Prevention and Treatment of Incisional Hernia: New Techniques and Materials

Eva Barbara Deerenberg

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Prevention and Treatment of Incisional Hernia: New Techniques and Materials

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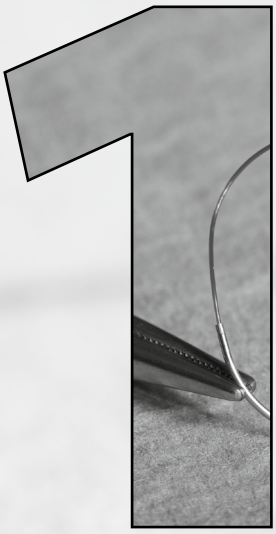

Introduction and outline of the thesis

Introduction

Ever since human beings have been walking in an erect position, abdominal wall hernias have likely been a problem. A hernia is a protrusion of abdominal content (preperitoneal fat, omentum, or abdominal organs) through an abdominal wall defect. Hernias usually develop in anatomically congenitally weak locations (e.g. inguinal, umbilical, and hiatal hernias) or as a result of prior surgery (incisional, parastomal, and trocar site hernias). After the discovery and introduction of asepsis and general anesthesia in the 19th century, there was a significant increase in the number of surgical interventions, and in the likelihood of surviving intra-abdominal surgery. As abdominal surgery became more common, the incidence of incisional hernia (IH) increased. In the present day, IH remains a common complication of surgery, and represents a large proportion of all ventral abdominal wall hernias; therefore, the subject of this thesis is IH. IH develops when the fascial tissue fails to heal at the incision site of a prior laparotomy. IHs are symptomatic in the vast majority of patients and associated with pain and discomfort, often resulting in a decreased quality of life and perception of body image(1). Additionally, incarceration and strangulation of abdominal contents can occur, for which emergency surgery is indicated, with associated morbidity and mortality(2). Furthermore, IHs are costly to treat(1, 3, 4) and recurrences do occur(5).

In decreasing order of incidence, IH can be diagnosed after upper midline incisions, lower midline incisions, transverse incisions, and subcostal incisions. Although midline incision is the type most associated with a high incidence of IH, it is still the incision most frequently used by abdominal surgeons. The midline incision provides surgeons with a rapid and wide access to the abdominal cavity, with minimal damage to the nerves, vascular structures, and muscles of the abdominal wall. IHs are also found to occur after paramedian, McBurney, Pfannenstiel, and flank incisions. Approximately 10-25% of all patients will develop IH after midline laparotomy(6-9). This incidence rises to 35% in patients with an aneurysm of the abdominal aorta(10-12); and incidences as high as 69% have been reported in high-risk patients after prospective long-term follow-up(13). During laparotomy, the creation of a stoma through the abdominal wall is necessary in approximately 25% of patients. A parastomal hernia (PSH) – a kind of IH – is a frequent complication following stoma creation, with a reported incidence of up to 48%(14, 15).

As far back as 1901, Eads recognized the high frequency of IH, and stated in the Annals of Surgery: *"The occurrence of ventral hernia as a sequence of abdominal section is so common that it should command our thoughtful consideration"*(16). Since then, extensive research on the aetiology and risk factors of abdominal wall hernias has been performed. During the 20th century, it was discovered that pathologic changes in connective tissue may render certain individuals particularly liable to hernia – a condition described as "herniosis"(17). The role of genetics, the collagen type 1 and 3 ratio, and matrix metalloproteinases in herniosis has been uncovered(18).

However, it is not only the patient characteristics and genetics that impair wound-healing that make patients susceptible to the development of IH. The effect of increased intra-abdominal pressure on the development and aggravation of abdominal wall hernias has also been recognized. In the last century, Jenkins focussed his research on a mechanical approach to IH development(19). During the postoperative period, abdominal distension can present as a problem, due, for example, to paralytic ileus. Almost all patients experience some period of paralysis, and approximately 40% of patients experience a paralytic ileus lasting more than five days(20). Jenkins' measurements showed that abdominal girth and the xiphoid-pubic distance may lengthen by up to 30% during abdominal distension. An adequate reserve of suture length in the wound is therefore necessary to allow for this lengthening to occur, to ensure the minimal resulting rise in tension between the sutures and the tissues. Jenkins calculated a suture length to wound length (SL:WL) ratio of 4:1 to be sufficient for a patient with postoperative abdominal distension and a 30% increase in wound length(19). Suturing the fascia of a midline laparotomy with a SL:WL of 4:1 reduces the tension on the suture, and, in turn, the risk of suture pull-out through the fascia. Applying an adequate SL:WL ratio significantly lowers the risk of IH(21, 22). In daily practice, most surgeons perform a continuous suture technique with slowly-absorbable suture material to close a midline laparotomy.

Conditions that impair wound healing and make patients susceptible to the development of IH include: wound infection, diabetes mellitus, obesity, immunosuppressive drugs, and smoking(4, 12, 23). Taking into account patient factors and surgical technique, the incidence of IH at the present time remains high, and prevention seems, therefore, of uttermost importance.

Despite the advances made in the prevention of IH, this still represents a common issue in general surgical practice. Non-surgical treatment for IH is mostly applied to patients that are unfit for surgery, and consists of abdominal binders to reduce the hernia and support the abdominal wall. The vast majority of IHs are symptomatic and require repair(1). In contrast to asymptomatic inguinal hernias, a watchful waiting strategy might not be a safe option for IHs(24). The risk of incarceration is high, and emergency repair is associated with a greater incidence of intraoperative bowel perforations, the development of enterocutaneous fistulas, and mortality(24). Elective surgical repair should be considered if: the hernia is symptomatic; the increased risk for incarceration outweighs the risk of the operation; when the size of the hernia complicates dressing or activities of daily living; or when decreased quality of life and perception of body image are a factor.

The surgical treatment of abdominal wall hernias has been performed since Hellenistic times, when Celsus performed hernial sac extirpations(18). Since then, many new surgical techniques, or modifications of established techniques, have been introduced. These repair techniques can broadly be divided into repair techniques without mesh (suture repair and autoplasty), and repair with mesh reinforcement. In 1899, Mayo described a transverse overlapping technique for repair of umbilical hernias(25), which was soon adopted as the standard technique for closing incisional and umbilical hernias. This technique was well adopted, but recurrence rates continued to frustrate surgeons. These procedures could not be performed for large abdominal wall defects, and new surgical techniques needed to be developed. With the introduction by Albanese and Ramirez of releasing incisions of the external oblique muscle, there was development of the components separation technique (CST) for large abdominal wall defects(26, 27). Besides several surgical techniques, transplantations of autologous or homologous materials were also explored. However, recurrence rates for hernia repair remained unsatisfactory high, and surgeons started to realize that ventral hernia repair might require the use of a foreign body.

Since 1859, when Edwin Drake first successfully obtained oil from the ground by drilling, the oil industry has flourished, and several new polymers have been developed and introduced to medicine. Perlon and nylon meshes (1944) were developed, and implanted during hernia repair. However, perlon was found to provoke an extreme inflammatory response, and nylon tended

to lose its strength and fall apart. American vascular surgeon Michael DeBakey discovered a new fabric called dacron (polyester) and used it to develop long-lasting vascular grafts. In 1956, the polyester vascular grafts were modified into synthetic meshes for hernia repair, and introduced to the market under the brand names Dacron and Mersilene. Around the same time, another American surgeon, Francis Usher, instigated collaboration with a petroleum company and developed a hernia mesh from the polymer Marlex. This first polyethylene Marlex mesh was further improved, and in 1963 the second generation Marlex mesh – of knitted polypropylene – was introduced, this compound being strong, biocompatible, and cheap. Over the following few years, Usher and other dedicated surgeons published good results for these synthetic meshes on recurrence rates and complications. But despite the positive reports, the surgical community, largely influenced by the high complication rates of earlier metal and plastic prostheses, saw little or no need for the routine use of these new meshes in hernia surgery.

In the following years, a third kind of synthetic mesh, made from expanded-polyetrafluoroethylene (e-PTFE), was developed by Gore. This new e-PTFE mesh was first used clinically in hernia repair in 1983. Although surgeons were starting to use meshes more and more in hernia repair, implantation was still reserved for complex or recurrent cases – particularly in ventral hernia repair. It took the publication of a randomized controlled trial from the Dutch REPAIR-group in 2000(23), for the worldwide surgical community to start to accept the use of meshes as the standard of care for ventral hernia repair. The impressive results of this RCT were published in The New England Journal of Medicine in 2000(23). Three-year follow-up revealed recurrence rates of 43% for suture repair, and 24% for mesh repair. Several years later, the long-term follow-up of this RCT showed a 10-year cumulative recurrence rate of 63% for suture repair, and 32% for mesh repair(5). In the following years, clinical trials were conducted on the different repair techniques and mesh prostheses for small and medium-sized ventral hernias, but the treatment of large IHs (over 10cm) has not yet been properly addressed. To improve the evidence-base for IH-surgery, the EHS developed a classification for IH which takes into account the location, size, and possible recurrence of the IH(28). This classification system has, since its introduction in 2009, been widely accepted and used in scientific publications about IH. However, a solid base of comparative research material on abdominal wall surgery has remained elusive, due to a strong heterogeneity in reported study population characteristics and outcome measurements.

The early meshes of polyester, polyethylene, polypropylene, and e-PTFE provided solid repair of the abdominal wall. However, these meshes were sometimes found to induce infectious complications, and adhesion formation when in contact with abdominal viscera. For these reasons, composite meshes with antibacterial and anti-adhesion coatings were developed, generating promising results. The anti-adhesive layer, added to a synthetic mesh, was designed to function as a barrier between the viscera and the mesh, reducing the risk of adhesion formation. However, implantation of synthetic meshes in infected environments remained problematic, with a high rate of mesh infections. Over the last decade, in response to this challenging indication, biological meshes of collagen have been developed, derived from animal or human donor tissue. These biological meshes were especially developed to be implanted in a contaminated or infected environment requiring closure. These biological collagen meshes are thought to be replaced by the patient's own collagen in time (remodeling), with associated low adhesion-formation, and a low infection risk. They are less suitable for bridging, however, because gradual absorption occurs, the risk of recurrence possibly being higher in such a case. The short-term results of biological mesh use for complicated abdominal wall repair seem promising, but long-term results on recurrence rates are not yet available. The Ventral Hernia Working Group have developed an incisional hernia grading system based on the characteristics of both the patient and the wound. It advises the use of a biological mesh in potentially contaminated environments (grade 3, i.e. patients with a previous wound infection, a stoma present, or involving an operation with violation of the gastrointestinal tract); and infected environments (grade 4, i.e. patients with an infected mesh or septic dehiscence)(29). Since long-term results are not yet available, and the cost of biological meshes is very high compared to synthetic meshes, evidence of superiority is necessary before widespread use of biological meshes can be justified.

Outline of the thesis

The **first aim** of this thesis is to determine the current incidence of IH, and the best surgical technique to prevent it. The **second aim** of this thesis is to study the treatment of IH, especially the repair of large IHs, and repair techniques using the novel biological and composite meshes.

In the **first part,** studies are presented on the current incidence of IH, and on the best surgical technique to prevent it.
In **Chapters 2** and **3,** the influence of exact suture techniques on the incidence of IH is examined. These chapters present the design (**Chapter 2**) and outcomes (**Chapter 3**) of a randomized controlled trial (RCT) comparing a commonly used 'large bites' technique (large tissue bites of at least a centimetre, with a stitch placed every centimetre) with a promising 'small bites' technique (small tissue bites of half a centimetre, with a stitch placed every half centimetre).
In **Chapter 4,** there is presentation of a systematic review and meta-analysis to evaluate the evidence from published RCTs examining suture materials or suture techniques on the incidence of IH.
In **Chapter 5,** the available evidence on the optimal materials and methods used to close abdominal wall incisions is used to report on European Hernia Society (EHS) guidelines.
In **Chapter 6,** a cross-sectional study on the incidence of IH and PSH in 150 patients with end-colostomy and midline laparotomy, is presented.
In **Chapter 7,** the aetiology of the combination of IH and PSH is further investigated. The effect of damage to the intercostal nerves due to herniation after colostomy formation with subsequent rectus atrophy and midline shift, is examined.

In the **second part** of this thesis, studies are presented on the surgical treatment of IH.
In **Chapter 8,** the results of a systematic review conducted to identify the best possible technique(s) for large IH repair, with regard to recurrence and complication rates, is reported on.
In **Chapter 9,** the EHS recommendations for abdominal wall surgery, for describing hernia variables, treatment variables, and for reporting outcomes, are presented.
In **Chapter 10,** several synthetic and biological meshes are compared in an animal experiment on adhesion formation and incorporation during long-term follow-up.
In **Chapter 11,** an animal experiment is described in which several synthetic and collagen meshes are implanted in a contaminated environment, and mesh infection and adhesion formation are evaluated.
In **Chapter 12,** the mesh-specific cellular responses are described.

In **Chapter 13,** an in vitro model to study the biomaterial-dependent reaction of macro-phages in an inflammatory environment is described.
In **Chapter 14,** the study of the infection susceptibility of several biological meshes in an experimental contaminated field is presented.
In **Chapter 15,** long-term results on the sustainability of abdominal wall repair with various biological meshes in an experimental setting, are presented.
In **Chapter 16,** a clinical case of bulging of a polyester mesh due to expansion of the pores is reported on.

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Part 1

Prevention and incidence of incisional hernia

Chapter

A multicenter randomized controlled trial evaluating the effect of small stitches on the incidence of incisional hernia in midline incisions (STITCH trial, NCT01132209)

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BMC Surgery 2011;11:20.

Abstract

Background

The median laparotomy is frequently used by abdominal surgeons to gain rapid and wide access to the abdominal cavity with minimal damage to nerves, vascular structures and muscles of the abdominal wall. However, incisional hernia remains the most common complication after median laparotomy, with reported incidences varying between 2-20%. Recent clinical and experimental data showed a continuous suture technique with many small tissue bites in the aponeurosis only, is possibly more effective in the prevention of incisional hernia when compared to the common used large bite technique or mass closure.

Design

The STITCH trial is a double-blinded multicenter randomized controlled trial designed to compare a standardized large bite technique with a standardized small bites technique. The main objective is to compare both suture techniques for incidence of incisional hernia after one year. Secondary outcomes will include postoperative complications, direct costs, indirect costs and quality of life.

Methods

A total of 576 patients will be randomized between a standardized small bites or large bites technique. At least 10 departments of general surgery and two departments of oncological gynaecology will participate in this trial. Both techniques have a standardized amount of stitches per cm wound length and suture length wound length ratios are calculated in each patient. Follow up will be at 1 month for wound infection and 1 year for incisional hernia. Ultrasound examinations will be performed at both time points to measure the distance between the rectus muscles (at 3 points) and to objectify presence or absence of incisional hernia. Patients, investigators and radiologists will be blinded during follow up, although the surgeon can not be blinded during the surgical procedure.

Conclusion

The STITCH trial will provide level 1b evidence to support the preference for either a continuous suture technique with many small tissue bites in the aponeurosis only or for the commonly used large bites technique.

Trial registration: Clinicaltrials.gov NCT01132209

Background

The median laparotomy is frequently used by abdominal surgeons to gain rapid and wide access to the abdominal cavity with minimal damage to nerves, vascular structures and muscles of the abdominal wall. However, incisional hernia remains the most common complication after median laparotomy, with reported incidences varying between 2-20%(1-5). Even higher incidences up to 30-35% have been reported in obese and aortic aneurysm patients(6-10). Incisional hernia can cause discomfort, impair quality of life or result in serious life-threatening conditions, such as incarceration or strangulation of the bowel(5). Median laparotomies and incisional hernias have been subject of investigation for a long period of time already. Although a lot is known about patient related risk factors and suture materials, technical risk factors such as suture techniques have not been investigated thoroughly(5, 11, 12).

For prevention of incisional hernia, many clinical trials and meta-analyses have demonstrated that a mass closure technique with a simple running suture is the best option to close a midline incision. A mass closure technique with a running suture is also easier and quicker to perform than layered techniques with interrupted sutures(5, 12-14). Furthermore, the use of slowly absorbable suture material compared with non-absorbable suture material decreases the incidence of incisional hernia, and it also lowers the incidence and intensity of postoperative pain and wound infection(12, 15, 16).

Suture length to wound length ratio and small bites

Several authors have stated that a suture length to wound length ratio (SL:WL) of four or more must be achieved, since a lower ratio is associated with an increased rate of incisional hernia(7, 17-20). It has often been recommended to place continuous stitches more than 10 mm from the wound edge in combination with a long stitch length(19, 21-28). A long stitch is the result of a large bite with the largest portion of fascia possible, aiming to increase tensile strength and to decrease the risk of fascial dehiscence. However, long stitches have been associated with high rates of both wound infection and incisional hernia(17, 29, 30). A long stitch length may be associated with higher risks of wound infection due to an increase in the amount of necrotic tissue within the wound. In experimental studies, the long stitch length has been found to compress or cut through soft tissue included in the stitch(31, 32). The risk

of incisional hernia may be higher because the stitch tends to slacken, which allows wound edges to separate.

Small stitches, placed 4–6 mm from the wound edge, only cut through the aponeurosis and not through the rectus abdominis muscle. Recent experimental data show that the small bites technique results in stronger wounds and faster healing than the routine large bite technique(33). Our experiments in a porcine model showed a 47% increase in breaking strength when small bites were used compared to the routine technique(32). A recent randomized of randomised clinical study by Millbourn et al. reported a decrease of incidence of incisional hernia of 70% 18% to 5.6%, $p<0.001$) and a decrease of 50%, (10.2% to 5.2%, $p=0.020$) of wound infection (34, 35). These results are very promising with regard to the prevention of incisional hernia and wound infection. The benefits of this technique need to be confirmed in a multicenter double-blinded randomized controlled trial.

In daily practice, most surgeons in the Netherlands use the large bite technique with large suture distances. With large bites, SL:WL ratio depends on the thickness of the abdominal wall including the muscles, the bite size, the number of stitches and the traction on the sutures during suturing. With large bites, an unanswered question remains with regard to how the SL:WL ratio of 4 should be reached. With a low traction force, fewer stitches are needed, but the slacking effect during the postoperative period may influence results.

With small stitches, SL:WL ratio is mostly dependent on the number of stitches. There is no sufficient evidence to prefer one suture closure technique over the other in order to prevent incisional hernia and fascia dehiscence.

Objective

The objective of the STITCH trial (Suture Techniques to reduce the Incidence of The inCisional Hernia) is to compare the small bites technique described by Millbourn et al. with a standardized large bites technique.

The overall objective of the study is reduction of the incidence of the most frequent complication of abdominal surgery, i.e., incisional hernia. We hypothesize that the small bites technique will result in a significant reduction of the incidence of incisional hernia, which may lead to a reduced morbidity and a better quality of life for patients and a significant reduction of costs.

Primary endpoint will be incisional hernia occurrence within one year after surgery, either clinically and/or ultrasonographically detected. Secondary

endpoints include postoperative complications, in particular surgical site infection, burst abdomen and wound pain in the first postoperative month.

Methods

Trial Design

The STITCH trial has been designed as a prospective, multicenter, double-blind, randomized controlled trial, in which the large bites technique will be compared with the small bites technique.

Participants

Patients scheduled for an elective abdominal operation through a midline incision will be asked for informed consent at the outpatient clinic or in hospital on the day preceding the day of surgery. Also, emergency laparotomies can be included in this trial if the patient is able to sign the informed consent. We intend to investigate the efficacy of the small bites technique in all risk groups. This also includes oncological gynaecological patients in centers with at least 50 median laparotomies a year.

Inclusion criteria:

- Signed informed consent
- Laparotomy through a midline incision
- Age 18 years or older

Exclusion criteria:

- Previous incisional hernia or fascial dehiscence with secondary healing after a midline incision
- Abdominal surgery through a midline incision within the last three months
- Pregnancy

Since the STITCH trial is an intervention study, it is not considered desirable to combine this trial with other intervention studies. In case of non-intervention (registration) studies, it will be judged on individual basis whether it is suitable and ethically correct to include a patient in both the STITCH trial and in another

study. Patients will be included in the STITCH trial in combination with one other trial (registration trials only), provided that it is possible to organize the informed consent and the follow up in a proper way for the individual patient for both trials.

Registration procedure

Included patient are registrated before surgery in an online data base (designed and managed by HOVON data center, Rotterdam, the Netherlands,) after signed informed consent via the Internet via TOP (Trial Online Process; see www.stitchtrial.nl). The patient namecode, date of birth, name of caller, name of responsible physician, sex and eligible criteria will be registered. Every participating institution has its own login code.

Randomisation procedure

The randomization process is started only 15 minutes before closure to prevent consequences due to the trial during the operation with the online TOP randomisation.

Patients will be randomized between closure with the large tissue bites technique or with the small tissue bites technique. Randomisation is stratified by center, and between surgeon or resident with a minimization procedure, ensuring balance within each stratum and overall balance. The randomization result will be given immediately by TOP. A confirmation email without randomization result will be send to the investigator.

Patients will be kept unaware of the type of closure until the endpoint of the trial. Surgeons or residents blinded for the procedure will perform outpatient clinic controls. Postoperative ultrasonography will be performed by radiologists blinded for type of closure. The randomisation procedure, blinding and objectification of incisional hernia by ultrasound will provide the best possible data to support preference for the large bites technique or the small bites technique over the other for closure of the abdominal wall.

Interventions

In this trial the large bites technique will be compared with the small tissue bites technique as developed in Sundsvall Hospital, Sweden(18). In the first group, the conventional large bites technique will be applied with bite widths of 1 cm and intersuture spacing of 1 cm with the use of one PDS plus II loop with a 48

mm needle. In the second group, the small bites technique will be applied with bite widths of 0,5 cm and intersuture spacing of 0,5 cm with the use of PDS plus II 2-0 with a 31 mm needle. In the small bites technique, twice as many stitches will be placed per sutured cm, with a smaller needle and thinner suture material. In the Swedish hospital where the small bites techniques has been in use for many years, this combination proved the easiest and safest method to perform the small bites technique(18, 34).

In both groups wound length is measured before closing of the fascia. After measurement of the wound length, the number of stitches is calculated. In the large bites technique at least one suture per cm wound length must be placed. In the small bites technique at least two sutures per cm wound length must be placed. The number of stitches is counted by the assistant during closure.

In both arms, suturing is initiated at both ends of the incision towards the middle where an overlap will be created of at least 2 cm. The remaining sutures will be measured and the suture length used for closure of the fascia and the SL:WL ratio will be calculated by the scrub nurse. In both arms, suture length to wound length ratios (SL:WL) of 4:1 are aimed at.

Implementation

In every hospital the OR nurses the surgeons or gynecologists and residents are instructed before the start of the trial in the individual institution during presentations and demonstration movies. During at least the first five inclusions the study coordinator will be present in the OR before randomization to assist randomization and control the correct applying of the standardized techniques. For every included patient a form with the detailed closing protocol in added to the clinical chart. Only when the surgeon is familiar with both the techniques, the nurses with the counting and measuring of the stitches and suture material and the study, centers are allowed to run the trial. Also for every included patient a form with the detailed closing protocol in added to the clinical chart. During the study unplanned audits are performed to control quality.

Outcome parameters

Primary outcome

- Primary outcome will be incisional hernia occurrence within one year after surgery, either clinically and/or ultrasonographically detected.

Secondary outcome

- Postoperative complications
- Pain
- Quality of life
- Cost effectiveness

We use the definition of the incisional hernia by the European Hernia Society: 'any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging'. The classification made by the European Hernia Society is used. [35] The classification of incisional hernias: Incisional hernias will be classified according to their localization, size, reducibility and symptoms.

Discharge dates and complications will be registered. Patients who fail to keep their annual clinic appointment will be given the option of a further appointment at a more suitable date or a visit to their home if they cannot make it to the outpatient clinic. The following data will be gathered at different points in time:

Preoperative data

- Date of birth
- Length and weight
- Current smoker (Yes or No).
- Medical history (including chronic obstructive pulmonary disease (COPD), diabetes mellitus, cardiac disease, prior laparotomies)
- Preoperative radiotherapy or chemotherapy
- Preoperative or perioperative corticosteroids
- Previous abdominal operations
- Other abdominal wall hernias
- American Society of Anaesthesiologists (ASA) classification
- Width of linea alba (if preoperative Computed Tomography Imaging is available)

Operation data

- Type of operation
- Suture length : wound length ratio
- Number of stitches
- Length of incision
- Closure time
- Blood loss
- Operation time
- Antibiotic prophylaxis
- Drains and location
- Thrombosis prophylaxis
- Pain medication
- Peroperative complications (intestinal lesions, bleeding, other)
- Epidural catheter

Postoperative data

- Blood transfusion
- Postoperative ventilation and duration
- Postoperative corticosteroids
- Postoperative radiation therapy
- Postoperative pain medication
- Postoperative ileus and duration
- Postoperative complications:
  - Centers for Disease Control criteria for Surgical Site Infection, according to the guidelines proposed by Mangram in 1999 (36).
  - Wound haematoma: accumulation of blood in the wound area, which warrants surgical exploration and intervention.
  - Pulmonary infections
  - Ventilation problems
  - Re-admission and indication
  - VAS pain score until day 6 postoperative

At 1 and 12 months, ultrasound imaging will be performed to examine the midline for any asymptomatic clinically not detectable incisional hernias. Size and location of any incisional hernias will be registered.

Outpatient clinic follow up

- Outpatient clinic visit at 1 and 12 months
  - Incisional hernia
  - Wound infection
  - Seroma formation
  - Other wound problems
  - Other abdominal wall hernia
- Ultrasound at 1 and 12 months
- VAS pain scores and Quality of Life forms preoperatively (day of operation or the day before) and at 1,3, 6 and 12 months

Ultrasound examinations

During the 1 month and 1 year follow up an ultra sound examination will be performed to measure the distance between the rectus muscles at 3 point in the incision and control for incisional hernia. A specific score is used for the ultrasound examination. At ten points, which include 4 measurements of the distance between the rectus muscle, the quality of the scar in the abdominal wall is objectified. With this method the conclusion if there is an incisional hernia can also be made on the score list. In this list is controlled for:

- An intact linea alba?
- Bulging without Valsalva maneuver?
- Bulging with Valsalva maneuver?
- Distance between rectus muscles in scar on 1/3 cranial part in cm?
- Distance between rectus muscles in scar on 1/3 caudal part in cm?
- Maximum distance between rectus muscles in scar in cm?
- Maximum distance between rectus muscles at place of bulging or defect in cm?
- Is there a defect? If yes, the size of the defect and location
- Is there fatty tissue in the defect?
- Is there a bowel loop in the defect?

The radiologist is asked to make prints of every measurement and finding.

Quality of life will be assessed based on standardized Quality of Life forms including the EuroQol-5D and Short Form-36 before and at 1 month, 3 months, 6 months, and 12 months after surgery.

Economic evaluation

We will perform an ex-post economic evaluation in which a new suture technique using small bites is compared with the traditionally applied large bites technique, from a societal perspective. The economic evaluation will be performed in accordance with Dutch guidelines(37).

To measure the economic impact of the new suture technique using small bites the cost-effectiveness will be assessed by calculating the incremental cost-effectiveness ratio, defined here as the difference in average costs between both suture techniques divided by the difference in average effects. The primary outcome measure will be the costs per reduced incisional hernia within 1 year. Secondary, a cost-utility analysis will be performed using costs per quality adjusted life year (QALY) as outcome measure, using the EQ-5D.

Costs for all separate actions and time used by all individual health care professionals, and all other materials will be measured from a societal perspective for both bites techniques, which means that both direct medical costs (e.g. intervention costs, intramural and extramural medical costs) and indirect costs (absence from work, patient costs) will be included in the analysis.

For the most important cost items, unit prices will be determined by following the micro-costing method (Gold et al, 1996), which is based on a detailed inventory and measurement of all resources used. Resource costs arise within the hospital and consist of outpatient visits, inpatient days, use of the operation room, radiology examinations, blood tests, etc. Real medical costs will be calculated by multiplying the volumes of health care use with the corresponding unit prices. For instance, the calculation of the costs of both suture techniques will consist of detailed measurement of investments in manpower, equipment, materials, housing and overhead. The salary schemes of hospitals and other health care suppliers will be used to estimate costs per hour for each health care professional. Taxes, social securities and vacations will be included.

Data on effects (reduction of incisional hernia), costs (time costs of new suture technique and material and development costs) and savings (reduced health care use of patients without incisional hernia) will all be collected in this study. Data on treatment (hospitalisation) and follow-up consultations will be collected retrospectively from (electronic) patient charts and hospital administration. This data will be collected by health care professionals using a data-collection form. Information will collected on:

- length of hospital stay
- length of stay in ICU
- reinterventions

Data on extramural care, work absence and other patient costs will be gathered via questionnaires at each follow-up (1 and 12 months).

For a description of the calculation of the effect measures see paragraph 'outcome parameters'. Discounting of future costs and effects is not relevant because of the limited time horizon of 1 year. When costs of a treatment are similar across subgroups, the absolute benefit determines the cost-effectiveness of a treatment for a specific subgroup. Randomized controlled trials are designed to evaluate the effects of treatment at the group level, and cost-effectiveness is usually calculated for this group as a whole. There could however be substantial and relevant between subgroup variability. It is therefore common to consider subgroup specific effects of interventions. The subgroup specific cost-effectiveness will be estimated by first deriving a prognostic index, based on the predefined predictors of incisional hernia: abdominal aneurysm aorta (AAA), obesity, diabetes, COPD, corticosteroid usage, radiotherapy, cardiovascular disease, smoking, age, cancer, other abdominal wall hernias and collagen disorders.

Sample size calculation

Millbourn et al. found a decrease in the incidence of incisional hernia from 18% to 5,6% in a randomized controlled trial. [34] In this trial, follow-up consisted of clinical instead of radiological examination for incisional hernia occurrence. In this trial, ultrasound examination will be used in order to be able to diagnose incisional hernia with higher sensitivity. It is expected that a relative decrease of the incidence incisional hernia after one year of 50% is reasonable. The mean reported one year incidence of incisional hernia in literature is 15%(1-5). In order to reduce the mean incidence of incisional hernia from 15 to 7.5%, power calculations showed that two groups of 259 evaluable patients each are needed (power=0.80, alfa=0.05). Loss to follow-up is estimated at 10% of included patients. A total of 576 patients (2 x 288) will be included in the study to correct for loss to follow-up. Overall effects will be calculated adjusted for predictive baseline characteristics, which will lead to a higher statistical power.

Statistical analysis

Descriptive statistics will include median and interquartile range for continuous variables, and absolute numbers (with %) for categorical variables. Randomized groups will be compared for imbalance without formal statistical testing. Analysis will be by intention-to-treat. Differences between randomized groups will be tested with appropriate statistical methods, including t-tests or Mann-Whitney tests for continuous variables (considering whether the normality assumption is rejected by the Kolmogorov-Smirnov test with Lilliefors correction test), and chi-square tests for categorical variables. The primary outcome (incisional hernia) will be analyzed with Kaplan–Meier analysis and a Cox regression analysis, to adjust for any loss to follow up between 30 days and 1 year after surgery. The primary analysis is a covariate adjusted Cox model, which includes the following predefined, well-establihed predictors of incisional hernia: abdominal aneurysm aorta (AAA), obesity, diabetes, corticosteroid usage, radiotherapy, COPD, smoking, age, cancer, inguinal hernia, cardiovascular disease and collagen disorders.

Subgroup effects will be assessed by tests of interaction to prevent overinterpretation of apparent differences in effectiveness. Quality of life data will be analyzed by paired T-tests, comparing baseline with follow-up measurements, and repeated measures analysis. A two-sided $p<0•05$ will be taken to indicate statistical significance.

Monitoring

The Erasmus University Medical center is the sponsor of this trial. Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death; is life threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, major safety finding from a newly completed animal study, etc. All SAEs will be reported to the accredited Medical Ethical Committee (MEC) that approved the protocol, according to the requirements of that MEC. Serious Adverse events are death and burst abdomen. Adverse Events are readmission and reoperations.

An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters every 3 months. The committee can unblind the data whenever deemed necessary based on reported adverse events. All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific adverse event. A copy of this report will be sent to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board. The Data Safety Monitoring Board will consist of an epidemiologist/ statistician and two independent surgeons.

Ethics

This study will be conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The Medical Ethical Committee of the Erasmus University Medical Center Rotterdam has approved the protocol. The Ethical Committees of the participating centers are applied for local feasibility. Prior to randomization, written informed consent will be obtained from all patients.

Discussion

A major issue in all suture studies is standardisation of technique. In a multicenter trial it is difficult to achieve standardisation because many surgeons and residents will contribute in this trial. The benefit of a large group of participants is that the results will be representable for daily practice.

In this trial two major parameters have been standardized: the difference between small and large bites and the amount of stitches per running cm of wound resulting in an appropriate SL:WL ratio.

In daily practice, most surgeons use the large bite technique with large suture distances. With large bites, SL:WL ratio depends on the thickness of the abdominal wall including the muscles, the bite size, the number of stitches and the traction on the sutures during suturing. With large bites there is an

unanswered question under which conditions an optimal SL:WL ratio of 4 should be reachable. With low traction on the suture fewer stitches are needed, but the slacking effect during the postoperative period will influence the results. For this reason in a RCT on suture techniques it is necessary to standardize the amount of stitches per centimetre of wound length.

Conclusion

The STITCH trial is a multicenter randomized trial (trialregister: http://clinicaltrials.gov/ct2/show/NCT01132209) comparing the costs and effectiveness of a standardized small tissue bites suture technique with a standardized large tissue bites technique in midline incisions. This trial will provide the surgical society the evidence needed to optimize a surgical technique used to prevent common surgical complications.

Appendix 1

Criteria for defining a Surgical Site Infection (SSI)

Superficial Incisional SSI

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

1. *Purulent drainage, with or without laboratory confirmation, from the superficial incision.*
2. *Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.*
3. *At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.*
4. *Diagnosis of superficial incisional SSI by the surgeon or attending physician.*

Do not report the following conditions as SSI:

1. *Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).*
2. *Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).*

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (e.g., fascial and muscle tissue) of the incision and at least one of the following:

1. *Purulent drainage from the deep incision but not from the organ / space component of the surgical site.*
2. *A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture negative.*

3. *An abscess or other evidence of infection involving the deep incision is found on direct examination, during re-operation, or by histopathological or radiological examination.*
4. *Diagnosis of a deep incisional SSI by a surgeon or attending physician.*

Notes:

1. *Report infection that involves both superficial and deep incision sites as deep incisional SSI.*
2. *Report an organ/space SSI that drains through the incision as a deep incisional SSI.*

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

1. *Purulent drainage from drain that is placed through a stab wound into the organ / space.*
2. *Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ space.*
3. *An abscess or other evidence of infection involving the organ / space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.*
4. *Diagnosis of a deep organ / space SSI by a surgeon or attending physician.*

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Chapter

Small bites versus large bites for closure of abdominal midline incisions: results of a double blinded multicenter randomized trial (STITCH-trial)

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Abstract

Background

Incisional hernia is a frequent complication of midline laparotomy and is associated with high morbidity, decreased quality of life, and high costs. We aimed to compare the large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.

Methods

We did this prospective, multicentre, double-blind, randomised controlled trial at surgical and gynaecological departments in ten hospitals in the Netherlands. Patients aged 18 years or older who were scheduled to undergo elective abdominal surgery with midline laparotomy were randomly assigned (1:1), via a computer-generated randomisation sequence, to receive small tissue bites of 5 mm every 5 mm or large bites of 1 cm every 1 cm. Randomisation was stratified by centre and between surgeons and residents with a minimisation procedure to ensure balanced allocation. Patients and study investigators were masked to group allocation. The primary outcome was the occurrence of incisional hernia; we postulated a reduced incidence in the small bites group. We analysed patients by intention to treat. This trial is registered at Clinicaltrials.gov, number NCT01132209 and with the Nederlands Trial Register, number NTR2052.

Findings

Between Oct 20, 2009, and March 12, 2012, we randomly assigned 560 patients to the large bites group (n=284) or the small bites group (n=276). Follow-up ended on Aug 30, 2013; 545 (97%) patients completed follow-up and were included in the primary outcome analysis. Patients in the small bites group had fascial closures sutured with more stitches than those in the large bites group (mean number of stitches 45 [SD 12] *vs* 25 [10]; p<0•0001), a higher ratio of suture length to wound length (5•0 [1•5] *vs* 4•3 [1•4]; p<0•0001) and a longer closure time (14 [6] *vs* 10 [4] min; p<0•0001). At 1 year follow-up, 57 (21%) of 277 patients in the large bites group and 35 (13%) of 268 patients in the small bites group had incisional hernia (p=0•0220, covariate adjusted odds ratio 0•52, 95% CI 0•31–0•87; p=0•0131). Rates of adverse events did not differ significantly between groups.

Interpretation

Our findings show that the small bites suture technique is more effective than the traditional large bites technique for prevention of incisional hernia in midline incisions and is not associated with a higher rate of adverse events. The small bites technique should become the standard closure technique for midline incisions.

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Introduction

Incisional hernia is a frequent complication of abdominal operations with an incidence of 10–23%, which can increase to 38% in specific risk groups(1-4). In the USA 4 million to 5 million laparotomies are done annually, suggesting that at least 400 000–500 000 incisional hernias can be expected to occur every year. Incisional hernia is associated with pain and discomfort, resulting in a decreased quality of life(5).Moreover, incarceration and strangulation of abdominal contents can take place, for which emergency surgery is indicated, with associated morbidity and mortality(6). About 348 000 operations for incisional hernia are done every year in the USA with US$3•2 billion in annual associated costs(7). Prevention of incisional hernia is therefore of paramount importance. Several suturing techniques for abdominal closure after a midline abdominal incision have been studied in the past few decades. Findings from meta-analyses have shown that a running technique with long-lasting monofilament suture material reduces the incidence of incisional hernia compared with interrupted suture techniques(3, 8). Nowadays, most surgeons, urologists, and gynaecologists use the running closure technique with large tissue bites to close midline incisions(9). In 2009, a study from Sweden(10) showed that a running suture technique with small tissue bites, developed by Israelsson, decreased the incidence of incisional hernia compared with a running suture technique with large tissue bites. In this study, small tissue bites were defined as placement of a stitch every 5–8 mm from the wound edge. This promising technique is contradictory to old surgical principles and needs to be thoroughly investigated before it can be widely implemented(11, 12). We did the STITCH study to compare the common conventional large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.

Methods

Study design

We did this prospective, multicentre, double-blind, randomised controlled trial at surgical and gynaecological departments in ten hospitals in the Netherlands. The trial protocol has been previously published(13). Patients aged 18 years

or older and scheduled to undergo elective abdominal surgery through a midline incision were asked to participate in the trial at the outpatient clinic or in hospital on the day before surgery. We excluded patients with a history of incisional hernia or fascial dehiscence after midline laparotomy, those who had undergone abdominal surgery through a midline incision within the past 3 months, those who were pregnant, or those who had participated in another intervention trial. The study protocol was approved by the institutional review board of Erasmus University Medical Center, Rotterdam, and by the review boards of each study centre before start of inclusion. All participants gave written informed consent. An independent data and safety monitoring board was constituted before the start of the trial. This board consisted of two independent surgeons and one biomedical statistician. All serious adverse events, defined as death and burst abdomen that happened during the study, were reported to the institutional review board of Erasmus University Medical Center. The progress of the trial and all adverse events were reported every 3 months to the data and safety monitoring board and the safety of the trial was examined.

Randomisation and masking

After provision of consent, patients were registered in an online database in which they were assigned a unique trial code. During surgery, about 15 min before closure, patients were randomly assigned (1:1), via a computer-generated randomisation sequence, to receive small tissue bites of 5 mm every 5 mm, or large bites of 1 cm every 1 cm (control group), for fascial closure. Randomisation was stratified by centre and between surgeons and residents with a minimisation procedure to ensure balance within each group and overall. Patients and study investigators were masked to group allocation. The data and safety monitoring board had access to unmasked data whenever deemed necessary.

Procedures

The principle of the small bites technique constituted placement of at least twice as many stitches as the incision length in cm with USP 2-0 PDS Plus II (Ethicon, Somerville, NJ, USA) with a 31 mm needle(10, 13-15). The suture technique was applied with tissue bites of 5 mm and intersuture spacing of 5 mm. In all cases the stitch incorporated the aponeurosis only and incorporation of fat or

muscle tissue was avoided. The conventional large tissue bites or mass closure technique was applied with tissue bites of at least 1 cm and intersuture spacing of 1 cm with USP 1 double loop PDS Plus II (Ethicon) with a 48 mm needle. In both groups, suturing was started at both ends of the incision towards the centre where an overlap of at least 2 cm of both the cranial and caudal sutures was created and both sutures were separately knotted. An additional knot from both the cranial and caudal sutures was allowed. The number of stitches was counted, wound length and length of the remaining suture measured, and ratio of suture length to wound length calculated by dividing the length of the suture used to close the fascia by the wound length. For both suture techniques, we aimed for a suture length to wound length ratio of 4:1 or higher(14). Patients were invited for follow-up at the outpatient clinic 1 month and 1 year after surgery. The 1 year follow-up visit was defined as a follow-up visit up to month 15 after surgery. During these visits patients underwent physical examination by a medical doctor and abdominal ultrasonography by a radiologist, both of whom were masked to group allocation. Any abdominal CT done after surgery was also used to identify the presence or absence of incisional hernia. Physical examination and assessment of CT of all patients was done by two medical doctors (EBD and JJH) specially trained for this trial. Patients who did not attend the outpatient clinic received a repeated invitation or were offered a home visit. In case of conflicting observations, the observation by radiological imaging was decisive. Patients were regarded as censored observations if they underwent re-laparotomy through midline incision, were deceased, or ended follow-up. Patients remained unaware of the type of closure until completion of follow-up. All participants were asked to fill out quality of life questionnaires preoperatively and at 1, 3, 6, and 12 months postoperatively. We assessed quality of life with the Short Form-36 (SF-36) and the EuroQoL-5D (EQ-5D) questionnaires(16, 17). EQ-5D includes a visual analogue scale to rate overall health status on a scale of 0 (worst imaginable health state) to 100 (best imaginable state). Additionally, in the first postoperative week, patients scored their pain on a visual analogue scale once a day.

Outcomes

The primary outcome was the occurrence of incisional hernia during follow-up. We used the definition of incisional hernia from the European Hernia Society (EHS):"any abdominal wall gap with or without bulge in the area of a postoperative

scar perceptible or palpable by clinical examination or imaging"(18). Secondary outcomes were short-term postoperative complications (eg, surgical site infection [scored as superficial, deep, or involving organ or space, as specified in the protocol(13)]), burst abdomen (fascia dehiscence), cardiac events, length of hospital stay, and health-related quality of life. Main endpoints regarding quality of life were differences between patients assigned to the small bites technique and those assigned to the large bites technique, and between patients with and without development of incisional hernia during follow-up.

Statistical analysis

We postulated a reduced incidence of incisional hernia in the small bites group. On the basis of the results of the Swedish trial(10), we calculated that 259 patients would be needed in each group to provide 80% power to detect a reduction of 50% (15% *vs* 7•5%) in the incidence of incisional hernia at a two-sided α level 0•05. We aimed for a total of 576 patients (n=288 per group) to correct for an estimated 10% loss to follow-up(10, 13). We analysed differences between groups with *t* tests for continuous variables and χ^2tests for categorical variables. For continuous variables, we tested equality of variance with Levene's test. Normal distribution of data was tested and confirmed by limited skewness and kurtosis. We analysed the primary outcome with cross-tables with χ^2testing and logistic regression to adjust for baseline covariates(19). We estimated final treatment effects with stratum of randomisation as a random effect in a generalised linear mixed model. We used a binomial error and logit link function in the glmer function of the lme4 package in R statistical sofware (version 3.1.0).

Considered baseline covariates were predefined potential predictors of incisional hernia: abdominal aneurysm aorta, body-mass index, diabetes mellitus, corticosteroid usage, preoperative chemotherapy, preoperative radiotherapy, chronic obstructive pulmonary disease (COPD), smoking, age, collagen disorders, non-incisional hernias (including inguinal hernia), and cardiovascular disease(13). For patients with missing covariate data for BMI, we imputed the mean BMI value. We assessed subgroup effects by tests of interaction to prevent over-interpretation of apparent differences in effectiveness for all baseline characteristics. We chose not to do Cox-regression analysis as specified in the protocol. Because most patients had available two-time measurements (1 month and 1 year postoperatively), we defined

incisional hernia as a binary endpoint if it took place up to 15 months after randomisation, with cross-table and logistic regression as the natural analyses, rather than Kaplan-Meier and Cox-regression analyses. Statistical comparison of quality of life between patient groups (small *vs* large bites technique and with or without incisional hernia during follow-up) was done by multilevel analysis (linear mixed-effects model with random effect for each patient). Time, randomisation (small *vs* large bites), and the interaction between time and randomisation were main effects, with adjustment for age and sex. Analysis was by intention to treat. We did statistical analysis with SPSS (version 20.0) and R statistical software (version 3.1.0).

This trial is registered with Clinicaltrials.gov, number NCT01132209, and Nederlands Trial Register, number NTR2052.

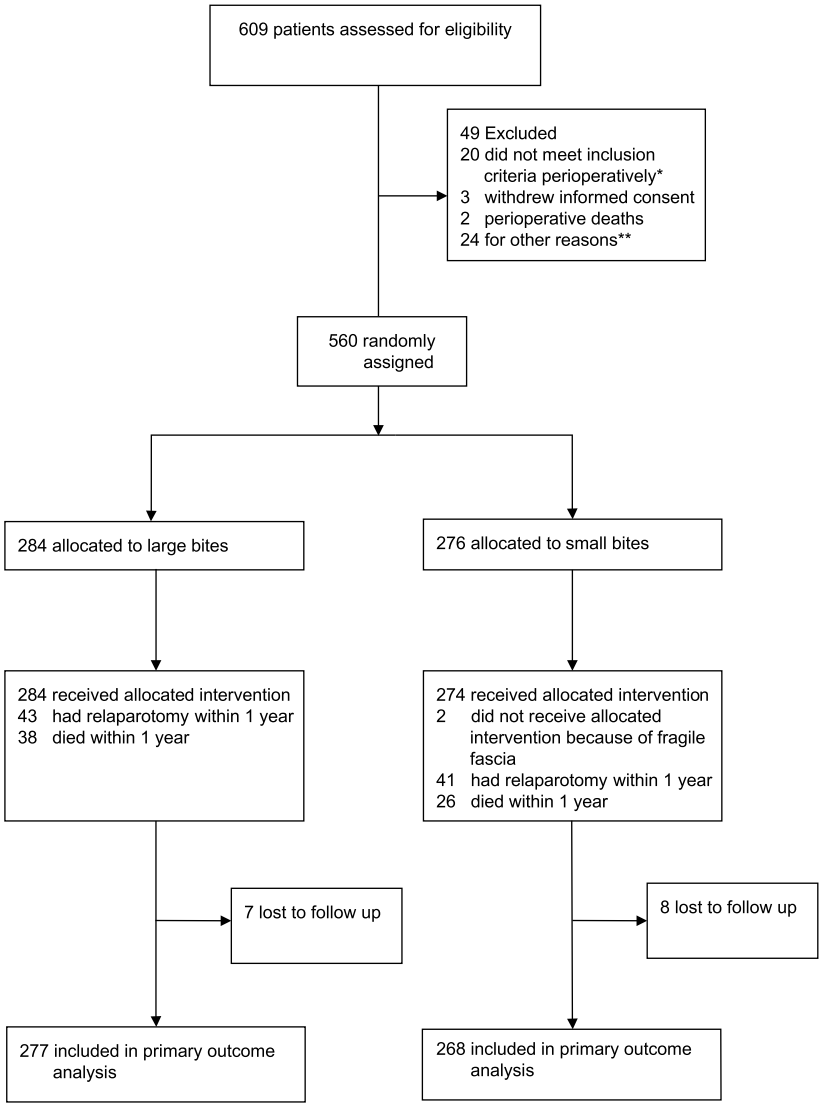
Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The figure shows the trial profile. Between Oct 20, 2009, and March 12, 2012, we randomly assigned 560 patients to the large bites group (n=248) or the small bites group (n=276). Follow-up ended on Aug 30, 2013; 545 (97%) completed follow-up and were included in the primary outcome analysis (figure). Baseline characteristics were similar between groups, except that slightly more patients with COPD were included in the small bites group (table 1). Most surgical procedures were for gastrointestinal oncological diseases and consisted of opening or partial resection of the gastrointestinal tract (table 1).

Figure: CONSORT flow-chart of study enrollment.(20)



*Not operated through midline incision, need to (partly) resect the abdominal wall or incisional hernia detected during incision. **Logistical reasons, computer randomisation issues, or surgeon was unfamiliar with this study.

Table 1: Baseline characteristics

	Large bites group (n=284)	Small bites group (n=276)
Sex		
• Male - n (%)	139 (48%)	137 (50%)
• Female - n (%)	145 (51%)	139 (50%)
Age - years (median, IQR)	63 (54-71)	62 (53-72)
BMI - kg/m²* (median, IQR)	24 (22-27)	24 (22-27)
Smoking - n (%)	65 (23%)	77 (28%)
Diabetes Mellitus - n (%)	39 (14%)	29 (11%)
COPD - n (%)	27 (10%)	44 (16%)
Cardiovascular disease - n (%)	116 (41%)	101 (37%)
Corticosteroid usage - n (%)	18 (6%)	28 (10%)
Non incisional hernias† - n (%)	34 (12%)	37 (13%)
Aneurysma abdominal aorta - n (%)	12 (4%)	13 (5%)
Previous laparotomy - n (%)	43 (15%)	49 (18%)
ASA classification - n (%)		
• 1	58 (20%)	61 (22%)
• 2	183 (64%)	162 (59%)
• 3 or higher	43 (15%)	53 (19%)
Preoperative chemotherapy - n (%)	75 (26%)	62 (22%)
Preoperative radiotherapy - n (%)	55 (19%)	59 (21%)
Type of surgery - n (%)		
• Gynecological	41 (14%)	41 (15%)
• Upper gastrointestinal	89 (31%)	74 (27%)
• Lower gastrointestinal	133 (47%)	140 (51%)
• Vascular	21 (7%)	21 (8%)

BMI=Body Mass Index. COPD=Chronic Obstructive Pulmonary Disease. ASA=American Society of Anesthesiologists. *Data for BMI were missing for 12 patients.†Eg, inguinal, umbilical, and epigastric hernias in history.

Peri-operative complications (gastrointestinal perforation, haemorrhage, or cardiopulmonary event) arose in 64 (11%) patients and were equally distributed between groups. The amount of blood loss and numbers of inserted drains were also equally distributed (data not shown). Approximation of subcutaneous tissue and method of skin closure did not differ between both groups (data not shown). Table 2 shows details of the suture techniques.

Table 2: Details of suture techniques

	Large bites group(n=284)	Small bites group(n=276)	p value
Number of stitches (mean; SD)	25 (10)	45 (12)	<0·0001
Total length of used sutures (cm) (mean; SD)	95 (34)	110 (39)	<0·0001
Wound length (cm) (mean; SD)	22 (5)	22 (5)	0·982
Rati of suture length to wound length (SL:WL) (mean; SD)	4.3 (1.4)	5.0 (1.5)	<0·0001
Time of fascial closure (minutes) (mean; SD)	10 (4)	14 (6)	<0·0001

Of 545 patients, follow-up assessments were done by clinical and radiological examination in 338 (62%) patients, by radiological examination in 76 (14%), and by physical examination in 131 (24%) patients. Follow-up methods were similar between groups. 1 year postoperatively, 57 (21%) of 277 patients had incisional hernia in the large bites group and 35 (13%) of 268 patients had incisional hernia in the small bites group (p=0•0220; adjusted odds ratio [OR] 0•52, 95% CI 0•31–0•87; p=0•0131). No subgroup effects were identified; all p values for interaction tests were greater than 0•20. In patients followed-up by both physical and radiological examination, incisional hernia was identified in 43 (49%) of 87 patients by both physical and radiological examination, in 41 (47%) of 87 solely by radiological examination, and in 3 (3%) of 87 solely by physical examination. In patients with incisional hernia, the mean fascial defect was 3•4 cm (SD 4•4). The size of the hernia defects did not differ significantly between groups (data not shown). Incisional hernias diagnosed by radiological examination alone were not significantly smaller than those diagnosed by both physical and radiological examination (mean 2•4 cm [SD 4•0] *vs* 4•2 cm [0•5]; p=0•0650.

Almost half of patients had postoperative complications, the incidence of which did not differ significantly between groups (table 3). Readmission rates and adverse events did not differ significantly between groups (table 3). Pain scores on the visual analogue scale did not differ significantly between groups in the first postoperative week (data not shown). 452 (94%) of 483 patients completed the SF-36 questionnaire and the EQ-5D questionnaire 12 months post-operatively. None of the SF-36 subdomains, the mental component summary (MCS) score, the physical component summary (PCS), or EQ-5D dimensions differed significantly between groups at 12 months (data not shown). Patients who developed incisional hernia during follow-up had lower general health SF-36 scores than did those without incisional hernia 12 months post-operatively (mean 60•16 [SD 18•27] *vs* 64•84 [48•70]; p=0•0326) and reported more problems in EQ-5D dimension of mobility (1•46 [1•06] *vs* 1•36 [0•46]; p=0•0318). We noted no significant differences for the other SF-36 domains, the MCS, the PCS, EQ-5D dimensions, or overall health status on VAS (data not shown).

Table 3: Secondary outcome parameters

	Large bites group (n=284)	Small bites group (n=276)	p value
Patients with postoperative complications - n (%)	129 (45%)	125 (45%)	1·000
Ileus - n (%)	33 (12%)	28 (10%)	0·590
Pneumonia - n (%)	40 (14%)	35 (1%)	0·710
Cardiac event - n (%)	30 (11%)	25 (9%)	0·573
Surgical Site Infection (SSI) - n (%)	68 (24%)	58 (21%)	0·419
• Superficial Incisional SSI*	33 (12%)	23 (8%)	0·207
• Deep incisional SSI*	12 (4%)	8 (3%)	0·496
• Organ/space SSI*	23 (8%)	27 (10%)	0·554
Burst abdomen - n (%)	2 (1%)	4 (1%)	0·444
Length of hospital stay (days) – mean (SE)	14 (24)	15 (35)	0·585

*detailed criteria for SSIs can be found in the published study protocol(13).

Discussion

Our findings show that suturing of the fascia after abdominal midline incision with a continuous small bites technique reduces the incidence of incisional hernia compared with suturing with the conventional large bites technique. The small bites technique with a single suture USP 2-0 is a safe technique in view of the low incidence of burst abdomen, and is easily learnt and performed with the small needle(15). With a mean additional closure time of 4 min, the small bites technique is not very time consuming; additionally, the technique is not associated with a difference in postoperative pain. Our results are generalisable to the general surgical population in view of the participation of residents and specialists of vascular, general, gastrointestinal and gynaecological surgical specialties.

Although the Swedish trial(10) was the first prospective trial comparing large and small bites, this study had methodological limitations. Patients were quasi-randomised (alternated per calendar week) and radiological examination of the abdominal wall was not done. As a diagnostic technique for the presence of incisional hernia, ultrasonography has a reported sensitivity of 70–98%; physical examination has a reported sensitivity of 58–74% in diagnosis of incisional hernia(21, 22). Furthermore, in 16–28% of patients with complaints of discomfort at their scar, but without a palpable defect during physical examination, an incisional hernia was diagnosed by ultrasonography(21, 22). Because almost half of incisional hernias in the present trial were diagnosed

solely during radiological examination, our results attest that radiological imaging is essential to assess the presence of incisional hernia. Guidelines on the closure of abdominal wall incisions from the European Hernia Society strongly recommend that prospective studies with incisional hernias as a primary outcome should integrate medical imaging in the follow-up(2, 9, 18, 21). In our trial, roughly three-quarters of patients received radiological imaging during follow-up. Some patients had such an obvious clinical incisional hernia that imaging would have added no extra information. In some patients, radiological imaging was not done, either because patients were visited at home or because of local logistical difficulties. We considered achievement of standardisation to be important. Two major parameters were standardised: the technique of small and large bites and the target number of stitches per running cm of wound length, resulting in an appropriate ratio of suture length to wound length.

Our study has some limitations. Our primary analysis was done after 1 year of follow-up. Previous studies(2, 4) have shown that incidence of incisional hernia increases during longer follow-up. Our follow-up of both clinical and radiological examination resulted in an incidence of 21% in the large bites group. These results are similar to those of other groups with longer follow-up(2, 4). Because radiological examination was done for the diagnosis of incisional hernia, small incisional hernias could have been diagnosed that would not have been detected by physical examination. We feel that the diagnosis of these smaller hernias explains the fairly high incidence in both groups at 1 year and might translate into a smaller increase in new hernias during longer follow-up. We do not expect that the effectiveness of the small bites will be affected with longer follow-up.

Another limitation might be that our results do not differentiate between an effect of the smaller bites or the use of different suture material. In this trial, we investigated the small bites technique described by Israelsson(14). For the small bites technique the UPS 2-0 PDS Plus II (Ethicon) single suture thread with a 31 mm needle was used, whereas the large bites procedure was done with a thicker PDS 1 loop with a 48 mm needle. Therefore, analysis of whether the small bites or the thinner needle and suture material reduces the incisional hernias in the small bites group needs further research.

We included only patients undergoing elective surgery. Evidence about the best closure technique in emergency laparotomy incisions is scarce, even in the EHS guidelines no recommendation is given(9). Whether results obtained

by studies for elective laparotomies can be extrapolated to emergency laparotomies remains a topic of discussion.

We hypothesise that the small bite suture technique in our trial, with twice the amount of stitches including the aponeurosis only, provides close to ideal conditions for fascia healing because of avoidance of necrosis of the rectus abdominis muscles and of optimum distribution of forces leading to a reduced incidence of incisional hernia. Experimental studies show that a suture technique with an equal distribution of forces on the fascia is necessary to achieve an optimum ratio of collagen type 1 to type 3. Too high tensile force per suture will result in more scar tissue(23, 24). The holding force of a suture depends on the collagen that deposits in the suture, which is best achieved by suturing of the aponeurosis without muscle or fat tissue(25). Experimental data show that the small bites technique is stronger than the large bites technique, which is consistent with the results of this clinical study(26).

In this era of minimally invasive and robotic surgery, many patients with high-risk profiles or undergoing major abdominal surgical procedures will still have to have open surgical procedures with midline incision. Compared with previous trials, we examined a relatively high-risk group, which is relevant and consistent with present surgical practice. Challenging patient and surgical characteristics could be an explanation of the overall complication rate and the fairly high incidence of surgical site infection in both groups. The higher incidence of surgical site infection in our trial than in the Swedish trial might be explained by the difference in patient condition (eg, previous midline incision, more patients with diabetes, perioperative chemoradiation, and malnutrition), more major surgical procedures, and use of a strict standardised wound scoring method in this trial(10, 27). Although surgical site infection was not the primary endpoint of our trial, our results emphasise that wound infection remains a frequent complication in this surgical population and should be monitored carefully.

We also reported health-related quality of life and pain of patients who received the small bites suture technique. Postoperative quality of life or pain did not differ between the two groups. Patients with incisional hernia in both groups had significantly lower scores on the general health dimension and had more mobility problems. Furthermore, most of our patients had malignant disease, which is associated with a reduced quality of life in general(5, 28, 29).

In conclusion, the small bites suture technique is more effective than the traditional large bites suture closure technique for prevention of incisional hernia in midline incisions. The small bites technique is not associated with more pain or adverse events and should be considered the standard closure technique for midline incisions.

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Chapter

The MATCH review; Meta-analysis on Materials and TeCHniques for laparotomy closure

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Abstract

Introduction

The aim of this systematic review and meta-analysis was to evaluate the evidence from published randomized controlled trials (RCT) comparing closure materials or suture techniques for emergency and elective laparotomies. The primary outcome was incisional hernia after 12 months and the secondary outcomes were burst abdomen and surgical site infection (SSI).

Materials and methods

A systematic computerized literature search was conducted using Medline, EMBASE, the Cochrane library, CINAHL, Scopus and Web-of Science including publications until May 2016. The quality of the RCTs was evaluated by at least 3 assessors using critical appraisal checklists from SIGN. Meta-analyses were performed with Review Manager v5.3.

Results

A total of 23 RCTs were included in the meta-analysis. There was no evidence from RCTs using the same suture technique in both study arms, that any suture material (fast absorbable/slowly absorbable/non-absorbable) is superior in reducing incisional hernias. There is no evidence that continuous suturing is superior in reducing incisional hernias compared to interrupted suturing (OR = 1.20 ; 95%CI : 0.84, 1.71). For continuous suturing in elective midline closure, the small bites technique results in significantly less incisional hernias than a large bites technique (OR = 0.41 ; 95%CI : 0.19, 0.86).

Conclusion

No suture material or suture technique was proven superior. This allows us to choose a continues suture (faster) technique using a slowly absorbable suture and small bites (or small needle) for closure of a midline laparotomy.

Introduction

Incisional hernia is a frequent problem after abdominal surgery with an incidence varying from 10% to 69% depending on the type of surgery, length and method of follow-up and patient characteristics(1-5). Incisional hernias develop due to insufficient healing of the abdominal wall after surgery. The defect in the abdominal wall allows for protrusion of intra-peritoneal content causing a variety of symptoms ranging from discomfort and impaired body image to incarceration and ischemia of the contents of the hernia sac. Besides significant morbidity and impaired quality of life, incisional hernias are costly to treat(6, 7). Well-known patient related risk factors for incisional hernia formation are smoking, obesity, relaparotomy and postoperative wound complications(8, 9). Additionally, the suture material and the surgical technique used to close a laparotomy wound are important surgical determinants of the risk of developing an incisional hernia. To reduce the incidence of incisional hernia, an international group of experts developed the European Hernia Society guidelines on the closure of abdominal wall incisions(10). The recommendations in this guideline for closure of midline incisions included a continuous suture technique, performed with a small bites technique and a slowly-absorbable suture material. These recommendations were mainly based on the evidence from systematic reviews on the subject(11-13). However, the randomized controlled trials (RCTs) included in these reviews generally compare a continuous suture technique with a slowly- or non-absorbable suture to an interrupted suture technique with a fast-absorbable suture. A comparison limited to those studies evaluating only one variable between study arms (same technique performed with different suture materials or different techniques performed with same suture material) was not performed. It was the hypothesis that in order to evaluate a certain suture material or technique, the same suture material should be used in both arms with various techniques and vice versa. Therefore this systematic review and meta-analysis was done to assess the evidence from published RCTs comparing closure materials or techniques for laparotomies with a primary outcome of incisional hernia after 12 months and with secondary outcomes of surgical site infection (SSI) and burst abdomen.

Materials and methods

A written study protocol was produced and registered on Prospero (CRD42015023689) before the initiation of the systematic review and meta-analysis. The data are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(14).

Inclusion and exclusion criteria

The aim of the systematic review and meta-analysis was to evaluate published RCTs comparing techniques and materials for fascial closure of a laparotomy. The primary outcome was incisional hernia and the secondary outcomes were SSI, burst abdomen/wound dehiscence and suture sinus formation. A minimum of 12 months follow-up was required. All types of incisions (transverse/midline/oblique/paramedian), all indications for surgery (both emergency and elective laparotomies) were included. Only human studies on adults $\geq$ 18 years of age were included. Studies on mesh closure of laparotomies and studies including historic suture materials such as catgut and stainless steel sutures for comparison were excluded.

Search strategy

A systematic computerized search was done independently by two authors (NAH and FM) in the following databases: Medline, EMBASE, Cochrane, SCOPUS, CINAHL and Web-of-Science. The search was not restricted to certain languages or years of publication. The last search was performed the 9th of May 2016. In Medline and EMBASE, the search strategy was based on the Medical Subject Heading (MeSH) terms: laparotomy, wound closure, sutures and abdominal wall hernias. The detailed search term for Medline was *((“Wound Closure Techniques”[Mesh] OR “Sutures”[Mesh] OR “Surgical Procedures, Operative”[Mesh] AND “Laparotomy”[Mesh] AND (Randomized Controlled Trial[ptyp] AND “humans”[MeSH Terms])) OR (“Wound Closure Techniques”[Mesh] OR “Sutures”[Mesh] OR “Surgical Procedures, Operative”[Mesh] AND “Laparotomy”[Mesh] AND “Hernia, Ventral”[Mesh] AND (Randomized Controlled Trial[ptyp] AND “humans”[MeSH Terms])))*.

Evaluation of papers and data extraction

Firstly, the records were screened by title and abstract by two assessors independently (ED, LV). Secondly, the full-texts were divided into two groups and each group was evaluated by two authors (NAH, ED, LV, RF) independently for eligibility with the use of critical appraisal checklist for randomized controlled trials developed by the Scottish Intercollegiate Guidelines Network (SIGN). Only papers rated as 'acceptable' or 'high quality' by SIGN were included in order to limit the risk of bias. Any disagreement between the two assessors were settled by discussion with a third evaluator (FM, MM). Data was extracted by two authors independently with regard to the predefined outcomes (NAH, FM) and checked by co-authors (LV, RF). Non-English full-texts were handled with same procedure by two individual assessors outside the author group.

Selection of outcomes to be included in the meta-analysis

In the meta-analysis, sutures were divided into fast-absorbable/slowly-absorbable and non-absorbable sutures regardless of whether the sutures were monofilament or multifilament. Suture methods were divided into interrupted versus continuous suturing and small bites versus big bites technique, regardless of a layered or mass closure technique was used. Emergency and elective laparotomies were pooled in the same analysis, as was all types of incisions (midline, transverse/oblique/paramedian). It was decided only to compare different suture types, when the same suture method was used in both arms. Likewise, suture methods were only compared, when the same type of sutures were used for both methods.

Statistical analysis

The outcomes were pooled in conventional meta-analyses and reported as weighted odds ratios (OR) with 95% confidence intervals (95% CI) using the random effects model and illustrated with forest plots. Heterogeneity was explored using I^2 statistics. Funnel plots were used to assess possible publication bias. The Cochrane risk of bias tool was used to assess the risk of bias. Kappa statistics were used to assess the agreement between two assessors. Statistical analyses were performed with Review Manager Software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Literature search

Out of 1,818 citations, a total of 23 RCTs with 10,130 patients were included in the meta-analyses (Figure 1). The level of agreement between the two assessors was moderate for screening abstracts and high for assessing eligibility of the full-texts. All studies were published in peer-reviewed journals from 1981 to 2015. One study was in French, and the remaining 22 studies were English. Study characteristics are listed in Table 1.

Risk of bias

Seven of the studies were considered high quality with the SIGN critical appraisal checklist, and the overall risk of bias was low. The most frequent source of bias was performance bias, as 12 of the studies did not report whether participants or personnel were blinded to the allocation. The funnel plots revealed no signs of publication bias.

Type of laparotomy

A total of 6 studies included only elective midline laparotomies(4, 12, 15-18). Nine of the studies included both emergency and elective midline laparotomies(2, 19-26), but none of them reported outcome data separately for the emergency or elective procedures. A total of 5 studies included emergency and elective procedures through all kinds of incisions(27-31), but again outcome data was not reported separately for emergency and elective procedures. Only two of the studies(30, 31) subgrouped the outcome data with regard to incision type and Sahlin *et al.* reported more incisional hernias and wound dehiscences in midline laparotomies, whereas Richards *et al.* found no significant differences regarding type of incision.

Reporting of suture technique

The suture technique differed widely between the studies, making it difficult to extract data on varying suture methods apart from continuous versus interrupted and small bites versus big bites technique. In 9 of the studies, the stitch size was not reported. Six studies(2, 4, 12, 15, 25, 32) reported that a 4:1 suture technique was used, but only half of them reported the specific measurements(4, 12, 25).

Table 1. Overview of included studies

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Agrawal et al.(32)	Acceptable	147 (40/47/45/42)	Emergency midline laparotomy	Non-absorbable continuous mass-closure (polypropylene 1-0) Non-absorbable interrupted mass-closure (polypropylene 1-0)	Absorbable continuous mass-closure (polyglactin 1-0) Absorbable interrupted mass-closure (polyglactin 1-0)	48 mo	4:1 ratio, N/A	Incisional hernia, SSI, dehiscence, suture sinus.
Berretta et al. (15)	Acceptable	191 (63/63/65)	Elective midline laparotomy	Non-absorbable monofilament continuous mass-closure (Premilene 1-0) Non-absorbable multifilament interrupted fascial closure (Ethibond 2-0)	Slowly-absorbable monofilament continuous mass-closure (PDS 1-0)	36 mo	4:1 ratio, N/A	Incisional hernia, SSI, dehiscence, scar pain
Bloemen et al.(2)	High quality	456 (233/233)	Emergency and elective midline laparotomy	Non-absorbable monofilament continuous single layer (Prolene 1-0)	Slowly-absorbable monofilament continuous single layer (PDS 1-0)	35 mo	4:1 ratio, 1 cm from fascial edge	Incisional hernia, SSI, suture sinus

Table 1. continued

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Bresler et al.(16)	High quality	235 (70/71/62)	Elective midline laparotomy	Slowly absorbable polydioxanone continuous suture (I or II)	Rapid absorbable continuous suture polyglactin	12 mo	N/A, N/A	Incisional hernia, SSI, dehiscence, suture sinus.
Cameron et al.(19)	High quality	284 (143/141)	Emergency and elective midline laparotomy	Non-absorbable monofilament interrupted mass closure (Prolene 1-0)	Slowly-absorbable monofilament interrupted mass closure (PDS 1-0)	15 mo	N/A, N/A	Incisional hernia, SSI, dehiscence
Carlson et al.(20)	Acceptable	225 (112/113)	Emergency and elective midline laparotomy	Non-absorbable monofilament nylon continuous mass closure (Ethilon 0-0 loop)	Slowly-absorbable monofilament polygluconate continuous mass closure (Maxon 0-0 loop)	24 mo	N/A, N/A	Incisional hernia, SSI, dehiscence
Colombo et al. (17)	Acceptable	614 (308/306)	Elective midline laparotomy	Slowly-absorbable monofilament polygluconate continuous (Maxon 1-0)	Absorbable multifilament polyglucolic acid Interrupted Smead-Jones (Dexon 1-0)	33 mo	N/A, 1.5-2 cm from fascial edge and 1.5-2 cm apart. Smead-Jones near 0.5 cm and far 2.0 cm.	Incisional hernia, dehiscence

Table 1. continued

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Corman et al. (21)	Acceptable	161 (49/53/59)	Emergency and elective midline laparotomy	Monofilament non-absorbable polypropylene interrupted single layer (Prolene) Multifilament non-absorbable uncoated nylon interrupted single layer (Nurolon)	Multifilament absorbable interrupted single layer (Vicryl)	19 mo	N/A, N/A	Incisional hernia, SSI, dehiscence, suture sinus.
Deerenberg et al. (4)	High quality	560 (284/276)	Elective midline laparotomy	Slowly absorbable monofilament, continuous single layer small bites (PDS 2-0)	Slowly absorbable monofilament, continuous mass closure big bites (PDS 1-0 loop)	12 mo	4:1 ratio, small bites 0.5 cm from fascial edge and apart, big bites 1 cm from fascial edge and apart	Incisional hernia, SSI, burst abdomen
Deitel et al. (18)	High quality	84 (42/42)	Elective midline laparotomy	Slowly-absorbable monofilament polygluconate continuous single layer (Maxon 1-0)	Absorbable multifilament polyglucolic acid continuous single layer (Dexon 1-0)	24 months, exact mean not reported	N/A, N,A	Incisional hernia, seroma, SSI
Donaldson et al.(33)	Acceptable	231 (80/74/77)	Emergency and elective paramedian laparotomy	Continuous polypropylene (Prolene 1-0)	Continuous chromic catgut 1-0 Continuous polyglycolic acid (Dexon 1-0)	12 mo	N/A, N/A	Incisional hernia, SSI, dehiscence, suture sinus.

Table 1. continued

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Gislason et al. (27)	Acceptable	599 (203/199/197)	Emergency and elective subcostal, transverse and midline laparotomy	Continuous mass polyglucanate (Maxon loop) Continuous mass polyglactin (Vicryl)	Interrupted polyglactin (Vicryl)	12 mo	N/A, 1.5 cm from fascial edge and 1.5 cm apart	Incisional hernia, burst abdomen
Gurjar et al.(22)	Acceptable	200 (100/100)	Ermergency and elective midline laparotomy	Continuous polypropylene, intermittent Aberdeen knot at every 4 stitch (Prolene 1-0)	Interrupted simple stitch polypropylene (Prolene 1-0)	12 mo	N/A, 2 cm from fascial edge and 2 cm apart	Incisional hernia, SSI, dehiscence
Gys et al.(28)	Acceptable	132 (67/65)	Emergency and elective subcostal and midline laparotomy	Non-absorbable polyamide continuous layered closure with (Ethilon 1-0)	Slowly-absorbable monofilament polygluconate continuous layered closure (Maxon 1-0)	12 mo	N/A, 1 cm from fascial edge and 1 cm apart	Incisional hernia, SSI, burst abdomen
Hsiao et al.(34)	High quality	340 (184/156)	Elective midline, subcostal, paramedian and transverse laparotomy	Slowly-absorbable monofilament polydioxane continuous layered closure with (PDS loop 0-0)	Absorbable multifilament polyglactin continuous layered closure (Vicryl 0-0)	24 mo	N/A, 1.5 cm from fascial edge and 1.5 cm apart	Incisional hernia, SSI
Krukowski et al.(23)	Acceptable	757 (374/383)	Emergency and elective midline laparotomy	Non-absorbable monofilament continuous mass closure (polypropylene)	Slowly-absorbable monofilament continuous mass closure (Polydioxane)	12 mo	N/A, stitch size 1 cm apart and 1 cm from edge	Incisional hernia, SSI, dehiscence

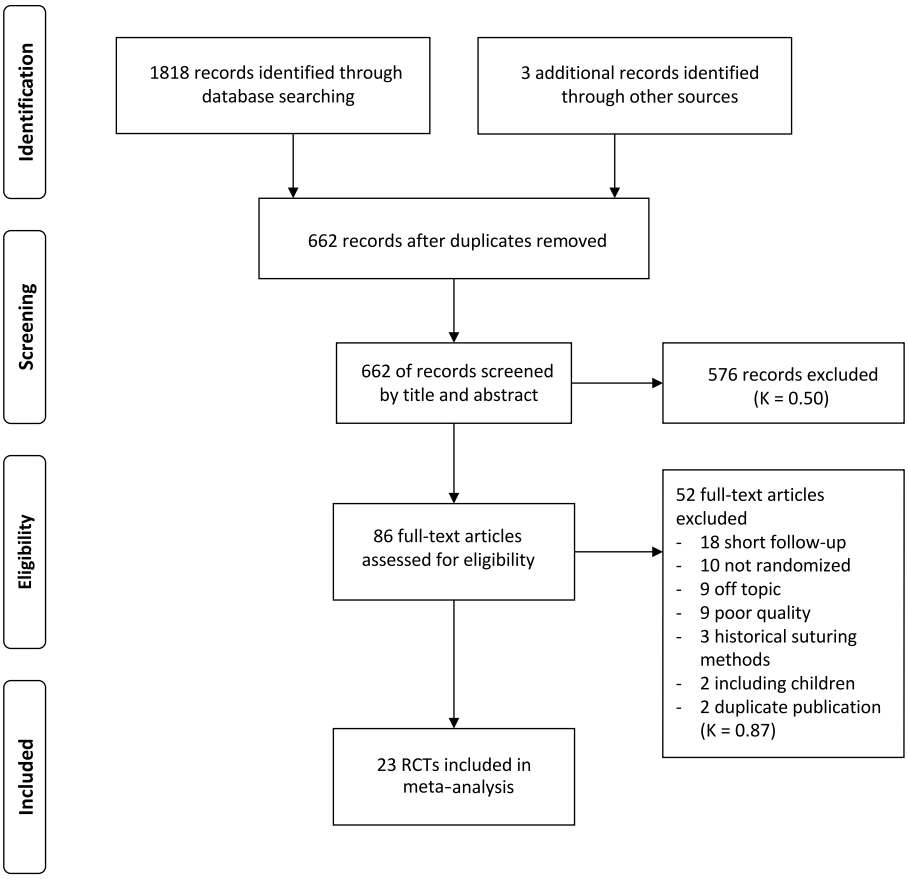
Table 1. continued

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Lewis et al.(24)	Acceptable	200 (105/95)	Emergency and elective midline laparotomy	Non-absorbable polypropylene, continuous layered closure (Prolene 1-0)	Rapid absorbable polyglycolic acid, interrupted Smead Jones (Dexon 1-0)	60 mo	N/A, 1 cm from edge, 1-2 cm apart	Incisional hernia, SSI, dehiscence
Millbourn et al.(25)	Acceptable	737 (381/356)	Emergency and elective midline laparotomy	Slowly-absorbable continuous single-layer small bites (PDS 2-0)	Slowly-absorbable continuous single-layer big bites (PDS 1-0)	12 mo	4:1 ratio, small bites 0.5 cm from fascial edge and apart, big bites 1 cm from fascial edge and apart	Incisional hernia, SSI, dehiscence
Osther et al.(29)	Acceptable	204 (100/104)	Emercency and elective midline, paramedian, transverse and oblique laparotomy	Slowly-absorbable polygluconate, single layer interrupted sutures (Maxon 0-0)	Rapid absorbable polyglycolic acid single layer interrupted sutures (Dexon 0-0)	12 mo	N/A, 1,5 cm from fascial edge and 1 cm apart	Incisional hernia, SSI, dehiscence
Richards et al.(30)	Acceptable	571 (286/285)	Emercency and elective midline, paramedian, transverse and oblique laparotomy	Non-absorbable continuous layered polypropylene (Prolene 0-0)	Rapid absorbable polyglycolic acid layered interrupted Smead-Jones (Dexon 0-0)	12 mo	N/A, 1,5 cm from fascial edge and 1 cm apart	Incisional hernia, SSI, dehiscence, haematoma
Sahlin et al.(31)	High quality	988 (345/339)	Emergency and elective midline, transvere and paramedian laparotomy	Slowly-absorbable monofilament polygluconate, continuous (Maxon 0-0)	Rapid absorbable multifilament polyglactin, interrupted (Vicryl 0-0)	12 mo	N/A, N/A	Incisional hernia, SSI, dehiscence

Table 1. continued

Paper	Quality assessment	Number of patients (group A/group B)	Type of laparotomy	Intervention	Comparison	Length of follow-up (months)	Suture to wound length ratio, stitch size	Outcome measures
Wissing et al.(26)	Acceptable	1539 (365/379/370/377)	Ermergency and elective midline laparotomy	Slowly-absorbable polydioxane single layer continuous (PDS 0-0) Non-absorbable single layer continuous (nylon 1-0)	Rapid absorbable multifilament polyglactin, single layer interrupted (Vicryl 1-0) Rapid absorbable multifilament polyglactin, single layer continuous (Vicryl 1-0)	12 mo	N/A, N/A	Incisional hernia, SSI, dehiscence, suture sinus, wound pain
Seiler et al.(12)	Acceptable	625 (210/205/210)	Elective midline laparotomy	Continuous slowly absorbable (MonoPlus) Continuous slowly absorbable (PDS)	Interrupted Vicryl	12 mo	4:1 ratio, N/A	Incisional hernia, SSI, burst abdomen

Figure 1. PRISMA flow diagram of search strategy and study selection



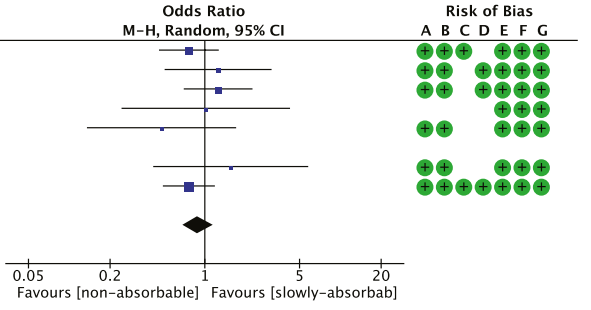
Primary outcome – incisional hernia

The vast majority of the studies defined incisional hernia with clinical examination as a protrusion of the laparotomy scar with the use of Valsalva's maneuver. Only five studies used radiological examination in the identification of incisional hernias(2, 4, 12, 15, 32). There was no reporting on differences of incisional hernia rates between elective and emergency laparotomies(2, 19-31). There were no significant differences on incisional hernia rates when comparing non-absorbable and slowly-absorbable sutures or slowly-absorbable and fast-absorbable sutures (Figures 2and 3). There was a tendency towards fewer incisional hernias, when using non-absorbable sutures compared with fast-absorbable sutures, but this was not significant (Figure 4).

Figure 2. Forrest plot of incisional hernia rates using non-absorbable versus slowly-absorbable sutures and the same suture technique.

Study or Subgroup	Non-absorbable Events	Total	Slowly-absorbable Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Wissing 1987	31	299	37	281	26.1%	0.76 [0.46, 1.27]	1987
Cameron 1987	11	90	10	100	8.2%	1.25 [0.51, 3.11]	1987
Krukowski 1987	28	295	22	285	19.8%	1.25 [0.70, 2.25]	1987
Gys 1989	4	64	4	65	3.3%	1.02 [0.24, 4.25]	1989
Carlson 1995	4	91	7	80	4.2%	0.48 [0.14, 1.70]	1995
Brolin 1996	20	109	11	120		Not estimable	1996
Beretta 2010	6	63	4	63	3.9%	1.55 [0.42, 5.79]	2010
Bloemen 2011	45	223	58	233	34.5%	0.76 [0.49, 1.19]	2011
Total (95% CI)		**1125**		**1107**	**100.0%**	**0.89 [0.69, 1.16]**	
Total events	129		142				

Heterogeneity: Tau² = 0.00; Chi² = 4.33, df = 6 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

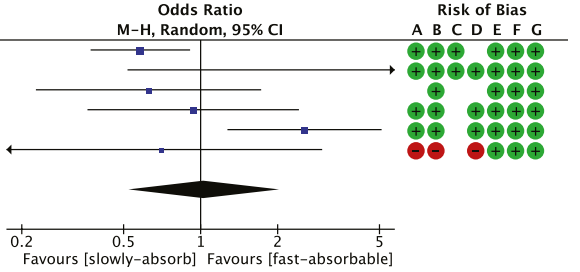


Risk of bias legend
(**A**) Allocation concealment (selection bias)
(**B**) Random sequence generation (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 3. Forrest plot of incisional hernia rates using slowly-absorbable versus fast-absorbable sutures and the same suture technique.

Study or Subgroup	Slowly-absorbable Events	Total	Fast-absorbable Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Wissing 1987	37	281	60	290	25.4%	0.58 [0.37, 0.91]	1987
Deitel 1990	4	42	0	42	4.5%	9.94 [0.52, 190.60]	1990
Osther 1995	7	67	11	70	17.4%	0.63 [0.23, 1.72]	1995
Bresler 1995	15	141	7	62	18.3%	0.94 [0.36, 2.42]	1995
Gislason 1995	19	164	16	327	22.0%	2.55 [1.27, 5.10]	1995
Hsiao 2000	3	156	5	184	12.4%	0.70 [0.17, 2.99]	2000
Total (95% CI)		**851**		**975**	**100.0%**	**1.03 [0.52, 2.03]**	
Total events	85		99				

Heterogeneity: Tau² = 0.42; Chi² = 15.46, df = 5 (P = 0.009); I² = 68%
Test for overall effect: Z = 0.09 (P = 0.93)



Risk of bias legend
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(**C**) Blinding of participants and personnel (performance bias)
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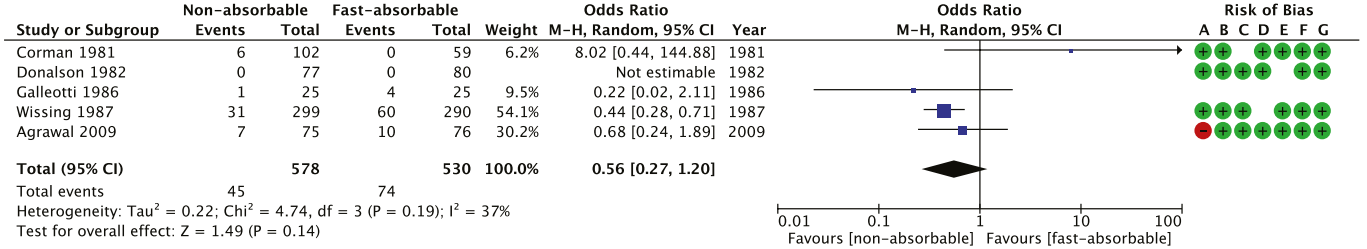
(**G**) Other bias

Figure 4. Forrest plot of incisional hernia rates using non-absorbable versus fast-absorbable sutures and the same suture technique.



Risk of bias legend
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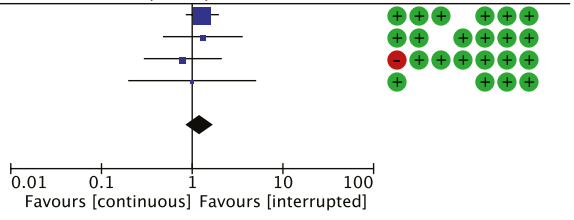
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

There was no significant differences between continuous and interrupted suture using the same suture material in both arms (Figure 5).

Figure 5. Forrest plot of incisional hernia rates using continuous versus interrupted suture technique using the same suture material in both groups.

Study or Subgroup	Continuous Events	Continuous Total	Interrupted Events	Interrupted Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Wissing 1987	60	290	48	286	67.6%	1.29 [0.85, 1.97]	1987
Gislason 1995	9	163	7	164	11.6%	1.31 [0.48, 3.61]	1995
Agrawal 2009	8	75	10	76	15.6%	0.79 [0.29, 2.12]	2009
Gurjar 2012	3	100	3	100	5.1%	1.00 [0.20, 5.08]	2012
Total (95% CI)		**628**		**626**	**100.0%**	**1.20 [0.84, 1.71]**	
Total events	80		68				

Heterogeneity: Chi² = 0.89, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)



Risk of bias legend
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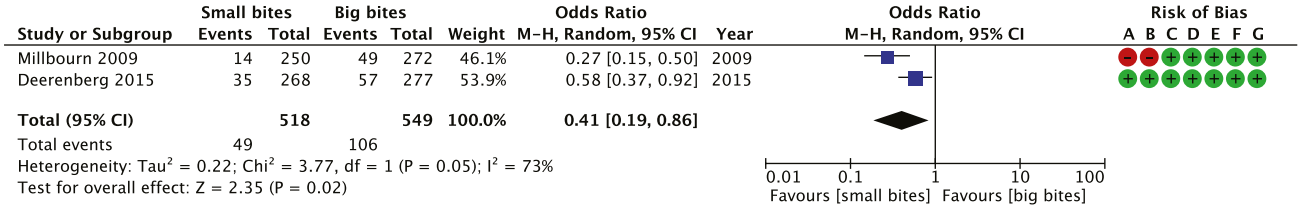
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Two studies(4, 25) including a total of 1,067 patients compared continuous suture with a slowly-absorbable suture using either the small bites or big bites technique, and there were significantly fewer incisional hernias using the small bites suture technique including only the aponeurotic layer (Figure 6).

Figure 6. Forrest plot of incisional hernia rates using small bites versus big bites suturing with the same suture material in both arms.



Risk of bias legend
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(**G**) Other bias

Secondary outcome – surgical site infection, wound dehiscence/burst abdomen, suture sinus

Various criteria were used for definition of SSI ranging from the definition by Center of Disease Control and Prevention with the classification into superficial, deep and organ/space infection to the surgeon's clinical assessment of the wound. Wound dehiscence and burst abdomen was poorly defined by the majority of the studies. Wound dehiscence seemed to include both skin dehiscence with intact fascia and fascial disruption. In the meta-analysis, we defined burst abdomen as cases where a fascial dehiscence was described. Only one study reported that SSI was more common after emergency laparotomy compared with elective laparotomy(27). Several studies found that the development of an incisional hernia was preceded by a SSI in up to 40% of the cases(25-29).

There were no significant differences on SSI and burst abdomen, when comparing the use of non-absorbable, slowly-absorbable and fast-absorbable sutures. Further, there were no differences on SSI and burst abdomen using a continuous or interrupted suture technique. Millbourn *et al*.(25) reported significantly fewer SSIs when using a small bites suture technique, however, Deerenberg *et al*.(4) found no significant differences on SSI between small and big bites technique (Figure 8). There were no significant differences regarding burst abdomen between small and big bites technique(4, 25).

Suture sinus formation, palpable knots and wound pain was reported to be a problem with the use of non-absorbable sutures as compared with fast- and slowly-absorbable sutures in several studies(19, 21, 23, 26, 28), whereas only one study found no significant differences on suture sinus between non-absorbable and slowly-absorbable sutures(20).

Discussion

The results of this systematic review and meta-analysis show that a small bites continuous suture technique with a slowly-absorbable polydioxanone (PDS) small sized suture decreases the incisional hernia rate compared to a large bite technique with a larger suture. There were no significant differences on incisional hernia rate when comparing non-absorbable, slowly-absorbable and fast absorbable sutures using the same suture technique. Furthermore, using an interrupted or continuous suture technique with the same kind of suture material did not affect incisional hernia rate.

Non-absorbable or slowly-absorbable sutures was not superior to fast-absorbable sutures in decreasing incisional hernia rate in this meta-analysis. In accordance, a recent systematic review by Bosanquet et al(3). did also conclude that there is no evidence that suture type has an intrinsic effect on incisional hernia rate. However, this finding is controversial compared with previous meta-analyses concluding that slowly-absorbable sutures are superior to fast absorbable sutures(11, 13). These previous meta-analyses differ from the current meta-analysis, which may explain the different conclusions. Firstly, only RCTs on midline laparotomies were included. Further, RCTs comparing a continuous suture technique using slowly-absorbable sutures with an interrupted suture technique using rapid absorbable suture were compared in the forest plots(11). Lastly, both meta-analyses included papers that were rejected in the current meta-analysis because of inadequate quality judged by the critical appraisal checklists.

Although no significant differences between sutures could be found on incisional hernia and SSI rate, we agree with the recommendations of the European Hernia Society to use a slowly-absorbable suture when closing the fascia(10). When considering the biology of wound healing, using a slowly or non-absorbable suture for fascial closure seems appropriate. Fascial healing starts by recruiting inflammatory cells. Two to five days after laparotomy fibroblasts enter the wound and start producing collagen. During the proliferation phase of the first three weeks, mainly type III collagen is produced and an extracellular matrix is created. Type III collagen consists of thin, weak fibers and is replaced by strong and thick type I collagen during the following maturation phase(35, 36). The last part of the maturation phase is remodeling or realignment of collagen fibers along tension lines and can take up to years. The half-life tensile strength of absorbable sutures like polyglactin 910 (Vicryl®) and polyglycolid acid (Dexon®) is around 2-3 weeks(37), suggesting an insufficient support of the healing fascial tissue. The half-life tensile strength of slowly-absorbable suture polydioxanone (PDS®) is 6 weeks(37). Since fascia needs at least 14 days to regain its strength(35, 38), using a fast-absorbable suture might not provide long enough support to the healing fascia, although this is not supported by our data. Since suture sinus formation, palpable knots and wound pain was reported to be a problem with the use of non-absorbable sutures(19-21, 23, 26, 28), a slowly-absorbable suture is preferred over a non-absorbable suture.

Although no significant differences could be found when comparing interrupted and continuous suture techniques using the same suture material, we agree with the recommendations of the European Hernia Society to use a continuous suture technique to close the fascia(10). The superiority of the combination of a continuous technique with a slowly-absorbable suture on the incidence of incisional hernia has been determined in high-quality systematic reviews and meta-analyses(11, 13). Furthermore, a continuous technique is faster than an interrupted technique thereby reducing the length of surgery(13).

Two RCTs proved that a small bites suture technique using 2-0 monofilamented slowly-absorbable stuture material significantly reduces incisional hernia rate compared to a large bite 1-0 suture technique(4, 25). This suture method was firstly described by Israelsson *et al*. and is also referred to as the 4:1 suture method, as the suture length should be at least four times as long as the laparotomy incision(39). Using twice the amount of stitches including the aponeurosis only, provides close to ideal conditions for fascial healing due to avoidance of necrosis of the rectus abdominis muscles and to optimal distribution of forces leading to a lower incidence of incisional hernia(4, 25, 40). Whether it is the size of the bites or the size of the suture, that is important in decreasing hernia rate is still unknown. Hypothetically, it is technically more difficult to perform the small bites technique with a larger needle and thicker suture.

The incidences of SSI reported in the included RCTs emphasize that wound infection remains a frequent complication after laparotomy and should be scored carefully. Furthermore, it was reported in the RCTs that incisional hernias were preceded by SSI in up to 40% of the cases(25-29), stressing that SSI is an important risk factor for incisional hernia formation. However, in this meta-analysis the suture material or suture method did not seem to influence the rate of SSI and burst abdomen.

Optimizing all surgical-technical factors in closing a midline laparotomy and the increasing use of minimally invasive surgery unfortunately does not reduce incisional hernia rate to zero. Patients undergoing open surgery for abdominal aortic aneurysm and obese patients have a higher risk of incisional hernia formation(8, 41). In these high-risk patients, other interventions might be needed to further reduce the incidence of incisional hernia. Patients with an abdominal aneurysm or obesity were found to benefit from prophylactic mesh augmentation with a significant reduction in the incisional hernia rate

with an odds ratio of 0.25(42, 43). Furthermore, many patients with high-risk profiles such as many previous laparotomies, emergency surgery and/or major abdominal surgical procedures will still have to undergo open surgical procedures through midline incisions. In these high-risk groups the avoidance of incisional hernia remains a challenge. Further studies on the optimal closure technique in emergency laparotomies are still needed, and should include the small bites technique in one study arm. To the best of our knowledge, there is only one ongoing RCT on midline emergency laparotomies comparing continuous all-layer suturing with slowly-absorbable suture to an interrupted technique with fast-absorbable sutures(44). The meta-analysis design is limited by the fact that the results depend on the included studies. Furthermore, one could argue that only studies on elective midline laparotomies should be included in order to minimize heterogeneity. On the other hand, the reality rarely represents with only elective midline laparotomies. Yet this is the first systematic review and meta-analysis to compare studies on the suture material using the same technique in both arms, which is essential to conclude anything on type of sutures. Likewise, to evaluate the suture technique, the same suture type must be used in both arms. Further, to minimize risk of bias, the SIGN checklists were used by two independent assessors for evaluation of the RCTs.

In conclusion, no suture material proved superior to other in the meta-analyses. However, a slowly-absorbable suture material seems wise to use as it keeps its strength until the fascial tissue is healed. Further, a slowly-absorbable suture does not increase the SSI rate compared to fast-absorbable sutures and decreases the risk of wound pain and suture sinus, which is a risk when using non-absorbable material. Moreover, there were no difference on an interrupted suture technique compared with a faster continuous technique. On the other hand, this meta-analysis significantly concludes that the best-evidenced technique for closure of a laparotomy incision is a small bites suture technique with a 2-0 slowly-absorbable suture including the aponeurosis only in a suture to wound length ratio of at least 4:1.

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Chapter

European Hernia Society guidelines on the closure of abdominal wall incisions

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Abstract

Background

The material and the surgical technique used to close an abdominal wall incision are important determinants of the risk of developing an incisional hernia. Optimizing closure of abdominal wall incisions holds a potential to prevent patients suffering from incisional hernias and for important costs savings in health care.

Methods

The European Hernia Society formed a Guidelines Development Group to provide guidelines for all surgical specialists who perform abdominal incisions in adult patients on the materials and methods used to close the abdominal wall. The guidelines were developed using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) and methodological guidance was taken from SIGN (Scottish Intercollegiate Guidelines Network). The literature search included publications up to April 2014. The guidelines were written using the AGREE II instrument. An update of these guidelines is planned for 2017.

Results

For many of the Key Questions that were studied no high quality data was detected. Therefore, some strong recommendations could be made but, for many Key Questions only weak recommendations or no recommendations could be made due to lack of sufficient evidence.

Recommendations

To decrease the incidence of incisional hernias it is strongly recommended to utilise a non-midline approach to a laparotomy whenever possible. For elective midline incisions, it is strongly recommended to perform a continuous suturing technique and to avoid the use of rapidly absorbable sutures. It is suggested using a slowly absorbable monofilament suture in a single layer aponeurotic closure technique without separate closure of the peritoneum. A small bites technique with a suture to wound length (SL/WL) ratio at least 4/1 is the current preferred method of fascial closure. Currently, no recommendations

can be given on the optimal technique to close emergency laparotomy incisions. Prophylactic mesh augmentation appears effective and safe and can be suggested in high-risk patients. For laparoscopic surgery it is suggested using the smallest trocar size adequate for the procedure and closure of the fascial defect if trocars larger or equal to 10 mm are used. For single incision laparoscopic surgery we suggest meticulous closure of the fascial incision to avoid an increased risk of incisional hernias.

Introduction

Background

Incisional hernias are a frequent complication of abdominal wall incisions, but a wide range of incisional hernia rates are reported(1-6). The weighted mean incisional hernia rate at 23.8 months was 12.8 % in a systematic review and meta-regression study(7), but incidence rates up to 69 % have been reported in high-risk patients with prospective long-term follow-up(8). The reported incidence is determined by several factors: the patient population studied, the type of abdominal wall incision, the length of follow-up and the method of incisional hernia diagnosis. Risk factors for incisional hernias include postoperative surgical site infection, obesity and abdominal aortic aneurysm(9-11). Nevertheless, it seems that the suture material and the surgical technique used to close an abdominal wall incision, are the most important determinants of the risk of developing an incisional hernia(4, 12). The development of an incisional hernia has an important impact on the patients' quality of life and body image(13). Furthermore, the repair of incisional hernias still has a high failure rate with long term recurrence rates above 30 %, even when mesh repair is performed(14-16). Optimising the surgical technique to close abdominal wall incisions using evidence based principles, holds a potential to prevent patients suffering from incisional hernias and the potential sequelae of incisional hernia repairs(17). The mean direct and indirect costs for the repair of an average incisional hernia in an average patient in France in 2011 was € 7,089(18). Thus, reducing the incisional hernia rate by optimising the closure of abdominal wall incisions holds a great potential for costs savings in the use of health care facilities and in reducing postoperative disability.

The European Hernia Society (EHS) originated from the "Groupe de la recherche de la paroi abdominal" (GREPA), which was founded in 1979 with the aim: "The promotion of abdominal wall surgery, the study of anatomic, physiologic and therapeutic problems related to the pathology of the abdominal wall, the creation of associated groups which will promote research and teaching in this field, and the development of interdisciplinary relations". During the autumn board meeting of the EHS in September 2013 in Italy it was decided to extend our mission to actively promote the prevention of incisional hernias by the Sperlonga statement: "Maybe we should first learn and teach how to prevent incisional hernias, rather than how to treat them?"

Objective

The objective is to provide guidelines for all surgical specialists who perform abdominal incisions in adult patients on the optimal materials and methods used to close the abdominal wall. The goal is to decrease the occurrence of both burst abdomen and incisional hernia. The guidelines refer to patients undergoing any kind of abdominal wall incision, including visceral surgery, gynaecological surgery, aortic vascular surgery, urological surgery or orthopaedic surgery. Both open and laparoscopic surgeries are included in these guidelines.

Methods

As EHS secretary of Quality, Filip Muysoms, under the auspices of the European Hernia Society board, proposed the Guidelines Development Group. The project was presented to the EHS board and accepted during the board meeting in Sperlonga, Italy, on September 28th 2013. The members of the Guidelines Development Group were chosen to recruit key opinion leaders and researchers on the subject from Europe. A geographical distribution across European countries was attempted and some younger surgeons having performed research on the subject were included in the Guidelines Development Group. Many of the members have contributed previously in producing guidelines on a national and international level. The Guidelines Development Group included abdominal wall surgeons, upper gastro-intestinal surgeons, hepato-biliary surgeons, colorectal surgeons and a vascular surgeon.

During a Kick Off meeting of the Guidelines Development Group in the Bonham Hotel in Edinburgh on October 28th 2013, the members attended a seminar on the methodological aspect of developing guidelines by Robin T Harbour, the Lead Methodologist of the Scottish Intercollegiate Guidelines Network (SIGN)(19). The AGREE II instrument was used from the start of the project to guide our methodology and structure of producing the guidelines(20). AGREE II gives as definition for the Quality of a guideline: "The confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice." During this first meeting Key Questions were formulated and translated into 24 patients-intervention-

comparison-outcome (PICO) formats. For each Key Question at least three Guidelines Development Group members were assigned as investigators and specific search terms were formulated.

On November 11th 2013, a meeting in Glasgow at the SIGN headquarters was held with the steering committee of the Guidelines Development Group to discuss the search strategy. A clinical librarian working for SIGN performed the primary literature research for all Key Questions. This involved a search for systematic reviews and/or meta-analyses on the Key Questions in Medline, Embase, NIHR CRD, NICE and The Cochrane library. The PRISMA flow diagram is shown in Figure1. The Guidelines Development Group members evaluated the systematic reviews for their relevance to the Key Questions and a qualitative assessment was done using the SIGN checklist No 1 for systematic reviews and meta-analyses(19). Only systematic reviews of High Quality were used as basis for the guidelines development. A second search (no filters) on the Key Questions was performed for relevant RCT's published after the end of the search performed for the systematic reviews involved. If no High Quality systematic review was identified for a Key Question, the working group members performed a separate systematic review using the PRISMA statement methodology(21). To avoid lengthening of this guidelines manuscript, the results of these systematic reviews will be submitted as a separate manuscript on behalf of "The Bonham Group", which are the members of the Guidelines Development Group. The members working together on a Key Question provided a Summary of Findings table from the results of the literature search, which were presented and discussed during the second group meeting.

The second Guidelines Development Group meeting was held in Edinburgh on April 25th 2014. For evaluation of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used(22). For each Key Question, a level of evidence was proposed using the GRADE approach and four levels of quality of the body of evidence were used: high, moderate, low, very low (Table 1). Based on the research evidence, the clinical experience and patient values the Guidelines Development Group formulated a recommendation for each Key Question. In the GRADE approach only three levels of recommendation are used: strong recommendation, weak recommendation and no recommendation.

The results of the guidelines proposed by the Guidelines Development Group were presented during the 36th Annual International Congress of the

European Hernia Society in Edinburgh on May 31st 2014. The manuscript was subsequently written by the first author in a uniform manner for all Key Questions and send for review and agreement by all co-authors. Prior to submission, the manuscript of the guidelines was externally reviewed by experts and evaluated using the AGREE II instrument.

Results

The results of the searches are shown in the PRISMA flow diagram in Figure 1. From the 97 records detected by the SIGN process, 69 records were excluded based on the title and abstract as not being relevant to the guidelines. The remaining 28 systematic reviews(4, 23-49) were assessed by full text for their relevance to the Key Questions and if retained were assessed qualitatively using the SIGN checklist No 1(19). Additional searches on PubMed and by checking the references of all manuscripts were performed by the members of the Guidelines Development Group assigned to each Key Question. Relevant studies published up until April 2014 were included to provide the Summary of Evidence tables.

Figure 1. PRISMA flow diagram for the search for systematic reviews and/or meta-analyses performed by Scottish Intercollegiate Guidelines Network (SIGN) for the Guidelines Development Group of the European Hernia Society guidelines on the closure of abdominal wall incisions. The search was performed in November 2013 and included searches in Medline, Embase, NIHR CRD, NICE and The Cochrane library

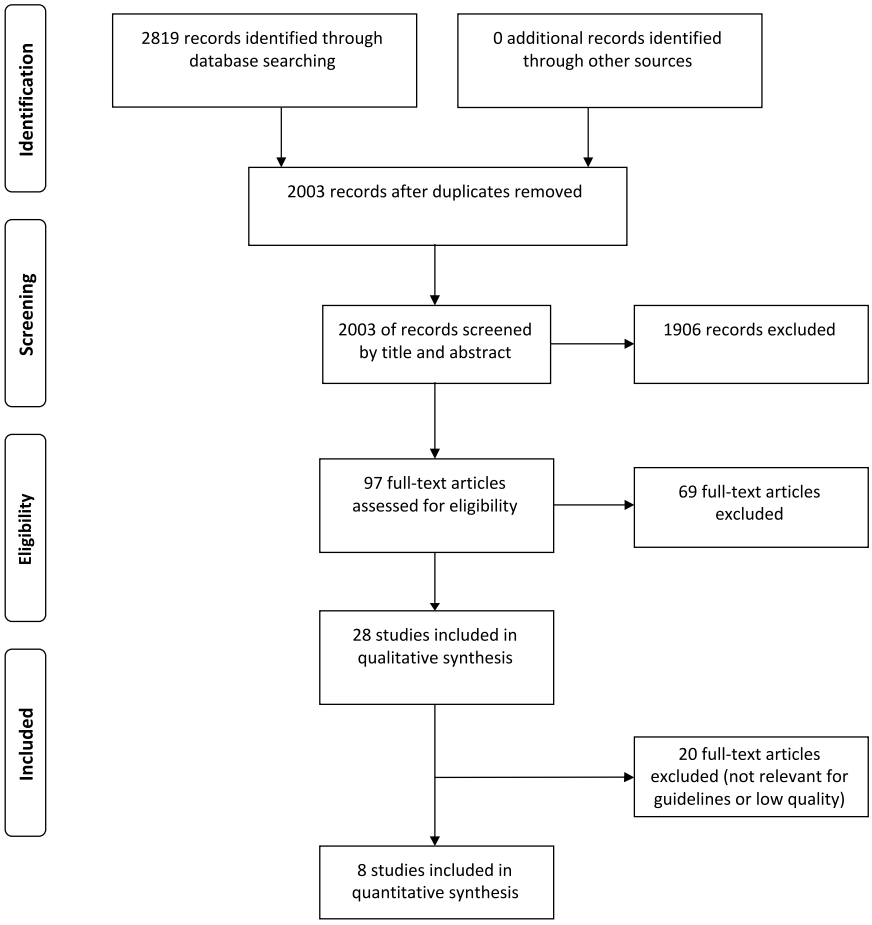


Table 1. Using the GRADE approach to guideline development(22) the Quality of the body of evidence is rated (high/moderate/low/very low) and the recommendations are graded as strong or weak

Grading the Quality of the body of evidence for each Key Questions using the GRADE approach			
Underlying methodology	**Quality rating**	**Symbols**	**Definitions**
Randomized trials; or double-upgraded observational studies.	High	■■■■	Further research is very unlikely to change our confidence in the estimate of effect
Downgraded randomized trials; or upgraded observational studies.	Moderate	■■■□	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Double-downgraded randomized trials; or observational studies.	Low	■■□□	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.	Very low	■□□□	Any estimate of effect is very uncertain.

Grading of recommendations using the GRADE approach	
Strong recommendation	Based on the available evidence, if clinicians are very certain that benefits do, or do not, outweigh risks and burdens they will make a strong recommendation.
Weak recommendation	Based on the available evidence, if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks, they must offer a weak recommendation.
No recommendation	If based on the lit

Which diagnostic modality is the most suitable to detect incisional hernias?

No systematic reviews on diagnostic modalities for incisional hernias were found. Fifteen records were included in the qualitative analysis(1-3, 6, 50-60). Only four studies were retained as High Quality and are listed in the Summary of Findings table (Table 2)(3, 50, 51, 60).

The quality of most studies investigating the diagnostic accuracy of imaging techniques was low to very low. Only some provided a sensitivity analysis. Because no studies compared different diagnostic modalities in a similar methodology and with similar study arms, no pooling of data was useful or possible. In general, most studies show that medical imaging will increase the rate of detection of incisional hernias compared to physical examination. In an everyday clinical setting this is usually not important, because most asymptomatic hernias do not require treatment and their diagnosis is thus not necessary.

CT scan is reliable and reproducible, whereas ultrasound is more operator-dependant. However, CT scan will induce a radiation load to the patients and ultrasound is more accessible in most health care settings. A good standardisation and dynamic evaluation by ultrasound of the abdominal wall is needed, as described by Beck et al.(51) as the dynamic abdominal sonography for hernia (DASH) technique.

The difference in accuracy between physical examination and imaging technique is most important in the context of comparative studies evaluating incisional hernia rate. Next to the method of incisional hernia diagnosis the length of follow-up is important. Fink et al.(5) reported in a follow-up study of two prospective trials an increase from 12.6 % at 12 months to 22.4 % at 36 months ($p < 0.001$) and concluded that follow-up for 3 years should be mandatory in any study evaluating the rate of postoperative incisional hernia after midline laparotomy.

Statement	It is recommended that prospective studies with incisional hernia as a primary outcome integrate medical imaging, either dynamic ultrasound or CT-scan, in the follow-up.	■■□□	strong

Statement	It is recommended that studies with incisional hernia as a primary outcome include follow-up of at least 24 months (and preferably 36 months).	■■□□	strong

Table 2. Summary of Findings table for Key Question A: which diagnostic modality is the most suitable to detect incisional hernias?

Bibliographic citation	Study type	SIGN assessment	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
Baucom et al. Journal of the American College of Surgeons 2013; 218(3):363-6.	prospective cohort study	High Quality ++	181	patients seen at a general surgery department who had a prior abdominal operation and an available CT scan within six months before the visit	Physical examination by a surgeon	CT scan reviewed by surgeon	not available	Physical examination had a low sensitivity (77%)and negative predictive value (77%). It fails to detect 23% of hernias and in 32% of the patients with a BMI ≥ 30 kg/m^2.
General comments: Adequate designed study to compare physical examination to CT scan diagnosis of incisional hernias. CT scan was used a "gold standard" for the sensitivity analysis.								
Beck et al. Journal of the American College of Surgeons 2013;216(3):447-53	prospective cohort study	High Quality ++	181	patients seen at a general surgery department who had a prior abdominal operation and an available CT scan within six months before the visit	dynamic abdominal ultrasound by surgeon	CT scan reviewed by surgeon	not available	Dynamic Ultrasound has a high sensitivity (98%) and specificity (88%). It has a positive predictive value of 91 % and negative predictive value of 97%. It is a good alternative to CT scan diagnosis.
General comments: Paper from the same group as Baucom et al. Concerns the same patient population. Adequate designed study to compare dynamic ultrasound to CT scan diagnosis of incisional hernias. CT scan was used a "gold standard" for the sensitivity analysis.								
den Hartog et al. Hernia 2009;13(1):45-8	prospective cohort study	High Quality ++	40	patients that had aortic surgery by midline incision at least 12 months before	Ultrasound by radiologist	CT scan (by 2 independent radiologists.	mean 3.4 years	Incisional hernia prevalence was 60.0% with CT scan and 42.5% with ultrasound. The sensitivity of US was 70.8% and the specificity 100%. Us has a positive predictive value of 100% and a negative predictive value of 69.6%. CT scan diagnosis of the incisional hernias has a good intra- and inter -observer reliability.

Table 2. continued

Bibliographic citation	Study type	SIGN assessment	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
General comments: Adequate designed study to compare ultrasound to CT scan diagnosis of incisional hernias. No comparison to physical examination. Limited number of patients. CT scan was used as "gold standard" for the sensitivity analysis.								
Schreinemacher et al. Arch Surg. 2011;146:94-9	retrospective cohort study with prospective examination	High Quality ++	111	patients that have a closure of a temporary stoma (42% ileostomies and 58% colostomies).	Ultrasound of the abdominal wall by surgeon	Physical examination by surgeon	median 35 months	Incisional hernia prevalence was 32.4% with ultrasound evaluation. Physical examination had a sensitivity of 58.3% and a specificity of 97.3%. The positive predictive value was 91.3% and the negative predictive value was 83%.
General comments: Both examinations were performed by the same person. Ultrasound was used a "gold standard" for the sensitivity analysis.								

Does the type of abdominal wall incision influence the incidence of incisional hernias or burst abdomen?

Laparotomy incisions can be classified as midline, transverse, oblique or paramedian incisions(61). Six systematic reviews have compared midline laparotomies to alternative incisions(26, 27, 31, 36, 38, 61), but only two were considered High Quality (26, 27). A recent systematic review by Bickenback et al.(26) compared midline, transverse (including oblique) and paramedian incisions. This review included all relevant studies from previous reviews and no additional RCT's were detected that were published after this review. The literature search of this systematic review(26) identified studies published until 2009 and 24 RCT's directly comparing different laparotomy incisions were included in the analysis. The incisional hernia rates after non-midline incisions were significantly lower compared to the incisional hernia rates after midline incisions, for both transverse incisions (RR = 1.77; 95 % CI:1.09–2.87) and paramedian incisions (RR = 3.41; 95 % CI: 1.02–11.45)(26). However, data on burst abdomen (deep wound dehiscence or fascial dehiscence) were not significantly different between the different incisions types.

A Cochrane review by Brown et al.(27) published in 2005 and updated in 2011, compared transverse versus midline incisions, but excluded studies comparing paramedian incisions. A decreased incisional hernia rate after transverse incisions was reported compared to midline incisions (OR = 0.49; 95 % CI: 0.30–0.79).

Both reviews concluded that non-midline incisions significantly reduced the risk of incisional hernia compared to midline incisions, but did not influence the risk of burst abdomen. Interestingly, the Cochrane conclusions were more moderate, due to methodological and clinical heterogeneity of the studies and the risk of potential bias.

Statement	Non-midline incisions are recommended where possible	strong ■■■□

What is the optimal technique to close a laparotomy incision?

Ten systematic reviews on the techniques and/or the materials to close abdominal wall incisions were identified (4, 32, 34, 37, 38, 42, 43, 48, 62, 63). The data from the different systematic reviews are very incoherent and conclusions

are often completely contradictory. The overall quality of most systematic reviews is low and therefore, several should be rejected as evidence to create guidelines. A major problem to identify the evidence from the literature is the fact that most prospective studies compared several variables between the study arms. Moreover, the populations studied are often very different: midline only or including other incisions, emergency or elective surgery, and different operative indications.

The current guidelines on techniques and materials are based on the systematic reviews by Diener et al.(4) and van't Riet et al.(48) which were evaluated as High Quality. Both systematic reviews included only studies involving midline laparotomies and the review by Diener et al. was the only one to distinguish between elective or emergency surgery. The systematic review by Sajid et al.(43) was used for the question on suture materials and a recent Cochrane review by Gurusamy et al.(62) was used for the question on peritoneal closure.

Using separate PICO's the shortcoming of many study designs to deliver clear answers becomes obvious. Another shortcoming in most studies on closure of laparotomies is the failure to monitor the technical details of the suturing technique, like the SL/WL ratio and the stitch size. As demonstrated by Israelsson(64) this might be an important confounding factor in studies comparing different suture materials. An updated systematic review taking into account the mentioned shortcomings of individual studies might be performed, but for these guidelines the conclusions are based on the data from the currently available systematic reviews. The protocol for an ongoing Cochrane review(65) was published in 2006 but the final data have not yet been published.

Statement	It is recommended that prospective randomized studies on the suture material to close abdominal wall incisions use the same suturing technique in both study groups.	strong

Statement	It is recommended that prospective randomized studies assessing the technique to close abdominal wall incisions use the same suture material in both study groups.	strong

Continuous suturing versus interrupted sutures

Both meta-analyses concluded that continuous suturing for closure of midline laparotomies was beneficial compared to interrupted closure (4, 48). Diener et al.(4) found a significant lower incisional hernia rate for continuous suturing (OR 0.59: $p = 0.001$) in elective surgery. Most of the included studies were at high risk of bias because the interrupted study arm used rapidly absorbable multifilament sutures and the continuous arm used either non-absorbable or slowly absorbable monofilament sutures. van't Riet et al.(48) included studies involving emergency laparotomies and did not find any difference in incisional hernia rate between interrupted and continuous suturing. Continuous suturing was recommended because it was significantly faster.

Statement	Continuous suturing for closure of midline abdominal wall incisions in elective surgery is recommended	■■□□	strong

Closure versus non-closure of the peritoneum

The Cochrane review by Gurusamy et al.(62) concluded that there was no short-term or long-term benefit in peritoneal closure. Five studies were included but were heterogeneous in type of incision (midline and non-midline) and included both elective and emergency laparotomies. In all studies the peritoneum was closed as a separate layer in the study arm with peritoneal closure.

Statement	Closure of the peritoneum as a separate layer during closure of laparotomy incisions is NOT recommended	■■□□	weak

Mass closure versus single layer closure

The search for the most appropriate layers to be sutured when closing a laparotomy is hampered by the lack of good definitions on what constitutes a

mass closure, layered closure or single layer closure. No clinical studies directly comparing different closure methods were found.

For future research the Guidelines Development Group proposes the following definitions:

- *mass closure*: the incision is closed with a suture bite including all layers of the abdominal wall except the skin.
- *layered closure*: the incision is closed with more than one separate layer of fascial closure
- *single layer aponeurotic closure*: the incision is closed by suturing only the abdominal fascia in one layer.

Statement	For closure of midline abdominal wall incisions in elective surgery, a single layer aponeurotic closure is suggested	■□□□	weak

Suture length to wound length ratio (SL/WL)

The beneficial effect of a high SL/WL ratio on reducing the incidence of incisional hernias has been recognised for a long time(66), but evidence from clinical prospective studies remains scarce and most of the work addressing the topic comes from the Clinic of Sundsvall in Sweden(64, 67, 68). A RCT, performed in Sundsvall, demonstrated the importance of the SL/WL ratio in reducing incisional hernia rate. The critical value was determined to be at a ratio of 4/1(64). Although a SL/WL ratio ≥4 is often mentioned in the protocol of prospective studies, many fail to document that the SL/WL ratio was recorded for the individual study patients.

Statement	A suture to wound length ratio (SL/WL) of at least 4/1 for continuous closure of midline abdominal wall incisions in elective surgery is suggested.	■■□□	weak

Statement	It is recommended that all prospective studies on the closure of laparotomy incisions will document the suture to wound length ratio (SL/WL) in all patients, as well as the number of stitches.		strong

Small bites versus large bites

Millbourn et al.(69) demonstrated that closure of a midline laparotomy with a "small bites" technique resulted in significant less incisional hernias (5.6% *vs* 18.0 %; p< 0.001) and less surgical site infections (SSIs) (5.2% *vs* 10.2%; p= 0.02). In the small bite technique the laparotomy wound is closed with a single layer aponeurotic suturing technique taking bites of fascia of 5 - 8 mm and placing stitches every 5 mm.

Statement	The "small bites technique" for continuous closure of midline incisions is suggested.	■■■□	weak

What is the optimal suture material to close a laparotomy incision?

Despite significant heterogeneity and confounders in most SRs identified, a study by Sajid et al.(43) focused solely on the suture material. Table 3 defines the suture materials used in the included studies.

Rapidly absorbable suture versus non-absorbable or slowly absorbable sutures

Diener et al. (4) reported a significantly lower incisional hernia rate with slowly absorbable sutures (OR 0.65: p= 0.009) in elective surgery. Subgroup analysis performed by van 't Riet et al.(48) comparing only continuous suturing studies, detected only one RCT by Wissing et al.(70) using continuous suturing in both study arms. This study, which included 21% of emergency operations, showed significantly more incisional hernias with rapidly absorbable sutures compared to non-absorbable sutures (p= 0.001) and compared to slowly absorbable sutures (p = 0.009).

Statement	The use of rapidly absorbable suture material for closure of midline abdominal wall incisions in elective surgery is NOT recommended.	■■■□	strong

Table 3 List of the most commonly used suture materials to close abdominal wall incisions and their characteristics

Suture	Producer	Material	Absorbable	Absorption time	Filaments	Antibiotics impragnated
Prolene	Ethicon	Polypropylene	Non		Mono	No
Surgipro	Covidien	Polypropylene	Non		Mono	No
Ethilon	Ethicon	Nylon	Non		Mono	No
Monosof	Covidien	Nylon	Non		Mono	No
Ethibond	Ethicon	Polyethylene	Non		Multi	No
Mersilene	Ethicon	Polyester	Non		Multi	No
Surgilon	Covidien	Nylon	Non		Multi	No
Maxon	Covidien	Polyglyconate	Slowly	180 days	Mono	No
PDS	Ethicon	Polydioxanone	Slowly	183–238 days	Mono	No
PDS plus	Ethicon	Polydioxanone + triclosan	Slowly	183–238 days	Mono	Yes
Monoplus	B Braun	Polydioxanone	Slowly	180–201 days	Mono	No
Monomax	B Braun	Poly-4-hydroxybutyrate	Slowly	390–1080 days	Mono	No
Vicryl	Ethicon	Polyglactin	Rapidly	56–70 days	Multi	No
Vicryl plus	Ethicon	Polyglactin + triclosan	Rapidly	56–70 days	Multi	Yes
Polysorb	Covidien	Polyglycolic acid	Rapidly	60–90 days	Multi	No
Dexon	Covidien	Polygglycolic acid	Rapidly	60–90 days	Multi	No

Non-absorbable versus slowly absorbable sutures

No difference in incisional hernia rate for continuous suturing of midline incisions with slowly absorbable versus non-absorbable sutures (p= 0.75) was identified(48). However, an increased incidence of prolonged wound pain (p< 0.005) and suture sinus formation (p= 0.02) with non-absorbable sutures was reported(48). Another MA (which included non-midline incisions) identified no difference in incisional hernia rate between slowly-absorbable polydioxanone and non-absorbable sutures (OR 1.10: p= 0.43)(43). Once again, non-absorbable sutures had a significant higher risk of suture sinus formation (OR 0.49: p= 0.01) (43).

Statement	Using slowly-absorbable suture material instead of non-absorbable sutures for continuous closure of midline abdominal wall incisions in elective surgery is suggested.	■■□□	weak

Monofilament versus multifilament sutures

Monofilament sutures are believed to be associated with a lower SSI rate than multifilament sutures(12). However, none of the SRs commented on this issue specifically. If the previous recommendation to use slowly absorbable sutures for closure of elective midline laparotomies is followed, this question becomes superfluous because the slowly absorbable sutures are all monofilament sutures.

Statement	We suggest using monofilament suture material for continuous closure of midline abdominal wall incisions in elective surgery.	■□□□	weak

Concerning the size of the suture, no studies comparing directly the size of the sutures used to close abdominal wall incisions were identified during our searches. For the "small bites" technique, Israelsson et al(12) suggest to use a suture size USP 2/0 (USP = United States Pharmacopeia).

Statement	No recommendation on the size of the sutures for closure of abdominal wall incisions can be given due to lack of data.	■□□□	no

Sutures impregnated with antibiotics

Sutures coated with Triclosan as an antimicrobial agent have been introduced to decrease the rate of surgical site infection in surgery. A recent meta-analysis has demonstrated a significant beneficial effect in the prevention of surgical site infection after all kinds of surgery(71). Surgical site infection is a risk factor for subsequent development of incisional hernias and therefore the use of antibiotics impregnated sutures to close laparotomies might be beneficial in the prevention of incisional hernias. Recently Diener et al.(72) published a large RCT on 1,224 patients undergoing an elective midline laparotomy comparing polydioxanone sutures with versus without triclosan impregnation. No reduction in the incidence of surgical site infection was reported (OR 0.91: CI 0.66–1.25; $p = 0.39$). Four other RCT's have compared sutures with or without triclosan in laparotomy closure, either with polyglactin sutures (Vicryl)(73, 74) or with polydioxanone (PDS)(75, 76). A meta-analysis on all five studies performed

by Diener et al. showed a significant decrease in surgical site infection (OR 0.67: CI 0.47–0.98). No data on incisional hernias are available from these studies.

Statement	Monofilament sutures impregnated with antibiotics for closure of elective midline incisions is NOT advised, because of insufficient data on their efficiency on prevention of surgical site infections and the lack of data on incisional hernias or burst abdomen.	■■■□	weak

Limitations of the statements in these guidelines on suture technique and suture materials

The statements are limited by the quality of the data on which they are based. In total, 61 RCT's have been identified that compared suture materials or techniques to close laparotomy incisions. Many studies have more than one variable between study arms and therefore analysing them in meta-analyses is difficult. Moreover, many studies have flaws in the methodology increasing the risk of bias. We would like to encourage researchers that plan studies on abdominal wall closure to improve the methodology of their study protocol. Preferably study arms are only different in the variable under investigation, either a suture technique or a suture material. Moreover we recommend documenting the technical details such as SL/WL ratio, the number of stitches used in the patients and to provide a follow up of at least 24 months.

Although some of the systematic reviews detected included non-midline incisions(43) or emergency operations(48), these guidelines are currently limited to elective midline laparotomies. For emergency operations and non-midline incisions there is currently not enough data available.

Statement	No recommendation on suture material or suturing technique for use in emergency surgery can be given due to lack of sufficient data.	■□□□	no

Statement	No recommendation on suture material or suturing technique for use in non-midline incisions can be given due to lack of sufficient data	■□□□	no

Suture needles and retention sutures

Blunt tip versus sharp needles

Only one SR assessing the type of needle used to close the abdominal wall(23) and one RCT comparing blunt needles with sharp needles were identified. The RCT reported no difference in SSI rate between blunt and sharp needles(77).

Statement	No recommendation on the type or the size of needle to close a laparotomy can be given due to lack of data.	■□□□	no

Is there a place for retention sutures when closing a laparotomy?

No SR on the use of retention sutures was found. Eight records were screened by full text(78-85). Three RCTs on the prevention of burst abdomen by using either retention sutures or a reinforced tension line suture in patients with increased risk for wound dehiscence and burst abdomen were identified(78, 81, 85). Follow up was too short to evaluate incisional hernia rate. The Summary of Evidence is listed in Table 4. Two studies showed favourable results(78, 81), but one study reported a high number of adverse events when using retention sutures(85).

Statement	No recommendation on the use of retention sutures in patients with multiple risk factors for burst abdomen can be given due to insufficient data.	■■□□	no

Postoperative care

Postoperative management and instructions for patients are not supported by high quality prospective data, but rely mostly on surgeons' habits, tradition and common beliefs (86-88). Long term follow up studies are needed to research the impact on the occurrence of incisional hernias of prescribing abdominal binders or restricting postoperative activity. The additional searches did not reveal any relevant study on long term outcome. Some studies on the short term benefits of abdominal binders were found.

Table 4. Summary of Findings table for Key Question M: is there a place for retention sutures when closing a laparotomy?

Bibliographic citation	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
Khorgami et al. J Surg Res. 2013;180:238-43.	RCT	300	Patients undergoing midline laparotomy with ≥ 2 risk factors of a list of defined risk factors for burst abdomen	extra retention sutures Nylon 1 (every 10 cm and with 5 cm bites of skin) kept for 3-4 weeks	continuous loop size 1 nylon suture (1 cm from the edge /1 cm intervals)	median 5 months	Wound dehiscence was 4.1% (6/147) in the intervention group and 13.5% (20/148) in the control group (p = 0.007). "We showed that prophylactic retention sutures could reduce wound dehiscence in midline laparotomy in high-risk patients with multiple risk factors without imposing remarkable postoperative complications. "
Agrawal Trop Gastroenterol. 2009;30:237-40.	RCT	190	Emergency midline laparotomy	reinforced tension line suture	continuous suture		Burst abdomen was 0.0% (0/90) in the intervention group and 13.0% (13/100) in the control group (p = 0.0026). "Closure of midline incision by RTL reduces the incidence of burst abdomen."
Rink et al Eur J Surg. 2000;166:932-7.	RCT	95 (92 midline)	Patients needing major abdominal surgery with infective or malignant intra-abdominal diseases. + at least one risk factor	extra retention sutures with sutures retention bridge for 12 days	interrupted Vicryl 1 sutures	12 days	"Retention sutures used to close abdominal wounds cause inconvenience, pain, and specific morbidity."

Subcutaneous drains in laparotomy incisions

Prophylactic routine placement of subcutaneous drains after laparotomy is occasionally used to decrease wound complications: infection, hematoma, seroma or wound dehiscence(88). However, there are several disadvantages to the routine use of subcutaneous drains. Namely, they cause patient discomfort and pain at removal, they hinder early mobilisation and demand additional nursing care. Therefore their use should be driven by a proven benefit.

One systematic review(89) and several RCTs (90-98) on the use of subcutaneous drains in abdominal surgery were found. They cover a wide range of operative indications: liver surgery, colorectal surgery, cholecystectomy, gynaecological surgery, caesarean section, and gastric bypass surgery. With few exceptions, most studies did not show a benefit for the use of subcutaneous drains. However, none of these studies had incisional hernias or burst abdomen as primary or secondary endpoint.

Statement	The routine placement of a subcutaneous drain during closure of abdominal wall incisions is NOT recommended.	strong ■■■□

Postoperative binders

One systematic review on the use of abdominal binders was found(86). The review included four RCT's (99-102) and a national survey by questionnaire on the use of abdominal binders in French surgical practice(86). One additional recent RCT was identified(103). The French survey reported that postoperative support of the wound with an abdominal binder is common practice after major laparotomies in many surgical departments (94% use them in some patients). It is expected to reduce postoperative pain and to improve early mobilisation of the patients. Moreover 83% of users expect a benefit in the prevention of abdominal wall dehiscence(86). No significant improvement for the short term benefits was found by the small RCTs from the review(98, 99, 101, 102). The additional study by Clay et al.(100) found a significant lower VAS (Visual Analogue Scale) score for pain at the fifth postoperative day and no adverse effect on postoperative lung function. No studies were found that had burst abdomen or incisional hernias as a primary or secondary endpoints.

Statement	No recommendation can be given on the use of postoperative abdominal binders due to lack of data on their effect on incisional hernias or burst abdomen rates.	■□□□	no

Postoperative restriction of activity

No prospective studies were found on the restriction of physical activity after abdominal incisions. Nevertheless, it is advocated by some surgeons in order to decrease the risk of incisional hernias, but there is no consensus on the level or the duration of the restriction(87). Postoperative restriction might have an adverse impact on the return to normal activity and delay the return to work.

Statement	No recommendation can be given on routine restriction of activity after abdominal surgery due to lack of data on the effect on incisional hernias or burst abdomen rates.	■□□□	no

Prophylactic mesh augmentation

Three Systematic reviews on the topic were found(24, 39, 104).

1. Nachappian et al.(39) did not assess of the quality of the individual studies and included non published data. Therefore this review did not qualify for inclusion in this guideline.
2. The systematic review by Bhangu et al.(24) is of High Quality and offers a good and extensive evaluation of the quality of the individual studies included. However, the quality of the non RCTs was usually low and these studies were not be used as evidence for these guidelines.
3. Timmermans et al.(104) published a good meta-analysis on five RCT's using polypropylene mesh, including a RCT published in 2013 by Abo-Ryia et al.(105).

One additional RCT published after the review by Timmermans et al.(106) was identified. In this RCT, one hundred and sixty patients were included. This is the first trial on non-selected elective midline laparotomies (with a majority of oncological patients). All the other trials have only included patients deemed

at high risk for incisional hernias. In this RCT by Caro-Tarrago et al. the mesh augmentation was performed with a light weight polypropylene mesh in the onlay position. A significant reduction in incisional hernias at 12 months was observed clinically and with CT scan in favour of prophylactic mesh, 1.5 vs 35.9 % ($p < 0.0001$). A significantly higher number of postoperative seroma was detected in the mesh group, 11.3 vs 28.8 % ($p < 0.01$). No major complications related to the mesh augmentation were reported.

The details of the six published RCT's using polypropylene mesh including 506 patients are listed in Table 5(105-110). Using Review Manager 5.2 software a new meta-analysis was performed. The data for this meta-analysis were extracted from the Timmermans et al. meta-analysis and the additional RCT(104, 106). A meta-analysis on the outcomes of incisional hernia, seroma and SSI was performed. The pooled analyses data are shown in a Forrest plot for each outcome in Figure 2. Prophylactic mesh augmentation is effective in the prevention of incisional hernias (RR 0.17: CI 0.08–0.37). An increased incidence of postoperative seroma is identified, but the majority of these are from the single study by Caro-Tarrago et al.(106) where the mesh was placed in an onlay position, with a weight of 45.9 % on the cumulative Risk Ratio for seroma (RR = 1.71; 95 %CI: 1.06–2.76) (Figure 2c).

Although the data are favourable and consistent for prophylactic mesh augmentation, the Guidelines Development Group decided that larger trials are needed to make a strong recommendation to perform prophylactic mesh augmentation for all patients within certain risk groups.

Statement	Prophylactic mesh augmentation for an elective midline laparotomy in a high-risk patient in order to reduce the risk of incisional hernia is suggested.	■■■□	Weak

Table 5. List of the randomized clinical trials and their characteristics on prophylactic mesh augmentation using a polypropylene mesh

								Incisional hernias			Effect size
RCT	**publ. date**	**LoE**	**SIGN**	**n**	**population**	**mesh position**	**FU months**	**diagnosis incisional hernia**	**NO Mesh**	**Mesh**	**Risk Ratio (95% CI)**
Gutiérrez (109)	2003	2b	+	88	High risk patients	onlay	36	clinical + selective CT scan	5/44	0/44	0.09 (0.01-1.60)
Strelczyk (110)	2006	1b	++	74	Obesity surgery	retro-muscular	28	clinical + ultrasound in all	8/38	0/36	0.06 (0.00-1.04)
El-Kadrawy (108)	2009	2b	+	40	High risk patients	pre-peritoneal	36	clinical	3/20	1/20	0.33 (0.04-2.94)
Bevis (107)	2010	1b	++	80	AAA	retro-muscular	25.4	clinical+ selective ultrasound	16/43	5/37	0.36 (0.15-0.90)
Abo-Ryia (105)	2013	2b	+	64	Obesity surgery	pre-peritoneal	48	clinical + selective ultrasound	9/32	1/32	0.11 (0.01-0.83)
Caro-Tarrago (106)	2014	1b	++	160	midline laparotomies	onlay	12	clinical + CT scan in all	30/80	2/80	0.07 (0.02-0.27)
Overall				506					71/257	9/249	0.17 (0.08 - 0.37)

Figure 2: Forrest plots of a meta-analysis performed by the Guidelines Development Group on prophylactic mesh augmentation with polypropylene mesh after laparotomy on the outcomes incisional hernia (2A), seroma (2B) and wound infection (2C).

Fig 2.A Incisional hernia

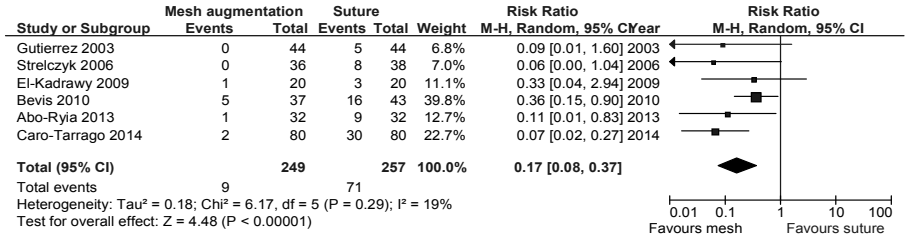


Fig 2.B Wound infection

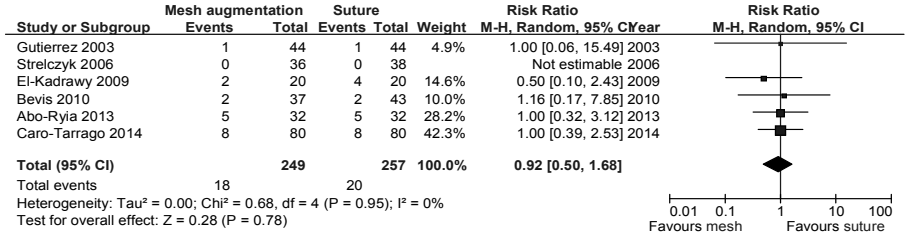
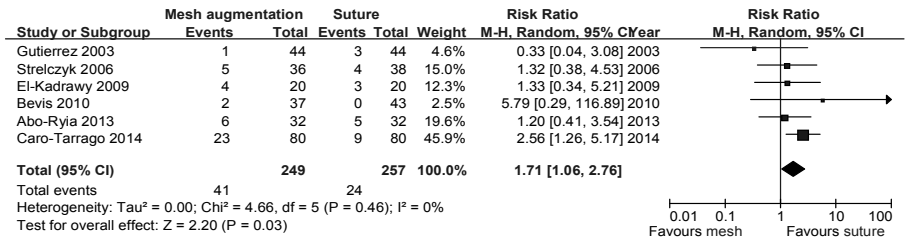


Fig 2.C Seroma



Which mesh type, which mesh position and which type of mesh fixation?

No comparative studies are published between different mesh type, mesh position or method of mesh fixation. Pans et al.(111) found no significant protective effect on incisional hernia rate by intra-peritoneal augmentation with a polyglactin mesh (Vicryl; Ethicon) on incisional hernia rate in a RCT on obesity surgery (*n* = 288). Llaguna et al.(112) placed a biological mesh (Alloderm; LifeCell) in a retro-muscular position in bariatric patients. In this non-randomised comparative study (*n* = 106 of which 44 with mesh) a significantly

lower incisional hernia rate was observed in the mesh group, 2.3 vs 17.7 % (p = 0.014). All other studies published used a polypropylene mesh, most often a small pore/heavy weight mesh: Prolene; Ethicon(107), Premilene; B. Braun(109), no name mentioned(105, 108, 110). Only Caro-Tarrago et al.(106) used a large pore/light weight mesh: Biomesh Light P8; Cousin Biotech.

There is a large variation between the studies on the mesh position for the prophylactic mesh augmentation. Onlay, retro-muscular and pre-peritoneal mesh positioning was performed in two studies each. No studies on the use of intra-peritoneal augmentation with a non absorbable synthetic mesh are reported. Only one study on the use of intra-peritoneal augmentation with an absorbable synthetic mesh is reported(111). The mesh was in all studies fixed with sutures to the fascia except for the study of Pans et al.(111) which used no fixation. No studies on mesh augmentation with glue or a self-fixating mesh are reported.

Statement	No recommendation on the optimal mesh position for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no

Statement	No recommendation on the optimal method of mesh fixation for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no

Statement	No recommendation on the type of mesh for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no

Trocar wounds for laparoscopic surgery and single port surgery

Trocar size and trocar type

The first search for systematic reviews resulted in 5 records(33, 40, 41, 46, 49) and 25 additional records were screened by full text(113-136). Several studies comment on the incidence of trocar-site hernia for various trocar sizes. However the quality of many studies is insufficient and challenge the validity of results.

Shortcomings of the individual studies include retrospective study design, short or unclear length of follow up and inappropriate or no information on diagnostic methods to detect incisional hernias. Most importantly, available data derive from studies in which the same patient serves as case and control; i.e. the incidence of trocar-site hernia is measured for different sizes of trocars inserted at different abdominal sites in the same patient. This may impose significant bias, related to the strength of the abdominal wall and the wound repair mechanisms at varying sites of the abdominal wall, in particular the linea alba to other parts of the abdominal wall.

Helgstrand et al.(33) performed a systematic review on the incidence of trocar-site hernia. Although they found a risk reduction after sutured closure and a lower hernia rate for 5-mm versus larger diameter trocars, no meta-analysis was undertaken. The poor quality and design of the majority of the included reports preclude further in-depth evaluation for supporting evidence. No RCT's have investigated the incidence of trocar-site hernia after insertion of blunt versus bladed trocars and no RCT's or case-control studies have investigated the incidence of trocar-site hernia with reference to trocar size or diameter. Available data derive from univariate and multivariate analyses of cohort studies, which have investigated the effect of potential risk factors for trocar-site hernia. Obesity, age above 60 years diabetes, long duration of surgery, and the need for fascia enlargement for specimen extraction were identified as risk factors for the development of trocar-site hernia(120, 136).

Statement	For laparoscopic procedures, using the smallest trocar size adequate for the procedure is suggested.	■■□□	Weak

Statement	For laparoscopic procedures, suturing the fascial defect, if trocars larger than or equal to 10 mm have been used, in the presence of established risk factors for incisional hernia formation is suggested.	■□□□	weak

Closure of trocar incisions

There are no good quality comparative studies investigating different suture materials or techniques for closure of trocar fascia defects. Armananzas et al.(113) reported in a recently published RCT a benefit for prophylactic intraperitoneal placement of a ventral patch at the umbilical site in high-risk patients to reduce the incidence of trocar-site hernia from 18.5% to 4.4% (OR 10.1: CI 2.15-47.6; p< 0.001). Larger sample-sized studies with a good risk-benefit assessment and longer follow-up are needed to confirm and support a stronger recommendation.

Statement	For laparoscopic procedures a mesh-augmented closure may be applied in patients at high risk for trocar-site hernia.	■■■□	weak

Single incision laparoscopic surgery and incisional hernia

The incidence of trocar-site hernia after single port surgery has been mostly investigated as a secondary outcome measure in the setting of RCTs and 3 High Quality MAs were found(137-139). Two MAs of RCTs have found no difference in the incidence of trocar-site hernia between single port and multiple port surgery, although a trend in favour of multiple port surgery was demonstrated(137, 139). The most recent MA included 19 RCTs involving 676 patients and found a higher incidence of trocar site hernia following single port surgery(138).

Statement	Emerging evidence suggests an increased incidence of trocar-site hernia for single-incision surgery as compared to conventional surgery; therefore meticulous closure of the incised fascia in single-port surgery is recommended.	■■■□	weak

Discussion

Limitations

Not many strong recommendations could be made due to lack of sufficient evidence on many of the PICO questions. It is somewhat confusing to notice that the first strong recommendation in these guidelines is to avoid midline laparotomies in favour of alternative incisions and that all other recommendations are only valid for elective midline incisions. Indeed most research is focused on midline laparotomies. A midline laparotomy is still the favoured approach for most surgeons. It allows quick entrance to the abdominal cavity and extension of the incision is easy if this is required for the operation. Nevertheless, the linea alba is probably the most vulnerable and least vascularized part of the abdominal wall. Some refer to incisional hernias as "a midline crisis". Optimising closure of abdominal wall incisions would appear to hold a large potential in reducing the incidence of incisional hernias and the subsequent need for incisional hernia repair. This has obvious benefits for the individual patient relating to an improved quality of life, avoidance of secondary operations and at a macro-economical level a significant reduction in costs for health care resources. It is not easy to see the impact of each recommendation separately. Therefore, implementation of the optimised abdominal wall closure is probably best done by teaching all involved specialists a standardised technique described as the "Principles" of abdominal wall closure(17). This incorporates all recommendations, although the Guidelines Development Group is aware that the level of evidence for the different aspects is sometimes low to very low. David Sackett, a pioneer in evidence-based medicine wrote: "… any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied"(140).

Discussions

For most Key Questions on the technique and material to close abdominal wall incisions, the grading of the Quality of Evidence and the choice of recommendation was straightforward. For several recommendations, while the quality of evidence was low, there was good consensus between the members of the Guidelines Development Group on the formulated statements. For prophylactic mesh augmentation there was disagreement

on the strength of recommendation (weak or strong). For this reason, an additional meta-analysis was performed (Figure 2). Although the effect size in favour of mesh augmentation is large and consistent over the studies, the Guidelines Development Group felt that larger trials are needed to support a strong recommendation for prophylactic mesh augmentation in high-risk patients. Indeed, the number of patients in the reported studies for each risk group separately (e.g. abdominal aortic aneurysm, obesity surgery, oncological surgery) seems too low to recommend prophylactic mesh augmentation in all these patient groups. Nevertheless, we are aware that several large RCT's are on-going and this grade of recommendation might be changed in the light of future publications.

No recommendations could be made on non-midline incisions due to insufficient evidence. Nevertheless, it seems reasonable to promote similar material (slowly absorbable suture) and techniques (continuous aponeurotic closure with small bites and SL/WL >4/1) for closure of non-midline incisions.

No recommendations could be made on the type or the size of the needle used to close abdominal incisions. No studies comparing the size of the sutures were identified in our searches.

No recommendation could be made for emergency surgery, which is often a contaminated procedure. The Guidelines Development Group consider that the use of retention sutures or of reinforced tension line sutures, should be prospectively studied in patients at high risk for development of burst abdomen. A risk model and score for burst abdomen has been developed by van Ramshorst et al.(141) and could be used as basis for including patients in these studies.

No recommendations could be made on the postoperative care after laparotomies. Long-term follow-up studies are needed to assess the impact on the occurrence of incisional hernias of prescribing abdominal binders or restricting or indeed encouraging early postoperative activity.

Applicability

To adopt the guidelines and "evidence based principles" for abdominal wall closure, surgeons must be convinced that these are valid recommendations with a large impact on the outcome for the patients. These guidelines are an attempt to create awareness amongst surgeons about these principles. Adaptation can be done by systematic quality control of the suturing technique

as described by van Ramshorst et al.(142). The EuraHS, European registry for abdominal wall hernias, has developed an online platform for registration and outcome measurement of abdominal wall surgery(140). An additional route in the database on the closure of abdominal wall incisions and for prophylactic mesh augmentation will be provided from 2015 onwards. It is hoped that such a registry database will facilitate the data collection for prospective studies.

Validity of the guidelines

Prior to submission of the manuscript the guidelines were evaluated and scored using the AGREE II instrument. Several large multi-centre studies on the closure of abdominal wall incisions are currently on-going. High Quality data on the use of the "small bites" technique in midline incisions, on the closure of laparotomies in emergency and on prophylactic mesh augmentation will be published in the coming years. The Guidelines Development Group has decided to update these guidelines in 2017 and present the results during the 39th Annual Congress of the European Hernia Society in Vienna in May 2017.

Conclusions

To decrease the incidence of incisional hernias it is recommended to utilize a non-midline approach to a laparotomy whenever possible. For elective midline incisions, it is strongly recommended to perform a continuous suturing technique and to avoid the use of rapidly absorbable sutures. It is suggested that the use of a slowly absorbable monofilament suture in a single layer aponeurotic closure technique without separate closure of the peritoneum and using a small bites technique with a SL/WL ratio at least 4/1 is the current recommended method of fascial closure. Currently, no recommendations can be given on the optimal technique to close emergency laparotomy incisions. Prophylactic mesh augmentation appears effective and safe and can be suggested in high-risk patients like, aortic aneurysm surgery and obese patients.

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Chapter

Parastomal hernia is an independent risk factor for incisional hernia in patients with end colostomy

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Abstract

Background

Incisional hernia (IH) is the most frequent complication after abdominal surgery with an incidence of 11-20% and up to 35% in risk groups. Known risk groups for IH are abdominal aortic aneurysm and obesity. Our hypothesis is that parastomal hernia (PSH) might also represent a risk factor for developing IH. Identifying risk factors can help determine the need for preventive measures like primary mesh augmentation.

Methods

In a multi-center cross-sectional study, all patients who were operated between 2002 and 2010 by means of a Hartmann procedure or abdominoperineal resection were invited for a follow-up visit to our outpatient clinic. Primary outcome measures were the prevalence of IH and PSH. All possible risk factors for IH were scored. A physical examination was performed and, when available, CT-scans were scored for IH and PSH.

Results

A total of 150 patients were seen in the outpatient clinic. The median follow-up was 49 months (30-75). IH had a prevalence of 37.1% and PSH had a prevalence of 52.3% during physical examination. During CT-scan examination prevalance was even higher, beeing 48.3% and 52.9%. IH and PSH were both present in the same patient in 30% of all examined, and in 35.6% after CT-scan examination. PSH was found to be a statistically significant risk factor for IH in univariate and multivariate logistic regression analyses of variance, with an Odds Ratio (OR) of 7.2 (95% CI 3.3 – 15.7). In addition, an emergency operation was found to be a risk factor for IH with an OR of 5.8 in the multivariate analyses.

Conclusions

Patients with a PSH have a seven times higher chance of developing an IH compared to patients without PSH.

Introduction

Patients diagnosed with abdominal pathology can be operated by open midline laparotomy. Incisional hernia (IH) is the most frequent complication following midline laparotomy, with an incidence of 11-20%(1-3). The presence of IH is associated with pain, impaired quality of life and potentially life-threatening complications such as incarceration or strangulation of the bowel(4, 5). In 25% of patients surgically treated for abdominal pathology, a stoma is necessary (6). Parastomal hernia (PSH) is a frequent complication following stoma creation, with an incidence of up to 48% (7). Clinical findings in our center suggest that PSH might be a risk factor for later IH. PSH disrupts the normal abdominal wall anatomy and might therefore induce a higher incidence of IH. Currently known risk factors for IH development are obesity and abdominal aortic aneurysm (AAA), with incidences of up to 35%(8-13). Identification of risk groups gives surgeons the possibility to adapt or change their techniques such as primary mesh augmentation in order to prevent IH occurrence(9, 14). A better understanding of the etiology of IH may also be obtained with greater insight into the association between PSH and IH. We hypothesized that the presence of a PSH would be a risk factor for the occurrence of IH occurrence.

Methods

A cross-sectional study was conducted at the Erasmus University Medical Center (EMC) in Rotterdam and the Albert Schweitzer Hospital (ASZ) in Dordrecht, The Netherlands. All patients who had been operated either using a Hartmann procedure (HMP) or abdominoperineal resection (APR) between 2002 and 2010 were screened for eligibility. Patients with HMP and APR were included because the end colostomy created during these operations is permanent (APR) or is not restored in most cases (HMP)(15). Patients who died and patients with anastomosis created in a second operation to restore the natural faecal route were excluded.

Those patients willing to participate provided their informed consent and were seen in our outpatient clinic. Follow-up examination was conducted by two physicians experienced in hernia investigation. Physical examination was performed to determine the presence of IH and/or PSH. IH was defined as

any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination and/or imaging(16). PSH was defined as any palpable defect or bulge adjacent to the stoma when the patient is supine with elevated legs or erect and coughing or straining(17). The length of the incision scar was measured and, when present, the position and size of the hernia was measured and scored using the European Hernia Society (EHS) classification system(18). If present, postoperative CT scans were scored for PSH and IH independently by two investigators.

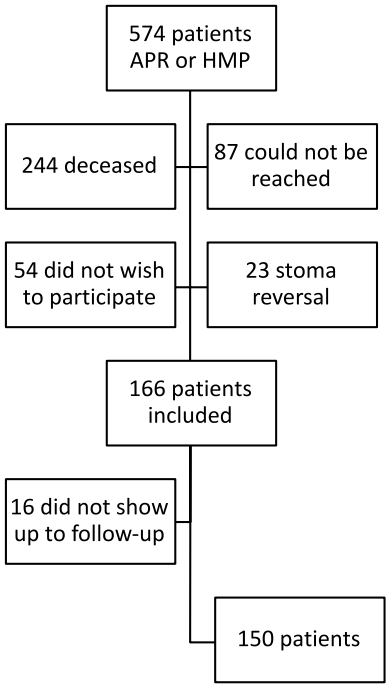
Information on possible risk factors for herniation was obtained: gender, age, weight, height, body mass index (BMI), current smoking (defined as 5 cigarettes per day or more), corticosteroid use (current user of any dose), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) (defined as current user of specific diabetic type of drugs or insuline use), previous midline incision, AAA, previous hernia (inguinal, umbilical, incisional, hiatal), postoperative complications (surgical site infection (SSI), burst abdomen, pneumonia, ileus), emergency operation, chemotherapy (defined as any type or dose of oral or intravenous chemotherapy), radiotherapy (defined as any type or dose of radiotherapy) and physical strenuous work.

Chi-Square (X^2) tests and Mann-Whitney U tests were used to compare risk factors for IH and PSH. Univariate and multivariate logistical regression analyses were conducted to predict Odds ratios (OR) of potential risk factors. Risk factors that were discovered in this study or are known in the literature will be added to the multivariate logistic regression analyses. All statistical calculations were done using IBM SPSS© 17 Software (SPSS, Chicago, Illinois, USA). Significance was assumed at $P < 0.05$.

Results

Between 2002 and 2010, a total of 574 patients received either APR or HMP. At the moment of our study: 244 of these patients were deceased; 87 could not be reached due to relocation or invalid contact information; and 54 patients did not wish to participate due to diminished physical condition or other reasons. Of the remaining 189 patients who were thus willing to participate 23 were excluded due to removal of the stoma and 16 did not show up for follow-up (Figure 1). Of the 150 included patients, 118 (78.7%) patients had undergone APR, 89 (59.3%) were male, the mean age was 67.4 years (SD 10.2), mean BMI

was 25.9 (SD 5.1) and median time to follow-up was 49 months (IQR 30-75). Of all the 150 operations, 119 patients were operated due to malignant disease and 31 times due to disease of benign nature (diverticulitis, crohns disease, colitis ulcerosa, fistulas etc). Most patients (92.4%) treated for malignant disease were operated by means of APR. Most patients (68.7%) treated for a disease of benign nature were operated by means of a HMP. In all midline closures a continuous closure technique with a slowly absorbable suture was used. The suture length to wound length ratio was not measured.



Risk factors

All possible risk factors were scored and the results are presented in Table 1. The presence of a PSH was a highly significant risk factor for IH occurrence ($p < 0.001$). HMP, age and length of the incision were also significant risk factors for developing IH. AAA and emergency operation both showed a tendency to increase the risk for IH. No differences were discovered between hospitals or follow-up period. During univariate analysis an OR of 7.2 (95% CI 3.3 – 15.7) was found for PSH on IH occurrence. When possibly confounding variables were controlled for in the logistic regression analyses (BMI, age, length of the incision, type of operation, emergency operation and radiotherapy), PSH

remained a statistically significant predictor of IH. Age and length of incision also remained significant predictors but had clinically irrelevant ORs (OR 1.05 and OR 1.1). In the logistic regression analysis an emergency operation was found to be a risk factor for IH with an OR of 5.8 (p = 0.016). HMP proved not to be a significant risk factor after controlling for possible confounding variables.

Table 1. Risk factors for incisional hernia.

	General (n=150)	No IH (N=94)	IH (N=56)	p-value***
Sex				0.732
- **Male**	89 (59%)	57 (61%)	32 (57%)	
- **Female**	61 (41%)	37 (39%)	24 (43%)	
BMI*	25.9 (5.1)	25.3 (4.1)	26.9 (6.2)	0.110
Age*	67.4 (10)	65.8 (10)	70.1 (10)	0.009
Follow-up (months)**	49 (30-75)	49.5 (28-67)	47.5 (31-81)	0.45
Hospital				1
- **ASZ**	67 (45%)	42 (45%)	25 (45%)	
- **EMC**	83 (55%)	52 (55%)	31 (55%)	
Surgery				0.004
- **APR**	118 (79%)	81 (86%)	37 (66%)	
- **Hartmann**	32 (21%)	13 (14%)	19 (34%)	
Reason Surgery				0.21
- **Malignant**	119 (79%)	78 (83%)	41 (73%)	
- **Benign**	31 (21%)	16 (17%)	15 (27%)	
Emergency operation	17 (11%)	7 (7%)	10 (18%)	*0.064*
Length incision*	21.7 (5)	20.9 (5)	22.9 (5)	0.029
Chemotherapy	61 (41%)	38 (40%)	23 (41%)	1
Radiotherapy	113 (75%)	76 (81%)	37 (66%)	*0.051*
Medical history:				
- **DM**	25 (17%)	14 (15%)	11 (20%)	0.5
- **COPD**	15 (10%)	10 (11%)	5 (9%)	0.787
- **Inguinal hernia**	20 (13%)	15 (16%)	5 (9%)	0.321
- **AAA**	3 (2%)	0 (0%)	3 (5%)	*0.05*
- **Diverticulitis**	16 (11%)	7 (7%)	9 (16%)	0.109
- **Previous midline**	36 (24%)	21 (22%)	15 (27%)	0.558
- **Smoking**	38 (25%)	26 (28%)	12 (21%)	0.439
Postoperative complications	39 (26%)	20 (21%)	19 (34%)	0.123
- **Wound infection**	21 (14%)	11 (12%)	10 (18%)	0.335
- **Burst abdomen**	4 (3%)	1 (1%)	3 (5%)	0.297
- **Ileus**	12 (8%)	7 (7%)	5 (9%)	0.763
- **Pneumonia**	7 (5%)	3 (3%)	4 (7%)	0.425
PSH	79 (53%)	34 (36%)	45 (80%)	< 0.001

*Values represent the mean and standard deviation.

**Values represent the median and interquartile ranges.

***p-values are two-sided. For dichotomous variables Chi-square test was performed and for continuous variables Mann-Whitney.

Prevalence

During physical examination, out of the total of 150 patients, 56 IHs (37.3%) and 79 PSHs (52.7%) were diagnosed (Table 2). Both hernia types were present in the same patient in 45 cases ($p < 0.001$). In 87 patients, a CT-scan was available and an objective evaluation of hernia presence could be performed. The available CT scans had been requested as follow-up method related to the initial disease of the patient. The CT revealed 42 IHs (48.3%) and 46 PSHs (52.9%). Both were present in 31 of the CT scans (35.6%), which was also statistically significant ($p < 0.001$). Physical examination for the diagnosis of IH reached a sensitivity of 0.79 and a specificity of 0.96. For PSH a sensitivity of 0.87 was reached with a specificity of 0.95.

Table 2. Physical examination and CT-scan examination.

	Prevalence	X^2 p-value*
Physical examination (n=150)		
- IH	56 (37%)	
- PSH	79 (53%)	
- IH and PSH	45 (30%)	< 0.001
CT-scan (n=87)		
- IH	42 (48%)	
- PSH	46 (53%)	
- IH and PSH	31 (36%)	< 0.001

*Association is tested by means of Chi-Square testing.

Discussion

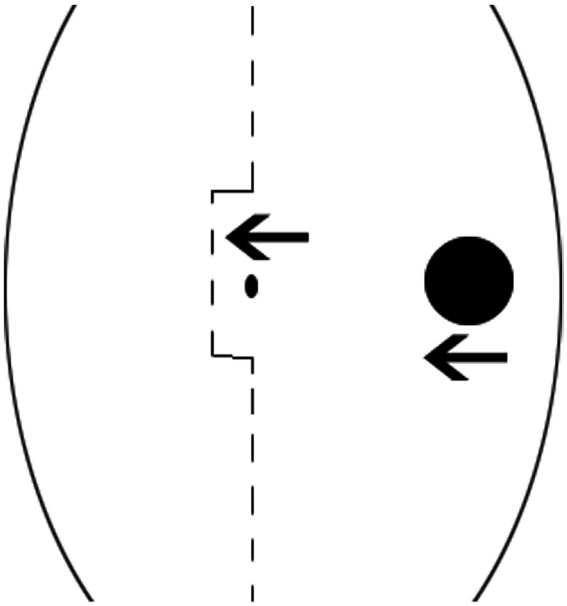
This study confirms our hypothesis that the presence of PSH represents a risk factor for the occurrence of IH. Patients who acquire a PSH had a seven times higher odds of developing an IH compared to patients without a PSH.

The prevalence of PSH in our study was 52.7%, which corresponds with existing literature and in our previous experience with colostomies (7). The incidence of PSH does not differ when open or laparoscopic colostomy creation are compared, suggesting that PSH is not affected by midline incision or hernia (7, 19, 20). A number of potential theories explaining the high rate of PSH have been suggested in the literature. Increased abdominal pressure can exit through the opening in the abdominal wall possibly promoting PSH. According to Laplace's law, the tangential forces working on the colostomy may enlarge the fascial opening and cause PSH (21). Additionally the creation of the colostomy opening is not a standardized procedure. An overly small

stoma opening can lead to obstruction while an overly large stoma opening can perhaps incite a higher frequency of PSH. These mechanisms can explain the high incidence of PSH found in general and also in our study. However, with a prevalence of over 37% at 49 months, the IH rate in our population is one of the highest found in the literature (3, 22, 23). Examination of the CT scans showed this number to be even larger - up to 48.3%. This high prevalence can probably be attributed to the presence of a PSH. When looking at the location where the IH occurred, it is striking to see that 55% of the IHs occurred at exactly the same level as the colostomy. For instance, patients with a colostomy at the M3 level (EHS classification) developed IH in most cases between 3cm above and 3cm below the umbilicus (M3). It can thus be hypothesized that the mechanical forces during inspiration and expiration change after colostomy creation. The midline incision tends to shift to the contralateral side due to reduced restraining force at the site of the colostomy. This explanation is visualized in Figure 2. The midline shift increases the tensile force on part of the sutures and can thus create direct postoperative separation of wound edges, which is a major predictor of IH (24, 25). The tensiles force and the midline shift will increase further after PSH development, with a further reduction of the restraining force as a result. Another possible explanation is atrophy of the rectus muscles on the colostomy side due to the disruption of nerve innervation during placement of the colostomy. This atrophy can create a weak spot at the level of the colostomy and thus induce IH. In the literature, it is also stated that some patients may be subject to herniosis and thus biologically prone to herniation (26-30). However, in the present study, no other possible symptoms of herniosis were found except the strong association between PSH and IH: Patients with a PSH and/or IH did not have more inguinal, umbilical or other incisional hernias. One can also hypothesize that *all* patients with a PSH have a form of herniosis in light of the fact that PSH can often be attributed to technical failures. Further research should thus examine both the biological and biomechanical aspects of hernia as the etiology may very well be a combination of the two.

In the present study, we found a difference in the hernia rates for the two types of surgery performed in our patient group. Surgical site infections have been shown to increase IH rates, which means that the nature of both of these operations could - in principle - contribute to the high incidence of hernias (31, 32). APR and HMP are by definition potentially contaminated surgeries.

Figure 2. Midline shift after enterostomy creation.



However, the 21 patients identified with SSI were equally divided across the patients with and without hernia; SSI therefore cannot be responsible for the high rates of hernia which we found. HMP showed a higher incidence (59.4%) of hernia compared to APR (31.4%). However, the results of the multivariate regression analysis showed - not HMP - but the emergency setting in which the HMP usually took place to constitute a risk factor for IH. Patients operated in an emergency setting had a 5.8 times higher odds of IH than patients not operated in an emergency setting. Relatively few articles have been published on this subject regarding emergency operations and hernia formation(33, 34). Patients operated in an emergency setting are generally in a more weakened state both pre-operatively and post-operatively, are more often subject of intra-abdominal contamination than other patients and also generally have high intra-abdominal pressure; the possibility of tension-free closure is thus reduced strongly (35).

Limitations

There are several weaknesses with regard to this study and most of them are due to the cross-sectional design. For instance, as all patients were seen at the

same time and in most cases no documentation of either IH or PSH could be found, it is unclear whether PSH or IH occurred first. Nevertheless an assumption was made on the basis of the patients' anamneses that PSH occurred first, but further prospective studies should be undertaken to confirm this assumed sequence. Also, no measurement of the suture length to wound length ratio was conducted, which could facilitate an increase in IH formation. In addition, in this study out of 574 patients *only* 150 patients were available for follow-up which could attribute to selection bias. The majority of these lost patients were due to death or due to them not being able to come to our outpatient clinic, possibly due a diminished physical state or to postoperative complications. A prospective trial could be able to control for this possible bias. Standard follow-up which includes radiological examination might also strengthen the results of future studies giving also give more insight into possible changes that occurred in the abdominal wall before and after operation and herniation.

Conclusion

This study confirms our hypothesis that PSH increases the chances of IH occurrence by seven times. Furthermore, patients operated in an emergency setting also have a 5 times higher chance of IH, as shown in the multivariate analyses of variance. Thus, PSH and - to a lesser extent - operation in an emergency setting can be added to the already known risk factors of IH development, namely AAA and obesity. Patients who are known to be prone to herniation can thus be treated prophylactically. Primary mesh augmentation in patients at risk for herniation has been shown to reduce the incidence of IH and PSH (9, 12), (36-39). Although colostomy operations are considered clean-contaminated or even contaminated operations, the contamination did not increase (mesh) infections in trials where mesh augmentation was used. In case of open colostomy creation it would be advisable to not only augment the midline or the colostomy with a mesh but augment both, in order to prevent IH and PSH formation. In case of PSH correction, an effort should be made to correct both the IH and PSH. Creating an mesh overlap over the midline, as demonstrated by Berger et al, would reduce the chance of IH development and PSH recurrence (40). Further research is nevertheless needed to identify other possible preventive measures to reduce postoperative hernias and better understand the mechanical and biological factors influencing the occurrence of IH.

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Chapter

Abdominal rectus muscle atrophy and midline shift after colostomy creation

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Abstract

Introduction

Incisional hernia (IH) can be attributed to multiple factors. The presence of a parastomal hernia has shown to be a risk factor for IH after midline laparotomy. Our hypothesis is that this increased risk of IH might be caused by changes in biomechanical forces, such as midline shift to the contralateral side of the colostomy owing to decreased restraining forces at the site of the colostomy, and left abdominal rectus muscle (ARM) atrophy owing to intercostal nerve damage.

Methods

Patients were selected if they underwent an end-colostomy via open operation between 2004 and 2011. Patients were eligible if computed tomography (CT) had been performed postoperatively. If available, pre-operative CT-scans were collected for case-control analyses. Midline shift was measured using V-Scope application in I-Space®, a CAVE™-like virtual reality system. For the ARM atrophy hypothesis, measurements of ARM were performed at, the level of colostomy, and 3cm and 8 cm cranial and caudal of the colostomy.

Results

Postoperative CT-scans were available for 77 patients; of these patients, 30 also had received a preoperative CT-scan. Median follow-up was 19 months. A mean shift to the right side was identified after preoperative and postoperative comparison; from -1.3 +/- 4.6 to 2.1 +/-9.3($p = 0.043$). Furthermore, during rectus muscle measurements, a thinner left abdominal rectus muscle was observed below the level of colostomy.

Discussion

Creation of a colostomy alters the abdominal wall. Atrophy of the left ARM was seen caudal to the level of the colostomy, and a midline shift to the right side was evident on CT-scan. These changes may explain the increased rate of IH after colostomy creation.

Introduction

Incisional hernia (IH) is one the most frequent postoperative complications after abdominal surgery (1-3). The reason for IH formation can be attributed to patient-related factors, such as high body mass index (BMI), smoking, corticosteroid use, abdominal aortic aneurysm (AAA), or other connective tissue disorders(4-8). Otherwise, IH formation can also be influenced by factors related to the surgeon or the surgical procedure, such as suture technique, surgical site infections and fascial dehiscence(9-11). More recently, we found that parastomal hernia appeared to be a risk factor for IH(12). Patients with a parastomal hernia had a 7.2 higher Odds Ratio for IH formation(12). In addition, 55% of all IH developed at the level of the colostomy. We hypothesized that the biomechanical forces in the abdominal wall would change after colostomy creation, inducing a greater rate of IH. One hypothesis was that the midline incision would shift to the right (or contralateral side) due to reduced restraining forces at the site of the colostomy. A midline shift would increase the tensile force on a part of the sutures and this shift would then cause separation of the wound edges, which is a major predictor of IH (13, 14). In addition, we hypothesized that would induce atrophy of the abdominal rectus muscle (ARM) due to transection or injury to the intercostal or subcostal nerves innervating the ARM (15). A radiologic anatomic study was performed to determine if colostomy creation induces a midline shift and ARM atrophy.

Methods

Inclusion and exclusion criteria

Patients were selected from the PACIFIC cohort, a multicenter study which was conducted at the Erasmus University Medical Center, Rotterdam, the Netherlands and the Albert Schweitzer Hospital, Dordrecht, the Netherlands(12). Patients were included in this cohort if they had undergone a left-sided, end-colostomy during an open Hartmann Procedure or abdominoperineal resection between 2004 and 2011. Patients were selected for this study if a CT had been taken postoperatively. If available, pre-operative CT-scans were also collected for case-control analyses. Patients were excluded if the time between operation and the postoperative CT was less than 1 month, if a patient had a transposition of the

ARM, if a patient had an ileostomy or, if a patient had multiple colostomies. Patients with a parastomal hernia or IH were not excluded from this study.

I-Space®

In order to evaluate a midline shift at the level of the colostomy, the I-Space®, a CAVE™ like virtual reality system, and V-scope software were used (16). This system was previously used and validated in a gynecologic and orthopaedic studies (17, 18). The CT-scans were uploaded to the I-Space® PACS, format converted, and then three dimensionally visualised and projected using the V-Scope application. This results in a "hologram" of the dataset being visualised floating in front of the viewers. The viewers wore a pair of lightweight glasses with polarising lenses that allowed the hologram to be seen with depth. A virtual pointer was used to interact with this "hologram" which made it possible to move into the hologram and to perform measurements (Figure 1 and 2) (19). The exact midline of the abdominal wall was determined by drawing a 3-dimensional line between the xyphoid process and the pubic bone, parallel to the spine. The distance of the abdominal rectus muscles to this midline (dARM) was measured to determine how the *exact* midline corresponded with the position of the rectus muscles. The midline shift was calculated as follows: (left dARM + right dARM) / 2 – left dARM). For instance, if the distance of the right ARM to the *exact* midline was 4 millimeter (mm) and the distance of the left ARM to the *exact* midline was 6 mm, this would constitute to: (6 + 4) / 2 – 6 = -1mm, which would mean that the rectus muscles have shifted 1mm to the left at the level of the colostomy.

ARM measurements

Measurements were performed at 5 different points at both the colostomy (left) side and the contralateral (right) side in order to evaluate the ARM thickness. These measurements were taken at 8cm, 3 cm cranial and caudal to, and at the level of the colostomy.

Statistical analysis was performed using the paired Student's t-test, Mann-Whitney-U test and the Spearman correlation coefficient, whenever appropriate(SPSS 14.0, Chicago, IL, USA). Numbers are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR). A p-value of <0.05 was considered statistically significant.

Figure 1. The I-Space® installed at the Erasmus is a CAVE™-like virtual reality environment where images can be projected as 3-dimensional hologram.

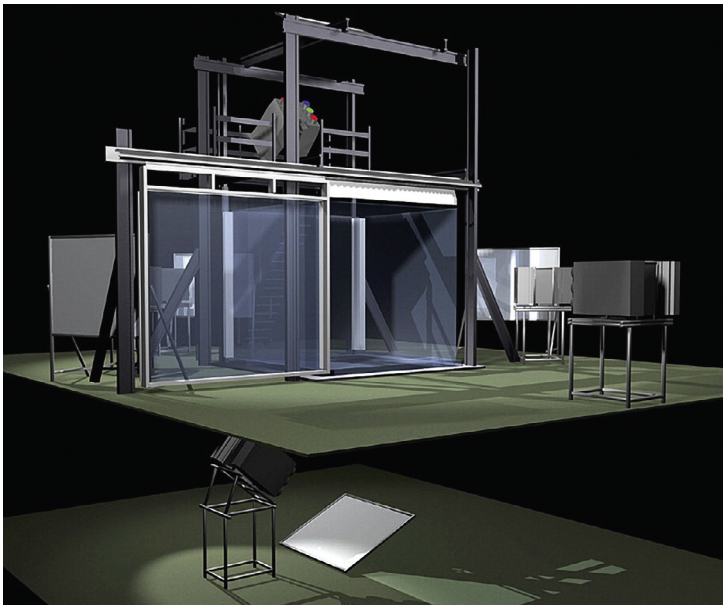


Figure 2. The distance between the ARM to the *exact* midline is being measured in a 3-dimensional hologram.

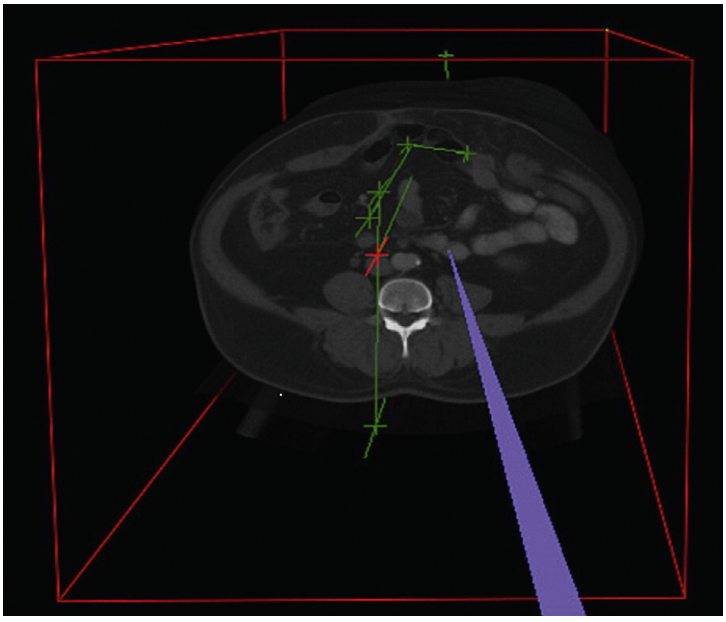
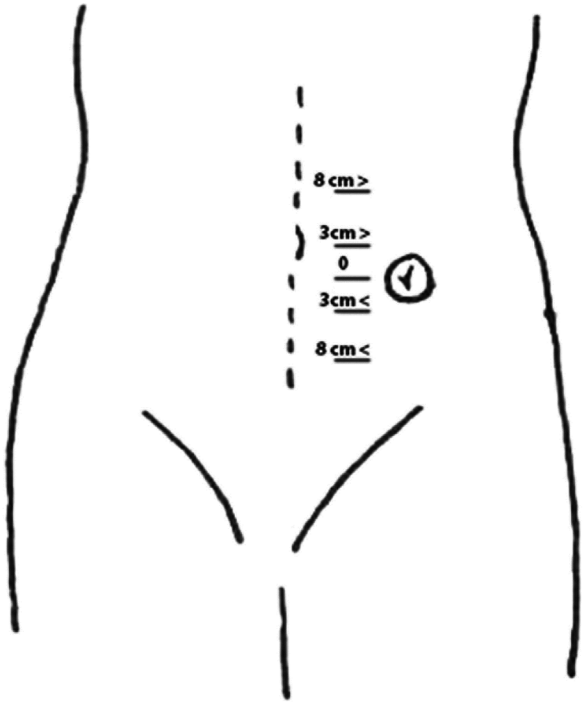


Figure 3. ARM thickness was measured at 8 centimetres (cm) above and below, 3 cm above and below and at colostomy level.



Results

Inclusion and exclusion criteria

A total of 160 patients from the PACIFIC cohort who had given informed consent were screened if a postoperative CT was available. At the time of our study, 32 patients were excluded (due to removal of the colostomy, multiple enterostomies, flap transposition of ARM, or a burst abdomen), 49 did not receive a postoperative CT, and in 2 patients the postoperative CT was taken within 1 month after surgery, leaving 77 patients eligible for this study.

General

The median time between creation of the colostomy and the postoperative CT-scans was 19 months (range 1 to 96). Of all patients 44, (57%) were men,

the median age was 66 (range 32 to 81), the median BMI was 25 (range 17 to 41), 10 patients (13%) had diabetes mellitus (DM), 10 (13%) had chronic obstructive pulmonary disease (COPD), 16 (21%) were current smokers and in 7 (9%), the colostomy was placed lateral to ARM. Older patients had a decrease in ARM thickness (r_s= -0.28 preoperatively, r_s= - 0.25 postoperatively); also, in female patients a general decrease in ARM thickness ($p < 0.001$) was observed. However, female sex and age did not have an effect on the midline shift. DM, COPD, smoking and pararectal placement of the colostomy were also not associated with a change in ARM thickness or midline shift.

I-Space®

The median preoperative midline shift was -0.8mm (n=30; IQR -4.8 to 0.9). Postoperatively the median postoperative shift was 4.5 mm (n=77; IQR -1.9 - 9.8) corresponding with a shift to the right. Comparing the preoperative CT-scans with the CT-scans that were taken postoperatively, there was a mean shift to the right side; from -1.3 +/-4.6 to 2.1 +/-9.3) ($p = 0.043$) (Table 1).

ARM measurements

When comparing the preoperative CT-scans with the postoperative CT-scans a thickening of the left ARM was observed at 3cm cranial, 3cm caudal, and at the level of the colostomy (Table 1). This thickening of the ARM was not seen on the right/contralateral side.

Table 1. Preoperative versus postoperative data.

	Preoperative*	**Postoperative***	**P-Value****
Midline shift at stoma	-1.3 (4.6)	2.1 (9.3)	0.043
Left ARM (n = 30)			
ARM thickness 8cm above stoma	8.1 (2.4)	8.5 (2.1)	0.203
ARM thickness 3cm above stoma	8.8 (2.6)	9.8 (2.6)	0.010
ARM thickness at stoma level	9.1 (2.8)	10.2 (2.5)	0.024
ARM thickness 3cm below stoma	9.6 (2.7)	10.3 (2.7)	0.086
ARM thickness 8cm below stoma	10.8 (3.2)	10.4 (3.2)	0.466
Right ARM (n = 30)			
ARM thickness 8cm above stoma	8.3 (2.4)	8.5 (2.6)	0.609
ARM thickness 3cm above stoma	8.9 (2.5)	9.6 (3.1)	0.081
ARM thickness at stoma level	9.3 (2.7)	9.6 (2.7)	0.448
ARM thickness 3cm below stoma	9.9 (2.7)	10.5 (3.3)	0.178
ARM thickness 8cm below stoma	10.9 (3.1)	11.1 (3.5)	0.609

* Values represent the means and standard deviation in mm

** p-values are two-sided. For continuous variables the paired student t-test was used.

When comparing the left and the right ARM, no difference was seen regarding ARM thickness preoperatively. However, postoperatively, a thickening of the left/ipsilateral ARM was seen at 8cm cranial, 3cm cranial and at the level of the colostomy (Table 2) compared with the right/contralateral ARM. When we stratified the postoperative group in groups, one with and one without parastomal hernia, the left ARM was thicker cranial and at the level of the colostomy in the parastomal hernia group but not in the group without parastomal hernia.

Table 2. Left ARM vs. right ARM data.

	Left ARM*	**Right ARM***	**P-Value****
No PH (n = 33)			
Postoperative 8cm above stoma	9.3 (2.1)	9.1 (2.3)	0.440
Postoperative 3cm above stoma	10.1 (3.3)	9.5 (3.2)	0.137
Postoperative level stoma	10.8 (3.1)	10.7 (3.4)	0.797
Postoperative 3cm below stoma	10.7 (2.8)	11.7 (3.6)	0.044
Postoperative 8cm below stoma	11.1 (3.6)	12 (3.7)	0.017
PH (n = 44)			
Postoperative 8cm above stoma	7.9 (2.3)	7.4 (2.3)	0.036
Postoperative 3cm above stoma	9.6 (2.4)	8.8 (2.9)	0.024
Postoperative level stoma	10.2 (3.0)	9.3 (2.5)	0.004
Postoperative 3cm below stoma	10.2 (2.8)	10.1 (3.6)	0.677
Postoperative 8cm below stoma	9.9 (3.3)	10.6 (3.9)	0.151

* Values represent the means and standard deviation in mm

** P-values are two-sided. For continuous variables the paired student t-test was used.

Caudal to the level of the colostomy, the left ARM was thinner than the right ARM. Again, the postoperative group was divided in two groups, one with and one without parastomal hernia. Caudal to the colostomy a thinner left ARM was observed in the group without parastomal hernia at 3cm caudal (10.7 +/-2.8 vs. 11.7 +/-3.6 (p = 0.044) and 8 cm caudal (11.1 +/-3.6 vs. 12 +/-3.7 (p=0.017) . In the group with a parastomal hernia no significant differences in ARM were seen.

Discussion

This is the first study to show that changes are present in the abdominal wall after colostomy creation. By using the I-Space® system, a midline shift was

seen to the right (contralateral) side of the colostomy. In addition differences were observed in the thickness of the ARM in the area near the colostomy.In literature, a decrease of the general thickness of the ARM in females and in older people has been described, and similar findings were observed in this study (20, 21). Little is known, however with regard to the effect of abdominal incisions on changes in the abdominal wall and even less is known regarding changes after colostomy creation (15, 22, 23). Two types of changes in the abdominal wall were observed in this study which might have an influence on wound healing and IH formation.

Midline shift

A significant shift to the contralateral side of the colostomy was observed when preoperative and postoperative CT-scans were compared. The observed midline shift appears to be caused by a decrease in restraining forces at the site of the colostomy. Without the pull of the abdominal wall muscles on the left (colostomy) side, a dysbalance of the muscles in favor of the muscles on the right (contralateral) side can result in the observed midline shift. This change would increase the force on some parts of the suture line. In addition, a curve instead of a straight wound line will also promote separation of the wound edges which is known to be a risk factor for IH (13). Although it is possible that in addition to the decrease in restraining forces, the excess of tissue due to colostomy creation might also induce a shift, this could not be tested in this study. During our initial mechanical modelling by testing using the Abdoman®, (the artificial abdomen of Erasmus University Medical Center and Technology University of Delft, the Netherlands) we observed that a midline shift also occurred without the excess volume of a colostomy and that the decrease in restraining forces were the main cause of midline shift. This findings are, however, preliminary and more research still needs to be conducted.

ARM measurements

Other observed findings were changes in ARM thickness. The left (colostomy) ARM at the level of the colostomy was significantly thicker postoperatively compared to the preoperative situation. On review of the CT-scans, it was more difficult to measure the ARM thickness in the vicinity of the colostomy; the medial part of the ARM seemed to fold over itself due to pressure of the colostomy, inducing the apparent observed increase in thickness.

A similar finding was observed when comparing the left (colostomy) ARM with the right ARM postoperatively. The left ARM was thicker at 8cm cranial, 3cm cranial and at the level of the colostomy. However, caudal to the colostomy, the left ARM was actually thinner. This change may be caused by left ARM atrophy due to the denervation or damage to the intercostal /subcostal nerve after colostomy creation. Colostomies created during abdominoperineal resection or Hartmann procedures are generally situated in the lower left quadrant and positioned at the level of the 12th intercostal nerve. The iliohypogastric nerve which travels caudal to the 12th intercostal nerve does not innervate the rectus muscle and cannot compensate for any potential damage. Injury to the intercostal nerve would induce atrophy of the left ARM at the level of the colostomy and caudal. This effect was partially obscured in this study due to overlap caused by the colostomy and possible herniation. The combination of an atrophy of the left ARM and the associated midline shift could be the cause of the increase of risk of IH observed in the PACIFIC-study(12). There has been discussion as to which position is preferential for colostomy placement. Currently, it is not known if colostomies should be placed through or lateral of the ARM. However, lateral of the ARM the intercostal nerves are less segmented and could be easier to detect and preserve (24). Additionally, a more cranial colostomy position could decrease atrophy to the ARM, because the 11th and 12th intercostal nerves are mainly responsible for ARM innervation (25). Furthermore, prophylactic mesh application at the level of the colostomy will decrease the chance of parastomal hernia formation and as a result will decrease possible long-term nerve damage due to compression(26). No literature, however, is currently available with regards to the effects of these prophylactic measures on ARM atrophy.

Limitations

The main weaknesses of this study are the retrospective design and the limited number of patients. Due to the limited number of available preoperative CT-scans in this cohort, we were not able to perform statistical analyses with regards to IH or parastomal hernia and the midline shift. In addition, it is unknown what the impact a 5mm shift would have on the forces on the abdominal wall. This is something that might be investigated in the future with

biomechanical experiments (for instance, using the Abdoman®). Currently our group is developing a Finite Element Model, in attempt to model the forces after incisions in the abdominal wall. Furthermore, it would have been interesting to have a preoperative CT-scan of all patients and standard follow-up CT-scans during the postoperative period and to see the development of the changes of the midline and the ARM. Also, measurement errors were minimized in this study by using the I-Space® program but could possibly be reduced even further by implementing a prospective study protocol. As stated before, it was difficult to measure the ARM in the vicinity of the colostomy due to folding of the ARM. The decrease in left ARM thickness caudal to the colostomy was apparent and in accordance with our hypothesis.

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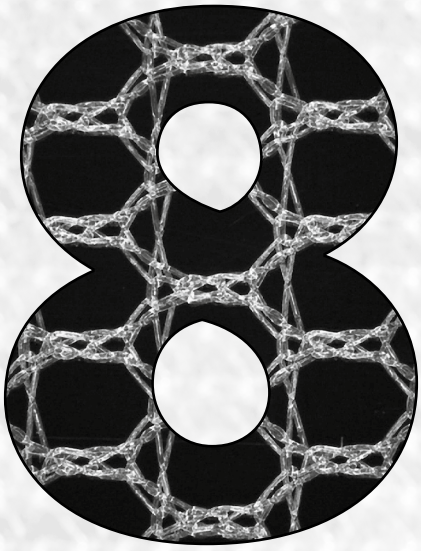
Part 2

Surgical treatment of incisional hernia

Chapter



A systematic review of the surgical treatment of large incisional hernia

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Abstract

Purpose

Incisional hernia (IH) is one of the most frequent postoperative complications. Of all patients undergoing IH repair, a vast amount have a hernia which can be defined as a large incisional hernia (LIH). The aim of this study is to identify the preferred technique for LIH repair.

Methods

A systematic review of the literature was performed and studies describing patients with IH with a diameter of 10cm or a surface of 100cm^2 or more were included. Recurrence hazards per year were calculated for all techniques using a generalized linear model.

Results

Fifty-five articles were included, containing 3945 LIH-repairs. Mesh reinforced techniques displayed better recurrence rates and hazards than techniques without mesh reinforcement. Of all the mesh techniques, sublay repair, sandwich technique with sublay mesh and aponeuroplasty with intraperitoneal mesh displayed the best results (recurrence rates of <3.6%, recurrence hazard <0.5% per year). Wound complications were frequent and most often seen after complex LIH repair.

Conclusions

The use of mesh during LIH repair displayed the best recurrence rates and hazards. If possible mesh in sublay position should be used in cases of LIH repair.

Introduction

Incisional hernia (IH) is one of the most frequent complications after abdominal surgery with an incidence up to 20%(1-3), and in high risk patients incidences over 35% have been reported (4, 5). In the United States, 4 to 5 million abdominal surgeries are performed every year which means that a number as high as 500.000 IH will develop annually. Within this group, a specific subcategory of patients with large incisional hernia (LIH) can be identified. The incidence of LIH is rising due to an increase in survival of intra-abdominal catastrophes and infections(6). Of all patients with IH 15-47% have a hernia which can be defined as a LIH (7). Patients with LIH often experience severe symptoms and associated co-morbidities. Patients with LIH may have complaints of severe back pain, disturbance of ventilatory function, chronic wounds or enterocutaneous fistulas, resulting in a major decrease in quality of life and daily activities(6, 8-10).

LIH repair is technically challenging and is associated with a longer hospital stay, impaired wound healing, a higher rate of reoperations and readmissions and increased recurrence rates(7, 11-14). In some cases approximation of the rectus fascia is not possible and the mesh can be used to bridge the defect or additional measures such as component separation or aponeuroplasty must be added. Bridging with the mesh in contact with the viscera increases the risk of postoperative complications such as adhesion formation, bowel obstruction and complicated reinterventions(15, 16). In the last decades laparoscopic LIH repair has been introduced, with an intraperitoneal onlay mesh (IPOM) bridging the defect. Using IPOM, augmentation of the abdominal wall is in most cases not performed and the entire mesh is in contact with the viscera, for which reason composite meshes are most often used to reduce adhesion formation.

Randomized clinical trials have been conducted on the different repair techniques of small and medium sized ventral(17-20), but the treatment of LIH has not yet been properly addressed. There is no consensus, based on evidence, regarding the optimal treatment option. The treatment of LIH is in fact a major problem, with associated potentially life-threatening complications. The aim of this study is to identify the best possible technique(s) for LIH repair with regards to recurrence and complication rates.

Methods

In literature many different definitions of LIH are proposed but consensus is lacking, as shown in table 1. Commonly used parameters to define large abdominal hernia include width, length, transverse size and the surface calculation of an ellipse (½ length x ½ width x π). For this review LIH is defined as ventral incisional hernia with a fascial defect of 10cm or more in any direction according to the definition of the European Hernia Society(21) or a defect surface of 100cm^2 or more.

Table 1. Definitions of large incisional hernias in the literature.

Author	Definition of large hernia
Tanaka EY, 2010(22)	≥ 10 cm width or length
Muysoms FE, 2009(21)	≥ 10 cm width
Ammaturo C, 2005(23)	≥ 10 cm width
Dumanian GA, 2003(24)	> 10-15 cm transverse size
Korenkov M, 2001(25)	≥ 10 cm width or length
Chevrel JP, 2000(26)	≥ 15 cm width

Search strategy

A systematic review of the literature was conducted to detect all treatment strategies of large incisional hernia. An electronic search of Embase, Pubmed and the Cochrane Central Register of Controlled Trials was performed on May 2nd, 2014. Additionally, a cross-reference search of review articles in leading journals and manual research of reference lists of all included studies was conducted to identify articles published on the treatment of LIH. There was no restriction on language, study type or publication year.

Study inclusion and exclusion criteria

Only treatment studies involving adult human subjects with LIH of the ventral abdominal wall were included. Ventral wall hernias include midline, transvers, subcostal, (para)umbilical and paramedian locations. LIH was defined as a fascial defect (hernial orifice) measuring 10cm or more in any direction or a surface of 100cm^2 or more. The following study types were included: RCT, prospective and retrospective cohort studies, case-control studies and case series.

Studies with one of the following characteristics were excluded: a mean follow-up of less than one year, less than 75% completion of follow-up of at least one year, or reporting on repair with a commercially not available mesh. Studies reporting series or cohorts of fewer than 10 patients operated over 3 years were excluded to eliminate small case series that were likely to be influenced by learning curves, and to minimize selection and publication bias of 'positive' results. LIH in the iliac region or after lumbotomy were excluded. Studies were excluded if a full-text version was not available. Whenever multiple publications from institutions reporting the same cohort were encountered, only the most recent and complete article was included. Two reviewers independently assessed the titles and abstracts of all reports identified by electronic and manual searches. Any disagreement was resolved by discussion and consensus with the last author of this article.

In the results discrimination between 'simple' and 'complex' LIH was made. Simple LIH was defined as a fascial defect over 10 cm (or surface over 100cm^2) with intact soft tissue and skin and, if recurrent, with a not-infected mesh in situ from previous repair, comparable to the 'minor' complex abdominal hernias from the classification system of Slater (27). Complex LIH was defined as a fascial defect over 10 cm (or surface over 100cm^2) and associated problems of substantial loss of tissue, intra-abdominal infection, or if recurrent with infected mesh. LIH was also considered complex if during LIH repair a concomitant parastomal hernia was repaired. The category complex LIH includes most of the 'moderate' and 'major' complex abdominal hernias from the classification system of Slater(27).

Statistical analysis

To compare recurrence rates between repair techniques a generalized linear model (GLM) is used(28). Since the occurrence of individual recurrence is not reported, the risk of getting a recurrence is assumed equal during each month of follow-up of the study for not-affected patients. Exponential survival curves are assumed, which are identical for all studies of a certain type of treatment, but which differ between treatments. Considering one study i, x_i represents the sample size, t_i the follow-up and y_i the number of patients not experiencing the recurrence. The exponential survival curve is given by $S(t)=exp(-at)$. a represents the angle of the slope of the curve and is estimated from the data of all inidividual studies reporting on one repair technique. The expected

value of y_i is $\mu_i = x_i \exp(-at_i)$, or $log\ \mu_i = \log x_i - at_i$. To estimate a, the GLM is used, assuming for y_i a Poisson distribution with expectation μ_i and a logarithmic link function. The linear predictor is $h_i = \log x_i + at_i$, with an offset $\log x_i$, and no intercept. Using the GLM function in the R system, a is estimated(29). A larger a means a smaller probability per month follow-up of getting a recurrence. The hazard (a) is transformed from a monthly risk to a yearly risk of getting a recurrence during long-term follow-up.

Results

The systematic database search identified 1749 records and 80 additional records were identified through additional cross-referencing. After removal of all duplicates 1467 unique records remained. All abstracts were screened for eligibility and for 410 records the full-text article was assessed. Fifty-five articles containing 3945 patients met the inclusion criteria and were selected for review and included in GLM analysis. The PRISMA flow-chart of the selection of relevant studies can be found in figure 1(30). Three techniques of open reconstruction without mesh were described comprising 460 patients. Six different techniques of open reconstruction with mesh were described comprising 3002 patients and 483 patients were repaired by laparoscopic approach. An overview of the different LIH repair techniques and results are shown in table 2.

1. Open reconstruction without mesh

a) Components Separation Technique (CST/Ramirez)

CST was firstly described by Albanese in 1951(82) and named as such after the publication of Ramirez in 1990(8). During CST the abdominal wall is augmented by creating relaxing incisions in the external oblique aponeurosis and separating the external oblique from the internal oblique muscles and elevating the overlying rectus muscle from the posterior rectus sheath (figure 2). In 7 studies, including one RCT, a total of 219 LIH were repaired using CST(9, 11, 31-35). In, approximately 40% of cases, patients had a complex LIH.

Postoperative mortality was 1.3%, and postoperative complications occurred in almost 50%. Infection or necrosis of the wound occurred in 20%, hematoma in 8%, seroma in 9%, and pulmonary complications in 7%. In one patient a rupture of the abdominal wall at site of the relaxing incisions occurred

for which mesh augmentation was performed. Recurrence after CST occurred in 16% of patients after mean 12-52 months follow-up.

Figure 1. The PRISMA flow chart of the selection of relevant studies.

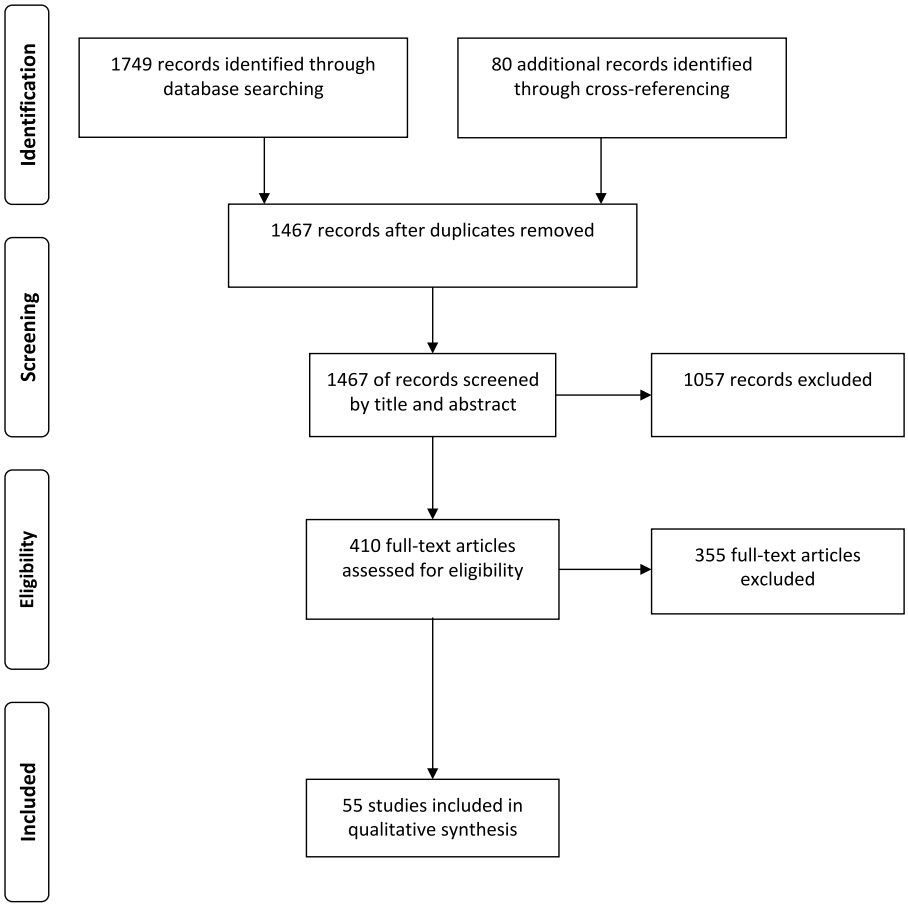
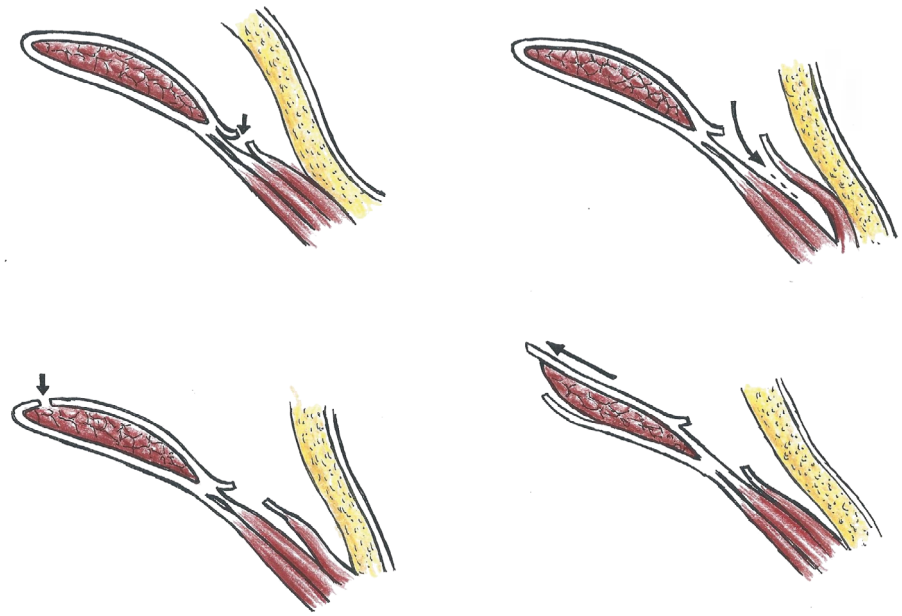


Table 2. Overview of different LIH repair techniques and results.

Technique	#	Simple LIH (%)	Complex LIH (%)	Wound complications (%)	Mesh infection (%)	Recurrences (%)	Mean FU
Open without mesh	460						
CST(9, 11, 31-35)	219	±60	±40	41	-	16	1-4 years
Aponeuroplasty(10, 36, 37)	195	45	55	13	-	12	4-10 years
Langenskiöld(38)	46	?	?	33	-	44	6 years
Open with mesh	3002						
Sublay(10, 39-48)	762	74	26	27	4.7	3.6	1-8 years
Aponeuroplasty + IPOM(49, 50)	630	?	?	9	1.3	3.2	3-8 years
IPOM (bridging)(11, 15, 46, 51-57)	514	±85	±15	19	3.7	8.3	1-6 years
MCST(47, 58-64)	511	43	57	48	0.6	10.0	1-5 years
Onlay(53, 65-69)	454	96	4	31	1.7	11.1	1-6 years
Sandwich(53, 70-73)	131	±90	±10	19	0.8	0.8	1-7 years
Laparoscopy	483						
IPOM (bridging) (74-81)	483	100	0	8	0.4	5.6	1-5 years

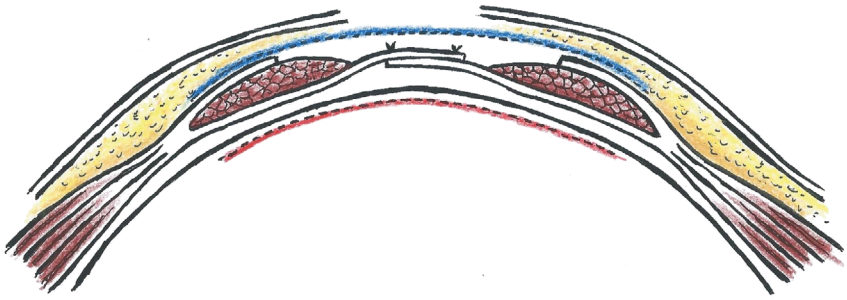
Figure 2. Components Separation Technique; relaxing incisions external oblique fascia(1), separating the external oblique from the internal oblique(2), elevating overlying rectus fascia from posterior rectus sheath(3) and bringing fascia from both sides together in midline for closure(4).



b) Aponeuroplasty

In 1941 Welti and Eudel introduced a technique which consists of incising both anterior rectus sheaths and suturing them overlapping together covering the hernia defect(83) (figure 3). In 3 studies a total of 195 LIH were repaired using aponeuroplasty(10, 36, 37). In 55% of cases, patients had a complex LIH (36, 37). In simple LIH cases postoperative seroma or hematoma formation developed in 6%. Recurrence occurred after aponeuroplasty in 2.2% of patients after a mean follow-up of over 4.5 year. In complex LIH patients the postoperative mortality after aponeuroplasty was 10.4% and 18.9% of patients developed postoperative wound infections. The recurrence rate after aponeuroplasty with complex LIH's was 21% after 10 years follow-up. The overall recurrence rate of LIH's repaired with aponeuroplasty was 12% after mean 4-10 years follow-up.

Figure 3. Aponeuroplasty technique; incising both anterior rectus sheaths and suturing them overlapping together. A mesh can additionally be implanted intraperitoneally (IPOM) (red dotted line) or onlay (blue dotted line).



c) Langenskiöld method

In 1982 Smitten et al published the results of the 'Langenskiöld' method of hernia repair, using strips of the hernial sac passed through the opposite abdominal wall as pulling threads to approximate the rectus muscles in the midline(38). Disappointing results included wound infection in one third of all patients and 20 out of the 46 patients (44%) with LIH developed a recurrence after a mean follow-up of 6 years.

2. Open reconstruction with mesh

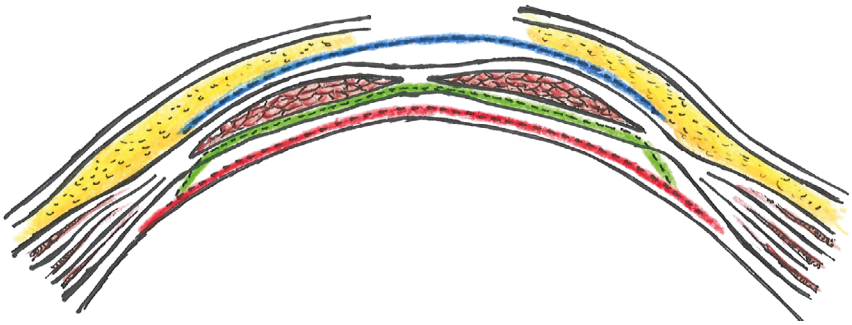
a) Open repair with sublay mesh (Rives-Stoppa technique)

French surgeons pioneered the use of a synthetic mesh in LIH repair performing closure of the rectus fascia using the preperitoneal (Stoppa, 1973) or retromuscular plane (Rives, 1973) (figure 4) (84, 85). In 11 articles a total of 762 LIH were repaired using the sublay technique.(10, 39-48). Currently sublay repair consists of dissection and closure of the posterior rectus sheath and placement of a non-absorbable mesh. Most authors report no problems with closing the posterior rectus sheath after dissecting the retrorectus plane. In a large hernia the defect can extend into the subumbilical abdominal wall (below the arcuate line) where no posterior rectus sheath is present and the mesh is (partly) positioned in the preperitoneal plane. Rosen extends the retromuscular dissection by incising the posterior rectus sheet just medial of the semilunar line and positioning the mesh in the retromuscular plain and more laterally in the preperitoneal plain (between the peritoneum and the transvers abdominis muscle)(47). In 26% of cases, patients had a complex LIH. Since not all studies

reported separately on the outcomes of simple and complex LIH, reported postoperative complications are of all patients with a sublay mesh.

Postoperative mortality following sublay repair was 2.1%. Wound complications were reported in 11%, seroma in 9% and hematoma in 7%. In 91 patients additional dermolipectomy or panniculectomy was performed, without increased complication rates(39, 41). Mesh infection or fistulas associated with wound infection developed in 4.7%, requiring removal of the mesh. In most cases of mesh infection, a polyester (PE) prosthesis was used(10). In contrast, mesh infection was observed in only 1 patient (<0.5%) after repair with polypropylene (PP)(40). After sublay repair some studies reported the occurrence of serious complications, such as respiratory failure or pulmonary infection in 4.8% (5/103 patients)(39, 41, 45) and prolonged ileus in 7.7% (5/65)(40) patients. The overall recurrence rate of LIH repair with sublay mesh reinforcement was 3.6% after follow-up from 1-8 years. Recurrence rates between simple and complex LIH did not differ.

Figure 4. Position of meshes in relation to the abdominal wall; onlay (blue dotted line), retromuscular (green dotted line) and preperitoneal (red dotted line) position. In our review 'sublay position' consists of meshes in retromuscular or preperitoneal position.



b) Open repair by aponeuroplasty and intraperitoneal mesh (IPOM)

In 2 studies, consisting of 630 patients, additionally to IPOM placement, both anterior rectus sheaths were incised and sutured overlapping together (figure 3) (49, 50). In all patients a (composite-)PE mesh was implanted. Neither of the articles reported the number of simple and complex LIH in their patient population.

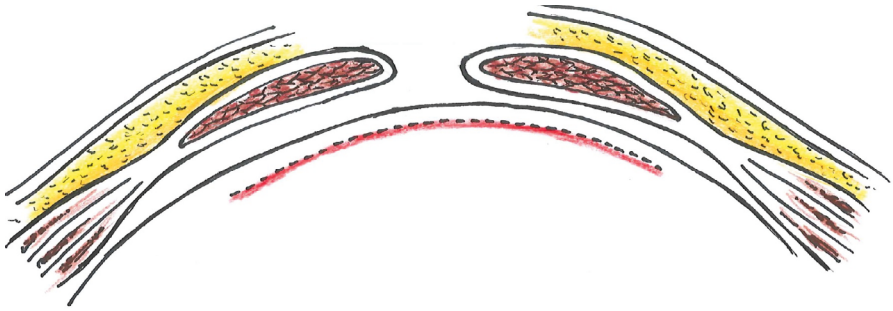
Postoperative mortality was 0.5%. Seroma or hematoma formation was reported in 5% and wound infection in 4%. In 1.3% of patients the mesh infected, requiring removal of the mesh. The recurrence rate of LIH repair with IPOM and aponeuroplasty was 3.2% after 3-8 years follow-up.

c) Open repair with intraperitoneal mesh by bridging (IPOM)

In cases were the hernia defect is too large or more complicated, IPOM as bridging technique can be used (figure 5). In 10 studies, a total of 514 LIH were repaired using the IPOM technique(11, 15, 46, 51-57). In one study a biological porcine mesh was used(57). Approximately 15% of patients had a complex LIH, but not all studies reported separately on the outcomes of simple and complex LIH repairs.

Postoperative one death was reported (mortality 0.2%). Wound infection and skin necrosis were reported in 9% of patients and seroma or hematoma formation in 10%. In 3.5% of cases, mesh removal was necessary due to infection. In the RCT of de Vries Reiling 39% (7 out of 18) of intraperitoneal ePTFE meshes became infected and required removal of the mesh(11). The recurrence rate of LIH repair with biological mesh in intraperitoneal position was 15.8% (3 out of 19 patients) after a follow-up of 18 months(57). The overall recurrence rate of LIH repair with IPOM was 8.3% after 1 to 6 years follow-up.

Figure 5. Intraperitoneal onlay mesh technique (IPOM); position of the mesh in relation to the abdominal wall.



d) CST with mesh (modified CST)

It can be opted to use an additional mesh during CST procedures. In the studies that investigated the modified CST (MCST), three variations on the classic CST were used for component separation, represented by the minimally

invasive, posterior and endoscopic CST. Minimally invasive CST uses tunnel incisions for external oblique aponeurosis release(58, 59). In endoscopic CST direct access to the ventral abdominal wall is provided by using balloon dissectors and laparoscopic visualization(60). In posterior CST the posterior rectus sheath is incised just medial to the intercostals nerves, exposing the transverses abdominis muscle and a release of the transverse abdominis is performed(61). In 8 articles a total of 511 LIH were repaired using the MCST(47, 58-64). Conventional modified CST was performed in 339 patients, minimally invasive CST in 95 patients, endoscopic CST in 22 patients and posterior CST in 55 patients. In 57% of the patients a complex LIH was present. The mesh was positioned in sublay position in 52%(47, 59-63), in IPOM 28% (58, 61, 62), or in onlay position in 20% (62, 64). In 11.5% of all patients midline closure of the fascia was not completely achieved and the mesh was used in a partially bridging position.

Postoperative mortality was 1.8% and postoperative complications occurred in 55%. Infection or necrosis of the wound occurred in 33%, hematomas in 4%, seromas in 11%, and pulmonary complications in 16%. In one study 3 mesh infections requiring excision of part of the biological mesh were reported(62). The reported recurrence rate for LIH after MCST was 10.0% after 1-5 years follow-up.

e) Open repair with onlay mesh

In 1979 Chevrel was one of the first who pioneered the use of a non-absorbable mesh on the anterior fascia of the rectus muscle as reinforcement of suture repair (figure 4)(86). In 6 articles a total of 454 LIH were repaired using the onlay mesh technique(53, 65-69). In 4% a complex LIH was present. In 26 patients additional relaxing incisions were used to achieve tension-free closure of the midline(67, 68). In 38 patients the defect was bridged with the onlay mesh(53, 66).

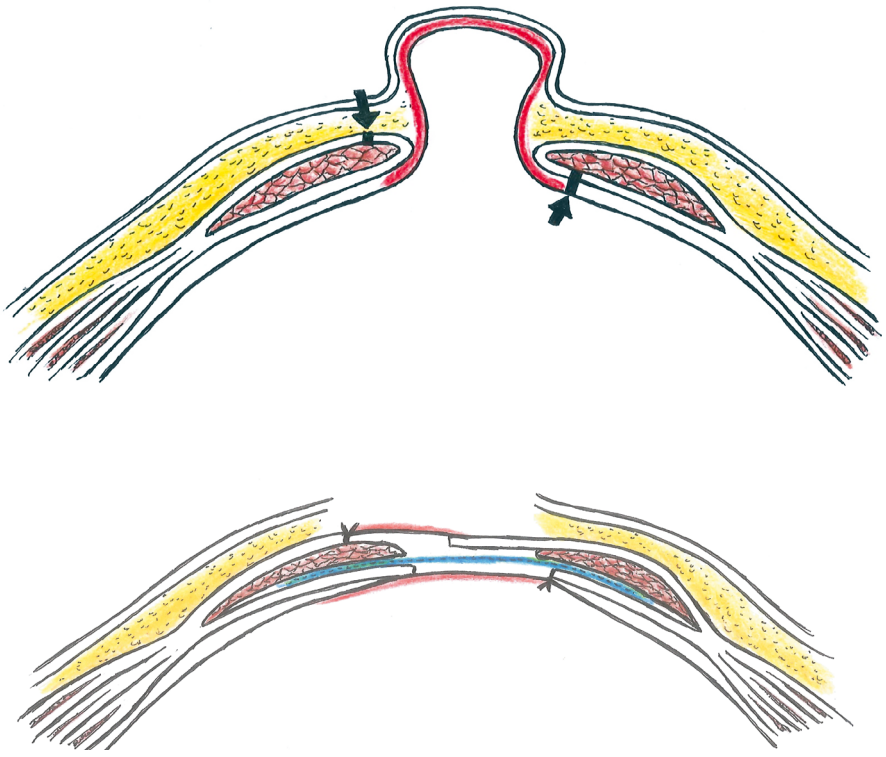
Postoperatively no mortality was reported. Wound infection occurred in 31% of patients and removal of the mesh was required in 1.7%. Seromas developed in 19% of patients, mainly in patients with a biological mesh. Respiratory and cardiovascular complications occurred in 6%. The overall recurrence rate of LIH repair with onlay mesh was 11.1% after a 15 to 77 months follow-up.

f) The sandwich technique

In the 'sandwich technique' the hernia sac is used as an extension of the posterior rectus sheath and the anterior rectus sheath. A non-absorbable mesh is implanted in the sublay position to reinforce the repair (figure 6). In 5 studies a total of 131 LIH were repaired using the sandwich technique(53, 70-73). In approximately 10% a complex LIH was present.

Postoperative complications of wound infection and seroma were reported in respectively 17% and 5% of simple LIH. One patient developed necrosis of both fascia and skin which led to mesh exposure and necessitated mesh explantation(73). In the small group of patients with complex LIH, no postoperative complications were reported. After a follow-up of 1 to 7 years, the only recurrence reported after the sandwich technique was of the patient needing mesh explantation.

Figure 6. The 'sandwich technique; a) half of the hernial sac (red) is used as an extension of the posterior rectus sheath and the contralateral half of the hernial sac as an extension of the anterior rectus sheath. b) A mesh is placed in retromuscular position (blue dotted line).



3. Laparoscopic repair

In the last decade the laparoscopic repair with intraperitoneal mesh (IPOM) has been gaining popularity (figure 5). In the included studies the mesh was positioned bridging the defect with an overlap ranging between at least 2 and 5 cm. In 8 studies a total of 483 LIH were repaired using laparoscopy(74-81). No patients were defined as complex LIH. During repair non-absorbable ePTFE, PE- or PP-composite meshes were used.

Postoperative wound complications were reported in 8% of patients; 6% of patients developing prolonged seroma (>6-8 weeks) and in 2 patients (0.4%) mesh infection was reported. The complication trocar site hernia was described by Ferrari in 2 out of 36 patients(74). Conversion to an open procedure due to dense adhesions, problems with fixation or enterotomy occurred in 5% of laparoscopic repair. Ji et al. describe a technique of adhesiolysis through an additional small (5-10cm) incision in case of dense adhesions as an alternative to complete conversion with good results.(79) The recurrence rate of laparoscopic LIH repair with intraperitoneal mesh was 5.6% after 14-62 months follow-up.

Table 3. Overview of recurrence hazards per year using GLM

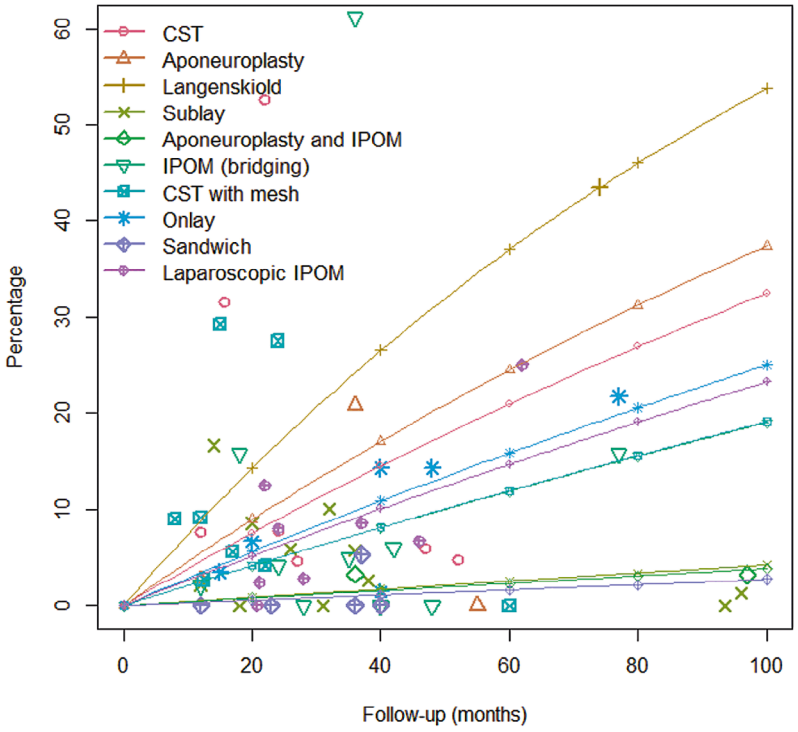
Technique	#	Hazard (*a*)	Std error	Recurrence hazard per year (%)
Open without mesh				
CST(9, 11, 31-35)	219	0.00392	0.00253	4.6
Aponeuroplasty(10, 36, 37)	195	0.00468	0.00251	5.5
Langenskiöld(38)	46	0.00771	0.00265	8.8
Open with mesh				
Sublay(10, 39-48)	762	0.00043	0.00069	0.5
Aponeuroplasty + IPOM(49, 50)	630	0.00039	0.00053	0.5
IPOM (bridging)(11, 15, 46, 51-57)	514	0.00211	0.00093	2.5
MCST(47, 58-64)	511	0.00212	0.00155	2.5
Onlay(53, 65-69)	454	0.00288	0.00101	3.4
Sandwich(53, 70-73)	131	0.00028	0.00273	0.3
Laparoscopy				
IPOM (bridging) (74-81)	483	0.00265	0.00181	3.1

4. Generalized linear model (GLM) of recurrence rates

The hazards (*a)* for the different repair techniques are shown in table 3 and figure 7. The open repair techniques without mesh have a recurrence hazard

of between 4.6 to 8.8% per year; components separation technique having the lowest recurrence hazard. All open repair techniques with mesh had lower recurrence hazards than techniques without mesh, ranging from 0.3-3.4% per year. The lowest recurrence hazards were seen for sandwich technique (0.3% per year), aponeuroplasty with IPOM mesh (0.5% per year) and mesh in sublay position (0.5% per year). The open and laparoscopic intraperitoneal bridging techniques showed high recurrence hazards of 2.5 and 3.1% per year, only exceeded by onlay mesh repair with 3.4% per year recurrence hazard for mesh repair techniques.

Figure 7. Data and curves of the recurrence percentage over time, as estimated by the generalized linear model. The large symbols represent the data; the curves are marked with the same symbols, but smaller.



Discussion

Recurrence rate

This review on surgical repair of LIH shows better long-term recurrence rates and hazards for techniques with mesh reinforcement compared to techniques without mesh reinforcement. To exemplify this finding, it was discovered that mesh reinforced CST and aponeuroplasty reported lower recurrence rates compared to their conventional use and implementation without mesh reinforcement. These results are comparable to the repair of small and medium sized IH (17, 19).

The best recurrence rates and hazards for LIH repair were reported after sandwich technique, sublay repair and aponeuroplasty with IPOM. After several years of follow-up the recurrence rates of these techniques were 3.6% or lower. These exceptional low recurrence rates were even lower than reported recurrence rates of 9-14% for small hernias repaired with sublay or intraperitoneal mesh as reinforcement(18). This might partially be explained by the experience of surgeons who published these series on LIH(10, 49, 50). Due to the complexity of problem we believe that patients with a LIH should only be operated by experienced hernia surgeons. In case of mesh repair, the sublay technique might be the best option for LIH repair as it is already widely implemented and displayed good recurrence rates and hazards. The mesh can be positioned in the sublay position after closing the posterior rectus sheaths or after the sandwich technique, which uses a part of the hernia sac as an extension of the posterior rectus sheath to create an extraperitoneal (sublay) space for the mesh. Although the hernia sac seems not as strong as the anterior or posterior rectus sheath, results of the sandwich technique seem promising. The aponeuroplasty technique is only described by one group and is currently not widely used. However, mesh repair might not be possible because of complex abdominal wall anatomy due to fibrosis, and/or co-morbidities such as obesity, pulmonary disease and old age. These cases should be treated case by case, and the best option might be conservative treatment.

Mortality

In the included studies the postoperative mortality of LIH repairs varied between 0.4% and 10.4%. Mortality was not associated with the used technique of repair. However, in patients with a simple LIH overall mortality

was 0.4%, increasing to 5.4% in patients with a complex LIH. The mortality after simple LIH repair is comparable to mortality of small incisional hernia repair (ranging 0.16-0.4%)(87-89). In patients with simple LIH or small hernias the cause of death is generally of cardiovascular origin. Patients with complex LIH frequently generally have more co-morbidities and mortality is related to multi-organ failure, bowel necrosis, bowel obstruction, mesh infection and sepsis(9, 31, 43, 45, 57, 62, 64).

Wound complications

Infection, seroma, hematoma and skin necrosis were observed frequently after LIH repair. Between simple and complex LIH a sizeable difference in wound complications was found. The degree of intra-operative contamination increases the risk of prosthetic infection and often results in a chronic affection with sinus formation or loss of prosthesis. For these reasons, the majority of patients with a complex LIH were repaired with an open technique without mesh implantation and overall wound complications for these techniques ranged between 13 and 48%. One of the more frequently used open non-mesh techniques in common practice is the CST. During CST the blood supply of the abdominal wall by the epigastric perforating arteries is endangered. Damage to these arteries may endanger the blood supply of the skin (then only depending on blood flow from the intercostal arteries) and interfere with wound healing and increase the risk of infection (6, 31, 90). Furthermore, the intercostal arteries might have been damaged during former operations, giving rise to even more complications(11, 90). Therefore, new endoscopic CST, minimally invasive CST and posterior CST have been developed and promising results of reduced wound infections and necrosis have been described(58-61).

Pulmonary complications

Postoperative pulmonary complications after LIH repair, such as insufficiency and pneumonia, were reported frequently, sometimes requiring reoperation or prolonged ventilatory support up to two weeks(9, 66). In patients with LIH lateral migration of the rectus muscles in conjunction with flank muscle contraction leads to a progressive decrease in the volume of the abdominal cavity and worsening protrusion of the viscera. Repositioning the viscera in a stiff abdominal cavity can lead to decreased perfusion of the intestine and elevation of the diaphragm, which in turn can lead to ventilatory difficulties

and rarely abdominal compartment syndrome(90, 91). The use of preoperative pneumoperitoneum or botox might be implemented in some cases although evidence is limited(44, 92-94).

In LIH repair overall postoperative complications are higher compared to smaller incisional hernia repair. The increased morbidity is partly caused by patient characteristics, such as more serious and extensive primary diseases, systemic collagen disease and the increased intra-abdominal and pulmonary pressure after repair. Frequently a large wound bed is created, increasing the risk of wound complications.

Limitations

The first limitation of this review is the lacking consensus on the definition of LIH (table 1). The criteria for LIH as proposed by the European Hernia Society (EHS)(21) were used: size of hernial orifice 10cm or more in any direction. Since some authors only report the hernia surface, articles describing hernias over 100cm^2 were also included. Recently a consensus paper on definition of complex abdominal wall hernias is published, but these detailed criteria are often not mentioned in articles and are especially usable for (future) prospective studies(27). That's why we used a more simple definition to differentiate between 'simple' and 'complex' LIH in this review.

Secondly, the follow-up between the studies included in this review varied from 1 to 10 years. Due to the delay between hernia repair and the development of a recurrence the period of follow-up is important. Since short term follow-up might cause underestimation of recurrence rate, only articles with a mean follow-up of at least 1 year were included. Still, comparing techniques for recurrence rates is difficult with different follow-up periods. For this reason the recurrence hazard per year for every repair technique was calculated. This model assumes an equal hazard for getting a recurrence during each month of follow-up of the study. But this is not consistent with the natural pattern of recurrence, and as a consequence the monthly or yearly hazard does not resemble the true percentage of recurrence. Furthermore, the assumption in the GLM is that count follow Poisson distributions. Overdispersion is quite common, and so one has to keep in mind that standard errors will be too optimistic. However, we think that the GLM is a useful tool in comparing recurrence rates for studies with different follow-up periods.

In the vast majority of articles recurrence was determined by physical examination. The use of radiological examination in the diagnosis of hernias is very useful in obese patients and for the detecting of smaller hernias. The sensitivity and specificity of ultrasonography and CT-scan for incisional hernias is very high(95). Since radiological examination was not standard performed the recurrence rates might be underestimated.

Another limitation was the availability of only a few prospective series and mainly retrospective series for inclusion. Postoperative complications are an important outcome parameter in comparing repair techniques but are likely to be underestimated, especially in retrospective studies(96). In addition possible patient selection bias and publication bias of good results might be present. Publication bias was reduced by excluding small series. For this reason not all possible techniques for large hernia repair are covered. Recently a systematic review was published which focussed on giant incisional hernia repair techniques(97). Although some of the conclusions drawn from that paper are similar to the conclusions made in this review, there are several limitations in that study. Firstly, a definition was used which does not correspond with the EHS guidelines. In addition, due to some of their exclusion criteria several articles were not included in their review. This resulted in them including only 14 papers whereas this review included 55. Furthermore their conclusions are based mainly on their expert opinion, whereas this study' conclusions are based on statistical analysis with a generalized linear model.

Also, the universal lacking consensus on terminology for mesh positions and the large variety of meshes for hernia repair on the market worldwide add difficulty in comparing repair techniques. Terms as 'inlay' 'underlay', 'overlay' and 'subfascial' are used without clarity about the position of the mesh to the abdominal wall. To minimize confusion the terminology proposed by the EuraHS working group was used (figure 4)(98). The choice of mesh material in abdominal wall repair is still debatable, especially in a complex LIH or infected environment. The studies included in this review reported more frequently mesh infections for PE meshes than PP meshes in LIH. This corresponds with the increased complication rate of PE meshes in smaller incisional hernia repair(99). The high rate of ePTFE mesh infections in complex LIH was the reason for premature termination of the RCT of the Vries Reilingh et al(11). Recently, biological meshes have been introduced into LIH repair which might induce better results with regards to infections and incorporation. The first

prospective trial has been conducted recently to evaluate their effectiveness in LIH repair and showed good results regarding mesh infection but a recurrence rate comparable to classic CST without mesh reinforcement(62). The ideal mesh for complex hernia surgery has still not been found and further research should be focus on this.

Finally, patient characteristics such as BMI, age and infection grade were often not described in the included studies and this could cause heterogeneity between groups. We tried to adjust for this limitation by excluding small series. However, this still poses a problem in this review and until new (randomized) trials become available the outcomes of this review should be interpreted critically.

Conclusion

Research on the treatment of LIH is challenging. LIH must be considered a separate category of incisional hernia, posing more problems than the smaller variety. Because of the high incidence of LIH and possibly also by the lack of centers for this complex pathology many different approaches have been proposed and are applied in daily practice until now. This heterogeneity in surgical care makes any validation of techniques difficult. To make results more comparable for future research, a widely accepted classification of hernias and repair techniques is needed. A global online registration system for all hernia repair has been developed and launched (EuraHS)(98).

Although available literature regarding LIH repair is relatively scarce, we feel that some of the limitations as previously discussed were adjusted for or reduced in this review due to its design and the statistics used. In this review it was observed that LIH repair with mesh reinforcement is superior with regards to long-term recurrence. Based on available literature sublay repair for LIH seems the preferred techniques it is already implemented widely and displayed good recurrence rates and yearly recurrence hazards. For all techniques increased postoperative complications were reported compared to smaller IH repair. IH repair, and especially LIH repair, is a surgical challenging procedure and in our opinion should be performed by specialists only.

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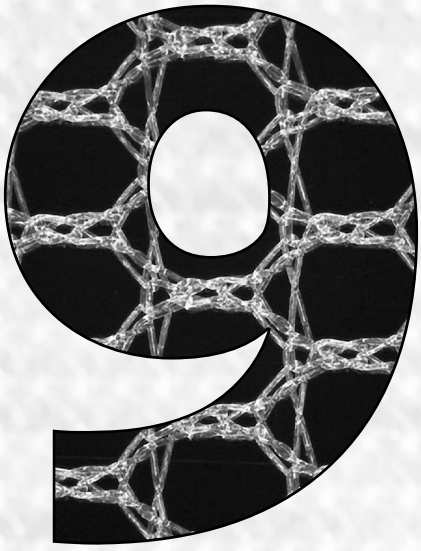
Chapter



Recommendations for reporting outcome results in abdominal wall repair. Results of a Consensus meeting in Palermo, Italy, 28-30 June 2012

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Abstract

Background

The literature dealing with abdominal wall surgery is often flawed due to lack of adherence to accepted reporting standards and statistical methodology.

Material and methods

The EuraHS Working Group (European Registry of Abdominal Wall Hernias) organized a consensus meeting of surgical experts and researchers with an interest in abdominal wall surgery, including a statistician, the editors of the journal Hernia and scientists experienced in meta-analysis. Detailed discussions took place to identify the basic ground rules necessary to improve the quality of research reports related to abdominal wall reconstruction.

Results

A list of recommendations was formulated including more general issues on the scientific methodology and statistical approach. Standards and statements are available, each depending on the type of study that is being reported: the CONSORT statement for the Randomized Controlled Trials, the TREND statement for non-randomized interventional studies, the STROBE statement for observational studies, the STARLITE statement for literature searches, the MOOSE statement for meta-analyses of observational studies and the PRISMA statement for systematic reviews and meta-analyses.

A number of recommendations were made, including the use of previously published standard definitions and classifications relating to hernia variables and treatment; the use of the validated Clavien-Dindo classification to report complications in hernia surgery; the use of "time-to-event analysis" to report data on "freedom-of-recurrence" rather than the use of recurrence rates, because it is more sensitive and accounts for the patients that are lost to follow-up compared to other reporting methods.

Conclusion

A set of recommendations for reporting outcome results of abdominal wall surgery was formulated as guidance for researchers. It is anticipated that the use of these recommendations will increase the quality and meaning of abdominal wall surgery research.

Introduction

The EuraHS (European Registry for Abdominal Wall HerniaS) working group was formed under the auspices of the European Hernia Society (EHS) board in 2009. An online platform for registration and outcome measurement of operations for ventral abdominal wall hernias has been developed. For this, a set of definitions and classifications were proposed(1). The EuraHS working group organized a consensus meeting to prepare recommendations relating to the reporting of outcome results in abdominal wall hernia repair. At the initiative of the first author, Filip Muysoms, current chairman of the EuraHS working group, and of Vincenzo Mandala, current president of the European Hernia Society, a consensus meeting was organized in Palermo, Italy from June 28th till June 30th 2012. The participants to this consensus discussion and meeting were the EuraHS Working Group members and some other experts, editors and a statistician. The participants to the consensus discussions are the authors of this manuscript.

Materials and methods

The scientific methodology of clinical studies including systematic reviews and meta-analyses were discussed with researchers and a statistician invited to the consensus meeting. Recommendations relating to study methodology, description of the patient population and statistical approach were proposed to research on abdominal wall surgery. For taxonomy of the statistical items two basic textbooks on medical statistics were used(2, 3). Specific recommendations on abdominal wall surgery for describing hernia variables, treatment variables and for reporting the outcome results in a uniform manner were formulated by consensus.

Results

Description of study methodology

A study describes a sample or cohort of patients. It is of utmost importance to know how the study population was decided upon, how the study was

conducted, what was the primary aim or endpoint of the study and how was the endpoint analysed. This knowledge is essential to know whether the results of this study can be extrapolated and generalized to the larger group of patients with the disease treated, so that the study result might influence the treatment of future patients. Knowledge of the sample procedures used to determine the study population from the screened patients allows the readers to identify potential sources of bias and thus assess the external validity of the study results. Some exemplary hernia-related different types of studies: cohort study by Dietz(4), comparative cohort study by Kurian(5), registry study by Helgstrand(6), randomized controlled trial by Bloemen(7), prospective non-randomized clinical trial by Feliu(8), systematic review by Hansson(9) a meta-analysis by Aslani(10).

Study types

All reported studies should have a clear description of the study type, which should be mentioned in the title and/or the abstract of the manuscript. There is a fundamental distinction between observational studies or interventional studies (Figure 1). An outcome variable(s) (aka dependent variable) will be studied in relation to one or more predictor variables (aka independent variables; aka risk factors) in an *observational study.* Analysis will focus on the association of the predictor(s) with the outcome(s) over a defined time period. A cohort study is a type observational study in which a group (cohort) is defined, e.g. all patients undergoing a particular operation or having a certain type of hernia. Most publications on ventral abdominal wall repair are classified as *non-comparative cohort studies* because there is no control group in the study. Rather the results are discussed in relation to other studies published on similar patient populations. In a *comparative cohort study or case-control study* at least two different populations are compared within the study. *A registry* is a type of cohort study that has a specific purpose, defined in advance. The data entered are carefully crafted to answer important questions about the condition or symptom being studied. Results from registry studies are often very informative because such care is taken to assure consistent data definition, consistent data entry and the enrolment of a large number of patients in relationship to the total affected population. A *cross-sectional study* is an observational study, which by definition is not longitudinal because subjects are studied at a single point in time. An example would be a study investigating the impact of the

patients' BMI on the incidence of incisional hernias in a population of patients with previous laparotomies.

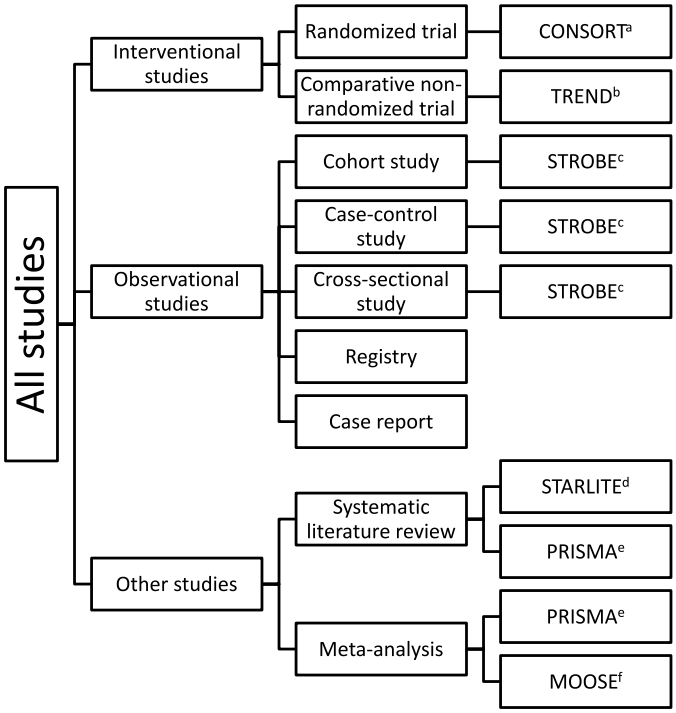
In an *interventional study* the result of an intervention on a specific outcome variable is examined. The patient samples compared in the study should ideally only differ in the predictor variable that is influenced by the intervention. Other variables, called confounders, should be equally distributed between the study groups. Randomization for the predictor variable in a *randomized controlled trial* (RCT) is the best method to ensure "equality" of the study groups provided the study population is large enough. For this reason RCT's are assigned a high level of evidence because if the randomisation is performed adequately they have the smallest risk of bias between the study populations. In a *comparative non-randomized clinical trial,* it is less clear why a specific patient receives the intervention or not.

In a *systematic review,* a comprehensive literature research is performed on a specific topic and a qualitative critical appraisal of the individual studies is performed. Only data from studies that are considered of sufficient methodological quality are summarized. In a *meta-analysis* the quantitative data of the individual studies are pooled and statistically analysed. A meta-analysis of RCT's is considered the highest level of evidence and thus allows for the highest grade of recommendation. But meta-analyses have considerable limitations to detect differences as they usually have higher variances than single studies, and thus have limitations to detect differences with low incidences.

A *case report* or case series describes an observation or a treatment, which is considered by the authors as rare or novel and thus worthy of publishing in a manuscript.

As shown in figure 1, guidelines are available on the web for specific types of studies which provide step by step instructions including a check list for authors to assure correct conduct and reporting of their work(11-16). The Cochrane Collaboration at www.cochrane.org summarizes the websites. Many journals only accept manuscripts that conform to these guidelines and require their reviewers and editors to use them when assessing the quality of submissions. Critical appraisal sheets to assess the quality of a study report can be found on the website of the Centre for Evidence Based Medicine from Oxford can be found to(17).

Figure 1. Types of clinical studies: it is recommended to include the type of study clearly in the title and/or the abstract of a manuscript. Reporting guidelines (colomn 3) are available on the web to help authors in preparing manuscripts for publication.



a: CONSORT statement: Consolidated standards of reporting trials. www.consort-statement.org(11)

b: TREND statement: Transparent Reporting of Evaluations with Non-randomized Designs. http://www.cdc.gov/trendstatement/(12)

c: STROBE statement: Strengthening the reporting of observational studies in epidemiology. www.strobe-statement.org(13)

d: STARLITE statement: Standards for reporting literature searches.(14)

e: PRISMA statement: Preferred reporting items for systematic reviews and meta-analyses. www.prisma-statement.org(15)

f: MOOSE statement: Meta-analysis of Observational Studies in Epidemiology.(16)

Prospective versus retrospective studies

In a *prospective study,* a cohort of patients is observed for a period of time to look at outcome, e.g. complications, and then relate this to the predictor variables, e.g. type of surgical technique. Interventional studies are prospective studies focused on the outcome of a specific intervention that is controlled but different in the study groups that are compared. A study qualifies as prospective if the outcome measurement of the primary endpoint is decided before the start of the study, and the endpoint measurements are performed in the future after the start of the study. Prospective studies are methodologically superior to retrospective studies because the measurements can be controlled and standardized. Moreover the data gathered are usually more homogeneous and complete.

In a *retrospective study* the investigator looks backwards in time and examines exposure to possible risk or protective factors in relation to an outcome that is established before the start of the study. Thus the study looks at measurements made before the study was started and therefore the data will be less controlled and less homogeneous.

The research question and the primary endpoint

The manuscript of an interventional study should clearly state the research question and/or aim of the study. This research question is translated into a *scientific hypothesis* that will be the basis for the study design and the number of patients required to answer the research question. A clinically relevant primary endpoint will be chosen for which the hypothesis is formulated. The *primary endpoint or primary variable* of a study is the outcome parameter to be measured and compared, either to the control group in a comparative study or to results from the literature in non-comparative studies. For abdominal wall repair, the primary endpoint is most often hernia recurrence, but many other outcome parameters are possible to formulate the hypothesis: acute or chronic pain, Quality of Life, complications, reoperation rates, wound infections, mesh infections, etc. A *superiority study* investigates if the intervention is superior in comparison to the control group. The results of the study will be compared to the *null hypothesis (H0),* that there is no difference between the groups in the primary endpoint measurement. The analysis has to be performed on Intention To Treat (ITT) basis. In ITT analysis, patient outcome is analysed according to the allocated treatment by randomization, regardless wether the patient actually

received the treatment or not(18). According to the International Conference on Harmonisation (ICH) guidelines of Good Clinical Practice (GCP) a statistical test decision of a study should be conservative. This is the rationale to use the ITT population for superiority studies and the PP population for equivalence studies. For non-inferiority trials the correspondence between ITT and PP should be used or a hybrid population.

In some specific clinical situations, an equivalence or non-inferiority design is preferred. An *equivalence study* investigates whether a new treatment is not worse than the control. The analysis will be performed on the Per Protocol Population (PP), i.e. the patients who adhered strictly to the protocol and actually received the intervention called for by the protocol. These different types of analysis aid investigators in determining if a new treatment or device is better or as good as, but cheaper than what is now available. Like most clinical studies, the use of a biomedical statistician at both the study design and study analysis stage is recommended.

The sample size

When designing a clinical trial it is important to estimate the number of patients needed to answer the research question. Performing a clinical trial is time-consuming and expensive. It is also ethically mandatory to keep the number of patients that allow for valid study results as small as possible. Therefore it is important to estimate the number of patients that should be included in the study at the onset to answer the clinical question and the scientific hypothesis the study is exploring. If the sample size is too small the study might not be able to reject the *H0*. In other words the study sample is too small to show a difference in the primary outcome, although in reality there is a difference (false negative; type II error). On the other hand if the sample size is too large, scares resources will be a spent unnecessarily. To calculate the sample size needed, there has to be agreement on several elements. First, the hypothesis type has to be clear: superiority, equivalence or non-inferiority. The expected mean value of the primary outcome parameter in the two groups and the difference in outcome considered clinically important has to be estimated, based on preliminary findings or results from similar studies in the literature. The significance level, i.e. the α or Type I error we accept (usually 5%) and the statistical power (usually 80% = 1- β, where β denotes the Type II error level) have to be defined. These assumptions will provide the number of patients

in each group needed to evaluate the primary endpoint. All studies have "dropouts", because the patients are lost to follow-up, die, or are not willing to continue participation. Therefore, the number of patients to enter in the study should be increased in line with the number of "dropout" patients anticipated, often 10% to 20%.

Interim analysis

Prior to the onset of the study, the protocol of the study should state if an interim analysis will be conducted. An interim analysis is usually done for safety reasons. Therefore, an analysis of the patients "as treated" is the best approach. There are different interim analysis procedures and the procedure should be chosen carefully and described in the study protocol.

During an interim analysis the progress of the study inclusions, the occurrence of serious adverse events and the quality of the raw data can also be evaluated. A decision can be made to prolong the inclusion time, to increase the sample size or to stop the trial prematurely. Ideally, an independent data monitoring committee (IDMC) takes such a decision. An example is the study by Itani et al. on ventral hernia repair comparing laparoscopic with conventional surgery(19). The infection rate was so much higher in the conventional group that the data safety monitoring board insisted the trial be stopped.

Description of patient population

The ultimate goal of a study is to generalize the findings in the study to the larger population of which the study population is a sample. To assess the external validity of a study, the exact method of determining the study sample or study cohort has to be clear.

Mono-centre versus multi-centre studies

There are advantages and disadvantages for both study strategies. *Mono-centre* interventional studies have a greater chance of having two comparable groups by excluding the variations in the confounding variables that arise from including patients treated in different centres. *Multi-centre* studies have a greater chance of correct inference and generalization of the study results to the larger population in the community. But multi-centre studies are logistically more difficult to perform. Moreover the homogeneity and the quality of the raw data are often inferior in the participating centres compared to the

centre of the primary investigator. On the other hand including patients from several centres will create a larger group of eligible patients and thus a higher likelihood of achieving the sample size in a shorter time period. For some less common conditions, a multi-centre approach is prerequisite to enrol a large enough cohort of patients. It is essential that the authors report variations in expertise related to the surgical technique under investigation.

Inclusion criteria, exclusion criteria and eligibility

To minimize selection bias all consecutive eligible patients during the study period should be considered for inclusion. The reasons for non-inclusion in the trial and the number of these should be monitored and reported. To know which patients are eligible a clear and detailed description of inclusion and exclusion criteria should be given. If reporting a subset of hernia patients, for example only those undergoing laparoscopic surgery, then clear reasons for why the subgroup were selected for that particular intervention, and how many patients over the same study period had an alternative intervention.

Dropouts and lost to follow-up

Inevitably subjects will become lost to follow-up and will not be available for measurement of the primary endpoint. Some patients will not receive the allocated treatment according to the randomization because of errors, a preoperative surgical decision, an intraoperative change in therapy or because the patient withdraws consent to participate. Nevertheless a description of the entire Intention To Treat (ITT) population has to be provided and every patient accounted for, preferably in a flow diagram. This will make it clear to the reader which patients are included in the study analysis. The baseline data of the study population with the distribution of the predictor variables and possible confounding variables should be provided for the ITT population in the first table of the manuscript. This table will allow evaluation of the concordance between different groups in comparative studies. The variables should be listed with their frequency or mean value, their range and their standard deviation. For analysis of the primary and secondary endpoints of the study the decision about the use of the ITT or PP population, is based on the type of statistical hypothesis (superiority versus equivalence).

Description of the hernia variables, operative procedure and mesh variables

The literature dealing with the treatment of abdominal wall hernias would benefit from using a common standard for description of the hernias themselves, the operation performed and the mesh materials used. The European Hernia Society has previously published classifications for inguinal and ventral hernias(20, 21). Moreover during the development of the EuraHS platform for registration of ventral hernias many definitions and recommendations for describing variables of interest were proposed by consensus amongst the EuraHS working group members(1). A general recommendation of the consensus meeting in Palermo is to use these existing classifications and terminologies to describe the hernia patients included in a study.

Hernia variables

It is recommended to use the EHS classifications for inguinal and ventral hernias. Primary ventral hernias and incisional ventral hernias should be distinguished and classified accordingly. The hernia size of ventral hernias is preferably an intra-operative measurement and the width and length will be described in centimetres (cm) as the mean and the standard deviation. If the hernia defect surface is reported, the method of calculation of the defect size in cm^2 should be given. By multiplying width and length, the true hernia defect size is smaller than the rectangle calculated and thus this value is an overestimation of the true abdominal wall defect size. Alternatively the formula of an ellipse can be used to get a better estimation of the true hernia defect size. For calculating the real surface area of a hernia defect or several defects of an incisional hernia many measurements are needed and calculations dependent on the form of the defect. Ammaturo and Bassi have published a method for calculating the wall defect surface and compare it to the surface of the anterior abdominal wall(22). This method involves the use of transparent paper, a computer scanner and software to calculate the exact surface. For routine use in surgical practice this is not practical.

In order to classify the dimensions of an abdominal wall hernia the consensus is to use the terminology proposed in the previous classifications. For primary ventral hernias three groups are created using the hernia defect diameter: small (<2 cm), medium (≥ 2 - 4 cm) and large (≥ 4 cm). For incisional hernias, there is not a common standard yet. The consensus panel recommends using the EHS classification and thus the width of the incisional hernia is the

distinguishing parameter between groups: W1 (< 4 cm), W2 (≥ 4 - 10 cm) and W3 (≥ 10 cm). If descriptive terminology like "large, giant, huge" are used, a clear description of the definition should be given. However, the use of such adjectives to define the hernia size is discouraged.

Operative techniques and mesh variables

Surgical technique and their outcome is an important issue in surgical studies. A detailed description of the surgical techniques used is important for the readers to understand the procedure(s) used in the patients studied. It should allow to reproduce the technique in future patients. Authors should be encouraged to use clear terminology like those proposed by the EuraHS working group(1). For prosthetic materials, fixation devices and other equipment, we recommend using not only the generic name of the material but also providing the product and company name. When comparing different meshes the classification of meshes proposed by Klinge and Klosterhalfen is recommended(23). A complete description of the size of implanted mesh, the overlap of the hernia defect and the detailed technique used for fixation will help the reader to understand the procedure used.

Assessment of outcome: recurrences, complications and quality of life

Recurrences

The outcome parameter recurrence is the primary endpoint in most studies of abdominal wall hernia surgery. A hernia recurrence is defined as: "A protrusion of the contents of the abdominal cavity or preperitoneal fat through a defect in the abdominal wall at the site of a previous repair of an abdominal wall hernia."(1). Recurrence is a *categorical dichotomous variable*, which means the outcome cannot be quantified, but is a yes or no response. The definition used in the study of what constitutes a recurrence should be given as well as the method of follow-up that is used to look for possible recurrence. If the primary endpoint of the study is recurrence, the consensus is that only clinical follow-up will be considered adequate. In an interventional study, blinding of the evaluator to the treatment arm will minimize investigator bias and improve the quality of the data and is to be strongly encouraged.

Basically, there are two options to describe the primary endpoint recurrence in a cohort of patients. The *"recurrence rate"* can be measured at a specific time point (Tx) during follow-up, as the number of patients of the

ITT population that have developed a recurrence between the operation date (T_0) and Tx. This will leave us with the problem of what to do with the patients that were *"lost to follow-up"*. This uncertainty about the status, i.e. recurrence or no recurrence, of the lost to follow-up patients will cause serious bias in the estimation of the calculated recurrence rate. A specific cohort of patients has no fixed recurrence rate because the recurrence rate will increase over time with longer follow-up. The result of a study with a recurrence rate at a specific point in time during follow-up should include 95% confidence intervals. It is recommended that the statistical analysis of recurrence rates at a specified time in a comparative study be performed with the Fisher exact test and logistic regression to include prognostic factors.

A more sensitive method of reporting the outcome is by *"time-to-event analysis"* as introduced by Kaplan and Meier several decades ago for survival analysis(24). The main reason to favour this approach is that patients lost to follow-up, the dropouts, are accounted for. In abdominal wall surgery, the event studied is most often recurrence and thus "survival rate" can be best described as the *"freedom-of-recurrence"*. For every patient in the study the time period of follow-up will be defined by the date of the hernia repair (T_0) to the date of recurrence or the date of the last follow-up recorded without recurrence (T_1). At T_1 the status of the patient will be recorded: recurrence or no recurrence. The difference between T_1 and T_0 is the time the patient was at risk of development of a recurrence and was under "surveillance". During the study period the number of patients at risk will gradually decrease with every patient that has a recurrence or that is lost to follow-up, i.e. censored cases. The outcome of time-to-event data for hernia recurrence is given by a Kaplan-Meier plot of the freedom-of-recurrence and by calculating freedom-of-recurrence rates at predetermined time endpoints. Statistical analysis of time-to-event data is performed using the log rank test or Cox's regression model if prognostic factors are included. Time-to-event analysis is more powerful than comparing recurrence rates, thus requiring a smaller sample size to test a specific scientific hypothesis of an interventional study.

Complications

The consensus group recommends using the Clavien-Dindo classification as was proposed previously by the EuraHS working group(25-27). A clear definition of the different complications evaluated and reported must be given, preferably

using published classifications. Of specific interest for abdominal wall surgery is postoperative seroma. The seroma classification proposed by Morales-Conde is recommended(28).

The method of follow-up

The method for assessment of the primary and other endpoints of the study should be described clearly in the manuscript. Indeed, the recurrence rate measured will be influenced by the method of follow-up. Figure 2 illustrates an increase in quality of follow-up which can range from the number of reoperations for recurrences seen to systematic investigation with medical imaging. The Palermo consensus group considered that follow-up without clinical examination of the patient is likely to give an important underestimation of the true recurrence rate and thus should be avoided. For other endpoints such as quality of life assessment, a follow-up by phone or mail might be adequate.

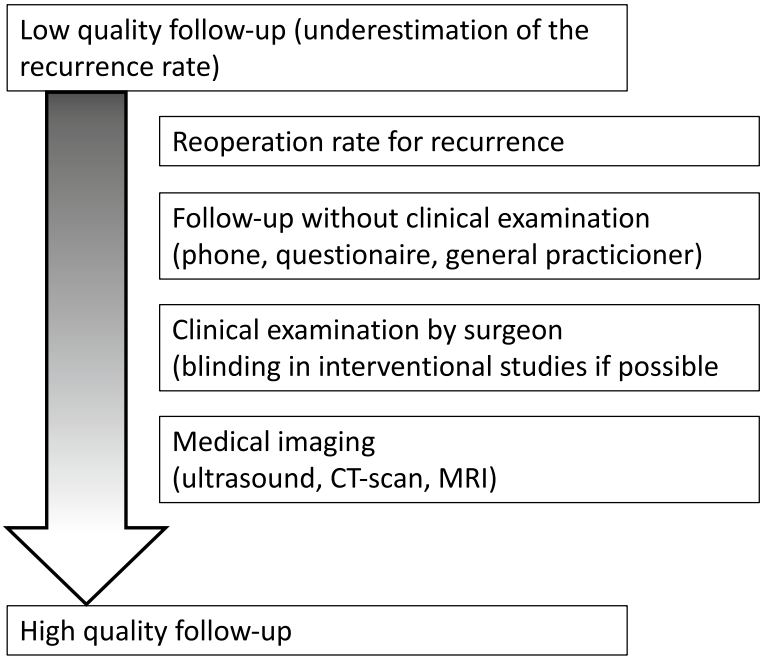
For large registries like the Danish Hernia Database, the Swedish Hernia Registry and the Herniamed database a clinical follow-up of all patients is not practical and achievable(29, 30). In the population based Danish Ventral Hernia Database the reoperation rate for recurrence is the primary outcome measurement as a "surrogate for recurrence". Helgstrand et al.(31) demonstrated using a questionnaire and subsequent selective request for clinical follow-up, that the reoperation rate underestimated the overall risk for recurrence by four- to fivefold. In the Herniamed registry patients are followed up using a questionnaire send to the patient at one, five and ten years(29). Patients reporting a problem are invited for an examination by a physician.

Blinding of the patient and the evaluator at the primary endpoint to the treatment group in an interventional study has some organisational and logistic difficulties, but should be considered when writing a study protocol because of the enhancement of the quality of the outcome data and the diminished risk of patient or investigator bias.

Ethical and financial considerations

Studies should be performed according to the guidelines of the International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP)(18). This includes the approval by the ethical committee of the center where the study is performed. Informed consent of the patients to be included in the study is mandatory.

Figure 2. The validity of data for recurrence after hernia repair is dependent on the method of follow-up performed. It is recommended to consider only follow-up including clinical investigation as adequate.



Registration of the study protocol in an international database like www.clinicaltrials.gov is recommended and is mandatory for acceptance in some peer reviewed journals.

For studies of abdominal wall surgery it is very important that financial sponsors of the study are disclosed. The manuscript should state how the study was initiated: as an Investigator Initiated Study (IIS) or initiated by a commercial sponsor of the study. Conflicts of interest should be clearly stated at the end of the manuscript. If a research grant was received for the study, the name of the sponsoring organisation or company should be disclosed. Also the involvement of the sponsor in initiating or conducting the study and in reporting the results should be clearly delineated.

The consensus group also encourages investigators to report negative trial results. If the study methodology is appropriate, a negative outcome should not hinder the acceptance for publication.

Discussion

The literature dealing with abdominal wall surgery often fails to meet good reporting standards and statistical methodology. Moreover the terminology used to describe the hernias and their therapies is very heterogeneous, often due to the lack of commonly accepted standards and definitions. This was the impetus for the formation of the EuraHS working group. By organising a consensus meeting including the editors of Hernia - the World Journal of Hernia and Abdominal Wall Surgery - and some specialists in statistics or systematic reviews, the aim was to suggest a set of recommendations to provide a standard for investigators writing a study protocol and to authors preparing a manuscript for submission. The recommendations are listed in Table 1.

The CONSORT statement is the common standard to use as guidance in performing and reporting RCT's (www.consort-statement.org). However, for ventral hernia repair, RCT's are not frequent and the majority of the literature is comparative retrospective studies or non-comparative cohort studies. For those studies the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) is the relevant guideline (www.strobe-statement.org) and the quality of the studies can be scored using the MINORS scale(32).

We consider that an author checklist specifically targeted at abdominal wall surgery based on accepted statements and scoring systems would increase the quality of submissions. Editors and reviewers can use a similar checklist for their evaluations.

The consensus panellists strongly believe that an effort is needed to increase the statistical and methodological basis of the abdominal wall research. Considering recurrence, which is the primary interest of most studies on hernia repair, it is recommended using time-to-event data of the freedom of recurrence to analyse and report study results. The number of dropouts from studies on hernia repair before the measurement of the primary endpoint is often high. Therefore the use of time-to-event data is more suitable in hernia repair studies.

To reduce the heterogeneity of the description of the variables studied and the surgical techniques performed, we recommend using previously published terminology and definitions. Understanding the study population and the surgical technique is essential for the inference of the results to the larger population of which the study population is part.

Table 1. Summary of recommendations for reporting outcome results in abdominal wall surgery as formulated by the panel of a consensus meeting held by the EuraHS working group in Palermo, Italy, June 2012.

Topic	Recommendation
Study type	The title and/or the abstract of the manuscript should have a *clear description of the study type*.
Reporting guidelines	Use standardised *reporting guidelines* (CONSORT, TREND, STROBE, STARLITE, PRISMA, MOOSE) to prepare a study protocol or manuscript.
Prospective *vs* retrospective	The abstract should report whether the study is *prospective or retrospective*, i.e. whether the data for the primary endpoint is assessed prospectively.
Primary endpoint or variable	Clearly define the *primary endpoint or variable* of the study, including the population analysed (ITT or PP) and a detailed description of how, when and by whom this primary endpoint was assessed.
Blinded assessment	State wether the evaluation of the primary endpoint was performed by a person *blinded* to the treatment group of the patient.
Sample size	Describe the method used for calculating the sample size and the software used for it.
Inclusion criteria, exclusion criteria and eligibility	Give a clear description of the study population by listing the inclusion criteria and exclusion criteria. Report the number of eligible patients not included in the study and the reasons for non-inclusion.
Dropouts	The percentage of patients not available for evaluation of the primary endpoint should be given, including the reasons for "lost to follow-up". The use of *a flow diagram* of the patients in the study is recommended.
Classifications	We recommend using the *EHS classification* for inguinal and ventral hernias.
Hernia size	The *width and the length* of the hernia from an intraoperative measurement are most appropriate. When the *hernia defect size* is reported the method of calculating this size should be given.
Surgical technique	The surgical techniques used in the study should be described in enough detail that the reader could perform the technique him or herself.
Meshes and devices	When referring to specific equipment items, we recommend the inclusion of the generic name (e.g. polypropylene), the product name and the manufacturer.
Mesh size and fixation	Report on the size of the implanted mesh, the overlap of the hernia defect and the fixation method in detail.
Time-to-event analysis	Time to event analysis using Kaplan-Meier estimates of "freedom of recurrence" is the preferred method for analysis of recurrences in hernia repair patients.
Recurrence rate	A recurrence rate should be given on the ITT population and reported with 95% confidence intervals. The duration of follow-up at which the recurrence rate was measured should be given.
Mean follow-up	If a *mean follow-up time* is given, the range should be given as well.
Method of follow-up	We recommend to consider *only clinically evaluated patients* as adequate follow-up to evaluate recurrence. In large patient registries clinical follow up in all patients is not achievable. Alternatively, follow-up with questionnaires and selective clinical follow-up is proposed.
Ethical considerations	Every study should mention the approval of the institutional ethical committee and informed consent of the patients.
Financial disclosures	Financial support of the study or the investigators should be mentioned by name of the organisation or company. Distinguish "Investigator Initiated Studies" from studies initiated by a commercial sponsor of the study.
Negative trial results	Negative findings or outcome of a study should not be a reason not to submit a manuscript. If methodologically correct, negative results can be informative.

The external validity of a study is the main goal of scientific research and exact description of the study parameters is thus important.

Several clinicians and researchers feel that for most clinical questions we have, we will never get answers from RCT's and meta-analyses because the amount of variables is too large. Their frustration is that at this moment guidelines are focused mainly on this type of EBM research. Registers may be an important source of information for health care. In our particular field of research, a population based register like the Danish Ventral Hernia Database or large surgical datasets of variables and outcomes like the Herniamed database and from the Würzburg Univesity, provides us with very interesting data(4, 29, 30). However, the statements resulting from the analysis of register data, even by sound scientific multivariate statistical analysis, can be limited by various sources of bias. The selective inclusion of patients and their data may introduce selection bias. Some confounding variables may not be included in the dataset of the register and thus result in confounder bias. Nevertheless we think that in practice registers may be good to generate scientific hypotheses and consider safety questions.

The EuraHS working group encourages researchers in abdominal wall surgery to use of the EuraHS platform to gather the data of their patients(1). The platform can be used for clinical studies like RCT's and observational studies or for prospective registration of consecutive patients. The platform can be used individually, as an institutional registry, or in groups of participants (e.g. as national registry). Use of the platform will conform to the recommendation of using the consensus-based definitions and classifications of the EuraHS working group.

Knowledge of study design and statistical issues is of minimal interest to many surgeons. We think that a series of short statistical reviews related specifically to abdominal wall surgery would be a good start to improve awareness of the importance of a sound statistical approach to hernia repair research. Moreover we would encourage the surgical societies to include courses on clinical research and statistical items in the program or in pre-congress courses during meetings of the societies.

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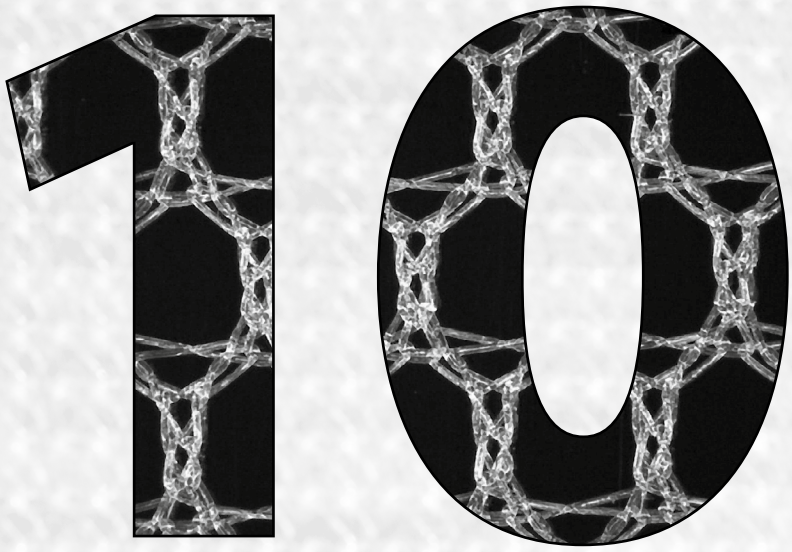
Chapter



Biologic meshes are not superior to synthetic meshes in ventral hernia repair: an experimental study with long-term follow-up evaluation

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Abstract

Background

In laparoscopic incisional hernia repair, direct contact between the prosthesis and the abdominal viscera is inevitable, which may lead to an inflammatory reaction resulting in abdominal adhesion formation. This study compared five different synthetic and biologic meshes in terms of adhesion formation, shrinkage, incorporation, and histologic characteristics after a period of 30 and 90 days.

Methods

In 85 rats, a mesh was positioned intraperitoneally in direct contact with the viscera. Five different meshes were implanted: Prolene (polypropylene), Parietex composite (collagen-coated polyester), Strattice (porcine dermis, non-cross-linked), Surgisis (porcine small intestine submucosa, non-cross-linked), and Permacol (porcine dermis, cross-linked). The meshes were tested in terms of adhesion formation, shrinkage, and incorporation after a period of 30 and 90 days. Additionally, collagen formation after 90 days was determined.

Results

Significantly less adhesion formation was observed with Parietex composite (5 %; interquartile range [IQR], 2–5 %) and Strattice (5 %; IQR, 4–10 %) in the long term. In contrast, organs were attached to Permacol with four of seven meshes (57 %), and adhesion coverage of Surgisis mesh was present in 66 % (IQR, 0–100 %) of the cases. After 90 days, the best incorporation was seen with the Parietex composite mesh (79 %; IQR, 61–83 %). After 90 days, major alterations in adhesion formation were seen compared with 30 days. Histologically, Strattice and Parietex composite showed a new mesothelial layer on the visceral side of the mesh. Microscopic degradation and new collagen formation were seen in the Surgisis group.

Conclusions

Parietex composite mesh demonstrated the best long-term results compared with all the other meshes. The biologic non-cross-linked mesh, Strattice, showed little adhesion formation and moderate shrinkage but poor incorporation. Biologic meshes are promising, but varying results require a more detailed investigation and demonstrate that biologic meshes are not necessarily superior to synthetic meshes. The significant changes that take place between 30 and 90 days should lead to careful interpretation of short-term experimental results.

Introduction

Incisional hernia remains a major clinical problem for 2–20 % of all patients undergoing abdominal surgery(1, 2). Even higher incidences reaching 30–37 % are reported among obese and aortic aneurysm patients(3, 4). Despite the high frequency of incisional hernia operations, long-term results remain disappointing.

Burger et al.(5) reported 10-year recurrence rates up to 63 % after primary suture repair and up to 32 % after mesh repair. In addition, the recurrence rates increase after each reoperation, underscoring the importance of the best evidence-based method at the first operation(6).

In recent years, laparoscopic incisional hernia repair has shown increased popularity. Although laparoscopic repair offers no advantages in terms of recurrence rates, it may be associated with a shorter hospital stay, lower perioperative complication rates, and a shorter mean operation time than open repair(7-9).

In laparoscopic hernia repair, direct contact between the prosthesis and the abdominal viscera is inevitable. This contact may lead to an inflammatory reaction resulting in abdominal adhesion formation(10), which can induce small bowel obstruction(11), chronic pain(12), infertility, enterocutaneous fistulas(13), and difficulties at reoperation(14). The latter is illustrated by Halm et al.(15), who showed that 21 % of patients with an intraperitoneal polypropylene mesh required small bowel resection for entrance to be gained into the abdomen at reoperation.

Currently, a wide variety of synthetic and biologic hernia reinforcement materials is available on the market, complicating the selection of an appropriate prosthesis(16, 17). The most commonly used meshes are made of polypropylene. This material is relatively inexpensive and easy to handle and does incorporate well into the abdominal wall. However, when placed in contact with the abdominal viscera, polypropylene meshes may be associated with severe adhesion formation(15). Therefore, intraperitoneal utilization should be avoided(18).

Alternatives can be found in composite and biologically derived prostheses. Composite meshes consist of a synthetic material and an anti-adhesive layer or coating on the visceral side of the mesh. Biologic grafts are collagen meshes derived from bovine, porcine, human skin, or other tissue such as submucosa or pericardium.

A recognizable difference exists between the meshes in performance characteristics such as cellular response, strength, biodegradability, and susceptibility to infection(19). Biologic meshes are thought to induce fewer adhesions because of increased "biocompatibility" and less foreign body reaction(16)]. On the other hand, these characteristics may result in less incorporation into the abdominal wall(19). Furthermore, some biologic grafts are chemically cross-linked to make them less prone to degradation in vivo. This progress should increase the strength and longevity of the mesh while providing the benefits of a biologic scaffold(20, 21).

This study aimed to help in the selection of the appropriate prosthesis from the wide choice of available hernia reinforcement materials. Therefore, we compared a commonly used synthetic mesh and a composite mesh with one cross-linked and two non-cross-linked biologic meshes in intraperitoneal position in a rat model. The meshes were tested in terms of adhesion formation, shrinkage, and incorporation after a period of 30 and 90 days. Additionally, collagen formation after 90 days was determined.

Materials and methods

Study design

In this study, 85 male Wistar rats were randomized into two groups: 50 animals in group A and 35 animals in group B. Both groups were in turn subdivided into five groups corresponding with the five meshes tested, thus resulting in 10 animals per mesh in group A and 7 animals per mesh in group B. After the animals had been humanely killed (group A after 30 days and group B after 90 days), adhesion formation, mesh incorporation, shrinkage, tissue response, and collagen formation were scored and compared.

Animals studied

Male inbred rats of the Wistar strain weighing 340–390 g were obtained from a licensed breeder in Harlan, The Netherlands and given 2 weeks to become customized to laboratory conditions before the start of the study. The animals were bred under specific pathogen-free conditions, kept under standard laboratory conditions in individually ventilated cages (temperature, 20–24 °C; relative humidity, 50–60 %; 12-h light and 12-h dark cycles), and fed with

standard rat chow and water ad libitum during the whole study period. The protocol of the study was approved by the Animal Experiments Committee of the Erasmus University Rotterdam.

Materials

Table 1 presents the materials and the brand names of the five meshes tested. Before use, the biologic scaffolds Strattice (Lifecell, KCl, Branchburg, NJ) and Surgisis (Cook Biotech, West Lafayette, IN, USA) were rehydrated or soaked as directed by the manufacturer. Monofilament polypropylene 5-0 (Ethilon; Johnson & Johnson Medical, New Brunswick, NJ, USA) sutures were used for mesh fixation to the abdominal wall and closure. Multifilament polyglyconate 5-0 sutures (Safil; Melsungen, Germany B. Braun) were used for closure of the skin.

Table 1. Meshes included in the study

Brand name	Basic material	Modification	Manufacturer
Prolene	Polypropylene	None	Ethicon, Johnson and Johnson (Somerville, NJ, USA)
Parietex Composite	Polyester	Collagen-polyethylene-glycol-glycerol coating	Covidien Surgical (Dublin, Ireland)
Strattice	Porcine dermis	Non-crosslinked	Lifecell, KCl (Branchburg, NJ, USA)
Surgisis	Small intestinal submucosa	Non-crosslinked	Cook Biotech (West Lafayette, IN, USA)
Permacol	Porcine dermis	Crosslinked	Covidien Surgical (Dublin, Ireland)

Procedure

The study was performed under aseptic conditions using a modification of a validated rat model previously described by Burger et al. (14, 22). At the start of the study, the animals were anesthetized using isoflurane/O_2 inhalation and buprenorphin analgesia (0.05 mg/kg) administered subcutaneously. The abdomen was shaved and cleaned with alcohol 70 %, after which a 5-cm midline skin incision was made and skin flaps were raised. Subsequently, the abdominal cavity was opened with a 4-cm midline incision through the linea alba. A sterile mesh measuring 2.5 × 3.5 cm was placed in an intraperitoneal position and fixed transmusculary with six nonabsorbable sutures. The abdominal wall and skin were both closed with a running absorbable suture.

Measurements

Adhesion formation

After 30 days (group A) and 90 days (group B), the animals were anesthetized and the ventral abdominal wall was opened through a U-shaped incision (including skin) around the mesh. Pictures of the mesh and current adhesions were taken using a 5.0-megapixel digital camera (Sony Cybershot, Tokyo, Japan). Subsequently, the animals were killed by cardiac incision, adhesions were cut, and the abdominal wall including the mesh was removed. Two independent observers assessed the adhesion coverage of the mesh surface using a scoring system. A grid was placed over the mesh, dividing it into 24 equal squares and facilitating accurate estimation of adhesion formation. In case of interobserver variance, the mean was scored. For objective scoring of the severity of the adhesions, the Zühlke scoring system was used. This system has a four-degree classification of adhesions based on histologic and morphologic criteria (Table 2). Adhesions merely attached to the mesh edge did not contribute to the total adhesion score. Finally, the animals were killed by cardiac incision.

Table 2. Zühlke score: macroscopic classification of abdominal adhesions.

Zühlke score	Characteristics
1	Filmy adhesion, easy to separate by blunt dissection
2	Stronger adhesion; blunt dissection possible, partly sharp dissection necessary; beginning of vascularization
3	Stronger adhesion; lysis possible by sharp dissection only; clear vascularization
4	Very strong adhesion; lysis possible by sharp dissection only; organs strongly attached with severe adhesions; damage of organs hardly preventable

Incorporation

Mesh incorporation was defined as the amount of the mesh edge (in millimeters) incorporated into the abdominal wall as a percentage of the circumference. In case of interobserver variance, the mean was scored.

Mesh shrinkage

Mesh shrinkage was defined as the projection of the mesh surface and measured with a caliper by two independent observers. By measuring the projection, curling and wrinkling of the mesh were included in addition to the actual size of the mesh. Shrinkage was defined as the relative loss of surface (%) compared with the original size of the mesh.

Tissue reaction

For each group, five meshes with the adjacent abdominal wall were fixed in 4 % neutral buffered formalin. After routine tissue processing, sections were cut and stained with hematoxylin and eosin (H&E) or picrosirius red.

H&E staining

Paraffin sections were dewaxed and stained with hematoxylin (Sigma-Aldrich, Seelze, Germany). After washing in tap water and demiwater, the sections were stained with eosin (Sigma-Aldrich). Subsequently, the sections were dehydrated in alcohol and xylene and mounted with Entallan (Merck, Darmstadt, Germany). Slides were analyzed with a light microscope (Olympus, Tokyo, Japan).

Picrosirius red staining

Paraffin sections were dewaxed, rehydrated, and stained with 0.1 % Sirius Red F3BA (Direct Red 80; Fluka Chemie, Zwijndrecht, The Netherlands) in a saturated picric acid solution for 1 h. Brief washing in 0.1 % acetic acid was followed by rapid dehydration in 100 % alcohol.

After a xylene bath, the slides were mounted with Entellan (Merck). Subsequently they were analyzed using a polarized light microscope (Olympus) with polarization filters whereby the collagen fibers show birefringence. This technique allows the orientation of the collagen fibers to be visualized, indicating the amount of collagen new formation(23).

In the H&E-stained samples, the degree of inflammation was scored using the following grading scale: grade 1 (mild inflammatory reaction with a few giant cells, occasional lymphocytes, and plasma cells), grade 2 (moderate reaction with giant cells and increased numbers of admixed lymphocytes, plasma cells, eosinophils, and neutrophils), and grade 3 (severe inflammatory reaction with micro abscesses).

Statistical analysis

Because the data were not normally distributed, adhesion formation, incorporation, shrinkage, and tenacity were compared using nonparametric tests (Kruskal-Wallis, Mann–Whitney). Therefore, all results were presented using the median and the interquartile range (IQR). After the amount of adhesion formation and the percentage of incorporated mesh edge had been assessed, these parameters were used to determine the Spearman's rank correlation

coefficient. All reported *p* values are two-sided and considered significant if lower than 0.05. Statistical analysis was performed using the PSAW 17 statistical software package (IBM SPSS statistics, Amsterdam, The Netherlands).

Results

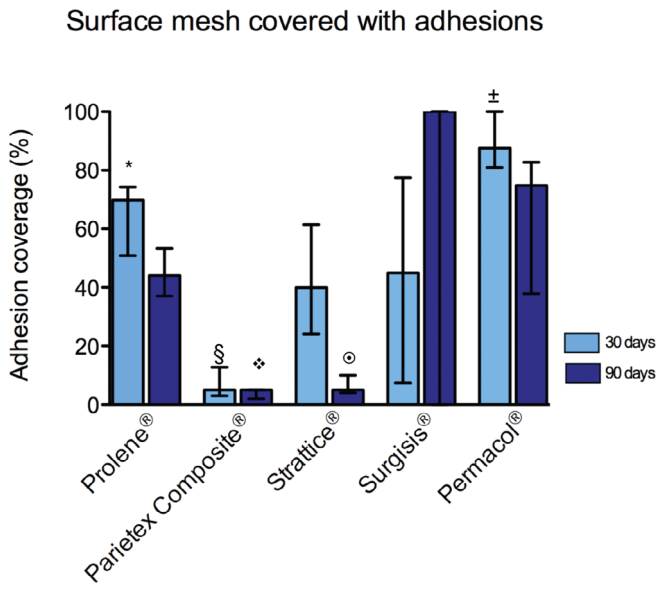
During this study involving 85 animals, no animals died prematurely.

Adhesions

At 30 days, Parietex composite showed a significantly smaller percentage of mesh surface covered with adhesions (9 %; IQR, 3.0–12.8 %) than any of the other meshes. Permacol resulted in significantly more adhesions than any of the other meshes (87.5 %; IQR, 81–100 %), and adhesion coverage with the Prolene mesh was significantly higher than with Strattice (40 %; IQR, 24.1–61.5 %) or Parietex composite meshes. Surgisis mesh showed 45 % coverage (IQR, 7.4–77.5 %) of the mesh surface.

At 90 days, the smallest amount of adhesions was seen with Parietex composite (5 %; IQR, 2–5 %) and Strattice (5 %; IQR, 4–10 %), significantly less with either Prolene (42 %; IQR, 36.8–53.6 %) or Permacol (74.8 %; IQR, 37.9–82.7 %) (Figure 1). Five Surgisis meshes showed 100 % adhesion coverage, whereas two meshes were completely adhesion free. Compared with the results at 30 days, Prolene, Strattice, and Permacol showed a significant reduction in the amount of adhesions at 90 days (Figure 1). Figure 2 shows representative views of all the meshes at the long-term follow-up evaluation.

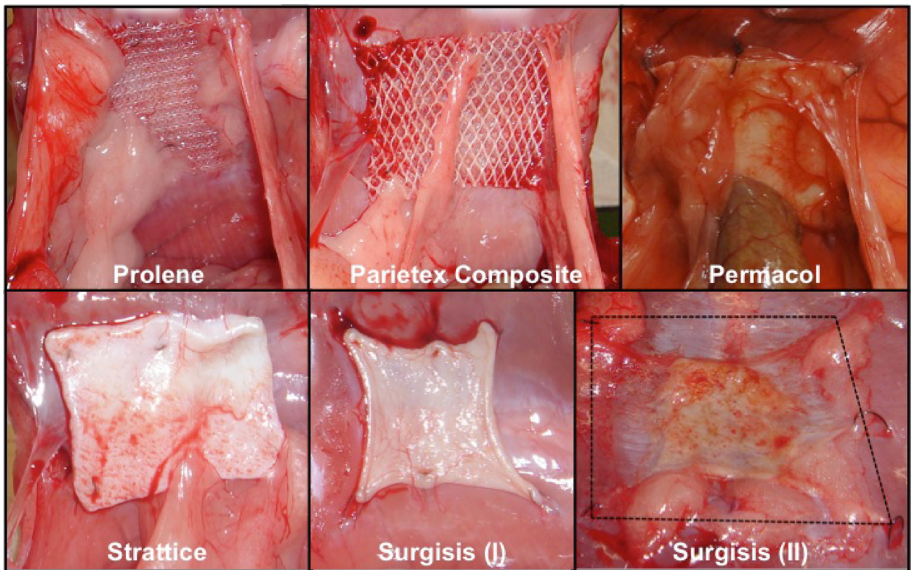
Figure 1. Adhesion coverage at 30 days compared with coverage at the 90-day follow-up assessment. Values are median (interquartile range). At 30 days: *$p < 0.050$ versus Strattice and Parietex composite; §$p < 0.050$ versus all other meshes; ±$p < 0.050$ versus all other meshes. At 90 days: ❖$p < 0.050$ versus Permacol and Prolene; ⊙$p < 0.050$ versus Permacol and Prolene. At 90 days, Prolene, Strattice, and Permacol showed a significant reduction compared with their status at 30 days (Mann–Whitney *U* test).



Mesh incorporation

At 30 days, no significant difference in mesh edge incorporation was seen between Parietex composite (70 %; IQR, 53–80 %), Prolene (50 %; IQR, 46.3–56.1 %), Surgisis (34 %; IQR, 16.7–66.5 %), Strattice (23 %; IQR, 5–70 %), and Permacol (48 %; IQR, 34.3–69.6) meshes. At 90 days, the percentage of Parietex composite mesh incorporated (79 %; IQR, 61.2–83.0 %) was significantly higher than that of Prolene (53 %; IQR, 31.0–61.2 %), Strattice (40 %; IQR, 9.5–57.4 %), or Permacol (21 %; IQR, 16.0–41.4). The percentage of Surgisis mesh edge incorporated was 66 % (IQR, 0–100 %). Five meshes showed complete incorporation, whereas two other meshes did not incorporate at all (Figures 2 and 3). For each mesh, no significant differences were observed between 30 and 90 days.

Figure 2. Representative views at the 90-day follow-up assessment. Parietex composite adhesions merely to the mesh edge do not contribute to the total adhesion score. Permacol cecum adhered to the mesh. Surgisis I without adhesions and with minimal incorporation (2 of 7). Surgisis II complete coverage with adhesions and full incorporation (5 of 7). Dashed line marks the original size of the mesh.



Shrinkage

At 30 days, Surgisis showed significantly more shrinkage (39 %; IQR, 37.1–50.6 %) than any of the other meshes. More shrinkage occurred with both Permacol (13.7 %; IQR, 8.6–22.6 %) and Strattice (16 %; IQR, 14.3–19.2 %) than with Parietex composite. No significant differences were seen between Prolene (11 %; IQR, 8.6–16.2 %) and Parietex composite (9 %; IQR, 5.7–13.6 %). At 90 days, Surgisis resulted in significant more shrinkage than any of the other meshes (65 %; IQR, 42.4–74.3 %) (Figure 4). The percentage of shrinkage shown by Strattice (28 %; IQR, 22.9–28.0 %) was significantly higher than that shown by Prolene (16 %; IQR, 11.4–18.5 %). After 90 days, Parietex composite mesh demonstrated shrinkage of 23 % (IQR, 9.7–31.7 %), and Permacol exhibited shrinkage of 17.7 % (IQR, 12.2–23.8 %). All the meshes except Prolene and Permacol showed significantly more shrinkage at 90 days than at 30 days.

Figure 3. Percentage of the mesh edge incorporated into the abdominal wall. At 30 days, no significant differences were found. Values are median (interquartile range). $^{\S}p < 0.050$ versus Prolene, Strattice, and Permacol. For each mesh, no significant differences were observed between 30 and 90 days (Mann–Whitney *U* test).

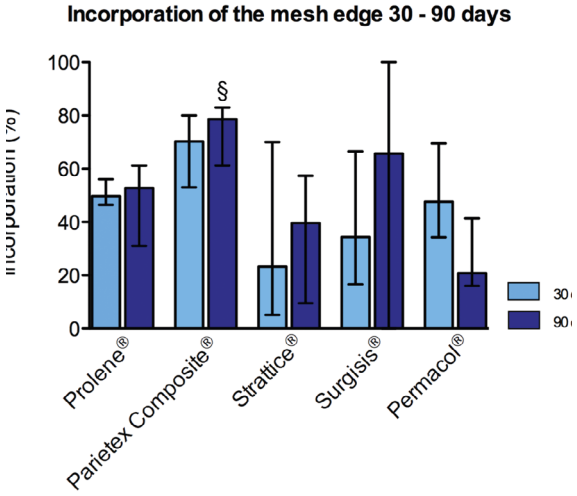
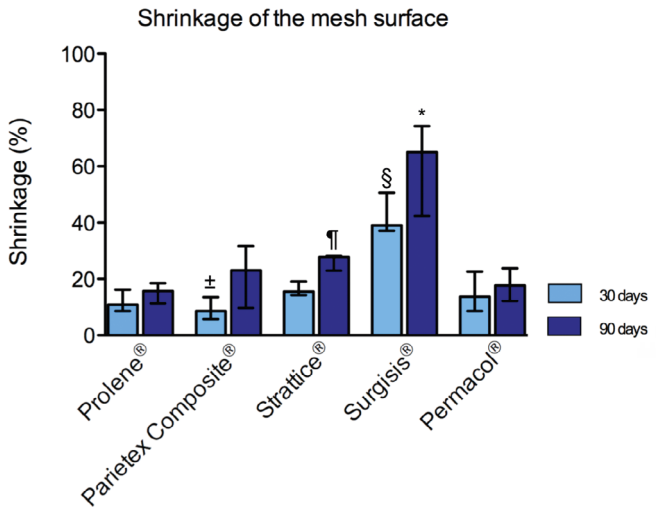


Figure 4. Shrinkage of the mesh surface compared with the original size. At 30 days: $^{\S}p < 0.050$ versus all other meshes; $^{\pm}p < 0.050$ versus Permacol and Strattice. At 90 days: $^{*}p < 0.050$ versus all other meshes; $^{\P}p < 0.050$ versus Prolene. Compared with 30 days, Surgisis, Parietex composite, and Strattice showed significant more shrinkage (Mann–Whitney *U* test)



Tenacity of adhesions

At 30 days, the Zühlke score for adhesions to the Permacol mesh was significantly higher than the score for Prolene ($p = 0.011$), Parietex composite ($p = 0.004$), or

Surgisis ($p = 0.007$). Organs were attached (Zühlke 4) to Permacol in 6 of 10 cases (60 %) and to Strattice in 2 of 10 cases (20 %). At 90 days, the Zühlke score of Permacol was significantly higher than the score of Parietex composite, Surgisis, or Strattice. No organs were attached to any of the meshes except Permacol (4 of 7, 57.1 %). The Zühlke scores for the Strattice (1; IQR, 1–2) and Surgisis (1; IQR, 0–1) meshes were significantly lower than for Prolene (2; IQR, 2–2).

Correlation between adhesion formation and incorporation

At 30 days, Strattice showed a significant correlation between adhesion coverage of the mesh and incorporation of the mesh edge ($\rho = 0.681$; $p = 0.030$). At 90 days, only Surgisis showed a significant correlation coefficient ($\rho = 0.828$; $p = 0.021$). In both cases, the correlation coefficient indicated that an increase of incorporation was correlated with an increase in adhesion formation.

Tissue reaction

At 30 days, histologic evaluation after H&E staining of the meshes demonstrated a grade 1 (mild) foreign body reaction to all the meshes except Permacol. This mesh showed a grade 2 inflammatory reaction, resulting in a thick fibrous layer between the mesh and the abdominal wall. Additionally, in some cases, a fibrous layer was visible on the abdominal side of the mesh, generally combined with strong adhesions (Figure 5).

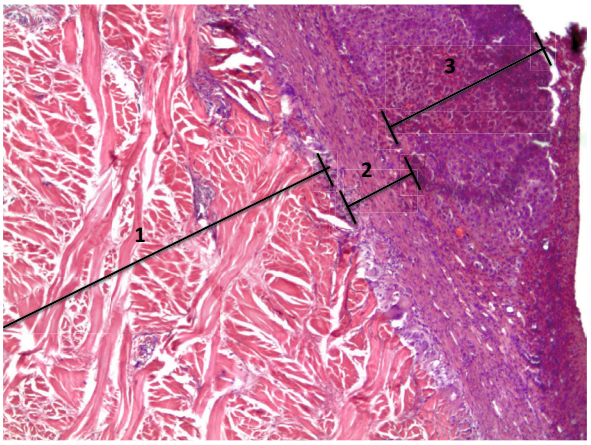
At 90 days, a grade 1 mild foreign body reaction was visible around all the meshes, with limited numbers of giant cells and lymphocytes present. Parietex composite meshes showed a larger influx of fibroblasts. Strattice and Parietex composite showed a new mesothelial layer on the visceral side of the mesh. On the Permacol mesh, a new mesothelial layer was alternating with a small layer of fibrous tissue.

Histologic samples after picrosirius red staining at 90 days are shown in Figure 6 Tissue surrounding the Prolene mesh indicates complete incorporation of the mesh by a layer of collagen around the Prolene fibers. All these collagen fibers have the same orientation and thickness. The collagen layer between mesh and muscles also was highly organized but in a different direction and with a different thickness because it is mostly of the same color.

In the case of Parietex composite, the mesh was completely covered with collagen in different orientations. The collagen directly surrounding the fibers has a different direction than the collagen of the layer between the

mesh and the muscles. In particular, the layer between material and muscles appeared to be very organized based on the homogeneity of color. The collagen fibers of the Permacol mesh itself showed a structured orientation of collagen fibers. The mesh and the muscle layer had almost no collagen between them, as indicated with a "c" in Figure 6. Furthermore, this layer was very organized in one direction. A small layer of collagen with fibers in several different orientations separated Strattice mesh from the abdominal muscles. Surgisis mesh was completely incorporated into connective tissue, with collagen fibers crossing the surrounding tissue and the Surgisis mesh (indicated by * in Figure 6).

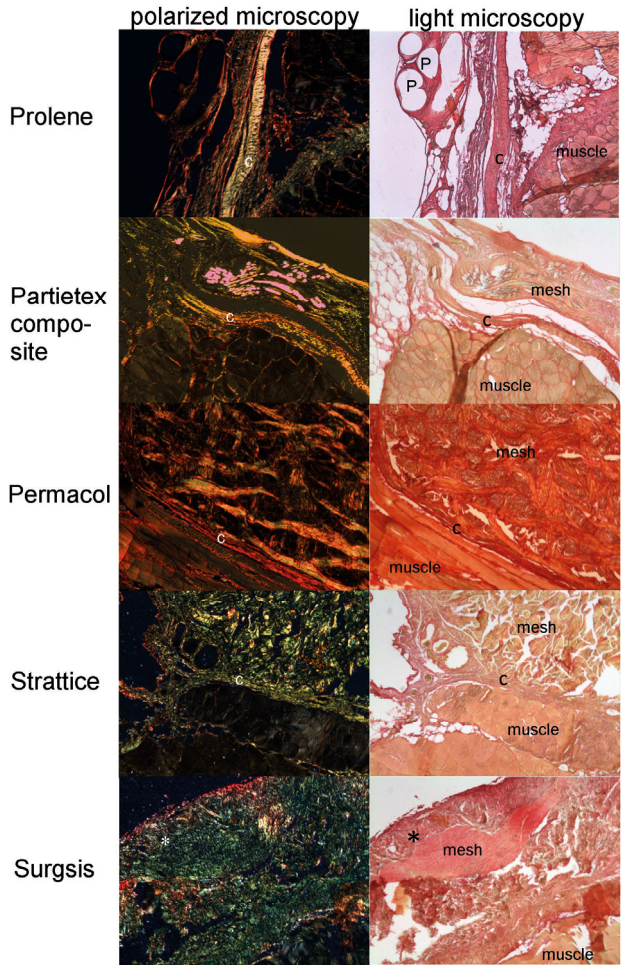
Figure 5. Histologic sample of Permacol mesh at the 30-day follow-up assessment. The liver is strongly attached to the mesh. *1* Permacol mesh. *2* Fibrotic layer. *3* Liver.



Discussion

The current study analyzed five different meshes in terms of adhesion formation, incorporation, and shrinkage after 30 and 90 days. For these three parameters, Parietex composite mesh demonstrated the best long-term results compared with all the other meshes. The biologic non-cross-linked mesh, Strattice, showed little adhesion formation and moderate shrinkage but poor incorporation.

Figure 6. Histologic samples after picrosirius red staining at 90 days. The collagen layer between mesh and abdominal wall is indicated by *c*. Collagen surrounding Surgisis mesh is shown by *asterisk*.



Adhesions are formed during the inflammatory phase in the first 7 days after surgery(24). This period is followed by the proliferation phase until about day 30, when some regression is observed, whereas the remaining adhesions become more organized to fibrous and vascularized tissue. In general, previous opinion maintained that this succeeding phase of remodeling was temporary and that inert scar tissue was finally formed. However, findings recently have shown that even after months to years, macrophages, fibroblasts, mononuclear cells, and neovascularization can be identified in abdominal adhesion tissue, suggesting a dynamic and ongoing process of remodeling(25-27). This is

supported by our study showing major alterations in the results after 90 days compared with 30 days. The amount of adhesion formation to the Strattice and the Prolene meshes was significantly diminished, whereas the extent of adhesions to the Surgisis mesh increased at 90 days.

The fact that the anti-adhesive collagen layer of the Parietex composite mesh is absorbed within 30 days is not congruent with our findings that very few adhesions on this mesh occur even in the long term(28). These data support recent long-term studies in which Parietex composite resulted in minimal adhesion formation(29, 30). The mechanism of this phenomenon is not completely understood, but perhaps the formation of a new mesothelial layer plays a pivotal role in this process. Histologic examination of tissue samples after H&E supports this hypothesis showing a new mesothelial layer on the Parietex composite and Strattice meshes. On Permacol mesh, a new mesothelial layer was alternating with a small fibrous layer, the latter most probably the result of adhesion formation.

In addition to adhesion prevention on the visceral side of the mesh, a fundamental characteristic of a mesh for intraperitoneal use should be a good incorporation on the ventral side. A macroporous surface and a (mild) foreign body reaction might be necessary for sufficient incorporation, although Petter-Puchner et al.(31) showed that macroscopic perforation of different biologic meshes did not improve incorporation. At 30 days, no significant differences in incorporation were seen between the meshes as a result of large variation in all the groups. At 90 days, however, Parietex composite showed a significantly higher percentage of incorporation than Strattice, Prolene, or Permacol. At this time point, Surgisis mesh resulted in a wide variation of results regarding all parameters. Five meshes were well incorporated and completely covered with adhesions, resulting in excessive shrinkage. In contrast, the other two meshes showed no incorporation or adhesion formation at all, with less shrinkage.

Further analysis showed a significant correlation between incorporation and adhesion formation. The cause of this correlation is a matter of speculation, although an explanation might be found in the foreign body reaction. This reaction necessary for ingrowth on the ventral side also can induce the formation of adhesions on the visceral side because this mesh does not have a specific anti-adhesive layer. As a consequence, limited adhesion formation goes with insufficient incorporation.

The literature clearly shows that Surgisis manifests enhanced shrinkage and is absorbed completely by the body. However, the speed of degradation is a matter of discussion(19, 31-33).

One advantage attributed to biodegradable meshes is their ability to support regeneration of the original tissue, but when the mesh degrades before adequate cellular infiltration, differentiation, collagen deposition, and neovascularization, the overall quality and strength of the newly formed tissue probably will be insufficient for abdominal hernia repair(19, 34).

Histologic examination of Surgisis after picrosirius red staining showed a transition layer with collagen fibers organized in different directions crossing the border between Surgisis and surrounding tissue. Together with degradation of the mesh, this suggests an ongoing remodeling process. Unfortunately, from the results of this study, it is not possible to conclude what influence the remodeling process has on the strength of the mesh and underlying tissue.

In our study, a wide variation in adhesion formation to the mesh was seen in the Strattice group at 30 days. In two cases, less than 5 % of the surface was covered with adhesions, whereas in two additional cases, organs were attached to the Strattice mesh. Remarkably, the amount of adhesions attached to the mesh dropped dramatically from 40 % at 30 days to 5 % at 90 days. In combination with a significant lower tenacity of adhesions compared with the Prolene mesh at 90 days, this may suggest less severe adhesion formation to Strattice mesh in the long term. This may be explained by the histologic result similar to that of Parietex composite meshes, showing a new mesothelial layer at the visceral side of the mesh.

Our result of a wide variation at 30 days is consistent with that of Mulier et al.(35), who also found a wide distribution in adhesion formation. However, they did not mention whether any organs were involved or not. At 90 days, 40 % of the Strattice mesh edge was incorporated into the abdominal wall. In contrast to the results at 30 days, correlation between adhesions and incorporation could not be found anymore because very few adhesions were seen. Histologic examination with picrosirius red staining showed almost no degradation of the mesh. Additionally, a small and sharply bordered layer of novel connective tissue was seen between the mesh and the abdominal wall, confirming the macroscopic observation of limited incorporation.

The amount of adhesions to Permacol mesh after 90 days (74.8 %) was significantly diminished compared with the amount after 30 days (87.5 %),

whereas the Zühlke score was not. This may be explained by the reduction in filmy adhesions, whereas, in contrast, bowel or liver adhered to 57 % of the meshes. In the literature, these extensive adhesions and limited adhesion formation to Permacol mesh are described(36, 37).

Mesh edge incorporation at 90 days was 21 %, and in contrast to Strattice and Surgisis, no correlation between adhesion formation and incorporation was found at either time point. Histologic examination after 30 days showed a substantial fibrotic layer between the Permacol mesh and the abdominal wall, and picrosirius red staining did not show a transition layer with degradation of the mesh or new collagen formation. Additionally, the macroscopic observation of liver adhered to the mesh was microscopically confirmed with a fibrotic reaction between liver and mesh (Figure 5).

These observations suggest that Permacol mesh placement results in a foreign body reaction comparable with that of synthetic meshes, resulting in formation of a fibrotic capsule rather than tissue regeneration. An explanation may be found in the chemical cross-linking process. The aim of this process is to increase the strength of the scaffold and to restrain the in vivo degradation process. A disadvantage may be that cross-linking results in biocompatibility, possibly leading to more adhesion formation. Therefore, based on results in this study, non-cross-linked mesh should be preferred to prevent strong adhesion formation.

We conclude from this study that biologic meshes are not necessarily superior to synthetic meshes with regard to adhesion formation, incorporation, or shrinkage. Our data confirm the outcome of earlier studies in which composite meshes showed clear advantages compared with other meshes on the market(38, 39). The difference in our results between 30 and 90 days appears to be highly significant and should lead to careful interpretation of short-term experimental results.

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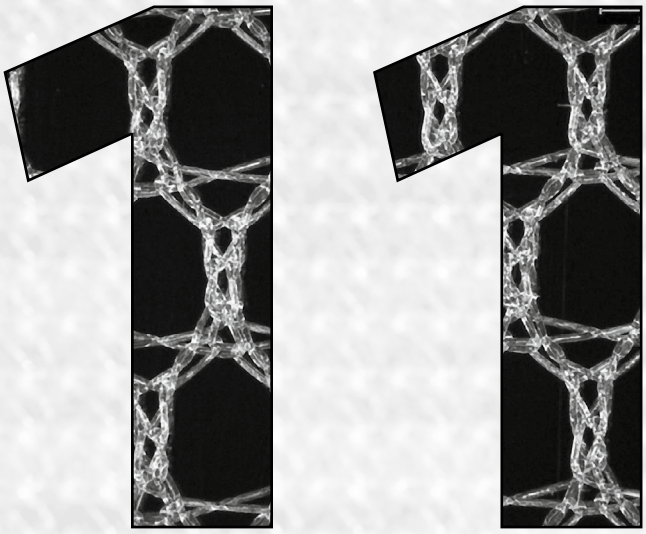
Chapter



Experimental study on synthetic and biological mesh implantation in the contaminated environment

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Abstract:

Background

Implantation of meshes in a contaminated environment can be complicated by mesh infection and adhesion formation.

Methods

The caecal ligation and puncture model was used to induce peritonitis in 144 rats. Seven commercially available meshes were implanted intraperitoneally: six non-absorbable meshes, of which three had an absorbable coating, and one biological mesh. Mesh infection, intra-abdominal abscess formation, adhesion formation, incorporation and shrinkage were evaluated after 28 and 90 days. Histological examination with haematoxylin and eosin and picrosirius red staining was performed.

Results

No mesh infections occurred in Sepramesh®, Omyramesh® and Strattice®. One mesh infection occurred in Parietene® and Parietene Composite®. Significantly more mesh infections were found in C-Qur® (15 of 16; $P \leq 0.006$) and Dualmesh® (7 of 15; $P \leq 0.035$). Sepramesh® showed a significant increase in adhesion coverage from 12.5 % at 28 days to 60.0 % at 90 days ($P = 0.010$). At 90 days there was no significant difference between median adhesion coverage of Parietene Composite® (35.0 %), Omyramesh® (42.5 %), Sepramesh® (60.0 %) and Parietene® (72.5 %). After 90 days the adhesion coverage of Strattice® was 5.0 %, and incorporation (13.4 %) was significantly poorer than for other non-infected meshes ($P \leq 0.009$). Dualmesh® showed shrinkage of 63 % after 90 days.

Conclusion

Parietene Composite® and Omyramesh® performed well in a contaminated environment. Strattice® had little adhesion formation and no mesh infection, but poor incorporation. Some synthetic meshes can be as resistant to infection as biological meshes.

Introduction

Mesh reinforcement during ventral hernia repair drastically reduces 10-year recurrence rates(1, 2). Non-absorbable synthetic materials are currently the most commonly used prosthesis for reinforcement of ventral hernias. Advantages of synthetic meshes are low recurrence rates, ease of use and relatively low costs. However, implantation of synthetic meshes can be complicated by mesh infection and adhesion formation. Mesh infection is a feared complication and reported in up to 16% of patients after abdominal wall repair(3). The risk of mesh infection is increased in a contaminated environment, which makes the use of synthetic mesh debatable(4). Mesh infection after implantation often necessitates its removal, which leaves the patient with a contaminated field and an abdominal wall deficit that is often larger than the original hernia. Macroporous meshes have been preferred because large pores permit infiltration of macrophages and allow rapid fibroplasia and angiogenesis, with reduced infiltration and growth of bacteria(5, 6). The drawback of macroporous meshes is the increased risk of visceral adhesions to the site of the repair, with associated small bowel obstruction, pain, infertility and enterocutaneous fistula formation(5, 7, 8). These adhesions arise as a result of fibrin deposition in the abdominal cavity, with subsequent formation of adhesions. The presence of contamination increases fibrin deposition, leading to an increased amount and tenacity of adhesions intra-abdominally and to the mesh(9). In a clean environment antiadhesive coatings have proved to reduce adhesion formation to macroporous meshes(8, 10, 11). The aim of the study was to compare commercially available synthetic and biological meshes in terms of infection rate, adhesion formation, incorporation and shrinkage after implantation in a contaminated environment.

Methods

One hundred and forty-four male Wistar rats weighing 250–350 g were obtained from a licensed breeder (Harlan Laboratories, Boxmeer, The Netherlands). They were bred under specific pathogen-free conditions, kept under standard laboratory conditions in individually ventilated cages, and fed freely with standard rat chow and water throughout the experiment. The

protocol of the experiment was approved by the Ethical Committee on Animal Experimentation of Erasmus University Rotterdam.

Peritonitis model

Rats were anaesthetized by isoflurane/oxygen inhalation and received buprenorphine analgesia (0.05 mg/kg subcutaneously). The abdomen was shaved and the skin disinfected with 70 % alcohol, after which the abdominal cavity was opened through a 3-cm midline incision. To induce peritonitis, a caecal ligation and puncture (CLP) model was used(12). The caecum was carefully manipulated outside the abdominal cavity and ligated just distal to the ileocaecal valve with a monofilament non-absorbable suture (4/0 Ethilon®; Ethicon, Johnson & Johnson, Somerville, New Jersey, USA), maintaining the continuity of the bowel. The caecum was punctured distally to the ligation with an 18-G needle. The fascia and skin were closed with a running absorbable suture (5/0 Safil®; B. Braun, Melsungen, Germany). After 24 h the abdomen was reopened, a culture swab was taken to confirm peritonitis, the necrotic caecum was resected and the abdominal cavity was rinsed with at least 20 ml phosphate-buffered saline at 37°C. A sterile mesh, measuring 2.5 × 3 cm, was implanted intraperitoneally with three transmuscular nonabsorbable sutures (5/0 Ethilon®) on both sides of the incision in all mesh groups. No mesh was implanted in the control group. After administration of gentamicin (6 mg/kg intramuscularly) the abdominal wall and skin were closed separately with a running absorbable suture (5/0 Safil®).

Implanted meshes

The rats were divided into eight groups, a control group that received no mesh and groups in which one of the following seven meshes was implanted intraperitoneally:

1. Non-cross-linked collagen (Strattice®; LifeCell, Branchburg, New Jersey, USA)
2. Polypropylene (Parietene®; Sofradim, Trevoux, France; part of Covidien, North Haven, Connecticut, USA)
3. Collagen–polyethyleneglycol–glycerol-coated polypropylene (Parietene Composite®; Sofradim)
4. Omega-3-fatty acid coated polypropylene (C-Qur®; Atrium, Hudson, New York,USA)

5. Carboxymethylcellulose–sodium hyaluronate coated polypropylene (Sepramesh®; Bard, New Providence, New Jersey, USA)
6. Expanded polytetrafluoroethylene (PTFE) (Dualmesh®; Gore, Flagstaff, Arizona, USA)
7. Condensed PTFE (Omyramesh®; B. Braun)

Measurements

Half of the surviving animals were killed after 28 days and half after 90 days. The abdomen was shaved, disinfected and opened through a U-shaped incision extending laterally and caudally to the mesh. Directly after opening the abdomen, a swab of the abdominal cavity was taken for culture. Mesh infection was defined as the presence of abscesses of the mesh, and parts of the mesh were cultured for microbiological evaluation. Adhesions were scored using a grid placed over the mesh, dividing it into 30 equal squares. The tenacity of the adhesions was graded using the Zühlke score, a four-degree classification of adhesions based on histological and morphological criteria(13). Pictures of the abdominal wall with mesh and any adhesions were taken with a 5.0-megapixel digital camera. The abdominal cavity was inspected for abscesses; when present, these were scored and cultured at four sites: the liver, abdominal wall, bowel and omentum(14). Mesh incorporation was defined as the percentage of the mesh edge incorporated into the abdominal wall, taking into account any shrinkage. Shrinkage was defined as the relative loss of surface compared with the original size of the mesh, measured with a caliper. The animals were killed by cardiac cut. All measurements were carried out by two independent observers and disagreements reconciled by discussion.

Histological evaluation

At least two representative samples of macroscopically non infected meshes with adjacent abdominal wall were excised by full-thickness (mesh and abdominal wall muscle) biopsy punches of 5 mm diameter. The samples were embedded in Tissue-Tek® (Sakura, Alphen aan den Rijn, The Netherlands) and immediately frozen in liquid nitrogen. Frozen sections of 6 µm were made using a cryostat (Leica; Davis Instruments, Vernon Hills, Illinois, USA). Sections were stained with either haematoxylin and eosin or picrosirius red (Direct Red 80; Fluka Chemie, Zwijndrecht, The Netherlands)(15). Samples were assigned a random number before evaluation and scored by two observers blinded to

the specific type of mesh. Fibrosis, lymphocyte infiltration and angiogenesis were scored macroscopically at 200× magnification using a light microscope (Olympus, Center Valley, Pennsylvania, USA). The following grading scale was used: 0, none present; 1, little; 2, moderate; and 3, extensive. The picrosirius red-stained sections were analysed for collagen and scored by means of the same scale for the presence of collagen around the mesh and abdominal wall.

Statistical analysis

Results are presented as median (interquartile range). Mesh infection, tenacity and percentage of adhesions, histological score, abscess formation, survival and weight were compared using Kruskal–Wallis, Mann–Whitney *U*, $\chi 2$ and Fisher's exact tests as the data did not show a normal distribution. If the overall test showed differences, pairwise tests were done to determine the groups causing the overall significance. Exact methods for significance were used when computational limits allowed these. All reported *P* values are two-sided and $P < 0.050$ was considered statistically significant. In view of the numbers, it was not possible to adjust the *P* values using Bonferroni's correction. Statistical analysis was performed using PSAW® statistical software package version 17 (IBM, Armonk, New York, USA).

Results

During the first 2 days of the experiment 22 (15.3%) of the 144 rats died. Necropsy was performed and septicaemia was found to be the cause of death in all rats (Table 1). On day 13 one rat in the C-Qur® group died from intestinal obstruction due to severe adherence of the bowel to the infected mesh. Abdominal cultures on day 1 confirmed bacterial contamination in all animals with Gram-positive (*Enterococcus, Staphylococcus, Streptococcus*) and Gram-negative (*Escherichia coli* and *Proteus*) microorganisms. All animals exhibited symptoms of sepsis including apathetic behaviour, ocular exudates, piloerection, diarrhoea and weight loss. The maximum percentage weight loss varied between 11.1 and 14.2%, and was more pronounced in the C-Qur® group ($P \leq 0.048$ compared with other groups).

Table 1. Postoperative mortality and number of animals analysed at 28 and 90 days after surgery

Group	Mesh material	#	Postoperative death	No. analysed	
				28 days	90 days
Control	-	18	2	8	8
Strattice	Non-crosslinked collagen	18	4	7	7
Parietene	Polypropylene	18	2	8	8
Parietene composite	Collagen–polyethyleneglycol–glycerol-coated polypropylene	18	4	7	7
Sepramesh	Carboxymethylcellulose–sodium hyaluronate-coated polypropylene	18	2	8	8
C-Qur	Omega-3-fatty acid-coated polypropylene	18	2	8*	8
Dualmesh	Expanded polytetrafluoroethylene	18	3	7	8
Omyramesh	Condensed polytetrafluoroethylene	18	3	7	8
Total		144	22	60	62

*One rat in the C-Qur® group died after 13 days. The results for this rat were analysed together with those for rats killed after 28 days in the C-Qur® group.

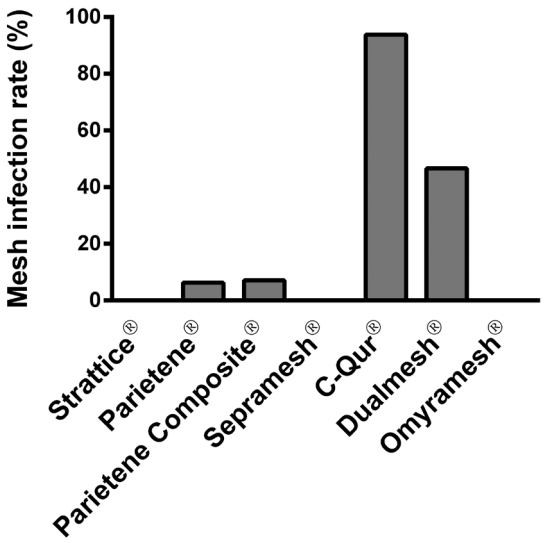
Mesh infection

At the time of death macroscopic infection of the mesh was present in 24 (22.6%) of 106 animals. The infection rate among C-Qur® meshes was high (15 of 16 rats) compared with all other meshes ($P \leq 0.006$) (Figure 1). Dualmesh® also showed a high infection rate (7 of 15 rats), significantly higher than all other groups apart from C-Qur® ($P \leq 0.035$). All infected meshes became large fibrotic pseudotumours. No additional mesh infection was discovered by microbiological culture of the meshes.

Abscesses

Intra-abdominal abscesses were found in 37 rats (62%) after 28 days and 27 (44%) after 90 days ($P = 0.049$).The majority of abscesses were located at the caecum or abdominal wall. There was no significant difference between groups in intra-abdominal abscesses ($P = 0.482$).

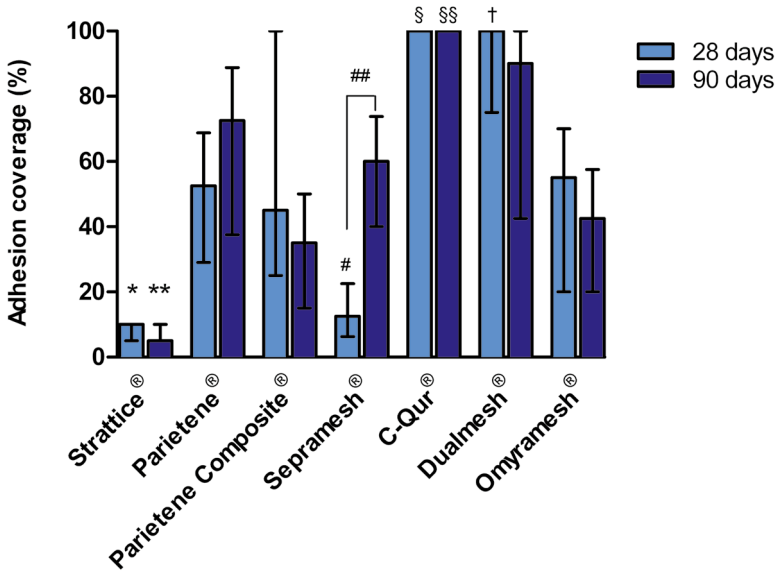
Figure 1. Comparison of mesh infection rates (combined 28 and 90 days). Values are percentage of macroscopically infected meshes among surviving animals.



Adhesions

After 28 and 90 days the surfaces of all infected meshes were completely covered with adhesions. Owing to the high infection rate in C-Qur® and Dualmesh® the median adhesion coverage was 90–100% (Figure 2). After 28 days significantly less adhesion to the mesh surface was found for Strattice® (median 10.0 (5.0–10.0) %) and Sepramesh® (12.5 (6.3–22.5) %) compared with all other meshes ($P \leq 0.004$ and $P \leq 0.017$ respectively). Median adhesion coverage was 45.0% for Parietene Composite®, 52.5% for Parietene® and 55.0% for Omyramesh®. Sepramesh® showed an increase in adhesion formation from a median of 12.5% at 28 days to 60.0% at 90 days ($P = 0.010$). After 90 days Strattice® (5.0 (5.0–10.0) %) had significantly less adhesion coverage than the other meshes ($P \leq 0.003$). At 90 days there was no significant difference between median adhesion coverage of Parietene Composite® (35.0%), Omyramesh® (42.5%), Sepramesh® (60.0%) and Parietene® (72.5%).

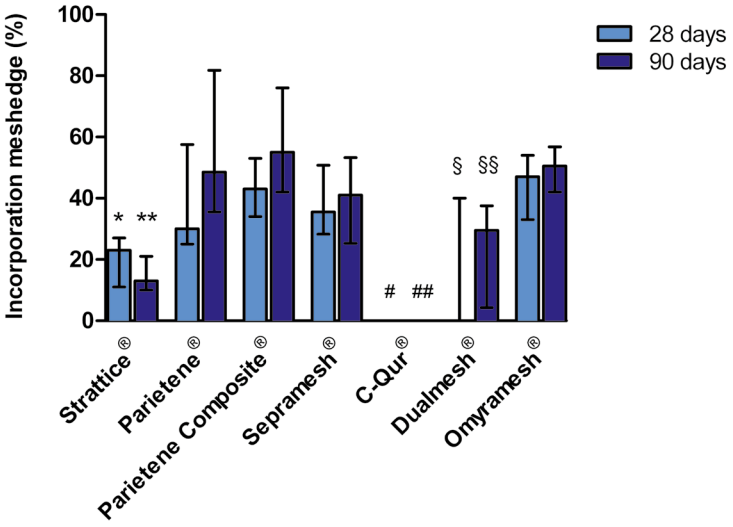
Figure 2. Comparison of percentage of mesh adhesions at 28 and 90 days' follow-up. Values are median (interquartile range).* At 28 days Strattice® had less adhesions compared to Parietene®, Parietene Composite®, C-Qur®, Dualmesh® and Omyramesh® (P<0.050), and §C-Qur® and †Dualmesh® more adhesions compared to Parietene® and Omyramesh®(P<0.050). **At 90 days Strattice had less adhesions than all other meshes (*P*<0.050); §§C-Qur® more adhesions compared to Parietene®, Parietene Composite®, Sepramesh® and Omyramesh® (*P*<0.050); # and ## Sepramesh® increase in adhesions from 28 to 90 days (P<0.050, all Mann–Whitney *U* test).



Incorporation

After 28 and 90 days C-Qur® showed no or very little incorporation into the abdominal wall owing to the high rate of mesh infection (Figure 3). Strattice® showed a poor incorporation of 22.7% at 28 days, which was lower than for Omyramesh® (47.1%; $P = 0.004$), Parietene Composite® (42.5%; $P = 0.004$) and Sepramesh® (35.6%; $P = 0.004$). The incorporation of Strattice® was not improved after 90 days (median 13.4%). This was significantly worse than the incorporation of Parietene Composite® (54.5%; $P = 0.003$), Omyramesh® (50.4%; $P < 0.001$), Parietene® (48.4%; $P = 0.009$) and Sepramesh® (40.9%; $P = 0.002$). At 90 days, Dualmesh® (29.4%) was incorporated more poorly than Parietene® ($P = 0.020$), Parietene Composite® ($P = 0.009$) and Omyramesh® ($P = 0.002$).

Figure 3. Mesh edge incorporation at 28 and 90 days' follow-up. Values are median (interquartile range). **P* < 0·050 *versus* Parietene Composite®, Sepramesh®, C-Qur® and Omyramesh® at 28 days; #*P* < 0·050 *versus* Parietene®, Parietene Composite®, Sepramesh® and Omyramesh® at 28 days; §*P* < 0·050 *versus* Parietene Composite® and Omyramesh® at 28 days; ***P* < 0·050 *versus* Parietene®, Parietene Composite®, Sepramesh®, C-Qur® and Omyramesh® at 90 days; ##*P* < 0·050 *versus* all other meshes at 90 days; §§*P* < 0·050 *versus*Parietene®, Parietene Composite®, C-Qur® and Omyramesh® at 90 days (Mann–Whitney *U*test).



Shrinkage

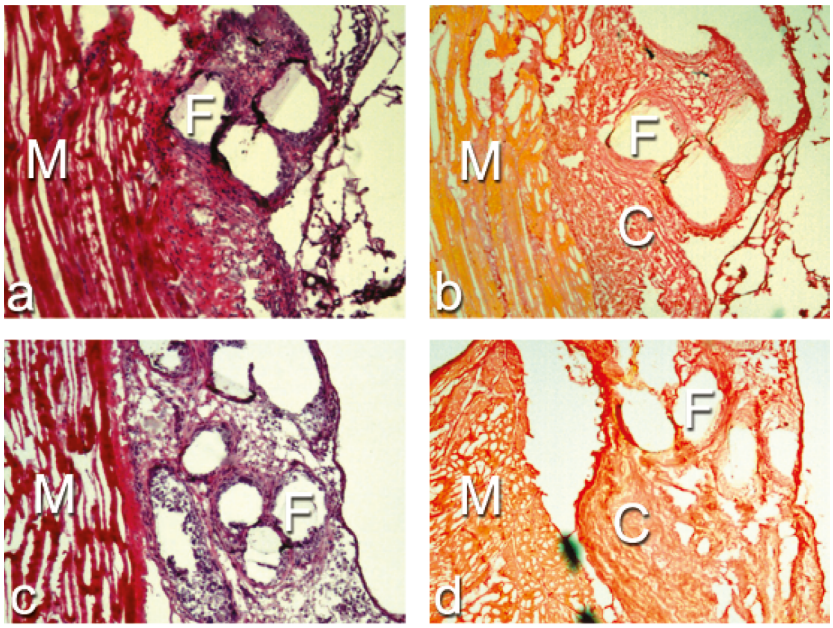
The shrinkage of C-Qur® could not be determined owing to the formation of large fibrotic pseudotumours in all but one of the meshes. The non-infected Dualmesh® showed the highest percentage loss of mesh surface, of 63% after 90 days ($P \leq 0.012$ compared with other meshes). All other meshes had a median loss of mesh surface of between 0 and 10% after 28 days. Strattice showed a progressive median loss of surface from 0% at 28 days to 23% at 90 days ($P = 0.003$). After 90 days the purely synthetic Dualmesh®, Omyramesh® and Parietene® showed shrinkage of between 0 and 15%. Parietene Composite® and Sepramesh® did not shrink after 90 days ($P \leq 0.026$ and $P \leq 0.014$ respectively compared with all other meshes).

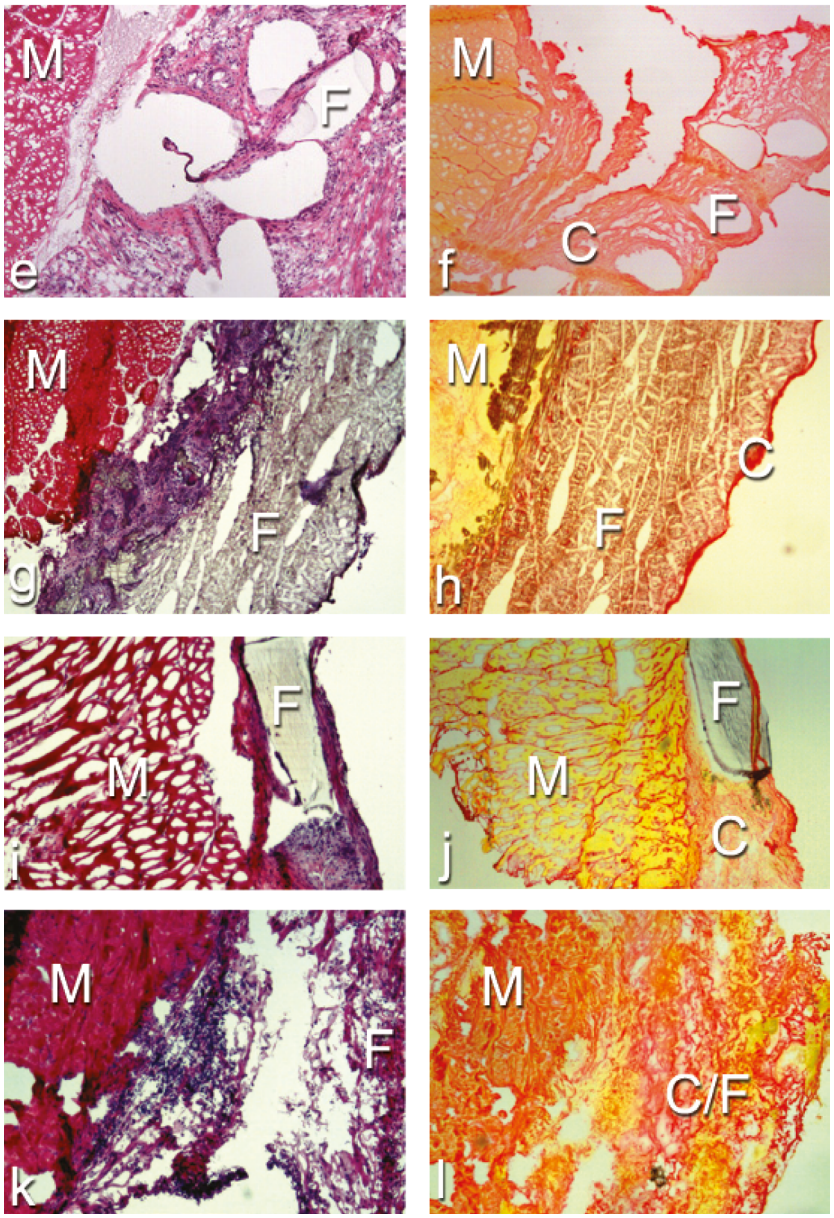
Histology

Fibrosis was observed in all mesh-surrounding tissues. This was especially pronounced for the four polypropylene based meshes and Omyramesh® (Figure 4). Dualmesh® showed a clear encapsulation of the mesh, almost

without cellular infiltration into it. A large number of vessels could be seen in the tissue surrounding Parietene Composite® and Omyramesh®. Because of wide intra-animal variation, no statistically difference was found for fibrosis, influx of lymphocytes, angiogenesis and collagen deposition (data not shown).

Figure 4. Histological samples after 90 days: **a,c,e,g,i** haematoxylin and eosin staining and **b,d,f,h,j** picrosirius red staining of histological samples after 90 days (original magnification ×40). **a,b** Polypropylene (Parietene®; Sofradim, Trevoux, France; part of Covidien, North Haven, Connecticut, USA); **c,d** collagen–polyethyleneglycol–glycerol-coated polypropylene (Parietene Composite®; Sofradim); **e,f** carboxymethylcellulose–sodium hyaluronate-coated polypropylene (Sepramesh®; Bard, New Providence, New Jersey, USA); **g,h** expanded polytetrafluoroethylene (Dualmesh®; Gore, Flagstaff, Arizona, USA); **i,j** condensed polytetrafluoroethylene (Omyramesh®; B. Braun, Melsungen, Germany); and **k,l** non-cross-linked collagen mesh (Strattice®; LifeCell, Branchburg, New Jersey, USA). The purple and pink cells in the haematoxylin and eosin-stained sections are fibroblasts and lymphocytes. The synthetic fibres of the Parietene® (**a,b**), Parietene Composite® (**c,d**), Sepramesh® (**e,f**) and Omyramesh® (**i,j**) are surrounded with fibrotic tissue with newly formed collagen. Around Dualmesh® (**g,h**) a cellular layer is observed, forming a capsule; cellular infiltration into the mesh is minimal. In the picrosirius red-stained section of the Strattice® mesh (**l**) it is impossible to differentiate between the collagen of the mesh and newly formed collagen (C/F). M, abdominal wall muscle; F, mesh fibres, C, newly formed collagen layer.

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Discussion

In this experimental contaminated environment, the collagen-coated polypropylene mesh Parietene Composite® and the condensed PTFE Omyramesh® had a low risk of infection, moderate adhesion formation and good incorporation. The biological Strattice® mesh did not become infected and showed remarkably little adhesion formation, but poor incorporation.

If a mesh is used in a contaminated environment, consensus exists that a biological collagen mesh or a synthetic macroporous, monofilament mesh may be advantageous(5, 16-18). Biological collagen meshes have been developed specifically for a contaminated environment and Strattice® did not show any mesh infection in this experiment. Biological meshes, particularly Strattice®, have shown improved clearance of bacteria, which decreases the possibility of infection and formation of adhesions(19). A prospective multicentre study of contaminated ventral hernia repair with Strattice® reported a similar low infection rate with little need to remove the mesh(20).

The macroporous Parietene®, Parietene Composite®, Sepramesh® and Omyramesh® had a low risk of infection. Large pores allow admission of macrophages, fibroplasia and angiogenesis, which improves the ability to clear infection(5, 6). In this study, however, the macroporous C-Qur® mesh showed a high infection rate. This polypropylene mesh is coated with anti-inflammatory omega-3 fatty acids. In an experimental clean environment macrophages were scarcely present in the mesh after implantation(11, 21). It might be hypothesized that the anti-inflammatory properties of the omega-3 fatty acid coating have prevented macrophage penetration, although no clinical or experimental literature on the characteristics of omega-3 fatty acids in the presence of bacteria has yet been published.

Dualmesh® showed a high infection rate, probably because of its partially microporous structure (smaller than 10 µm). The increased risk of infection after surgery with Dualmesh®, and the need to remove the prosthesis in case of infection, is notorious in the clinical situation(22-24). Mesh infection is caused by infiltration and proliferation of bacteria within the pores and interstices of synthetic materials. Small pores prevent infiltration of immune cells and make microporous meshes more susceptible to infection(5, 25).Additionally, the hydrophobic visceral surface of Dualmesh® decreases adhesion of tissue cells, allowing bacteria a free passage to the implant surface(16).

Intra-abdominal adhesion and abscess formation are important causes of morbidity and mortality following contaminated abdominal surgery. During peritonitis fibrin is deposited in the abdominal cavity, inducing adhesion formation and providing possible niduses for abscess formation(9). Biological Strattice® mesh showed low adhesion formation after 90 days, confirming previous experimental results(26-28). Sepramesh® showed a significant increase in adhesion formation between 28 and 90 days, implying that the cellulose–hyaluronate coating is absorbed before a neoperitoneal layer is formed. These results confirm that adhesion formation in the presence of mesh is not complete after 7 days(8, 11). The surface of Parietene Composite® and Omyramesh® were least covered with adhesions after 90 days. Low adhesion formation on the collagen-coated Parietene Composite® has been described in a clean environment(8, 11). The present results suggest that the collagen coating remains present until a neoperitoneum has formed, even in a contaminated environment. The low adhesion formation on Omyramesh® confirms experimental findings with this relatively new mesh in a clean environment(29, 30). The low adhesion formation might be explained by its smooth, monolayer, non-fibrous, macroporous structure. The plain polypropylene Parietene® mesh was largely covered with adhesions. Clinically, uncoated polypropylene meshes are known to induce severe adhesion formation with attachment of intestine to the mesh when implanted intraperitoneally(7, 31). In 21 % of patients with an intraperitoneal uncoated polypropylene mesh, adhesions made bowel resection necessary during re-exploration in one study(7).

The non-infected, partially microporous, expanded PTFE Dualmesh® had an alarmingly high shrinkage rate (median 63 % after 90 days). Such shrinkage has frequently been reported experimentally, but this does not seem to be correlated with a higher recurrence rate clinically(8, 23, 32). A fibrous capsule surrounding the mesh was observed, almost without cellular infiltration into the mesh. Contraction of this capsule was probably the cause of shrinkage, which might have been more pronounced in the small meshes used in the present experiment compared with the much larger meshes used clinically. Of the macroporous meshes, the plain polypropylene Parietene® showed the most shrinkage (15 % after 90 days), confirming experimental results(32, 33).

The biological Strattice® mesh had a 23 % loss of surface after 90 days, probably caused by collagenase activity. Premature weakening of the biomechanical properties of the scaffold combined with insufficient

incorporation can possibly result in loss of the prosthesis and hernia recurrence(34). Until evidence of biomechanical strength after hernia repair with biological meshes has been provided, synthetic meshes are preferred for primary repair.

Translation of experimental results to the clinical situation should be done with caution. However, the CLP model is suitable for studying the behaviour of synthetic and biological meshes experimentally in a contaminated environment. In this model, as in clinical infections, peritonitis arises from a complex interaction of the immune system with inflammatory, haemodynamic and biochemical alterations similar to human sepsis, with a consistent increase in cytokine levels(35-38). Another advantage of this experimental model is the use of rats of the same age and sex, and specified pathogen-free bacterial status. This minimizes biological and microbiological variability, and makes it suitable for comparing characteristics of different meshes in a similar contaminated environment(38). A limitation of the model is the size of the mesh and mesh pores in relation to the abdominal wall, which is different between rats and humans. This might lead to an overestimation of shrinkage. The meshes in this experiment were fixated with six sutures. In humans the number of fixation points in relation to the mesh size would be much higher. This might have influenced incorporation, as described in previous experimental mesh studies(8, 11). Finally, the concentration of the antiadhesive coatings and its systemic effects during breakdown in this model might be different from the human situation.

The experimental results of synthetic mesh implantation in a contaminated environment make strict contraindication in humans questionable. Although there are no meshes without disadvantages, certain permanent synthetic meshes might be somewhat infection-resistant and therefore useful for permanent hernia repair in a contaminated environment.

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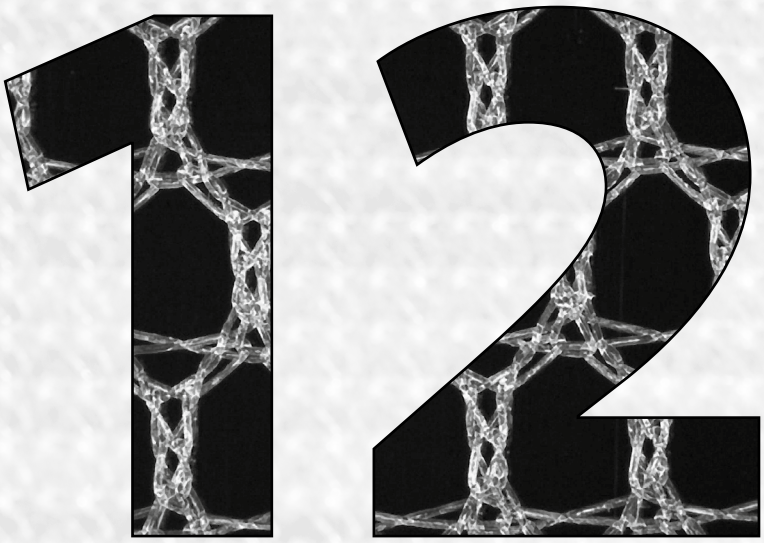
Chapter



Mesh-specific inflammatory cell response in a contaminated environment

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Submitted

Abstract

Background

The use of meshes for abdominal hernia surgery in a contaminated environment is compromised due to a high risk of complications. Little is known about differences in the foreign body reaction between materials in contaminated environments. Therefore we compared the presence of macrophages and their attractors after implantation of different meshes in a contaminated environment in vivo.

Methods

28 and 90 days after implantation, biopsies of the abdominal wall with implanted meshes (Parietene®, Parietene Composite®, C-Qur®, Sepramesh®, Dualmesh® and Omyramesh®) were harvested from a peritonitis rat model. Biopsies were analysed with immunohistochemistry for macrophage markers CD68, iNOS, and CD206, and for T-cells with CD3. Toluidine-staining was used for mast cells.

Results

More CD3- and CD68-positive cells were found in samples with meshes than in the control group without a mesh. After 90 days, Parietene Composite® and Sepramesh® were surrounded by more iNOS-positive cells than the control group. C-Qur® and Dualmesh® were surrounded by more CD206-positive cells than the control group at day 28. The M1/M2 ratio was low for all meshes.

Conclusions

Mesh-specific cellular responses are evident in a contaminated environment and therefore these data can help the surgeon to select suitable meshes for implantation.

Introduction

Meshes are occasionally used in a clean-contaminated or even in a contaminated environment, like fascial defects after bowel resection, near stomas or after removal of an infected mesh. Generally spoken, in clinical application the risk of complications like infection of the mesh is higher in a contaminated field and therefore surgeons are hesitant to use meshes in these cases(1, 2). The extent of the inflammatory response of the body, also known as foreign body reaction, depends on the type and consistency of the mesh(3-5).

Using an in vitro model, we have recently described mesh-dependent reactions of macrophages in a contaminated environment(6). Many researchers investigate the foreign body reaction in a sterile environment. After implantation, all types of meshes used for abdominal wall hernia surgery induce a foreign body reaction. After implantation of the mesh, inflammatory cells, starting with neutrophils and mast cells are attracted to the wound site(3). Mast cells attract macrophages to the wound site and the number and degranulation of mast cells is important for the extend of the foreign body reaction. After implantation of the mesh, inflammatory cells, starting with neutrophils and mast cells are attracted to the wound site(3). Mast cells attract macrophages to the wound site and the number and degranulation of mast cells is important for the extend of the foreign body reaction(3, 4, 7, 8). Besides mast cells, T-cells are also important attractors of macrophages(3, 4, 9).

After being recruited, macrophages will dominate the wound site(3, 5). Macrophage phenotypes can range between pro-inflammatory (M1) and repair/anti-inflammatory (M2). M1-macrophages produce pro-inflammatory factors such as interleukin (IL)-6, tumor necrosis factor (TNF)α and express inducible nitric oxide synthase (iNOS)(10). M2-macrophages produce anti-inflammatory factors such as IL-1 receptor antagonist (IL-1RA), chemokines such as CCL18, and growth factors such as vascular endothelial growth factor (VEGF). M2-macrophages express among others the surface protein CD206, which is the mannose receptor important for recognition of pathogens(10).

How the foreign body reaction in a contaminated environment will depend on the type of material is not yet completely understood. In a contaminated environment, macrophages are expected to change mainly into the M1-phenotype because the infection and presence of bacteria needs to be eliminated(11). M1-macrophages negatively influence incorporation of the

mesh, by producing matrix degrading enzymes and inhibitors of extracellular matrix(5). Van Putten et al.(12) found that the foreign body reaction against collagen discs is delayed in the presence of bacterial cell wall components. Whether the presence of bacterial components also delays the foreign body reaction against synthetic meshes is not known.

Using an in vitro model, we have confirmed mesh-dependent reactions of macrophages in a contaminated environment(6). Previously we studied the in vivo behavior of seven commercially available meshes (1 biological and 6 synthetic meshes) in a contaminated environment in rats and found differences in mesh infection, adhesions and incorporation of the biomaterial(13). In this experiment polypropylene was used, a mesh often used in patients and also polypropylene based meshes with a hydrophilic collagen-coating, omega 3-fatty acid-coating, and a hyaluronate-carboxymethylcellulose coating, which are described to have a lower complication rate in a clean environment(14). Expanded (microporous) and condensed (macroporous) expanded polytetrafluoroethylene (PTFE) meshes were also included. Expanded PTFE has a high infection risk due to the small micropores whereas condensed PTFE is believed to have a good outcome in a contaminated environment due to its macroporous structure(15, 16).

In this study, the cellular immune responses to different synthetic meshes in a contaminated environment in vivo are compared in more detail. As macrophages are the key players in the foreign body reaction, the presence of T-cells and mast cells as macrophage attractors and the phenotypes of macrophages with immunohistochemistry are investigated. This knowledge can help the surgeon to choose the best materials to use in an environment with high risk of contamination.

Materials and methods

Contaminated model in vivo

The rat experiment protocol is according to the Animal Research: Reporting In Vivo (ARRIVE) guidelines and was approved by the Ethical Committee on Animal Experimentation of Erasmus University Rotterdam, the Netherlands (EMC 2075-105-10-03). We used samples of an earlier presented study in which in 144 (8 groups, 9 rats per group, two time points) male Wistar rats

(Harlan Laboratories, Boxmeer, the Netherlands) weighing 250-350 grams a contaminated environment was created by caecum ligation and puncture(13). Briefly, the caecum was ligated just distally to the ileocaecal valve maintaining the continuity of the bowel and punctured distally to the ligation with an 18-G needle leading to leakage of fecal fluids with bacteria into the abdominal cavity to induce peritonitis. After 24 hours the abdomen was re-opened and peritonitis was confirmed by microbiological culture, resulting in a contaminated wound. One of the following meshes (2.5 x 3 cm) was implanted intraperitoneally with 6 transmuscular non-absorbable sutures (5/0 Ethilon, Johnson & Johnson: New Brunswick, New Jersey, United States):

1. Parietene® (polypropylene (PP), Covidien- Sofradim Production, Trevoux, France)
2. Parietene Composite® (PP with an onesided absorbable, hydrophilic collagen-coating, Covidien- Sofradim Production, Trevoux, France)
3. C-Qur® (PP with omega 3-fatty acid-coating and triglycerides, Atrium, Hudson, New York, USA)
4. Sepramesh® (PP, with a hyaluronate-carboxymethylcellulose coating, Bard, New Providence New Jersey, USA)
5. Dualmesh® (expanded polytetrafluoroethylene (PTFE), Gore, Flagstaff, Arizona, USA)
6. Omyramesh® (condensed PTFE, B Braun, Melsungen, Germany)
7. Strattice® (collagen derived from porcine skin, LifeCell, Branchburg, New Jersey, USA)

A control group was included following completely the same protocol, only no mesh was implanted after re-opening the abdomen. After implantation, all rats received one dose of gentamicin (6 mg/kg) intramuscularly. Two to four rats per group died from sepsis(13).

Harvesting

At 28 days and 90 days after implantation of the materials, the animals were euthanized by cardiac cut and a swab was taken to culture bacteria; C-Qur® resulted in 95% (15 out of 16) of the samples positive for bacteria, Dualmesh® 50% (7 out of 15) and Parietene® and Parietene Composite® both 5% (1 out of 15), in the other groups no infections were found. One biopsy per animal was taken from the incorporated mesh with surrounding tissue. In the rats without

a biomaterial a biopsy of the abdominal wall was taken at the same place where in the other rats the mesh was implanted. In some animals, incorporation of the material was insufficient and because there was no adjacent tissue, no biopsy could be taken. For Strattice® at both time points, Sepramesh® at day 28 and C-Qur® and Omyramesh® at day 90 only 1 or 2 samples could be taken because of insufficient incorporation and therefore these conditions were excluded for analysis. Biopsies were snap-frozen in Tissue-Tekc (Sakura, Alphen, Rijn, The Netherlands) with liquid nitrogen and stored at -80oC till sectioning. Sections of 6 µm were cut on a cryostat (Leica; Davis Instruments, Vernon Hills, Illinois, USA) and stored at -80oC.

Staining

Immunohistochemistry

Frozen sections were defrosted and fixed in acetone. After fixation sections were washed in PBS and incubated with 10% normal goat serum (Sigma-Aldrich, St Louis, MO, USA) to block non-specific binding. After incubation sections were washed with phosphate buffered saline and incubated with primary antibodies against CD206 (2.5 µg/mL, Abcam, 64693, Cambridge, UK), iNOS (2 µg/mL, Abcam, 15323), CD3 (1:100, Abcam, 16669), CD68 (5 ug/ml, Acris Antibodies GmbH, BM 4000, Herford, Germany). We choose the antibiodies based on literature(4, 10, 17). Irrelevant IgG was used as a negative control. Link biotinylated goat-anti-mouse (Biogenex, HK-325-UM, Fremont, CA, USA) was used at a second antibody, Label streptavidin-AP (Biogenex, HK-321-UK) as a tertiary antibody with neufuchsin as substrate. Sections were counterstained with hematoxylin (Sigma). Lung and spleen tissue were used as a positive controls. Sections were mounted with vectamount (Vector Laboratories, Burlingame, CA).

Toluidine blue (mast cells)

Sections were defrosted and fixated in acetone. After washing in demineralised water the sections were placed in a toluidine blue solution (1% Toluidin blue (Fluka (Sigma), 89640) in 50% isopropanol and 50% demineralised water) for 30 minutes at 37°C. Sections were washed for 1 minute in pure isopropanol. Sections were air-dried and mounted with vectamount (Vector Laboratories).

Analyses

Stained sections were analysed by light microscopy (Olympus, Tokyo, Japan). Per staining, sections were blinded and the number of cells in 5 areas at the interface of the mesh and tissue was ranked. In the case of the control group, cells were counted subcutaneously, at the place where in the other groups the mesh was implanted. Samples were ranked based on the number of positive cells, ranks were ranging from 1 to 58 (due to a total of 58 analysed samples). Control group day 28: 8 samples, day 90: 7 samples. Parietene® 8 and 5 samples respectively, Parietene Composite® 5 and 4 samples, C-Qur® day 28: 5 samples, Sepramesh® day 90: 4 samples, Dualmesh® day 28: 3 samples, day 90: 4 samples, Omyramesh® day 28: 5 samples. Ranking was performed by two independent observers (NG and NK). The ranking of one observer was compared with the ranking of the other observer. If there was a difference in ranking per sample of more than 15, the samples were analysed again. After that, the mean ranking per sample was calculated from the ranking of one observer and the other observer. Then the samples were unblinded and were used for further analysis. The number of iNOS-positive cells was divided by the number of CD206-positive cells leading to an M1/M2 ratio. The natural logarithm of this ratio was calculated for visualisation. Data is presented as box plots with medians and whiskers showing the interquartile range.

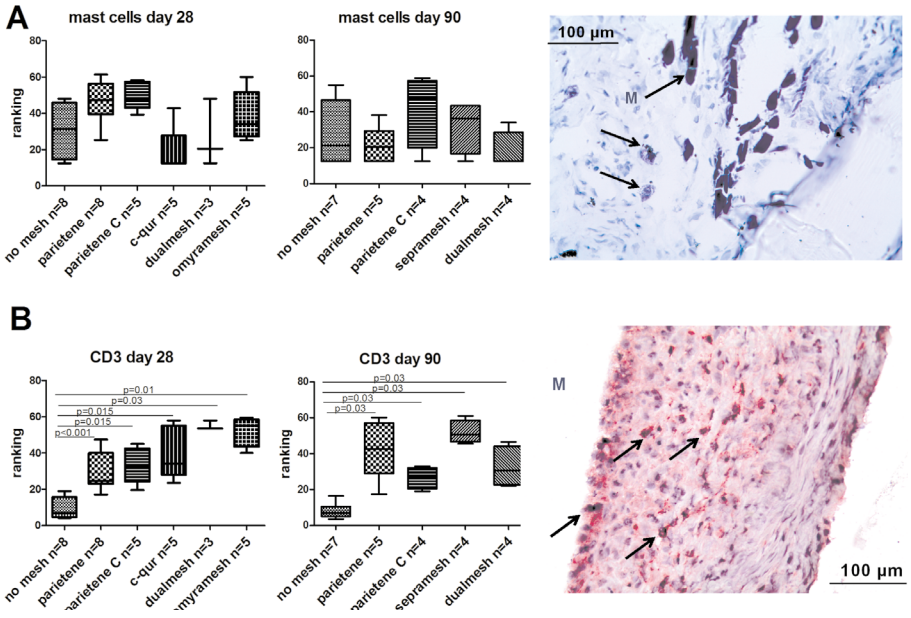
Statistics

The medians of the groups were compared with a Kruskal-Wallis test (independent samples median test) and Mann-Whitney in SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) False Discovery Rate was used for mathematical correction by multiple comparisons. $p<0.05$ was considered statistically significant.

Results

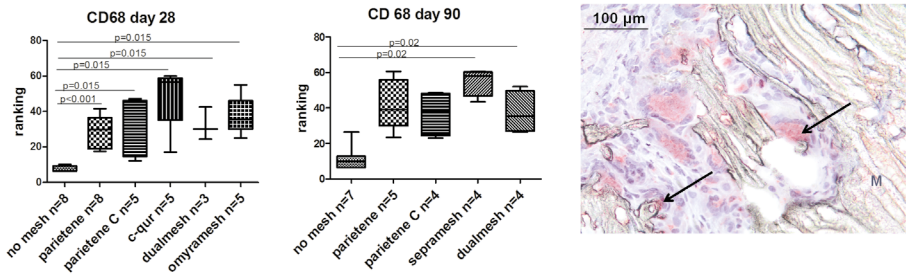
The number of mast cells and T-cells were analysed in the tissue adjacent to the meshes, since these two cells are the main attractors of macrophages. We found no significant differences in the numbers of mast cells between the biomaterials or compared to the control group (Figure 1a).

Figure 1. A) Analysis of the presence of mast cells at day 28 and day 90 after implantation of a mesh. Graphs show the mean rank per type of mesh, numbers behind the groups indicate sample size. An example of the toluidine staining is shown in which positive cells are indicated by arrows. M indicates mesh. **B)** Analysis of the presence of T-cells with antibodies against CD3 after 28 and 90 days. An example of the CD3 staining is shown in which positive cells are indicated by arrows. M indicates mesh. Graphs show the mean rank per type of mesh, p-values are indicated in the graphs, numbers behind the groups indicate sample size.



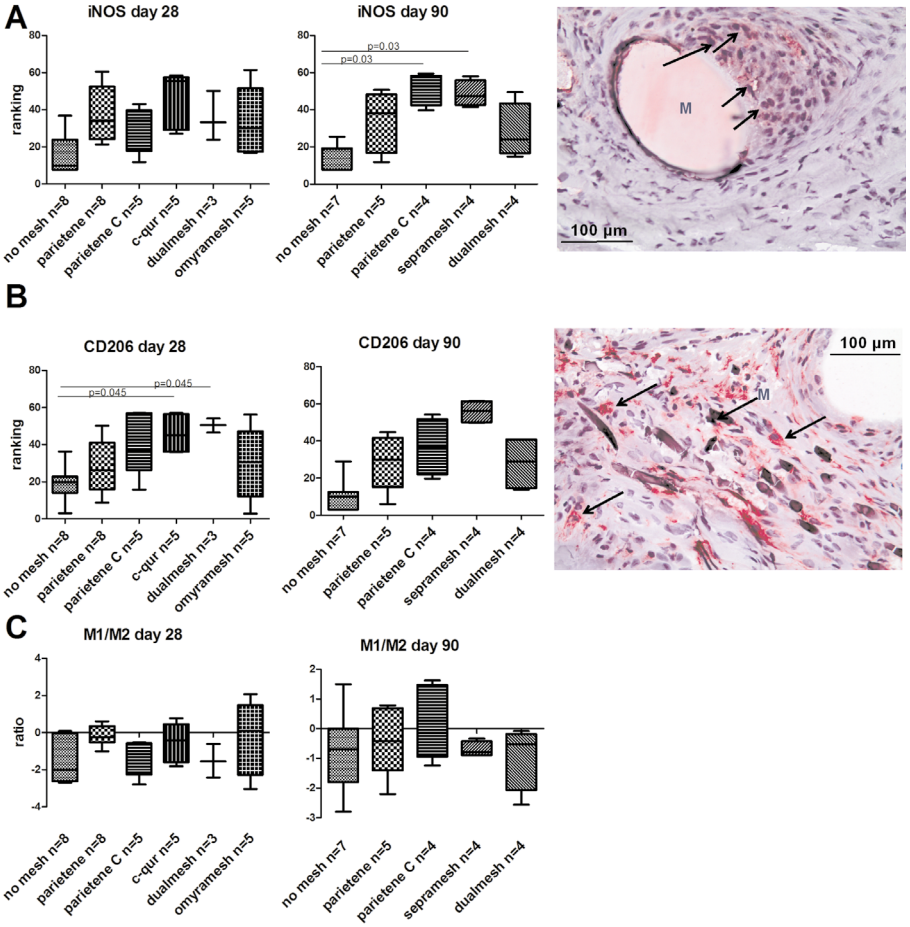
All meshes had more CD3-positive T-cells at day 28 than the control group (p= or < 0.03). There were also mesh-dependent differences: Parietene® was surrounded by less CD3- positive cells than Dualmesh® (p=0.03) and Parietene Composite® was surrounded by less CD3-positive cells than Omyramesh® (p=0.03). After 90 days still all samples with meshes contained more CD3-positive cells than the control group (p=0.03) (Figure1b). To investigate the total number of attracted macrophages, samples were stained for CD68 as a general macrophage marker. After 28 days more macrophages were found adjacent in the groups with a mesh than in the control group (p= or < 0.015). The same finding was still observed after 90 days, but this was only statistically significant for Sepramesh® (p=0.02) and Dualmesh® (p=0.02) (Figure 2).

Figure 2. Analysis and ranking for the presence of CD68-positive macrophages 28 and 90 days after implantation of a mesh. An example of CD68-positive cells is shown in which positive cells are indicated by arrows. M indicates mesh. Graphs show the mean rank per type of mesh, p-values are indicated in the graphs, numbers behind the groups indicate sample size.



To investigate how the different meshes influence the macrophage phenotype, we stained the samples with antibodies against iNOS for M1-macrophages and with antibodies against CD206 for M2-macrophages. At day 28 we did not find significant differences between the conditions, however after 90 days, Parietene Composite® and Sepramesh® were surrounded by significantly more iNOS-positive cells than the control group (p=0.03). There were no statistically significant differences between the meshes (Figure 3a). After 28 days we found more CD206-positive cells surrounding C-Qur® and Dualmesh® than in the control group (p=0.045). After 90 days, no significant differences were observed (Figure 3b). To determine for each mesh whether it induces a more pro- or antiinflammatory reaction the M1/M2 ratio was calculated based on iNOS positive and CD206-positive cells (Fig.3c). All meshes except Parietene Composite® after 90 days, had a negative mean ratio, indicative for a predominant M2, or anti-inflammatory, reaction. However no statistically significant differences in M1/M2 ratios were observed between the meshes.

Figure 3. A) Analysis and ranking for the presence of iNOS-positive M1 macrophages 28 and 90 days after implantation of a mesh. An example of iNOS-positive cells is shown in which positive cells are indicated by arrows. M indicates mesh. Graphs show the mean rank per type of mesh, p-values are indicated in the graphs, numbers behind the groups indicate sample size. **B)** Analysis and ranking for the presence of CD206-positive macrophages 28 and 90 days after implantation of a mesh. An example of CD206-positive cells is shown in which positive cells are indicated by arrows. M indicates mesh. Graphs show the mean rank per type of mesh, p-values are indicated in the graphs, numbers behind the groups indicate sample size. **C)** The M1/M2 ratio based on the number of iNOS- positive cells divided by the CD206-positive cells, the natural logarithm of this ratio was calculated for visualisation. p-values are indicated in the graph, numbers behind the groups indicate sample size.



Discussion

Surgeons often hesitate to use biomaterials in a contaminated environment, like fascial defects after bowel resection, near stomas or after removal of an infected mesh. Nowadays, most used biomaterials in this environment are biologic materials, which are very expensive compared to synthetic biomaterials. However, a critical review describes that there is not enough evidence to state that biologic biomaterials perform better than synthetic biomaterials(1). Therefore a close look to synthetic biomaterials in a contaminated environment is needed. Little is known about the mesh-specific phenotypes and presence of macrophages after implantation of a mesh in a contaminated environment.

In this study, different meshes were implanted in a rat model in a contaminated environment. The attractors of macrophages, namely T-cells and mast cells, and the different phenotypes of macrophages were analyzed. In these experiments mesh-specific cellular responses were seen. All meshes induced the influx of T-cells and macrophages, still present after 90 days compared with the control group without a mesh. High levels of T-cells and macrophages indicate a chronic inflammatory reaction when meshes were implanted in a contaminated environment(3, 4). Both PTFE-meshes were surrounded by the most T-cells whereas the polypropylene biomaterials Parietene® and Parietene Composite® had the lowest number of T-cells. The latter is indicative for resolution of the inflammatory reaction, possibly leading to a fibrotic reaction for Parietene® which is often seen in vivo. This macroscopically represents in a firm incorporation and shrinking of this mesh suggesting fibrosis(3, 13, 18, 19). Parietene Composite® performed well macroscopically with a low amount of adhesions and a low percentage of infection in a contaminated environment(13), most likely due to the collagen layer which is known to reduce adhesions(14).

We found high numbers of CD206-positive and iNOS-positive macrophages around C-Qur®-and Dualmesh®-samples after 28 days, indicative for a chronic inflammation reaction. Indeed macroscopically these meshes had the highest infection rate and a bad incorporation in the abdominal wall(13). This might be explained by the presence of endotoxins released by bacteria during the infection, which are known to delay the foreign body reaction(12). Dualmesh® is a partially microporous mesh with a higher risk of infection than PP and polyethylene(15, 20). This can be explained by the small pore size

allowing bacteria to infiltrate when macrophages cannot(21). Also small pores induce a M1 pro-inflammatory reaction, known to induce tissue turnover and thereby negatively influencing incorporation of meshes in the abdominal wall(5, 22). This was macroscopically confirmed(13). Higher numbers of M2 macrophages are associated with a better outcome in wound healing than with a predominant M1-reaction(17, 23). We found high levels of CD206(M2)-positive cells around Parietene Composite® and Sepramesh® which are meshes known for a good biocompatibility in vivo with low adhesion formation(14). C-Qur® is coated with triglycerides and Omega 3-fatty acids.

Cardiovascular research showed that triglycerides can enhance an inflammatory response in endothelial cells. Whether this is also the case in the foreign body reaction is not investigated, however this can be a possible explanation for the found chronic inflammation reaction(24). We expected more distinguished differences between the meshes regarding the M1/M2 ratio, however macrophages are a heterogeneous population of cells, M1 and M2 being two extremes in the spectrum(25, 26). Subtle differences in this ratio might have been missed. Due to poor incorporation of some of the meshes we did not have equal group sizes leading to a lower probability of finding significant differences. Sepramesh® at day 28, C-Qur® and Omyramesh® at day 90, and Strattice® at both time points had a very low sample size due to no ingrowth in the surrounding tissues which made it impossible to draw conclusions. Therefore these meshes for these time points were not included in our analysis. No differences were found for mast cells. This is likely due to the time point of analysis for we did our first analysis 28 days after implantation. The amount and presence of mast cells is indicative for an acute inflammatory reaction(7, 27) and therefore differences could not be detected in these experiments. Future studies with increased sample numbers and time points are needed to obtain more insight in the precise foreign body reaction and thereby the different performances of meshes in a contaminated environment.

For surgery in an environment at risk of contamination, the choice of a specific mesh is important. More insight in mesh-dependent cellular immune responses can help surgeons choose between the various commercially available meshes for implantation in a contaminated environment.

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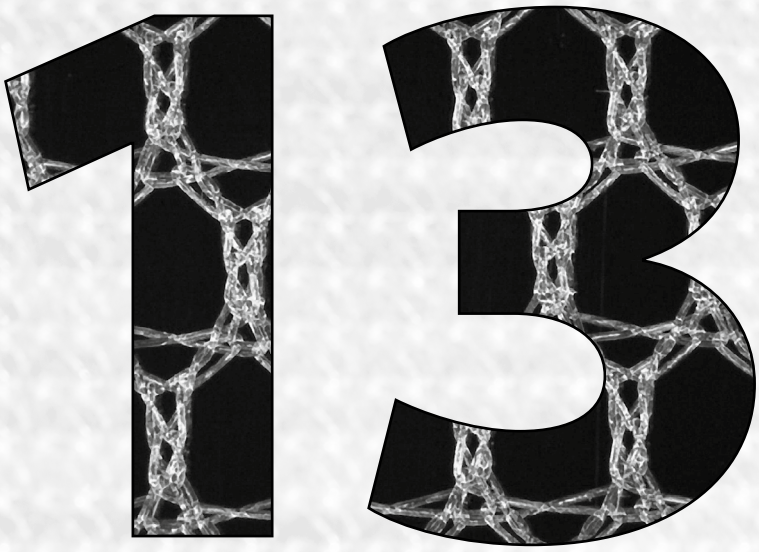
Chapter



Mesh-specific inflammatory cell response in a contaminated environment

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Submitted

Abstract

Background

Macrophages play an important role in the reaction to biomaterials, which sometimes have to be used in a surgical field at risk of contamination. The macrophage phenotype in reaction to
biomaterials in an inflammatory environment was evaluated in both an *in vivo* and *in vitro* setting.

Methods

In the *in vivo* setting, polypropylene (PP) biomaterial was implanted for 28 days in the contaminated abdominal wall of rats, and upon removal analysed by routine histology as well as immunohistochemistry for CD68 (marker for macrophages), inducible nitric oxide synthase (iNOS – a marker for proinflammatory M1 macrophages) and CD206 (marker for anti-inflammatory M2 macrophages). For the *in vitro* model, human peripheral blood monocytes were cultured for 3 days on biomaterials made from PP, collagen (COL), polyethylene terephthalate (PET) and PET coated with collagen (PET+COL). These experiments were performed both with and without lipopolysaccharide and interferon γ stimulation. Secretion of both M1- and M2-related proteins was measured, and a relative M1/M2 index was calculated.

Results

In vivo, iNOS- and CD206-positive cells were found around the fibers of the implanted PP biomaterial. *In vitro*, macrophages on both PP and COL biomaterial had a relatively low M1/M2 index. Macrophages on the PET biomaterial had a high M1/M2 index, with the highest increase ofM1 cytokines in an inflammatory environment. Macrophages on the PET+COL biomaterial also had a high M1/M2 index.

Conclusion

Macrophages in an inflammatory environment *in vitro* still react in a biomaterial-dependent manner. This model can help to select biomaterials that are tolerated best in a surgical environment at risk of contamination.

Introduction

Biomaterials are used widely in reparative and regenerative medicine. However, in an environment at risk of contamination, surgeons are reluctant to use biomaterials owing to a higher risk of complications. A feared postoperative complication of biomaterial implantation is infection of the biomaterial and surrounding tissue by bacteria, reported in up to 16 per cent of patients[1]. The risk of infection is even higher in some circumstances, such as in surgery of the gastrointestinal tract or nasal cavity, as well as in the presence of peritonitis. The risk of infection also depends on the type of biomaterial, such as its configuration, hydrophobicity and whether it is made from monofilament or multifilament[1-3]. All biomaterials elicit a foreign body reaction, and the degree of this reaction varies depending on the nature of the biomaterials. At present, the foreign body reaction in an environment with a high risk of contamination is not well characterized.

Macrophages play a pivotal role in the foreign body reaction[1, 4, 5]. The phenotype of the macrophages can change in response to environmental factors, giving rise to different populations of macrophages with distinct functions, which can force the foreign body reaction into tolerance of the biomaterial or into a state of inflammation. Classically activated macrophages, or M1 macrophages, have been characterized and desribed most thoroughly. They propagate proinflammatory responses by producing cytokines such as interleukin (IL) 1b, tumour necrosis factor (TNF) a and IL-6[6-8]. Another macrophage phenotype is represented by the alternatively activated macrophages, referred to as M2 macrophages. These cells can arise when exposed to IL-4 or immune complexes. They express scavenger receptors and IL-1 receptor antagonist (IL-1RA). M2 macrophages also produce IL-10 and chemokines, such as CCL18 and macrophage-derived chemokine (MDC, or CCL22)[6-8], and are able to produce growth factors, thus promoting angiogenesis and tissue repair(6). During wound healing, M1 macrophages are normally present from day 1, and accumulate and dominate the wound site after 2–3 days. After cleaning the wound site by phagocytosis, macrophages change towards an M2 phenotype. Persistent inflammation can cause an imbalance of M1 to M2 macrophages and lead to fibrosis. Synthetic biomaterials can induce the formation of fibrous wound healing tissue within 2–4 weeks. Macrophages

cannot phagocytose this synthetic biomaterial, leading to the formation of giant cells situated at the biomaterial surface[10].

In a contaminated environment macrophages adapt to an M1 phenotype[(9)], needed for control of the acute infection by phagocytosis. However, prolonged M1 phenotype of macrophages can lead to tissue damage, and may compromise the integration of the material in the body by the release of inflammatory cytokines(10). Therefore, the foreign body reaction is altered in a contaminated environment.

New biomaterials should be developed for use in an environment where the risk of contamination of the biomaterial is high. Biological materials, such as collagen-based biomaterials processed from human or porcine dermis, are thought to be tolerated in an environment at high risk of contamination and have a low postoperative complication rate[(11, 12)]. Biomaterials with low actual surface area, such as monofilament biomaterials, were well tolerated in a contaminated field in an experimental study[2], and in several clinical studies have been associated with fewer postoperative infections(13, 14). However, there is no consensus yet, and only a few comparative studies[13,14] are available. In a recent study[15] employing an experimental rat model, the foreign body reaction in rats was biomaterial-dependent in a contaminated environment. Some biomaterials had poor incorporation into the abdominal wall with a high infection rate, whereas others, such as monofilament polypropylene biomaterials, had good incorporation into the abdominal wall and a low inflammatory reaction[(15)].

The aim of this study was to investigate the reaction of macrophages to biomaterials in an environment at risk of contamination. First, the phenotype of macrophages surrounding a monofilament polypropylene biomaterial was analysed *in vivo*, as this material has been shown previously to induce the mildest foreign body reaction[(15)]. Second, the macrophage phenotype and reaction were characterized in more detail in an *in vitro* model. In this model bacterial contamination was simulated, thereby permitting comparison of the macrophage reaction in a contaminated and a clean environment. Contamination was simulated using a combination of lipopolysaccharide (LPS) and interferon (IFN) γ, and the macrophage reaction was studied by measuring a panel of proteins indicative of the macrophage phenotype.

Methods

Rat peritonitis model and tissue collection

The protocol of the rat experiment was approved by the Ethical Committee on Animal Experimentation of Erasmus University Rotterdam, The Netherlands, and is in accordance with the Animal Research: Reporting *In Vivo* Experiments (ARRIVE) guidelines. A contaminated environment was created by the caecal ligature puncture model, in which the caecum is punctured to provide leakage of faecal fluid into the abdominal cavity, thus causing peritonitis. After 24 h the abdominal cavity was re-opened, peritonitis was confirmed by microbiological culture, and a monofilament polypropylene (PP) biomaterial (Parietene™; Covidien – Sofradim Production, Trévoux, France) was placed intraperitoneally in four rats(15). Some 28 days after implantation, a sample of the abdominal wall with the incorporated biomaterial was harvested using biopsy punches (5 mm diameter). As controls, abdominal walls from rats with peritonitis, but with no biomaterial, were collected. All tissue samples were fixed in 4 per cent formalin and embedded in paraffin.

Histology and immunohistochemistry

Tissue sections were cut and stained with haematoxylin and eosin in accordance with standard procedures. To identify macrophage types, immunohistochemical staining with the following antibodies were used; CD68, a general macrophage marker; CD206, a marker for M2 macrophages[8], and inducible nitric oxide synthase (iNOS) as a marker for M1 macrophages(10). Briefly, paraffin sections were dewaxed and, to block the sections for aspecific binding, the sections were pretreated with heat-mediated antigen retrieval solution (Target Retrieval Solution; Dako, Glostrup, Denmark) at 90°C for 20 min. Sections were incubated with CD68 (1 : 100; Acris, Herford, Germany), CD206 (1 : 100) or iNOS (1 : 50) (both Abcam, Cambridge, UK) for 60 min, and subsequently incubated with link and label (Concentrated MultiLink® and Concentrated HRP Label (peroxidase-conjugated streptavidin); BioGenex, Fremont, California, USA); 3,3′-diaminobenzidine was used as substrate. Sections were dried overnight and mounted with VectaMount™ (Vector Laboratories, Burlingame, California, USA). Matching irrelevant isotype antibodies were used as negative controls, and tissues known to contain the specific markers were employed as positive controls. Sections were also Gram-stained to visualize potential bacteria. All

slides were analysed with an Olympus BX50 light microscope (Olympus, Tokyo, Japan).

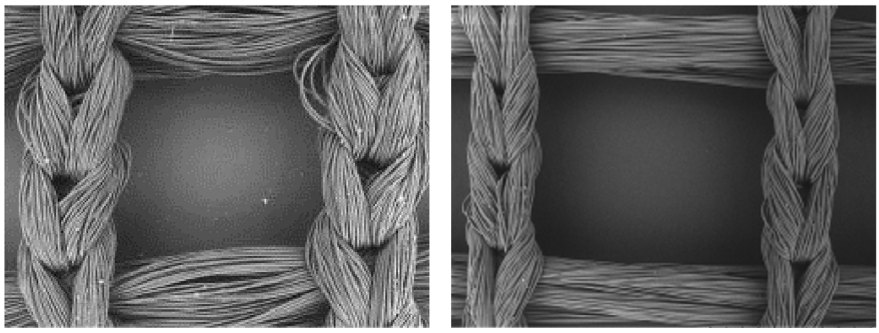
Monocyte isolation

Ficoll density gradient (Ficoll-Paque™ PLUS; GE Healthcare, St Giles, UK) was used to isolate monocytes from the buffy coat of four healthy donors (men and women aged 25–65 years). All buffy coats were obtained from the blood bank (Sanquin, Rotterdam, The Netherlands). Some 30 ml of 1 : 5 diluted buffy coat with 0.1 per cent bovine serum albumin (BSA) in phosphate-buffered saline (PBS) was layered on 15 ml Ficoll. After 15 min centrifugation at 1000*g* with no brake, the interphase band containing peripheral blood mononuclear cells was aspirated and washed in PBS/BSA 0.5 per cent 2 mmol/l EDTA and labelled with 100 µl anti-$CD14^+$ magnetic beads (CD14 microbeads human, MACS Separation columns LS and MidiMACS™ Separator; all from Miltenyi Biotec, Bergisch Gladbach, Germany), and isolated according to the manufacturer's guidelines. This positive selection of monocytes will not activate the cells[16]. Purity of the isolation was assessed by fluorescence-activated cell sorting (FACS) analysis, in which 1×10^6 monocytes were incubated for 15 min at room temperature with the following antibodies: FITC-conjugated CD14 and peridinin chlorophyll protein complex (PerCP)-conjugated CD45 (all BD Biosciences, Franklin Lakes, New Jersey, USA). After incubation, cells were washed in PBS/BSA 0.1 per cent and FACS analysis was performed with CellQuest™ Pro on a FACSCalibur™ (both BD Biosciences); the purity of the freshly isolated $CD14^+$ monocytes was above 95 per cent (data not shown). In the case of donors 1, 2 and 4, the yield of monocytes was not sufficient to allow for testing of all four biomaterials in the experiments.

Culturing macrophages on biomaterials

Four different biomaterials were chosen to study macrophage response in relation to the biomaterial (all from Covidien – Sofradim Production): a multifilament PP biomaterial (Parietene™), hydrophobic with a contact angle of 95°; a collagen-based material (COL) (Permacol™), processed from porcine skin and cross-linked with hexamethylene di-isocyanate; a multifilament polyethylene terephthalate (PET) biomaterial, hydrophilic with a contact angle of 80.9°; and a multifilament PET biomaterial with an absorbable, continuous and hydrophilic collagen film on one of its sides (PET+COL) (Parietex™ Composite). The PET and PP biomaterials have a similar weave (Figure 1).

Figure 1. Detailed picture of wave pattern of polypropylene (A) and polyethylene terephthalate multifilaments (B)



The materials were cut into 1.5 × 1.5-cm pieces with a sterile scalpel. Before cell seeding, materials were incubated in 100 per cent non-heat-inactivated fetal calf serum (FCS) (Lonza, Verviers, Belgium) for 2 h to provide protein attachment. Freshly isolated monocytes were adjusted to a concentration of 0.7×10^6 cells/ml in a total volume of 25 ml in a 50-ml PP tube (Falcon™; Becton, Dickinson, Franklin Lakes, New Jersey, USA). Twelve samples were incubated per 25 ml for 2 h at 37°C. Subsequently, samples were placed in a 24-well non-adherent plate (NUNC™, non-treated multiplate; Thermo Scientific, Rochester, New York, USA) and cultured for 3 days in serum-free X-VIVO™ 15 medium with 20 per cent FCS (Lonza). To simulate an inflammatory environment caused by bacterial infection, macrophages on biomaterials were cultured with 10 ng/ml LPS (Sigma-Aldrich, St Louis, Missouri, USA) and 1 ng/ml recombinant human IFN-γ (PeproTech, Rocky Hill, New Jersey, USA), and compared with macrophages on the same materials without simulation. The medium was refreshed after 48 h of culturing, and after a further 24 h in culture the supernatant was harvested for protein analysis.

Analysis of the production of inflammatory and anti-inflammatory cytokines

Proteins were measured in 25 µl cell culture supernatant using a multiplex system (Millipore, Billerica, Massachusetts, USA)[17]. IL-1β, IL-6, TNF-α, monocyte chemotactic protein (MCP) 3 and macrophage inflammatory protein (MIP) 1α, IL-1RA, RANTES (regulated on activation, normal T cell expressed and secreted, or CCL5), and macrophage-derived chemokine (MDC, or CCL22) were measured according to manufacturer recommendations. The CCL18 DuoSet®

ELISA (R&D Systems, Minneapolis, Minnesota, USA) was used to analyse CCL18 in 100 µl cell culture supernatant according to the manufacturer's instructions. These nine proteins were selected based on previous experiments, where the read-out parameters were chosen after stimulation of macrophages towards either the M1 or M2 phenotype[16]. To correct for the numbers of macrophages on the different biomaterials, the cells were lysed in 0.1 per cent Triton in PBS (Sigma-Aldrich) and samples were frozen at −80°C before being analysed with CyQUANT® cell proliferation assay kit (Invitrogen, Carlsbad, California, USA). DNA content was measured according to the manufacturer's recommendation.

Statistical analysis

The *in vitro* experiments were performed in triplicate with four different monocyte donors. All data are presented as scatterdot plots, with each dot representing an individual sample. The mean of the four donors is indicated by a line in the graphs. When evaluating the effect of an inflammatory environment, the data are presented as the ratio of the LPS/IFN-γ-stimulated condition *versus* the non-stimulated condition for each biomaterial. To calculate the ratio between LPS/IFN-γ-stimulated samples and non-stimulated samples, the stimulated samples were divided by the mean of the non-stimulated samples per donor. To compare the effect of the four biomaterials on the macrophage phenotype in an inflammatory environment, a relative M1/M2 index for each material was determined by calculating for each cytokine the percentage of production relative to the mean production on the four materials. This was followed by taking the mean of the percentages of the M1 cytokines (MIP-1α, TNF-α, MCP-3, IL-1β, IL-6) divided by the mean percentages of the M2 cytokines (MDC, RANTES, IL-1RA and CCL18) per sample. Groups were compared in SPSS® for Windows® version 20.0 (IBM, Armonk, New York, USA) using the Kruskal–Wallis test (independent samples median test) and Mann–Whitney *U* test, because the data were not normally distributed. Correlation between proteins was analysed by Spearman correlation. The Bonferroni correction was used. Differences were considered statistically significant when $P < 0.050$.

Results

Macrophage phenotype in vivo

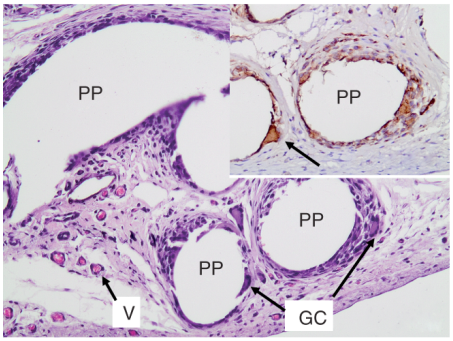
The PP biomaterial was well integrated in the surrounding tissues 28 days after implantation into the contaminated abdominal wall of rats. On histological examination, all samples displayed dense tissue surrounding the fibres of the biomaterial, with many multinucleated CD206-positive giant cells. iNOS and CD206-positive cells were also observed in this dense layer. In addition, many blood vessels were observed in the connective tissue surrounding the biomaterial (Figure 2).

To investigate the influence of a biomaterial, samples of abdominal wall tissue from control rats with contamination but without implanted biomaterial were also stained with haematoxylin and eosin, CD68, CD206 and iNOS at 28 days. These samples had no infiltration of lymphocytes and only a few macrophages, some of which were iNOS- or CD206-positive (Figure 2).

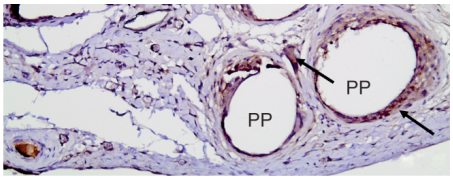
Biomaterial-dependent effect on macrophage phenotype in an in vitro model

LPS and IFN-γ were chosen to simulate bacterial infection in the *in vitro* model. LPS is a bacterial wall fragment and IFN-γ is known to activate the immune system and macrophages following bacterial infection[22]. To investigate how macrophages react on biomaterials in this simulated inflammatory environment *in vitro*, production of IL-1β, IL-6, TNF-α, MCP-3, MIP-1α, IL-1RA, RANTES, MDC and CCL18 was measured. The production of these proteins in an inflammatory environment was compared with that in a non-stimulated environment. Although the inflammatory environment increased the production of most proinflammatory proteins by macrophages, there were still differences in relation to the tested biomaterials (Figure 3). Macrophages on PET biomaterial induced the biggest increase in proinflammatory proteins. The stimulated *versus* non-stimulated ratio for anti-inflammatory proteins was approximately 1, indicating no increase in the production of these proteins in an inflammatory environment, except for RANTES, which was produced in greater amounts by macrophages on PET biomaterial in an inflammatory environment (Figure 4).

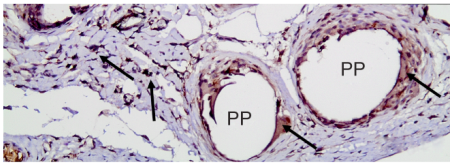
Figure 2. a,d Haematoxylin and eosin (CD68 shown in inset), **b,e** inducible nitric oxide synthase (iNOS) and **c,f** CD206 staining 28 days after implantation of polypropylene (PP) in a contaminated environment in the rat. CD68-, iNOS- and CD206-positive macrophages can be seen surrounding the PP fibres. **a–c** PP biomaterial from a contaminated abdominal wall. **d–f** Abdominal wall without biomaterial from the same model. Representative sections and samples are shown. Brown colour represents positive staining; arrows indicate positive cells. GC, giant cell; V, vessels. (Original magnification ×200).



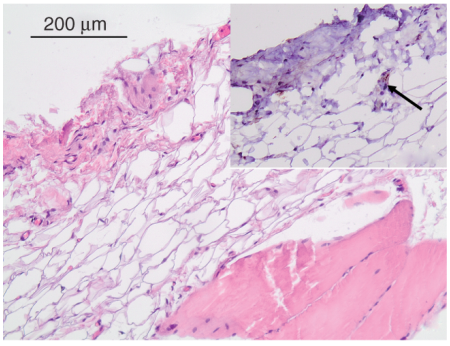
a Haematoxylin and eosin-stained, PP biomaterial



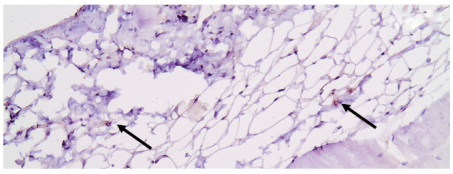
b iNOS-stained, PP biomaterial



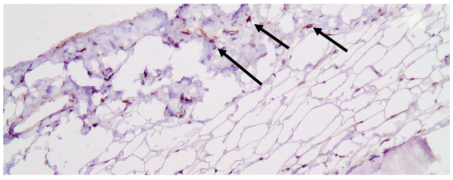
c CD206-stained, PP biomaterial



d Haematoxylin and eosin-stained, no biomaterial



e iNOS-stained, no biomaterial



f CD206-stained, no biomaterial

Figure 3. Production of proinflammatory cytokines by macrophages seeded on different biomaterials in an inflammatory (as induced by lipopolysaccharide/interferon γ) compared with a non-stimulated environment after 3 days of culture. **a** Tumour necrosis factor (TNF) α, **b** interleukin (IL) 1β, **c** monocyte chemotactic protein (MCP) 3; **d** IL-6, **e** macrophage inflammatory protein (MIP) 1α. The dotted line indicates the basal level of expression, where there is no difference between stimulated and non-stimulated environments, and the bars denote the mean value. Monocytes from a total of four donors were divided over the different biomaterials in triplicate samples. Cells from all donors could not be tested on every biomaterial owing to a low yield of monocytes. Protein production was corrected for DNA before comparison of stimulated and non-stimulated environments. PET+COL, polyethylene terephthalate with a collagen coating; COL, collagen; PET, polyethylene terephthalate; PP, polypropylene. **P* < 0·001, †*P* < 0·050 (Kruskal–Wallis and Mann–Whitney *U* tests), indicating a significant increase in proinflammatory cytokines compared with baseline values.

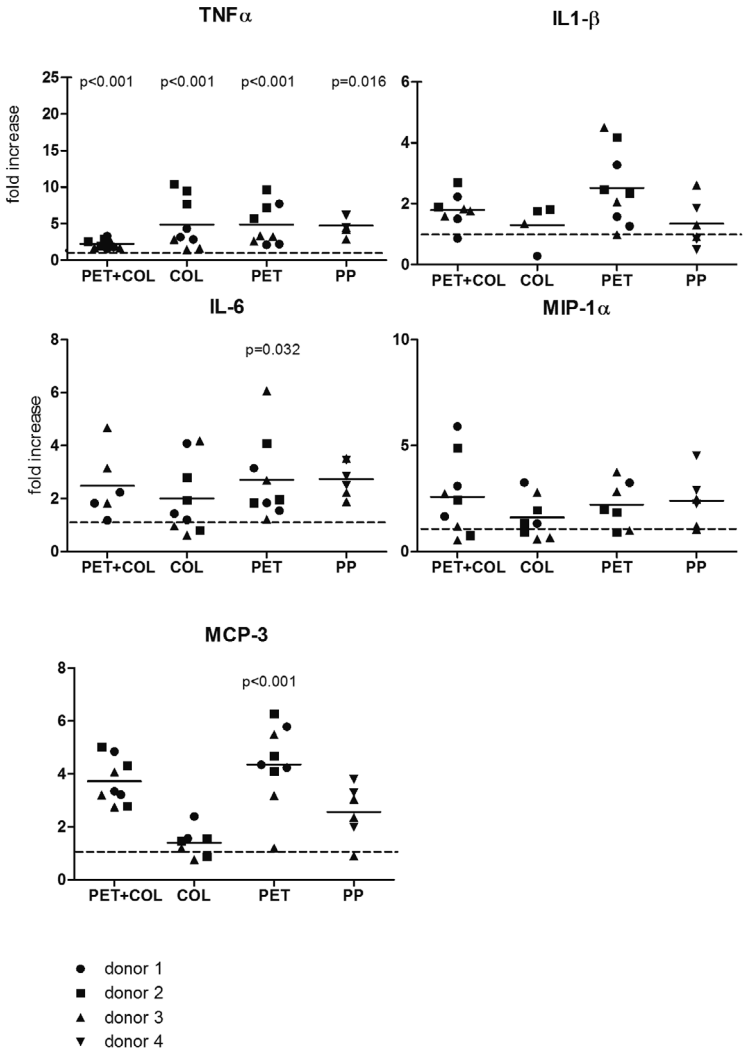


Figure 4. Production of anti-inflammatory cytokines by macrophages seeded on different biomaterials in an inflammatory environment (as induced by lipopolysaccharide/interferon γ) compared with a non-stimulated environment after 3 days of culture. **a** CCL18, **b** interleukin 1 receptor antagonist (IL-1RA), **c** RANTES (regulated on activation, normal T cell expressed and secreted), **d** macrophage-derived chemokine (MDC). The dotted line indicates the basal level of expression, where there is no difference between stimulated and non-stimulated environments, and the bars denote the mean value. Monocytes from a total of four donors were divided over the different biomaterials in triplicate samples. Cells from all donors could not be tested on every biomaterial owing to a low yield of monocytes. Protein production was corrected for DNA before comparison of stimulated and non-stimulated environments. PET+COL, polyethylene terephthalate with a collagen coating; COL, collagen; PET, polyethylene terephthalate; PP, polypropylene. *$P < 0{\cdot}050$ (Kruskal–Wallis and Mann–Whitney U tests), indicating a significant increase in anti-inflammatory cytokines compared with baseline values

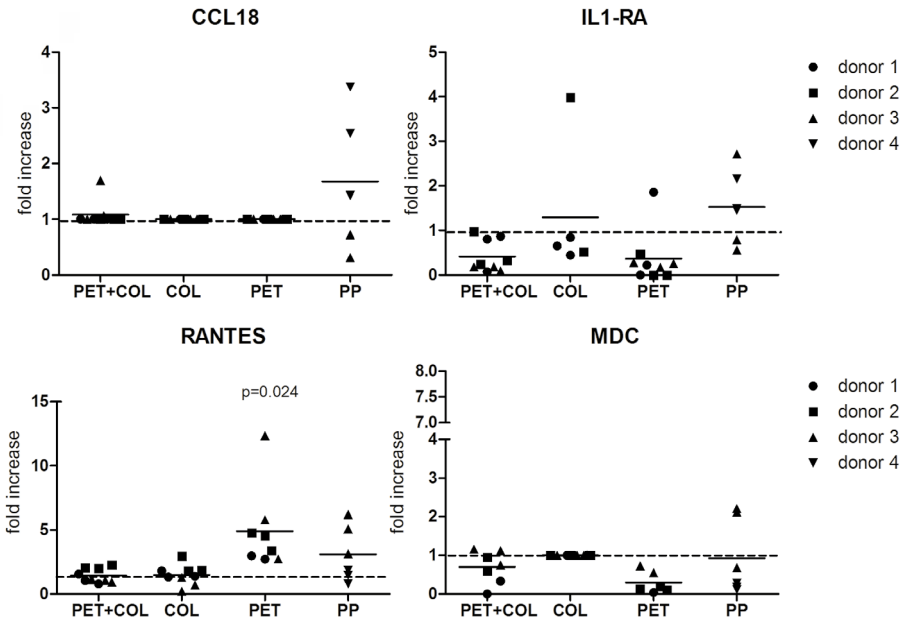
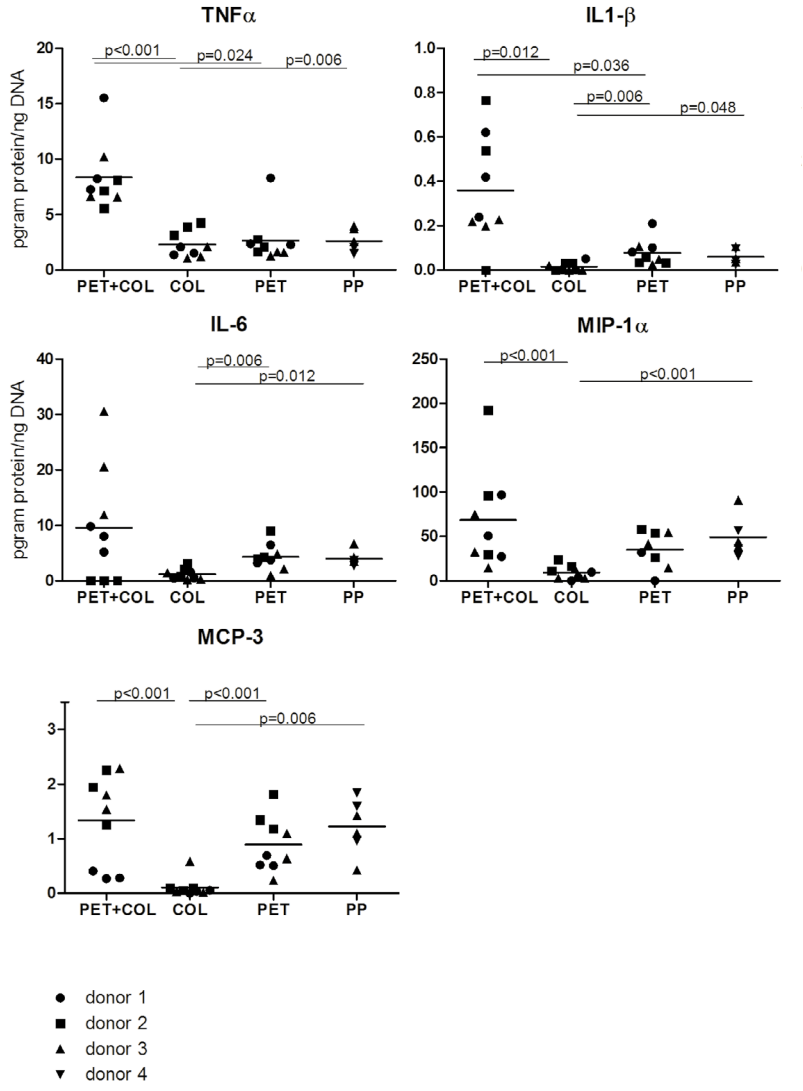


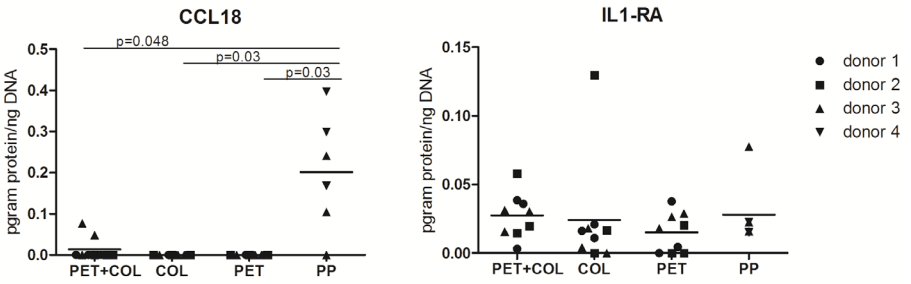
Figure 5. Comparison of secretion of proinflammatory cytokines by macrophages seeded on different biomaterials on the third day of culture with lipopolysaccharide/interferon γ, corrected for DNA. **a** Tumour necrosis factor (TNF) α, **b** interleukin (IL) 1β, **c** monocyte chemotactic protein (MCP) 3; **d** IL-6, **e** macrophage inflammatory protein (MIP) 1α. Monocytes from a total of four donors were divided over the different biomaterials in triplicate samples. Cells from all donors could not be tested on every biomaterial owing to a low yield of monocytes. PET+COL, polyethylene terephthalate with a collagen coating; COL, collagen; PET, polyethylene terephthalate; PP, polypropylene. **a** **P* < 0•001 (PET+COL *versus* COL), †*P* < 0•050 (PET+COL *versus* PET), ‡*P* < 0.050 (COL *versus* PP); **b** †*P* < 0•050 (PET+COL *versus* COL and PET), ‡*P* < 0•050 (COL *versus* PET and PP); **c** **P* < 0•001 (COL *versus* PET+COL and PET), †*P* < 0•050 (COL *versus* PP); **d** †*P* < 0•050 (COL *versus* PET and PP); **e** **P* < 0•001 (COL *versus* PET+COL and PP) (Kruskal–Wallis and Mann–Whitney *U* tests)

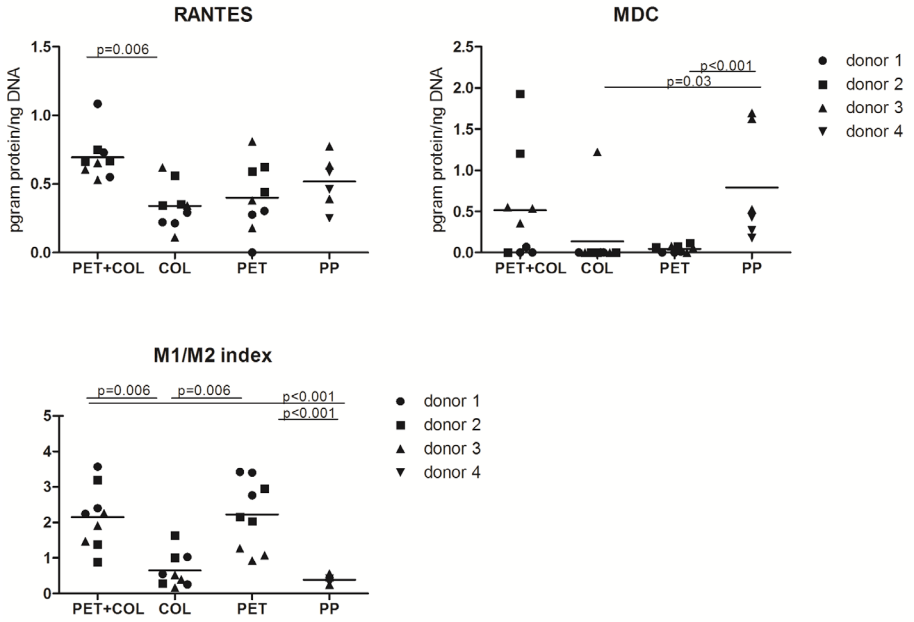


To compare the reaction of macrophages on the four different biomaterials in an inflammatory environment, the total amount of protein corrected for DNA is shown (Figure 5). The greatest induction of proinflammatory cytokines TNF-α, IL-1β, MCP-3 and MIP-1α was induced by macrophages on PET+COL biomaterial in the inflammatory environment. The lowest induction of proinflammatory and anti-inflammatory cytokine production was seen on the COL biomaterial (Figure 5). Macrophages on PP biomaterial produced significantly more CCL18 and MDC than macrophages on other biomaterials, with the exception of MDC on PET+COL biomaterial. Macrophages on PET+COL biomaterial induced a significantly higher RANTES production compared with macrophages on COL (Figure 6). Macrophages on PP and COL biomaterial had the lowest M1/M2 index, whereas macrophages on PET and PET+COL biomaterials had the highest M1/M2 index in the inflammatory environment (Figure 6).

Taking all the samples together, after correction for multiple testing, significant correlations with $P < 0.050$ were found between MCP-3 and MDC ($r_s = 0.80$), IL-6 and IL-1β ($r_s = 0.59$), MIP-1α and MCP-3 ($r_s = 0.64$), MIP-1α and IL-1β ($r_s = 0.60$), TNF-α and IL-1β ($r_s = 0.59$), and MIP-1α and RANTES ($r_s = 0.72$).

Figure 6. Comparison of secretion of anti-inflammatory cytokines by macrophages seeded on different biomaterials at the third day of culture with lipopolysaccharide/interferon γ, corrected for DNA. **a** CCL18, **b** interleukin 1 receptor antagonist (IL-1RA), **c** RANTES (regulated on activation, normal T cell expressed and secreted), **d** macrophage-derived chemokine (MDC); **e** M1/M2 macrophage index. Monocytes from a total of four donors were divided over the different biomaterials in triplicate samples. Cells from all donors could not be tested on every biomaterial owing to a low yield of monocytes. The M1/M2 index for each sample was calculated as the percentage of the mean for each cytokine. The mean of M1 cytokines (macrophage inflammatory protein 1α, tumour necrosis factor α, monocyte chemotactic protein 3, interleukin (IL) 1β, IL-6) was divided by the mean of M2 cytokines (MDC, RANTES, IL-1RA and CCL18). PET+COL, polyethylene terephthalate with a collagen coating; COL, collagen; PET, polyethylene terephthalate; PP, polypropylene. **a** †$P < 0{\cdot}050$ (PP *versus* all other biomaterials); **c** †$P < 0{\cdot}050$ (PET+COL *versus* COL); **d** *$P < 0{\cdot}001$ (PP *versus* PET), †$P < 0{\cdot}050$ (PP *versus* COL); **e** *$P < 0{\cdot}001$ (PP *versus* PET+COL and PET), †$P < 0{\cdot}050$ (COL *versus* PET+COL and PET) (Kruskal–Wallis and Mann–Whitney *U* tests).





Discussion

As tolerance to biomaterials in surgical areas at risk of postoperative contamination is not understood completely, surgeons are reluctant to use biomaterials in these circumstances. Biomaterials should be explored for safer use in surgical environments prone to the development of postoperative infection. Macrophages are key players in the foreign body reaction, thus influencing the fate of biomaterials. In the present study the effect of biomaterials on macrophage phenotypes in an experimental model of postoperative contamination in rats, and in an *in vitro* model of inflammation, were studied.

Implantation of the monofilament PP biomaterial in a contaminated environment in the rat *in vivo*[15] revealed that PP fibres became surrounded by a small layer of dense tissue with many macrophages and other leucocytes. Compared with a contaminated abdominal wall without PP, which by day 28 displayed only a few inflammatory cells, the implanted PP mesh appeared to extend the postoperative inflammatory reaction. No residual bacteria were observed on the Gram staining (data not shown), in agreement with previous

results of negative microbiological cultures of the biomaterial 28 days after implantation[15]. This means that the extended inflammatory reaction is not caused by the presence of bacteria. The macrophages surrounding the PP mesh displayed mainly an M2 phenotype, which is associated with tissue repair and angiogenesis, thus indicating a remodelling phase of wound healing[10]. In earlier *in vivo* rat studies, monofilament PP biomaterial evoked an anti-inflammatory/fibrotic reaction with formation of fibrotic tissue around the mesh fibres, a low infection rate, and good incorporation into the abdominal wall, in both a contaminated(15, 18).

For the *in vitro* analysis, the M1/M2 index was calculated to summarize the effects of a biomaterial on macrophages. However, it should be appreciated that dividing macrophages into either M1 or M2 phenotypes is a simplification, as several intermediate states exist[28]. In the *in vitro* inflammatory environment, macrophages on the multifilament PP biomaterial induced the expression of anti-inflammatory proteins at a higher rate than the other biomaterials tested, thus resulting in a low M1/M2 index. The low M1/M2 index in the case of PP is caused mainly by a high protein production of CCL18, which is known for its association with fibrosis[23].

Macrophages on the COL biomaterial produced a relatively low amount of proinflammatory and anti-inflammatory cytokines, indicative of a mild reaction to the biomaterial. A mild foreign body reaction against collagen-based biomaterial has also been observed *in vivo* by others(11, 12, 14, 19).

Macrophages on the PET biomaterial had a relatively high M1/M2 index in the *in vitro* model, indicating a predominantly proinflammatory reaction of macrophages. PET and PP biomaterials are knitted according to similar weaves, resulting in comparable surfaces (figure 1). The difference *in vitro* is thus mainly in the contact angle/hydrophobicity, and therefore the proinflammatory reaction; thus the high M1/M2 index can be caused partly by the polymer type itself.

The PET+COL composite biomaterial tested is the mesh type generally preferred for intraperitoneal hernia surgery, as it minimizes the formation of postoperative tissue adhesions[20, 21]. A high M1/M2 index was found for PET+COL biomaterial, indicating a high proinflammatory reaction in an inflammatory environment. In fact, this material evoked the highest absolute production of proinflammatory cytokines. This acute reaction can be explained by phagocytic activity of macrophages, trying to break down and digest

the thin collagen layer[22]. A proinflammatory reaction was induced by the macrophages on PET+COL, even in a non-stimulated environment. When this environment was compared with an inflammatory environment *in vitro,* only a slight further increase in proinflammatory protein production was observed. This indicates that the PET+COL material itself has a great influence on the reaction of macrophages.

In a previous study[16], the M1/M2 index in a sterile environment was analysed *in vitro*. Most interestingly, the present data indicate that the macrophage response remains biomaterial-specific even in an environment with simulated contamination. When comparing sterile and contaminated environments, the largest differences were observed for TNF-α production. TNF-α is an acute-phase protein, and reacts quickly in the present *in vitro* system. However, this does not indicate that the fourfold increases in MCP-3 or the threefold increases in IL-6 are less relevant, as these factors might have a different potency or kinetics.

In vivo there is a great difference between multifilament and monofilament biomaterials, as the former allow for more cells to attach and fill the biomaterial. Monofilament biomaterials are less prone to infection because they provide fewer niches for bacterial infiltratration[2,3]. In the present study, monofilament biomaterials were not tested in the *in vitro* system owing to the low number of macrophages attaching to these in comparison with multifilament biomaterials.

The variation between macrophages isolated from different donors is not unexpected because it is known from clinical practice that patients respond differently to biomaterials. However, variations between the samples from one donor were also observed, which can be explained by the fact that monocytes are a heterogeneous population with different sensitivities to biomaterials or cytokines. However, taken together, distinct differences in macrophage reactions to biomaterials were observed.

The present study describes the very acute reaction to biomaterials, with analysis after 3 days of culture. The acute reaction is indicative of the subsequent outcome. It is obvious that the *in vivo* conditions are more complex than the *in vitro* situation. Most importantly, this study shows that an *in vitro* model system can be used to evaluate and simulate the foreign body reaction in an inflammatory environment, which can aid in selecting and developing new biomaterials that are well tolerated under conditions with a high risk of postoperative biomaterial infection.

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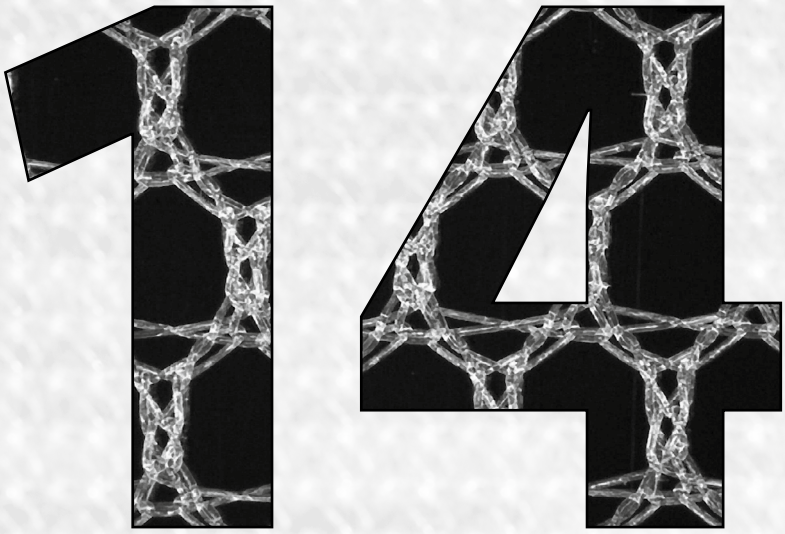
Chapter



Infection susceptibility of crosslinked and non-crosslinked biological meshes in an experimental contaminated environment

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Abstract

Background

This experimental study investigates infectious complications and functional outcome of biological meshes in a contaminated environment.

Methods

In 90 rats peritonitis was induced, and after 24 hours, a biological mesh was implanted intraperitoneally including 2 non-crosslinked mesh groups (Strattice and Surgisis) and 2 crosslinked mesh groups (CollaMendFM and Permacol). Sacrifice was after 90 and 180 days.

Results

More mesh infections occurred in crosslinked meshes compared with non-crosslinked meshes (70% vs 4%; $P < 0.001$). Mesh infection was the highest in crosslinked CollaMendFM (81.2%) and lowest in non-crosslinked Strattice groups (0%). Incorporation into the abdominal wall was poor in all meshes (0% to 39%). After 180 days no residue of non-crosslinked Surgisis mesh was found. After 180 days, shrinkage was 0.8% in crosslinked Permacol and 20% in Strattice groups. Strattice showed the least adhesion formation (median 5%).

Conclusions

Infection rate of biological meshes in a contaminated field was the highest in crosslinked meshes. All biological meshes showed poor incorporation, which makes long-term abdominal wall repair questionable.

Introduction

Many factors are of influence on the functional outcome of abdominal wall repair, such as patient characteristics, site of implantation, the presence of contamination, and the chosen mesh material. Especially in the presence of bacterial contamination, repair of abdominal wall defects is a continuing challenge for surgeons. Contamination can be caused by intra-abdominal and surgical site infection, incarcerated and strangulated hernia, concomitant bowel surgery, the presence of a colostomy, acute evisceration, and open abdomen. Introduction of synthetic meshes in abdominal wall repair significantly decreased recurrence rates(1, 2). However, implantation of a synthetic prosthesis into a contaminated environment generates an increased risk for infection(3, 4). Mesh infection often necessitates removal of the mesh, leaving an abdominal wall deficit, sometimes larger than the original hernia, and closure can only be accomplished with contact of the mesh with the intra-abdominal content. Recommendations on mesh selection have been developed by the Ventral Hernia Work Group in 2008(5). In case of ventral hernia repair with mesh implantation in patients with grade-3 and -4 risk of surgical site infection, biological mesh is recommended.

Biological meshes are extracellular scaffolds, processed from animal (bovine or porcine) small intestine submucosa, pericardium, or dermis. The donor tissue is said to be cleared of cells and immunogenic particles, after which a scaffold of extracellular matrix (ECM) remains. After implantation, the scaffold is gradually vascularized and remodelled into the host tissue while degradation of the ECM takes place(6, 7). To increase biomechanical strength, chemical crosslinking of the biological mesh can be conducted. Crosslinking stabilizes the 3- dimensional structure of the ECM. This improves withstanding of enzymatic degradation of the ECM, which can be accelerated because of inflammation or infection at the implantation site(8-10). Initial animal and clinical data seemed promising; however, compelling evidence is lacking as these data mainly report on clean cases and short follow-up with only a small portion in contaminated cases(11). Furthermore, recent clinical reports have been published on infectious complications of both non-crosslinked and crosslinked meshes(12-17).

The objective of this experimental study was to investigate the infectious complications and functional outcome of crosslinked and non-crosslinked

biological meshes in a contaminated environment in a model of abdominal wall repair in the rat.

Methods

Animals

Experimental protocols were approved by the Ethical Committee on Animal Experimentation of the Erasmus University Rotterdam. Ninety male rats of the outbred Wistar strain were obtained from a licensed breeder (Harlan, the Netherlands) and accustomed to laboratory conditions 2 weeks before the start of the experiment. The animals were bred under specific pathogen-free conditions, were kept under standard laboratory conditions in individually ventilated cages in pairs, and had free access to standard rat chow and water throughout the experiment.

Peritonitis model

Rats were anaesthetized with isoflurane and O2 inhalation (Pharmachemie, Haarlem, the Netherlands) and received buprenorfin analgesia 0.05 mg/kg subcutaneously (Reckitt Benckiser Healthcare (UK) Limited, Kingston upon Thames, United Kingdom). Procedures were performed under aseptic conditions. The abdomen was shaved and the skin disinfected with 70% alcohol, after which the abdominal cavity was opened through a 3-cm midline incision through the skin and linea alba. To induce peritonitis, the cecal ligation puncture model was performed in all rats(18, 19). The cecum was carefully manipulated outside the abdominal cavity and ligated just distal to the ileocecal valve with a monofilament non-absorbable nylon suture (Ethilon 4-0; Ethicon, Somerville, NJ), maintaining the continuity of the bowel. Distally, the cecum was punctured once with an 18-ga needle. The fascia and the skin were closed with running absorbable polyglycolic acid sutures (Safil 5-0; B Braun, Melsungen, Germany). After 24 hours of recovery, the animals were re-anesthetized, the abdomen was reopened, a culture swab taken to confirm peritonitis, the necrotic cecum resected, and the abdominal cavity was rinsed with at least 20 mL phosphate-buffered saline at 37°C. A sterile mesh, measuring 2.5 x 3 cm, was implanted intraperitoneally with 6 transmuscular non-absorbable sutures (Ethilon 5-0) in all mesh groups. In the control group no mesh was implanted.

After administration of gentamicin 6 mg/kg intramuscularly (Centrafarm, Etten Leur, the Netherlands), the abdominal wall and skin were separately closed with a running absorbable suture (Safil 5-0). Buprenorfin analgesia 0.05 mg/kg was administrated twice daily on the days animals were operated and the first day after mesh implantation.

Implanted meshes

The control group received no mesh, and in the mesh groups, 1 of 4 biological meshes was implanted within the peritoneal cavity. Prostheses were prepared according to the manufacturer's instructions before implantation. Four commercially available biological meshes were implanted:

1. Non-crosslinked porcine dermis Strattice® (LifeCell, Branchburg, NJ)
2. Non-crosslinked porcine submucosa Surgisis® (Cook, Bloomington, IN)
3. Crosslinked porcine dermis CollaMendFM® (C.R. Bard [Davol, Inc],Warwick, RI)
4. Crosslinked porcine dermis Permacol® (Covidien, Norwalk, CT).

Measurements

Animals were divided in groups according to implanted mesh and intended time of sacrifice, 90 or 180 days after implantation of the mesh. During the experiment, animals were weighed daily and scored for their wellness using an objective 12-point scoring system during the first 14 days of the experiment, thereafter once a week(20). In case of severe infectious complication, weight loss of 20% or more, or a wellness score of less than 5 out of 12 points, animals were euthanized before the intended end of the experiment and analyzed together with the surviving animals of the group. On all euthanized and deceased animals necropsy was performed.

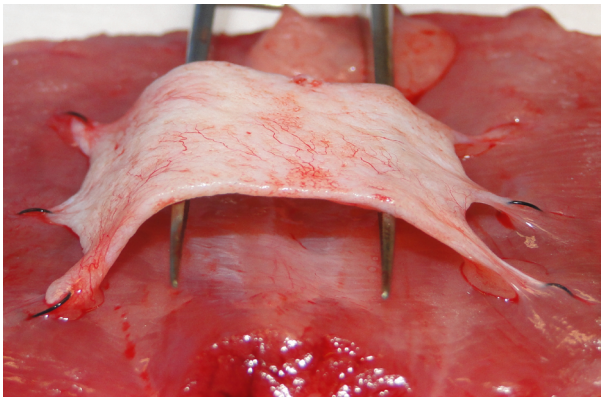
During sacrifice, the animals were anaesthetized with isoflurane and O2 inhalation; the abdomen was shaved, disinfected, and opened through a U-shaped incision extending laterally and caudally to the mesh. Macroscopically, mesh infection was defined as the presence of abscesses of the mesh. Parts of the mesh were cultured for microbiological evaluation. In all mesh groups, mesh surface and coverage of the mesh surface with adhesions were scored using a grid placed over the mesh, dividing it into 30 equal squares and facilitating accurate estimation of adhesion formation. Tenacity

of adhesions was scored using the Zühlke score, a 4-degree classification of adhesions based on histologic and morphologic criteria(21). Pictures of the abdominal wall with the mesh and the present adhesions were taken (5.0 megapixels digital camera, Sony Cybershot, Tokyo, Japan). The abdominal cavity was inspected for abscesses, and when present, scored and cultured at 4 sites of the peritoneum (liver, abdominal wall, bowel, and omentum) using an objective abscess size scoring system(22). Mesh incorporation was defined as percentage of the mesh edge incorporated into the abdominal wall, taking into account any surface reduction (Figure 1). If only the sutures secured the mesh to the abdominal wall and no ingrowth of the mesh was seen, ingrowth was scored as 0%. Surface reduction was defined as the relative loss of surface compared with the original size of the implanted mesh measured with a calliper. All measurements were performed by 2 independent observers and disagreements reconciled after discussion. The animals were euthanized by cardiac cut at the end of the experiment during anaesthesia.

Statistical analysis

Mesh infection, tenacity, and percentage of adhesions, abscess formation, survival, and weight were compared using nonparametric tests as the data did not show normal distribution (Kruskal-Wallis, Mann-Whitney, chi-square, and the Fisher exact tests). Therefore, all results are presented using the median and the interquartile range (IQR). In case the overall test showed differences, the pairwise tests were done to determine the groups causing the overall significance.

Figure 1. Example of (absent) incorporation of the edge of biological mesh in the abdominal wall.



Exact methods for significance were used when computational limits allowed these. All reported P values are 2-sided and considered significant if less than 0.05. In view of the small sizes of the groups, it was not possible to adjust the P values using the Bonferroni correction. Statistical analysis was performed using PSAW statistical software package, version 17 (IBM SPSS statistics).

Results

During the 2 days after implantation of the mesh, 18 of the 90 rats (20%) were prematurely taken out of the experiment because of a low wellness score. Postoperative mortality was not statistically different between the groups. In all rats necropsy was performed and septicemia was found to be the cause of death. Abdominal cultures at day 1 confirmed bacterial contamination in all animals with gram-positive (Enterococcus, Staphylococcus, Streptococcus) and gram-negative microorganisms (Escherichia coli and Proteus). All animals demonstrated signs of sepsis including apathetic behaviour, ocular exudates, piloerection, diarrhea, and weight loss. Mortality in the groups is depicted in Table 1. Maximum percentage weight loss was significantly higher in CollaMendFM after postoperative day 5 compared with the other groups (median: CollaMendFM, 12%; Strattice, 11%; Surgisis, 9%; Permacol, 9%; $P < 0.020$).

Table 1. postoperative mortality and animals analysed at both time points per group.

Group	Material	Animals	Postoperative mortality	90 days	180 days
Control	No mesh	18	2	8	8
Strattice	Non-crosslinked dermis	18	4	7	7
Surgisis	Non-crosslinked submucosa	18	5	6	7
Permacol	Crosslinked dermis	18	5	7	6
CollaMendFM	Crosslinked dermis	18	2	9	7
Total		90	18	37	35

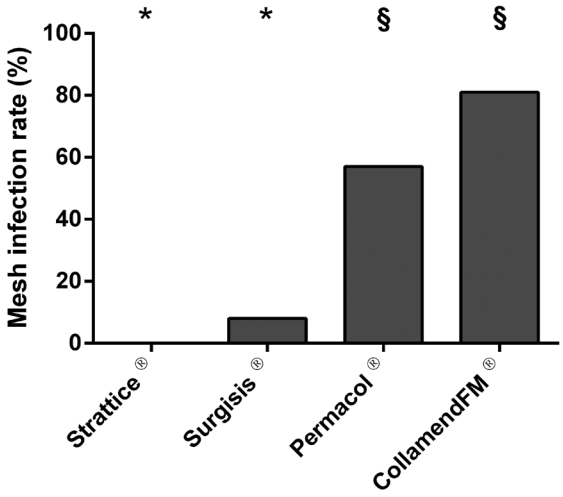
*One rat in the Permacol group and 7 rats in the CollaMendFM group were euthanized before the intended end point. The results of these rats were analyzed together with the rats sacrificed at the intended end point.

Mesh infection and abdominal abscesses

Seven animals (44%) with a CollaMendFM mesh and 1 animal (7%) with a Permacol mesh were euthanized before the intended time point because

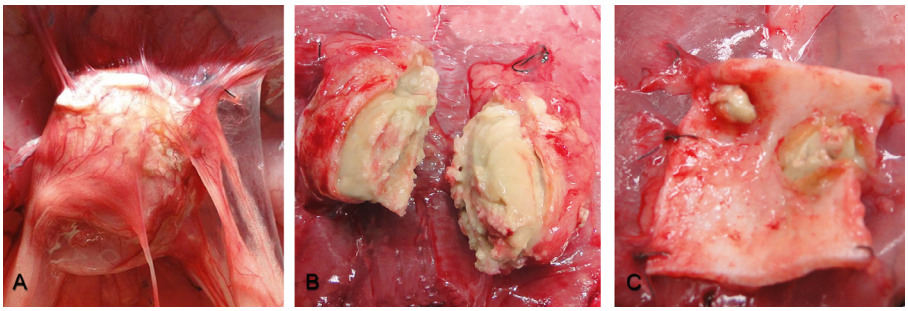
of clinically evident mesh infection with transcutaneous migration of the prosthesis. At sacrifice, macroscopic infection of the mesh was present in 22 of 57 animals (39%). In Figure 2, the percentage of mesh infections per mesh group is shown. The mesh infection rate was significantly higher for crosslinked meshes compared with non-crosslinked meshes (70% vs 4%; P < 0.001). In 16 animals, the mesh was encapsulated by a large abscess, and in 6 animals, abscesses in parts of the mesh were found (Figure 3). No additional mesh infections were discovered by microbiological culture of the meshes performed during sacrifice.

Figure 2. Comparison of combined percentage (90 and 180 days) of mesh infection. Values are percentages of macroscopically infected meshes of surviving animals. * non-crosllinked and § crosslinked meshes.



Intra-abdominal or abdominal wall abscesses were found in 42% of all surviving animals at sacrifice. Most abscesses were located at the ligation of the cecal stump. There was no significant difference in amount and size of intra-abdominally (non-mesh related) observed abscesses (P 5.321) between the meshes. Although when differentiated between crosslinked and non-crosslinked meshes, more abscesses were observed in the animals with crosslinked meshes implanted (P =0.011).

Figure 3. Macroscopic evaluation of mesh infection with meshoma of a Permacol mesh (A, B) and formation of mesh abscess in a Permacol mesh (C).



Surface reduction

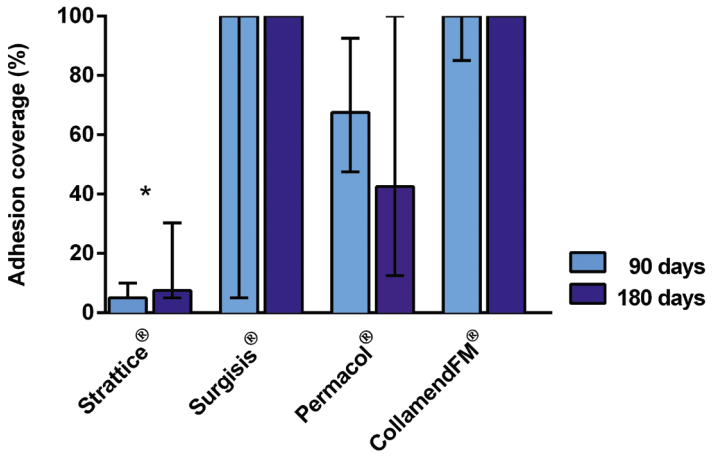
The 22 animals with infected meshes were excluded from this analysis because surface of the mesh could not be accurately measured. The CollaMendFM groups were excluded from analysis because, after excluding the animals with infected meshes, an insufficient number of animals were left to perform statistical testing. Loss of surface of Surgisis was significantly higher at both time points compared with Strattice and Permacol ($P < 0.036$). Both at 90 and 180 days, only in 2 animals a very thin residue of the Surgisis mesh could be found macroscopically. Loss of surface after 90 days was significantly higher in the Strattice compared with the Permacol group (median [IQR], 23% [10 to 46] vs 3% [0 to 7]; $P = 0.033$). In the Strattice group, loss of surface after 180 days was median 20% (IQR, 10 to 41) and median 1% (IQR, 0 to 3) for the Permacol group ($P = 0.075$). After grouping the scaffolds by crosslinking, surface reduction of the mesh was lower in the crosslinked group (median [IQR], 2% [0 to 4]) compared with the non-crosslinked group (23% [10 to 46]; $P < 0.001$).

Incorporation

Overall incorporation of the biological meshes into the abdominal wall at 90 and 180 days was poor (range, 0% to 39%). At 90 days, incorporation of all meshes was median 4% (IQR, 0 to 21) and at 180 days median 0% (IQR, 0 to 11). Due to the high infection rate, the CollaMendFM mesh showed incorporation of median 0% at 90 and 180 days (IQR, 0 to 24; IQR, 0 to 17, respectively). Most Surgisis meshes could not be identified at 90 and 180 days, leading to an overall incorporation of 0% (IQR, 0 to 0). Strattice showed incorporation of median 14% (IQR, 10 to 21) at 90 days, decreasing to median 10% (IQR, 6 to 12) at 180 days

(P = 0.128). Permacol was incorporated median 21% (IQR, 3 to 39) at 90 days, decreasing to 6% (IQR, 0 to 31) at 180 days (P = 0.320). At both time points, incorporation was not different between Strattice and Permacol (P = 0.513 and P 5.506). There was no difference in incorporation between crosslinked and non-crosslinked meshes (P = 0.537).

Figure 4. Comparison of the percentage of each mesh covered with adhesions after 90 and 180 days' follow-up. Values represented as median (interquartile range). Strattice has significant lower adhesion formation than Surgisis, Permacol and Colla-MendFM at 90 and 180 days, *P < 0.05.



Adhesions

In the control group, 6 of 15 rats (40%) showed visceral adhesions to the midline scar with a maximum Zühlke score of 2. Adhesion coverage per mesh group is depicted in Figure 4. At 90 and 180 days, median 100% of the original implantation site of the Surgisis was covered with adhesions (90 days IQR, 76% to 100%; 180 days IQR, 100% to 100%). CollaMendFM was covered with median 100% adhesions at 90 and 180 days (90 days IQR, 95% to 100%; 180 days IQR, 100% to 100%). Strattice had little adhesion formation to the mesh at 90 and 180 days (both time points median 5%; IQR, 5% to 10%), which was significantly lower than the other meshes (P < 0.038). At 90 days, median 68% (IQR, 48% to 93%) of mesh surface of Permacol was covered by adhesions and at 180 days, median 42% (IQR 13% to 100%). Alteration in adhesion coverage between 90 and 180 days in all mesh groups was not significantly different (P > 0.356).

Tenacity of adhesions was higher after 90 days for CollaMendFM (median Zühlke score, 4; IQR, 3 to 4) compared with Permacol (median Zühlke score, 3; 3 to 3) and Strattice groups (median Zühlke score, 3; IQR, 3 to 3, respectively; P = 0.012 and P = 0.031). After 180 days, the tenacity of adhesions decreased and was lowest for Strattice (median Zühlke score, 2; IQR, 2 to 3), which was significantly lower than that for Permacol (median Zühlke score, 3; IQR, 3 to 3), CollaMendFM (median Zühlke score, 3; IQR, 3 to 4) and Surgisis (median Zühlke score, 3; IQR, 3 to 3, respectively; P = 0.013, P = 0.007, and P = 0.008, respectively). After grouping the scaffolds by crosslinking, the percentage of the mesh covered with adhesions and the tenacity of the adhesions to the mesh were found to be higher in the crosslinked group (P = 0.01 and P = 0.024, respectively).

Comments

Crosslinked biological meshes were found to have a significantly higher percentage of mesh infection (70% vs 4%; P < 0.001) and intra-abdominal abscesses (P = 0.011) than non-crosslinked biological meshes. Infectious complications required euthanasia before the intended time point in almost half of animals in the crosslinked CollaMendFM group, as described in previous animal experiments(23-27).These results are in accordance with clinical reports of infectious complications of biological meshes instigating the debate on the indications for their clinical use(12-15, 17, 28, 29). The development of infection in crosslinked meshes seems comparable to mesh infection in microporous synthetic meshes by preclusion of immune cells(30). Crosslinking appears to decrease the pore size of biological meshes to a pore size small enough to provide a suitable housing for bacteria while preventing access of macrophages, fibroblasts, blood vessels, and collagen fibers into the pores(31, 32). This may lead to encapsulation rather than remodelling of the mesh(33, 34).

However, not all crosslinked meshes have similar densities of crosslinking because of differences in processing. Another interference of mesh integration could be the sterilization technique. CollaMendFM and Surgisis inhibiting tissue integration and reducing tensile strengths(35, 36).

However, the influence of sterilization techniques on these parameters is still largely untested. This could be of importance considering the differences

found in performance between the crosslinked meshes. In previous studies, the possible effect of crosslinking on the occurrence of infectious complications was not addressed. This experiment is the first step in acquiring more knowledge on the effect of crosslinking on the occurrence of infectious complications after implantation of biological meshes in a contaminated environment.

In abdominal wall repair with a biological mesh, resistance to degradation is critical to prevent recurrence of hernia. During the remodelling process, after implantation a delicate balance exists between ECM degradation and deposition of host collagen. The donor material of the ECM seems to influence the rapidity of degradation of the mesh. High levels of hydroxyproline in collagenase assay suggest low resistance of the submucosa-based mesh to enzymatic degradation(37). This was illustrated in the present and previous experiments by the complete disappearance of the small intestine submucosa–based Surgisis, which makes long-term hernia repair questionable(34, 38). Meshes derived from dermis were observed to have little surface reduction in the present experiment, with a 20% reduction in non-crosslinked Strattice and 1% in crosslinked Permacol after 6 months.

Chemical crosslinking is performed to make biological meshes more resistant to matrix metalloproteases and native and bacterial collagenase. Our experiment also showed decreased surface reduction in the crosslinked group; however, when only dermal meshes were investigated, there was no difference in surface reduction between non-crosslinked and crosslinked meshes. In the present experiment, under contaminated conditions, crosslinked meshes showed poor incorporation in the abdominal wall. The best incorporation was 21% by Permacol after 90 days, which was decreased to only 6% at 180 days. This disappointing incorporation of crosslinked meshes can be explained by delayed collagen degradation, leading to decreased angiogenesis and inflammation due to foreign body reaction resulting in poor tissue integration and adhesion formation(14, 24, 26, 27). This foreign body reaction can be provoked by exposure of antigenic epitopes known to hinder successful xenotransplantation. For example, galactose-alpha-1,3-galactose (alpha-gal) is proven to be present in the ECM of non-crosslinked Surgisis(39). Crosslinking can initially mask these antigenic epitopes, but with mesh degradation, epitopes become exposed(40, 41). Exposure of epitopes leads to production of antibodies in humans and primates activating humoral immune and complement response(39, 42). Adhesion formation seems to be

related to foreign body reaction to the mesh and sutures and the presence of mesh infection in the present experiment. The amount of adhesions found in this experiment is consistent with earlier experimental reports(19, 26, 27). One clinical study evaluated adhesions by laparoscopic re-exploration after ventral hernia repair and found similar surface area and tenacity of adhesions in the biological meshes compared with synthetic meshes(43).

To create a contaminated environment, we used the cecal ligation puncture model, which was originally designed as a sepsis model. In this model, as in clinical infections, peritonitis arises from a complex interaction of the immune system with inflammatory, hemodynamic, and biochemical alterations with a consistent increase of cytokine levels(44-47). Additionally, in this model genetically identical rats were used of the same age and sex and specified pathogen-free bacterial status. This minimalizes biological and microbiological variability and makes the model suitable for comparing the behaviour of various meshes in a contaminated environment but does not reflect daily practice(46).

A limitation of the model in this experiment is that only a single dose of aminoglycoside is administrated, where this does not reflect the treatment of humans with abdominal sepsis. Administration of antibiotics in rats with fecal peritonitis does reduce bacteremia, bacteria concentration, and mortality rates(48). But previous experiments proposed a drawback regarding the use of antibiotics because of the possible marked bacterial cell death causing the release of toxic components against the immunologic system and the triggering of uncontrolled activation of this system(49-51). Previous animal experiments found that when antibiotics were added to the surgical treatment, the inflammatory response is minimized, but there is no difference in survival or amount of intra-abdominal abscesses(52, 53). Therefore, surgical control of the source of infection remains the most important treatment in abdominal sepsis. However, the adjunct of systemic antibiotics to surgical treatment is firmly established in the postoperative period in humans because it reduces the systemic effects of peritonitis and could influence late complications like abscess or fistula formation(54). Therefore, translation of experimental results to the clinic situation should be done with caution.

In the clinical setting, biological meshes are often implanted in the intraperitoneal or sublay position. A limitation of the present animal study is that thickness and size of the mesh in relation to the abdominal wall is dissimilar

between rats and humans. Furthermore, the chosen intraperitoneal placement of the mesh could have influenced incorporation of the mesh in the abdominal wall because the mesothelial layer of the peritoneum is less vascularized than the retromuscular space(55). On the other hand, closure of the peritoneal layer is often deficient when attempting sublay positioning of the mesh in humans, making the used model clinically relevant.

Conclusions

In conclusion, this experiment demonstrates a high infection rate and increased adhesion formation of crosslinked biological meshes (Permacol and CollaMendFM). Resistance to infection of non-crosslinked Strattice could allow implantation in the contaminated environment. However, the poor incorporation of all biological meshes and complete degradation of Surgisis makes long-term biomechanical strength of hernia repair questionable. Implantation of biological prostheses could be a valid choice in staged contaminated abdominal wall repair. Prevention of mesh infection associated with high costs for intensive care treatment, reoperation, and prolonged hospital stay might justify the high costs of a biological mesh.

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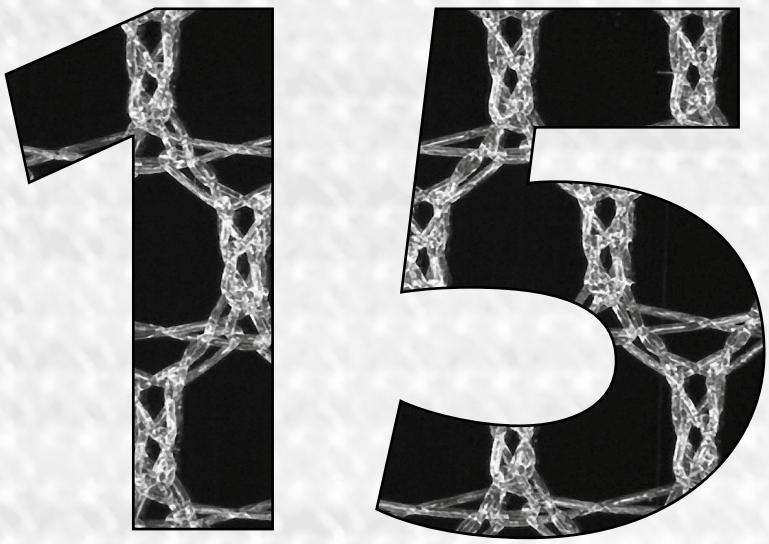
Chapter



Problematic incorporation of biological meshes in ventral hernia repair during long-term follow-up

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Submitted

Abstract

Background

This study investigates long-term incorporation, adhesion formation, mesh infection and shrinkage after implantation of biological meshes in non-contaminated environment.

Methods

In 64 rats a mesh-model was used to implant various meshes intraperitoneally: 2 non-crosslinked mesh groups (Strattice and Surgisis) and 2 crosslinked mesh groups (CollaMendFM and Permacol). Sacrifice was after 90 and 180 days.

Results

High numbers of infectious complications were observed (12.5% transcutaneous prosthesis migration and 23.4% macroscopic mesh infection). Incorporation of meshes was poor (0% to 36.8%) on POD 180. Mesh shrinkage was highest in Surgisis (POD 90 57%, $P<0.01$). On POD 180, shrinkage did not differ between the meshes. Surgisis had the highest adhesion score on POD 90 (90%, $P<0.023$). Adhesions covering the mesh was least in Strattice (5%, $P<0.029$).

Conclusions

Experimental intraperitoneal implantation of biological meshes is accompanied by various infectious complications with little incorporation and will most likely not adequately prevent the formation of recurrent incisional hernia.

Introduction

The number of patients undergoing elective abdominal wall hernia repair with mesh in the United States was approximately 48,000 in 2010(1). The subsequent economic burden is justified by the increased quality of life and core physiology after hernia repair(2, 3). Many different mesh types have been introduced on the market with different indications. Synthetic meshes are suggested to be contraindicated in clean-contaminated and contaminated fields following reports on increased susceptibility to infection, fistula formation and adhesion formation. Biological meshes were introduced aiming to reduce infectious complications by complete integration in the host tissue and ingrowth of mononucleair cells. Early short term results after implantation of biological meshes were promising, although mainly investigated in a clean environment. Thereafter reviews concluded that biological meshes should be incorporated in the surgeons armentarium which resulted in widespread implantation of these grafts(4-7).

The Ventral Hernia Working Group of the European Hernia Society recommended use of biological mesh in case of a potentially contaminated or infected wound due to the risk of infectious complications. Consensus on the use of biological meshes has not been reached and surgeons over the world struggle with these recommendations in daily practice(8-10). In clinical studies with Strattice and Surgisis meshes recurrence of hernia was high which could be due to use of non-crosslinked meshes(11, 12). In a previous animal model infection rate was increased in crosslinked meshes and incorporation of all biological meshes was poor in a contaminated environment(13). Sustainable hernia repair and low rates of mesh infection when using biological meshes is essential to compete with synthetic meshes in a clean environment.

Long-term follow-up on biological meshes in clinical and animal studies is still scarce. This study aimed to compare two commercially available crosslinked with two non-cross-linked biological meshes in intra-peritoneal position in a rat model. The meshes were tested on infectious complications, adhesion formation, shrinkage and incorporation after a period of 90 and 180 days.

Materials and methods

Animals

Sixty-four male rats of the outbred Wistar strain weighing 288-422 grams were obtained from a licensed breeder (Harlan, the Netherlands) and bred under specific pathogen-free conditions. The animals were accustomed to laboratory conditions one week before the start of the experiment. They were kept under standard laboratory conditions in individually ventilated cages and fed with standard rat chow and water ad libitum throughout the experiment. Experimental protocols were approved by the Ethical Committee on Animal Experimentation of the Erasmus University Rotterdam.

Implanted meshes

Animals were divided into 8 groups and 4 different commercially available biological meshes were implanted. Prostheses were prepared according to the manufacturer's instructions before implantation.

1. Non-crosslinked porcine dermis Strattice (Lifecell, Branchburg, NJ)
2. Non-crosslinked porcine submucosa Surgisis (Cook, Bloomington, IN)
3. Crosslinked porcine dermis Permacol (Covidien, Norwalk, CT)
4. Crosslinked porcine dermis CollamendFM (C.R. Bard/Davol, Inc, Warwick, RI).

Mesh model

Rats were anaesthetized with isoflurane/O_2 inhalation (Pharmachemie, Haarlem, the Netherlands) and received buprenorfin analgesia 0.05 mg/kg subcutaneously (Reckitt Benckiser healthcare limited, Kingston upon tames, United Kingdom). Procedures were performed under aseptic conditions. The abdomen was shaved and the skin disinfected with 70% alcohol, after which the abdominal cavity was opened through a 3 cm midline incision through the skin and linea alba. A sterile mesh, measuring 2.5x3 cm, was implanted intraperitoneally with three transmuscular non-absorbable sutures (Ethilon, 5-0) on both sides of the incision in all mesh groups. Thereafter the abdominal wall and skin were separately closed with a running absorbable suture (Safil , 5-0).

Measurements

In case of severe infectious complications animals were euthanized before the intended endpoint. These animals were analysed together with the surviving animals sacrificed at the intended endpoint. Half of the surviving animals were sacrificed after 90 days and half after 180 days. During sacrifice the abdomen was shaved, disinfected and opened through a U-shaped incision extending lateral and caudal to the mesh. Mesh incorporation was defined as percentage of the mesh edge incorporated into the abdominal wall, taking into account any shrinkage (example in Figure 1). In all mesh groups mesh surface and coverage of the mesh surface with adhesions was scored using a grid placed over the mesh, dividing it into 30 equal squares and facilitating accurate estimation of adhesion formation. Tenacity of adhesions was scored using the Zühlke-score, a 4-degree classification of adhesions based on histological and morphological criteria(14). Pictures of abdominal wall with mesh and the present adhesions were taken (5.0 megapixels digital camera; Sony Cybershot). Macroscopically mesh infection was defined as the presence of abscesses of the mesh. Shrinkage was defined as the relative loss of surface compared with the original size of the implanted mesh measured with a calliper. All measurements were performed by 2 independent observers and disagreements reconciled after discussion. The animals were euthanized by cardiac cut.

Statistical analysis

Incorporation, mesh infection, tenacity and percentage of adhesions, abscess formation, survival, weight and shrinkage were compared using non-parametric tests (Kruskal Wallis, Mann Witney, Chi-square, Fisher's exact and Spearman's rho) since the data did not show a normal distribution. Therefore all results are presented using the median and the interquartile range (IQR). In case the overall test showed differences, the pairwise tests were done to determine the groups causing the overall significance. Exact methods for significance were used when computational limits allowed these. All reported p-values are two-sided and considered significant if less than 0.05. In view of the small sizes of the groups, it was not possible to adjust the p-values using Bonferroni's correction. Statistical analysis was performed using PSAW statistical software package, version 17 (IBM SPSS statistics).

Results

Mesh infection

During the experiment 8 animals were euthanized due to clinically evident mesh infection with transcutaneous migration of the prosthesis between day 49 and 87. In all euthanized rats, 7 animals of the CollamendFM group and 1 of the Surgisis group, necropsy was performed and large mesh abscesses were found intra abdominally. In total 15 of 64 rats (23.4%) were found to have macroscopic infection of the mesh at time of sacrifice. In Figure 1 the amount of mesh infections per mesh-group is shown. Strattice had a significantly lower number of mesh infections compared to CollamendFM at 90 days ($P<0.001$). At 180 days CollamendFM showed a significantly higher rate of mesh infection compared to all other meshes ($P<0.004$). Maximum percentage of weight loss was significantly higher in CollamendFM compared to all other groups (median 6, compared to Strattice 2; Surgisis 3; Permacol 3.5, $P=0.001$).

Mesh incorporation

Animals with mesh infection were not included in this analysis because no incorporation of the mesh was found in these animals. Incorporation of the meshes was not significantly different between the groups at 90 days (median 13.2%, IQR 0-24.2%). Data per mesh is shown in Figure 2. No Surgisis meshes could be identified at 180 days and incorporation was scored as 0%. Therefore at 180 days the incorporation of Surgisis (0%, 0-0) was significantly lower than Strattice (13.7%, 10.3-22.4; $P<0.001$) and Permacol (20.7%, 5.7-24.5; $P<0.001$). For each mesh no difference in incorporation of the mesh was observed between 90 and 180 days.

Adhesions

At 90 days Surgisis had the highest percentage of mesh adhesions to the mesh implantation site (90%, 32.5-100) which was significantly more than all other meshes ($P<0.023$). Data per mesh is shown in Figure 3. Strattice showed a significantly smaller percentage of mesh surface covered with adhesions (5.0%, 5.0-5.0; median Zühlke 2) compared to all other meshes ($P<0.029$). When only considering non-infected meshes there was no longer a difference in adhesion coverage between Strattice and CollamendFM .

Figure 1. Comparison of combined percentage (90 and 180 days) of mesh infection. Values are percentage of macroscopically infected meshes of surviving animals. * Non-crosslinked and § crosslinked meshes.

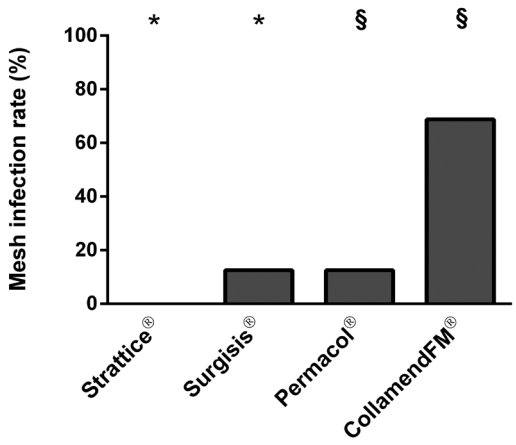
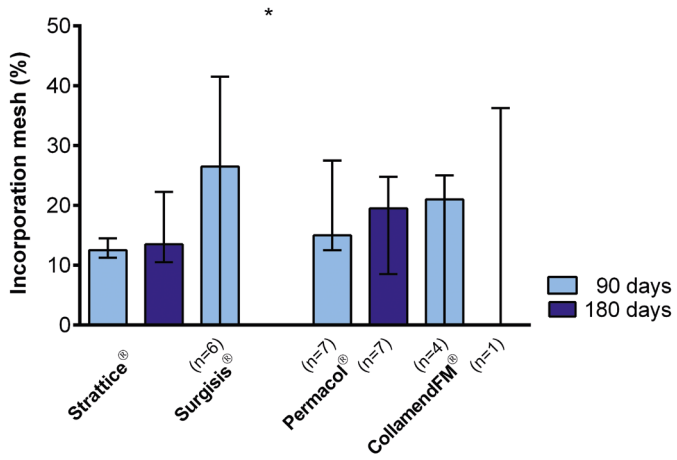
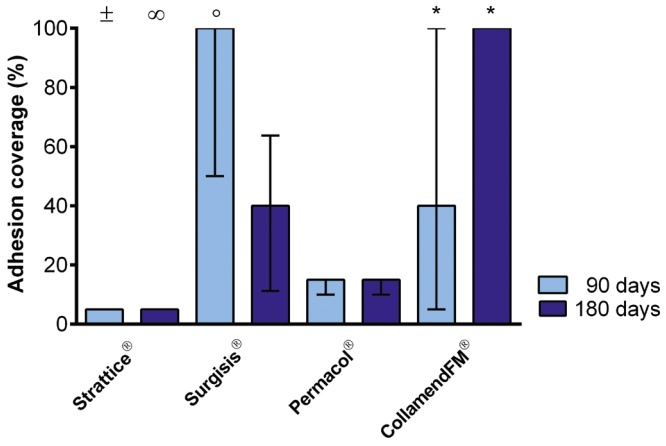


Figure 2. Percentage of the mesh edge incorporated into the abdominal wall, only non-infected meshes included. Values are median (interquartile range). At 180 days: *no Surgisis mesh could be identified and P<0.001 compared to Strattice and Permacol (n=7).



At 180 days CollamendFM had the highest rate of adhesions coverage (median 100, IQR 100-100; median Zühlke 3) of the mesh due to the high amount of infected meshes. This was significantly more than all other meshes (P<0.029). Adhesions were found at median 40% (IQR 11.2-63.7) of the size of the original implantation site of the Surgisis . Of the non-infected meshes Strattice had the least adhesions (5%, 5.0-5.0) which was significantly less than Surgisis (P<0.001) and Permacol (P<0.001).

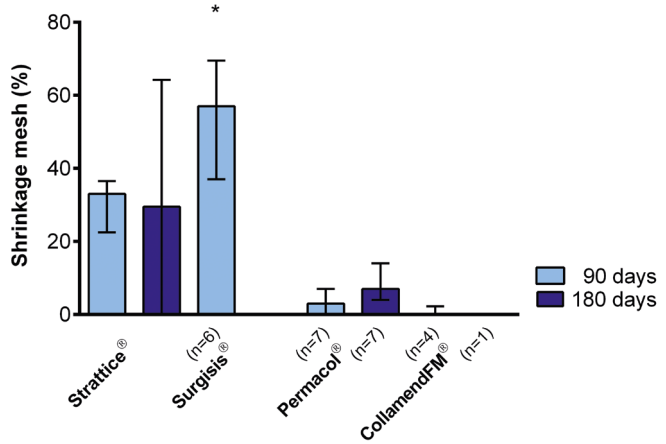
Figure 3. Comparison of percentage of each mesh covered with adhesions at the 90 and 180 days follow-up assessment. Values are median (interquartile range). *n=7. At 90 days: ± P<0.023 compared to all other meshes; ° P<0.029 compared to all other meshes. At 180 days: ∞ P<0.029 compared to all other meshes.



Shrinkage

Surface of the mesh could not be accurately measured in infected meshes therefore these were excluded from the analysis. Shrinkage of the mesh was highest in Surgisis at 90 days were a residue of median 43% of the original size was found (shrinkage 57%, IQR 37.0-69.5). Data per mesh is shown in Figure 4. This shrinkage of Surgisis was significantly higher than Strattice (33.0%, 22.5-36.5; P=0.02), Permacol (3.0%, 0.0-7.0; P=0.003) and CollamendFM (0.0%, 0.0-2.2; P=0.016). At 180 days there was no difference between the mesh groups.

Figure 4. Percentage of shrinkage of the mesh surface, only non-infected meshes included. Values are median (interquartile range). At 90 days: *P<0.016 compared to all other meshes.



Correlation between adhesion formation and incorporation

At 90 days CollamendFM showed a significant correlation between adhesion coverage of the mesh and incorporation of the mesh edge (ρ=-0.973; P=0.01). At 180 days there was no correlation. When the animals in group 90 days and 180 days were combined CollamendFM showed a correlation coefficient of ρ=-0.612; P=0.05. This correlation coefficient indicates that in CollamendFM meshes increase of adhesion formation was correlated with a decrease of incorporation.

Discussion

Based on the results of our long-term animal study we advocate more reluctance on implantation of biological meshes for abdominal wall repair. When biological meshes are implanted in an intraperitoneal position, incorporation in the abdominal wall is poor and adhesion formation and infection susceptibility remain a problem. The best results in our study were found with implantation of non-crosslinked Strattice. Adhesion coverage was low as 5%, but incorporation after 180 days was only 13.7%. Crosslinked Permacol had the better long-term incorporation (20.7%) but adhesion coverage of 15%. Worst results were found with crosslinked CollaMend and non-crosslinked Surgisis. After implantation of CollaMend infection of the mesh occurred in over 60% leading to a very low incorporation and increased adhesion formation. Non-crosslinked Surgisis dissolved completely within 180 days but induced substantial adhesion formation. These characteristics of biological meshes at long-term follow-up make the strength of the abdominal wall repair questionable. Moreover the adverse effects are comparable to intraperitoneally used (coated) synthetic meshes.

It is a recurrent phenomenon in research where initial studies on new technology describe positive results (whether or not industry driven) and subsequently critical reviews are published only after years of trial and error. The first studies on biological meshes were mainly case series with large variation in sample size, mesh material, implantation technique, follow-up and study endpoints(7, 15). Although the majority of cases were implanted in a non-contaminated environment they have also led to recommendations for the use in contaminated surgical fields. In recent years authors have started to publish their doubts on biological meshes(15, 16).

The aim of biological mesh implantation is to create a functional abdominal wall by deposition of native collagen during mesh degradation ('remodelling'). In our current study incorporation of the mesh was highest in Permacol however with only 20.7% incorporation (20.7%, 5.7-24.5), followed by Strattice (13.7%, 10.3-22.4). The steps in this dynamic process include inflammatory response, cellular penetration and neovascularisation of the mesh, fibroblast infiltration and collagen deposition(17). It appears that all meshes induce varying levels of foreign body reaction and fibrosis. Multiple characteristics of the mesh influence this response: mesh material, weight, pore size, crosslinking and sterilisation technique. More data is becoming available on histopathologic responses to specific synthetic and biological meshes in animal models(16, 18, 19). Novitsky et al observed that crosslinked meshes caused extensive foreign body reaction with fibrous encapsulation and no evidence of integration or remodelling of the mesh(16). Dissimilarities have been found between crosslinked and non-crosslinked meshes suggesting that improved integration into host tissue in non-crosslinked matrix is due to a moderate mononucleair cell reaction(20). Possible cause of this foreign body reaction is due to presence of nucleair material in the mesh or exposure of antigentic epitopes following implantation(21-25). It is suggested that some crosslinking processes damage the extracellular matrix and negatively influence the host response leading to encapsulation, decreased fibroblast penetration in the matrix and little collagen synthesis(20, 23, 26-28). Similar results have been found in patients who underwent removal of porcine biologic mesh where no to little evidence of neovascularisation or neocellularisation was detected in crosslinked meshes(17). Non-crosslinked Strattice mesh showed highest degree of new collagen deposition and organization in the study by Novitsky et al. which is comparable to the results in our current study(28).

Clinical studies like the multicentre RICH study showed similar results with a recurrence hernia rate of 19% after 1 year and 28% after 2 years(11). Likewise, Rosen et al recorded a recurrence rate of 31.3% with a follow-up of 21.7 months after implantation of biological mesh(29). These results can hardly be called sustainable hernia repairs and are not that dissimilar to synthetic meshes(6, 30). Increasingly synthetic meshes are being implanted in clean-contaminated and contaminated surgical field with quite favorable results(31-34) . Recent studies in grade II contaminated wounds showed lower recurrence rate after implantation of synthetic meshes compared to biological meshes with similar adverse event(35).

Possible factors affecting the collagenesis and consequential recurrence rate of hernias are high rates of postoperative infectious adverse-events. Ambivalent results have been published previously: Basta et al reported a 51.4% incidence of wound complications leading to recurrence hernia rate of 18.9% with postoperative wound infection being the only predictor of recurrence with an odds ratio of 22.1(36). Increased infection rate of biological meshes could be due to bacterial niches in biomesh pores and bacterial formation of biofilms(37).

Perhaps the advantage of biological meshes over synthetic material is the possibility of performing aggressive salvage procedures with removing parts of an infected mesh in situ to avert removal of all material with subsequently recurrence of hernia.

An important factor when choosing a mesh are the associated costs. Biological meshes are substantially more expensive than synthetic meshes(4, 6). However costs can be reduced when delayed primary closure with implantation of a biological mesh is possible during one hospital admission. In this way the number of admissions and in-hospital days can be reduced compared to staged repair(38). Additional benefit is earlier restoration of abdominal wall function which may lead to accelerated return to work.

A limitation of our study might be the implantation of the mesh in an intraperitoneal position. After intraperitoneal placement of the mesh there is no close vascular supply to facilitate neovascularisation and fibroblasts have difficulty reaching the mesh(39). However in previous animal studies intraperitoneal or extraperitoneal implantation of the mesh did not affect host tissue incorporation or mesh degradation(19). Contact of the mesh with the intraperitoneal compartment can often not be avoided due to the large dimensions of the hernia defect(11, 36). In the retrospective analysis of the RICH study there was no difference in hernia recurrence rate when the retro-rectus plane was compared to intraperitoneal placement. In 2 trials sublay procedures are found to result in less wound complications and seromas compared to onlay procedures(40, 41). It is suggested that further randomized trials on the optimal placement is needed to guide decision-making(17, 38).

Another limitation is that this research was performed in animals without any predisposing collagen disease or hernia defect.

Conclusions

We advocate more caution with implantation of biological meshes for abdominal wall repair. There seems to be no evidence for previously purported hypothesis that biological material enables ingrowth of cells and vessels resulting in a sustainable hernia repair. Implantation of biological mesh does not seem to reduce infection rate which is a significant factor for the recurrence of incisional hernia. Biological meshes might not have the required characteristics for implantation in clean environment with high infection rate and low incorporation of the mesh in the current experiment.

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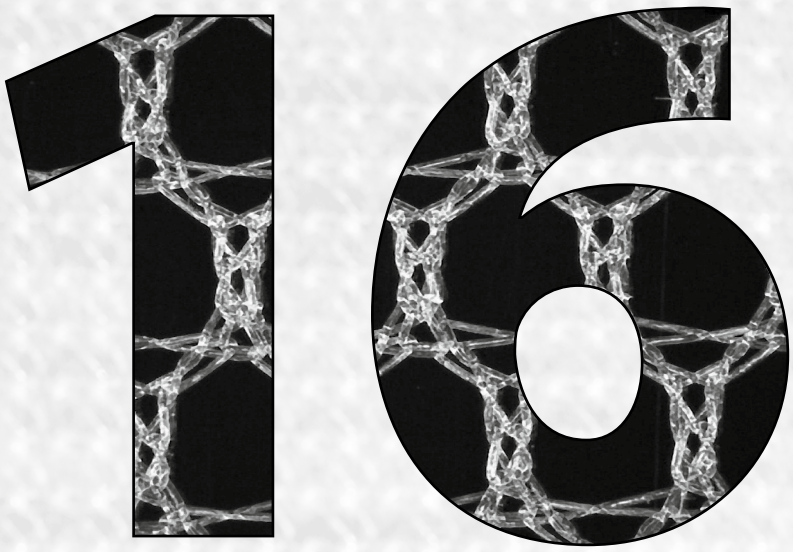
Chapter



Mesh expansion as the cause of bulging after abdominal wall hernia repair

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Abstract

Background

Recurrence is the most important complication of abdominal wall reconstruction. It is possible the repair itself is intact, but bulging or expansion of mesh causes recurrent swellings of the abdominal wall.

Case summary

In this report, we present bulging of a polyester mesh due to central pore expansion.

Discussion

Repetitive stress and variations in intra-abdominal pressure can change tensile strength and stretches mesh materials. Clinical distinction between recurrent hernia and mesh bulging is difficult but therapeutically irrelevant in symptomatic patients.

Conclusion

A swelling after abdominal wall repair can be caused by bulging of the mesh. A progressive bulging might be the result of failure of the mesh implant due to elongation. Mesh characteristics should be considered when choosing a feasible and suitable mesh for abdominal wall reconstruction.

Introduction

Recurrence is the most important complication of abdominal wall reconstruction. In order to reduce recurrence rates meshes are used as reinforcement of augmentation or bridging of large abdominal wall defects. Numerous meshes are available worldwide, differing in material, pore size, weight, tensile strength, elasticity and biocompatibility. These characteristics influence the risk of failure of repair. Swelling or bulge in the area of previous abdominal wall reconstruction is suggestive for recurrence, although not obligatory to be so(1, 2). It is possible that the repair is still intact and bulging of the mesh causes swelling. Bulging can be the result of an insufficient surgical technique. The problem is more frequently seen after repair of large defects(1), especially when mesh are used to bridge the defects(1, 3) and more frequent after laparoscopic repair(2-4). In this article we present the phenomenon of symptomatic bulging due to failure of a polyester mesh.

Time-line

2004 necrotizing fasciitis
2005-2008 4-staged repair of abdominal wall with polyester mesh
2012 symptomatic bulging of repair due to enlargement of the mesh. Excision part of mesh.
2015 recurrent symptomatic bulging of the mesh. Excision polyester mesh and replacement by polypropylene mesh

Case

A 43-year-old male was referred to the outpatient clinic with severe bulging of the complete right hemi abdomen. One year before he developed necrotizing fasciitis, extending from the right knee to the right thoracic wall resulted in a resection of the right abdominal wall. The patient was left with multiple scars from the right upper leg to the right thorax consisting mainly skin grafts. The abdominal wall consisted skin grafts and peritoneum. The patient experienced reduced quality of life and discomfort. A four-staged repair over three years

was performed in order to reconstruct the abdominal wall. Finally in 2008, the defect was closed in with two (sutured together) collagen-coated polyester meshes of 20*30cm (Parietex Composite®, Covidien, France). A coated mesh was implanted since contact with the visceral organs was inevitable with the loss of abdominal wall and bridging position of the mesh. The soft tissue defect was repaired at the sides of the hernia with skin obtained by using multiple tissue expanders. The soft tissue defect was covered with a free vascularized latissimus dorsi flap with large full thickness skin graft (figure 1).

Four years after the final repair the patient returned to the outpatient department with progressive swelling of the right lower abdomen (figure 2).

Figure 1. Abdominal wall after four-staged repair with Parietex Composite® mesh and latissimus dorsi flap (2008).

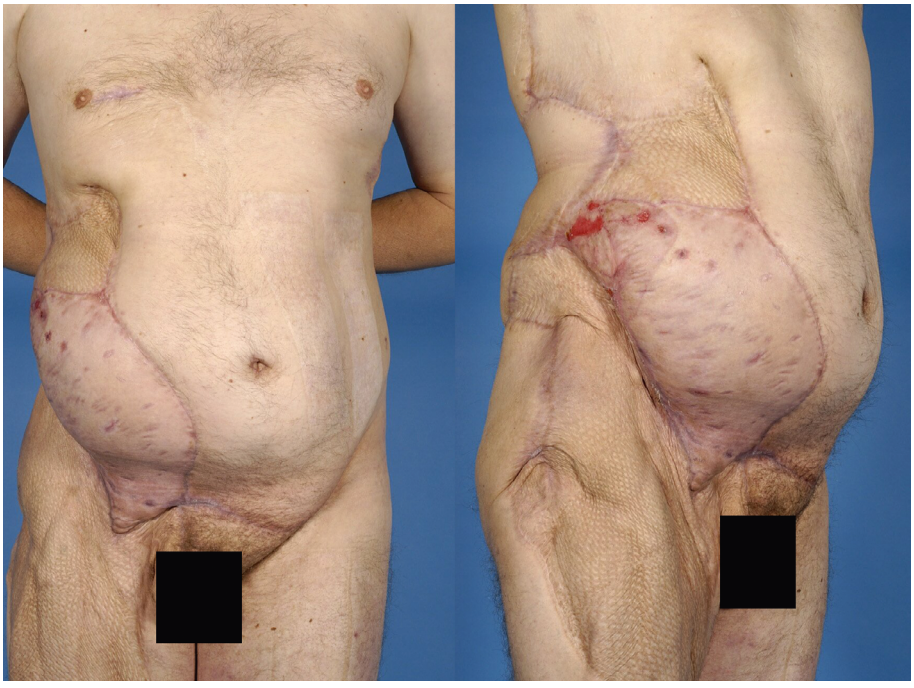
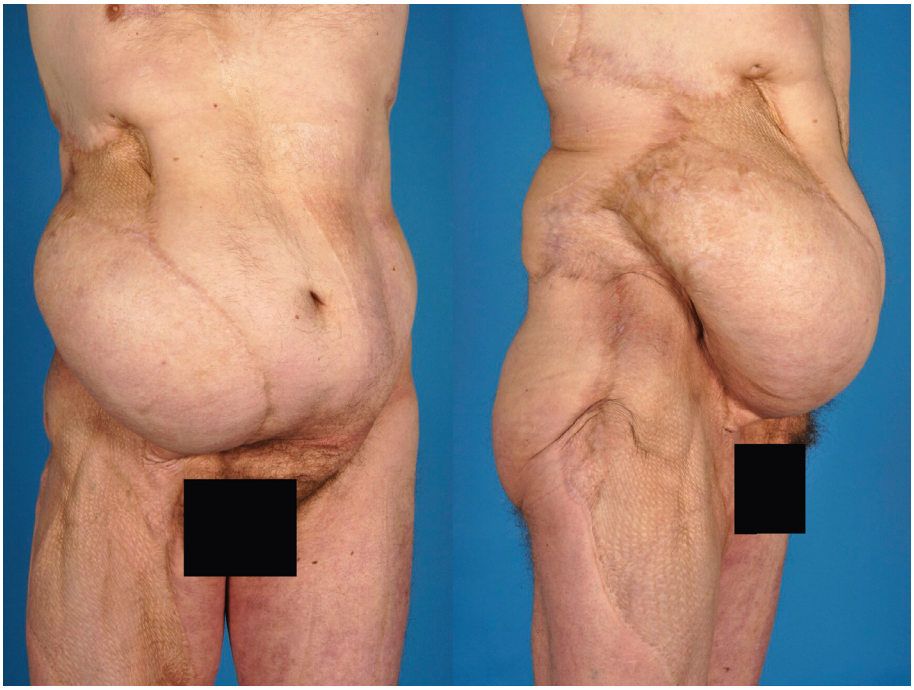
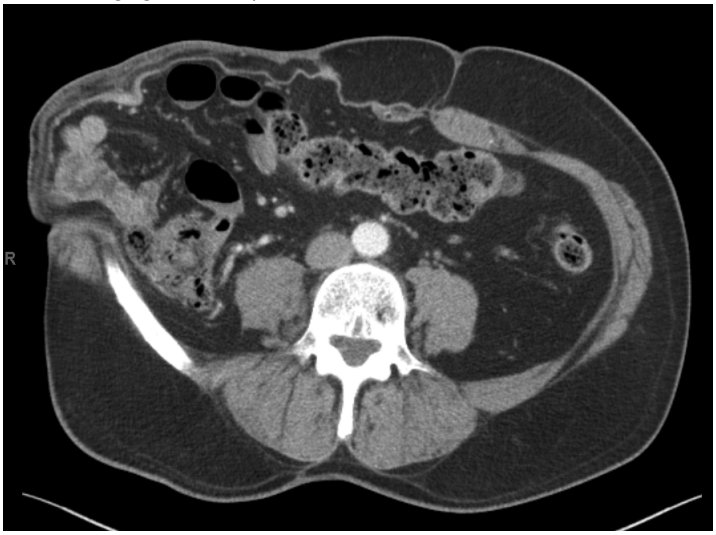


Figure 2. Increased bulging of the abdominal wall four years after reconstruction (2012).



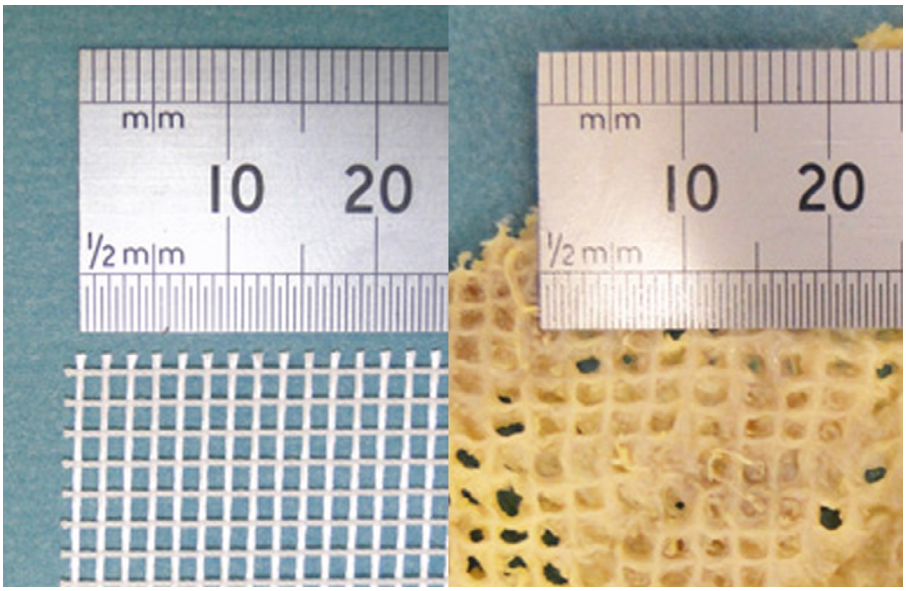
He suffered from abdominal pain and protrusion that interfered with his work. A CT-scan was performed, showing an intact repair, but enlargement of the mesh (figure 3).

Figure 3. CT-scan of bulging mesh four years after reconstruction (2012).



A surgical procedure was planned to repair the bulging abdominal wall. During surgery the bulging was found to be caused by expansion of an intact mesh. The elongation was caused by a striking central pore expansion from 1.5 to 2.5 mm (figure 4).

Figure 4. Pore size of explanted polyester mesh compared to original mesh (2102). (A) Pore size (1.5 mm) of original mesh (Parietex Composite®, Covidien, France). (B) Increased pore size (2.5 mm) of explanted mesh (Parietex Composite®, Covidien, France).



Surgical excision of the central part of the mesh was performed to tighten the mesh and reduce the bulging. 30 months later the patient developed swelling of the right abdominal wall again. The patient was planned for repair. During the procedure the mesh was still in tact but there was ongoing expansion of the mesh. The mesh has been removed and replaced by a 20*30 polypropylene collagen-coated mesh (Parietene Composite®, Covidien, France) in bridging position. A heavy-weight polypropylene mesh was implanted to provide the maximum tensile strength to prevent failure of the repair(5). Follow-up of over 1 year did not show any bulging.

Discussion

In this case symptomatic bulging at the hernia repair site was caused by elongations of the mesh due to pore enlargement. Each mesh used for hernia repair has certain features that determine the mechanical properties. During normal daily activities, mesh material is exposed to stress subsequent to changes in intra-abdominal pressure. The intra-abdominal pressure can raise up to 100 mmHg during coughing and can reach 250 mmHg during vomiting or jumping(6, 7). When abdominal wall defects are repaired using a bridging technique the material has to withstand the tensile stress at the borders.

Normal daily activities require a tensile strength of 16 N/cm and strenuous activities a maximum tensile strength 42-47 N/cm(5, 8). Medium-weight and heavy-weight meshes made of polyester, polypropylene or (expanded) polytetrafluoroethylene (ePTFE) provide the maximum tensile strength to prevent failure of the repair(5). In our patient polyester mesh was a valid choice for the first repair with regard to the tensile strength. The elasticity of a mesh should correspond to the elasticity of the abdominal wall to prevent foreign body sensation or discomfort of stiffness. Biomechanical studies have shown low stretch properties of meshes, only up to 3.5% during normal daily activities due to the very large diameter of the filaments(5). However, other biomechanical studies show that repetitive stress can change the tensile strength and stretches mesh materials(9). These studies did not test the polyester meshes, but in our case, elongation of polyester filaments is clearly demonstrated.

Bulging is an important adverse effect after abdominal wall repair. Incidences of bulging vary from 1.6% to 17.4%(2-4). Clinical distinction between recurrence and bulging of mesh is difficult(1-3). Differentiation is therapeutically irrelevant in symptomatic patients, because both conditions surgical repair is indicated. Asymptomatic patients however do not require repair in the case of mesh bulging, except for cosmetic reasons. Radiologic imaging can be used to establish the right diagnosis. The use of CT-scans to distinguish between bulging or recurrence can be challenging because polypropylene meshes are visible lines with densities similar to adjacent muscle and can better be identified with ultrasound(10-12). When performing surgical repair for symptomatic bulging it is often not necessary to remove the implanted mesh, when incorporation is sufficient. With open approach the

mesh can be partly excised to tighten the repair or the mesh can be removed and replaced. In this case however, bulging was an ongoing process, that finally resulted in mesh explantation and placement of a new mesh. In asymptomatic patients a watchful waiting approach seems justified(2).

Conclusion

A swelling after abdominal wall repair can be caused by bulging of the mesh. A progressive bulging might be the result of failure of the mesh implant due to elongation. The distinction between a recurrence and bulging of the mesh remains difficult even with radiological examinations but is therapeutically irrelevant in symptomatic patients.

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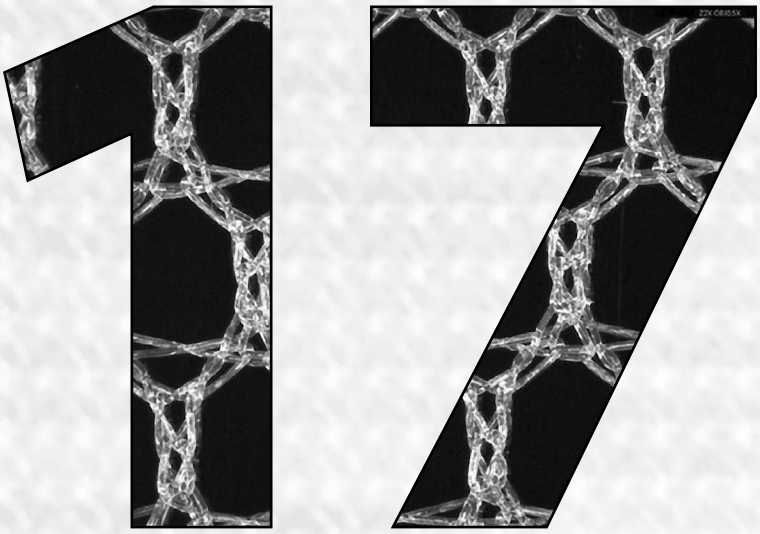
Chapter



General discussion and future perspectives

General discussion

An attempt has been made to reduce the incidence of incisional hernia (IH) through optimizing all techniques for closing abdominal wall incisions. The STITCH trial confirmed the positive results of the Swedish research group of Israelsson, that developed the 'small bites' suture technique(1). Although in our systematic review and meta-analysis, a superior suture material for suturing the abdominal fascia could not be detected, evidence from earlier systematic reviews and meta-analyses demonstrated a combination of a continuous suture technique with a non-absorbable or slowly-absorbable suture material to be superior to an interrupted suture technique with a fast-absorbable suture on the incidence of IH(2, 3). Furthermore, a continuous technique is, of course, faster than an interrupted technique(2).

Evaluating the evidence from the existing literature, the European Hernia Society formulated guidelines on the optimal method of closing abdominal wall incisions. It is advised to use a continuous suture technique with a slowly-absorbable suture, since using a non-absorbable suture is associated with increased incidence of prolonged wound pain and suture sinus formation(3). Furthermore, a 'small bites' technique with a suture to wound length radio of at least 4:1 is recommended, in part based on the results of the STITCH trial, providing level 1 clinical evidence.

When taking into account the biology of wound healing, using a slowly- or non-absorbable suture to suture the fascia seems most logical. Fascial healing starts with the recruiting of inflammatory cells. Two to five days after laparotomy, fibroblasts enter the wound side and start producing collagen. During the proliferation phase of the first three weeks, mainly type III collagen is produced and an extracellular matrix is created. Type III collagen consists of thin, weak fibres, and is replaced by strong and thick type I collagen during the following maturation phase(4, 5). The last part of the maturation phase is the remodeling or realignment of collagen fibres along tension lines – a process which can take years. The half-life tensile strength of absorbable sutures like polyglactin 910 (Vicryl®) and polyglycolid acid (Dexon®) is around 2-3 weeks(6), suggesting an insufficient support of the healing linea alba after this time. The half-life tensile strength of the slowly-absorbable suture polydioxanone (PDS®) is 6 weeks(6). Since healing fascia needs at least 14 days to regain its strength(4, 7), using a fast-absorbable suture will probably not provide support for long enough.

Since the research of Jenkins, it has been known that force distributions on the healing abdominal fascia play an important role in the development of IH(8). In patients that received an end colostomy during midline laparotomy, an increased prevalence of IH in those with parastomal hernia (PSH) was found after a mean follow-up of four years. A possible cause for this could be damage to the innervation of the abdominal wall during colostomy creation, leading in turn to atrophy of the abdominal rectus muscle. Furthermore, a non-symmetrical force distribution on the midline laparotomy wound occurs through the creation of a colostomy on the left side of the abdomen. The presence of PSH can increase the risk of the development of IH through both mechanisms.

Unfortunately, optimizing all techniques for closing a midline laparotomy does not reduce the IH rate to zero; in high-risk patients, other interventions might be needed to further reduce its incidence. Prevention of the development of IH with the use of a prophylactic mesh has been investigated for this group. Patients with an abdominal aneurysm or obesity have been found to benefit from prophylactic mesh augmentation; the incidence of IH in these patients was significantly reduced, with an odds ratio of 0.25(9, 10). It is not clear if mesh augmentation in an onlay or sublay position is superior in the prevention of IH in high-risk patients. An RCT (PRIMA trial) was initiated to study the best mesh position for preventing IH in high-risk patients(11). Short-term results showed that primary mesh augmentation is safe, with an increase in seroma formation only, after onlay mesh augmentation, and without any increased risk in surgical site infection(12). The results on the incidence of IH after 2 years follow-up are expected in the near future. Since PSH is also a risk factor for IH, prevention of PSH will also reduce the incidence of IH. Another RCT (PREVENT trial) was initiated to investigate the use of a prophylactic mesh reinforcement of a colostomy on the incidence of PSH(13). In this trial, a retromuscular polypropylene mesh was put in place during colostomy creation. The results of 1-year follow-up show a significant reduction in the incidence of PSH – from 24 to 4.5% – and no adverse events were found(14). Using prophylactic mesh augmentation of the abdominal wall during laparotomy or colostomy creation seems a safe and effective means of preventing hernias.

An additional effect in reducing IH might come from influencing patient-related factors. Unfortunately, it is not (yet) possible to influence genetic susceptibility, or the connective tissue disorders that increase the risk of IH in some patients. However, influencing co-morbidities, nutritional status, and lifestyle choices is possible. As physicians, we should try to optimize patient factors that influence wound healing positively and negatively before performing surgery. In collaboration with other medical specialists, diabetes regulation should be optimized to improve wound healing; steroid use should be critically evaluated; and chronic pulmonary obstructive disease (COPD) and other lung pathologies should be optimized to minimize postoperative coughing, risk of pneumonia, and steroid use. Furthermore, the patient's nutritional status should be evaluated in collaboration with a dietician. Optimization of metabolic state prior to major surgery leads to improved surgical outcomes by improving both wound healing and immune function(15). Patients with severe malnutrition and gastrointestinal dysfunction may benefit from preoperative parenteral nutrition. In morbidly obese patients, weight loss should be encouraged before elective surgery, since obesity is a risk factor for the development of IH(16-18). Lifestyle counselling should be provided, and patients should be strongly recommended to stop smoking – smoking is a risk factor for IH, has a detrimental effect on wound healing, increases the risk of surgical site infection, and is associated with increased coughing(19-21).

An IH generally tends to become symptomatic and require treatment(22). For small and medium-sized hernias, the superiority of open mesh repair over suture repair has been proven by recurrence rates(23-25). However, for large hernias (over 10 cm in diameter), no consensus currently exists. The systematic review performed on the treatment of large 'giant' IHs revealed the best results for open repair with mesh in the sublay position. Large IH repair often requires some form of components separation technique (CST). During CST, the blood supply of the abdominal wall by the epigastric perforating arteries is endangered. Damage to these arteries may jeopardise the blood supply to the skin (which then depends solely on blood flow from the intercostal arteries) and thus interfere with wound healing and increase the risk of infection (26-28). Furthermore, the intercostal arteries might have been damaged during former operations, giving rise to even more complications(26, 29). With this in mind, new endoscopic CST, minimally invasive CST, and posterior CST

have been developed, and promising results in terms of reduced wound infection and necrosis, have been described(30-33). In patients with a large IH, lateral migration of the rectus muscles in conjunction with flank muscle contraction, leads to a progressive decrease in the volume of the abdominal cavity and worsening protrusion of the viscera. Repositioning the viscera in a stiff abdominal cavity can lead to decreased perfusion of the intestine and elevation of the diaphragm, which in turn can lead to ventilatory difficulties – and rarely, abdominal compartment syndrome(26, 34). The use of preoperative pneumoperitoneum or botox might be indicated in some cases, although evidence is limited(35-38).

These results are in accordance with the results of reviews and meta-analyses on the subject for IH of all sizes(25, 39, 40). However, all authors report the same problem: the heterogeneity of the studies. Little evidence is available from RCTs on the subject of IH repair, and clear definitions of mesh positions, techniques, and outcome parameters are lacking, with substantial research flaws both methodologically and statistically. To improve the evidence-base for IH-surgery, the European Hernia Society Working Group has developed a classification for IH which takes in account the location, size, and possible recurrence of the IH(41). This classification system has, since its introduction in 2009, been widely accepted and used in scientific publications regarding IH. However, a solid comparison of research on abdominal wall surgery has remained elusive, due to the strong heterogeneity of reported study population characteristics and outcome measurements. To address this issue, improve research on hernia repair, and enable comparison of the literature, the EHS initiated a consensus meeting, and recommendations were duly formulated. Besides true recurrence, bulging is also an important adverse effect of abdominal wall repair, and the incidence of this is likely to have increased with the rise in laparoscopic hernia repairs(42). Clinical distinction between recurrence and bulging of mesh, is difficult(42-44). Differentiation is therapeutically irrelevant in symptomatic patients, because in both conditions surgical repair is indicated. Asymptomatic patients, however, do not require repair in the case of mesh-bulging, except for cosmetic reasons, and a watchful waiting approach seems justified in such cases(42).

The subject of a large part of the research on the treatment of IH is the search for the ideal mesh. Currently, a wide variety of synthetic and biological meshes are available on the market, complicating the selection of an

appropriate prosthesis. The most commonly used meshes in hernia repair are made of non-absorbable materials, in particular polypropylene and polyester. These materials are relatively inexpensive, easy to handle, and incorporate well into the abdominal wall. However, when placed in contact with the abdominal viscera, complications of adhesion formation can occur, associated with abdominal pain, small bowel obstruction, bowel erosion, enterocutaneous fistulas, and complicated future abdominal surgery(45-48). Contact with viscera is more common in laparoscopic repair and during the repair of complex or large abdominal wall hernias, with loss of domain or the inability to close the fascia completely. Furthermore, mesh infection can follow either open or laparoscopic hernia repair. Incidences of mesh infection after open repair range between 6-10%; and 0-4% after laparoscopic repair(49-51). Implantation of a mesh in a contaminated environment increases the risk of surgical site infections, including mesh infection(50, 52). For mesh use intraperitoneally or in contaminated fields, alternatives can be found in composite and biological meshes. Composite meshes are synthetic meshes with an additional layer or coating on the visceral side of the mesh. Biological meshes are collagen scaffolds derived from human or animal donors.

The results of the experiments described in part 2 of this thesis show a wide range of performance for biological meshes between clean and contaminated environments. Besides the infection susceptibility of some biological meshes, incorporation is found to be a problem for all biological meshes. This poor incorporation makes sustainable hernia repair questionable. The results of our animal experiments are in accordance with published results of recurrence rates of up to 80% in human hernia repair with biological meshes(53-59). Human studies reporting on the outcomes for biological meshes in hernia repair are scarce, report small numbers, are mostly single-institution based, and vary widely in follow-up time, operative technique, and patient selection(53). Furthermore, conflict of interest statements are often not reported(53). A limitation of our experiments might be the implantation of biological meshes in an intraperitoneal position. After intraperitoneal placement of a mesh, there is no close vascular supply to facilitate neovascularisation, and fibroblasts have difficulty reaching the mesh(60). However, in previous animal studies intraperitoneal or extraperitoneal implantation of the mesh did not affect host tissue incorporation or mesh degradation(61). In the retrospective analysis of the RICH study, there was no difference found in hernia recurrence rate when

the retro-rectus plane was compared to intraperitoneal placement of non-crosslinked biological Strattice® mesh in patients(56).

Biological meshes can roughly be divided into non-crosslinked and crosslinked meshes. After implantation, the scaffold of extracellular matrix (ECM) is gradually vascularised and remodelled into the host tissue while degradation of the ECM takes place(62, 63). To increase biomechanical strength, chemical crosslinking of the biological mesh can be conducted. In the experiments in this thesis, a high incidence of mesh infection of crosslinked biological meshes was found. These results are in accordance with clinical reports of infectious complications with use of biological meshes(54, 64-69). The development of infection in crosslinked biological meshes seems comparable to mesh infection in microporous synthetic meshes by preclusion of immune cells(70). The crosslinking of meshes appears to involve the decreasing of pore size in biological meshes such that it promotes a suitable housing for bacteria, while preventing access of macrophages, fibroblasts, blood vessels, and collagen fibres into the pores. The greater the percentage of crosslinking, the more a biological mesh behaves like a microporous mesh. Additionally, crosslinking may lead to encapsulation rather than remodelling of the mesh. It is suggested that some crosslinking processes damage the extracellular matrix and negatively influence the host response, leading to encapsulation, decreased fibroblast penetration into the matrix, and little collagen synthesis(71-75). Similar results have been found in patients who have undergone removal of porcine biologic meshes, where little or no evidence of neovascularisation or neocellularisation was detected in crosslinked meshes(76).

The first studies on biological meshes were mainly case series, with large variations in sample size, mesh material, implantation technique, follow-up, and study endpoints(52, 77). Although the majority of cases were implanted in a non-contaminated environment, these studies have also led to recommendations for use in contaminated surgical fields. In 2010, the Ventral Hernia Working Group (VHWG) recommended use of a biological mesh in cases of a potentially contaminated or infected wound, due to the risk of infectious complications(52). This publication, among other optimistic reports, led to the incorporation of biological meshes into the surgeon's armentarium, which resulted in widespread implantation of these grafts(52, 78-80). In recent years, authors have started to publish their doubts on biological meshes(53, 59, 77, 81). Biological meshes are often used when a hernia defect must be closed

in a contaminated environment: grade 3 and 4 hernia repairs of VHWG(52). Although no high-quality evidence exists to support the use of biological meshes in these situations, this decision can be defended. However, the use of biological meshes in clean or clean/contaminated environments – grade 1 and 2 of VHWG(52) – cannot be justified by the evidence. Recent studies on grade 2 hernia repairs showed a lower recurrence rate after implantation of synthetic meshes compared to biological meshes, with similar adverse events(82). Furthermore, several synthetic meshes have been shown to be infection-resistant in these circumstances(58). An important factor when choosing a mesh is the associated cost; biological meshes are substantially more expensive than synthetic meshes(53, 78, 80). The mean price of a biological mesh in 2016 was $19.15 per cm^2 ; and the mean price of a non-biological mesh was $5.41 per cm^2 – an average of 3,5-fold less cost(53). The 2016 costs of the biological meshes used in the experiments in this thesis were: Strattice® $30.29 per cm^2; Permacol® $18.24 per cm^2; Surgisis® $13.42 per cm^2; and CollaMendFM® $13.25 per cm^2(53). However, in VHWG grades 3 and 4(52), costs can be reduced when delayed primary closure with implantation of a biological mesh is possible during one hospital admission. In this way, the number of admissions and in-hospital days can be reduced, compared to staged repair(83). An additional benefit is earlier restoration of abdominal wall function, which may lead to accelerated return to work.

Future perspectives

Prevention of IH is a very important issue, and one that deserves a great deal more attention in the surgical community. As Hans Jeekel wisely stated during the 2016 EHS conference: "Don't judge a surgeon before you've seen him or her close the abdomen". Proper opening and closing of the abdominal wall should become a mandatory part of surgical training. Anatomical education and detailed instructions on the best evidence-based closing techniques will improve the general skills of surgical residents and reduce incidence rates of IH. Improvements in anatomical knowledge of the abdominal wall will also benefit laparoscopically oriented surgeons. Since laparoscopic abdominal surgery requires placement of trocars, there is a risk of vascular or nerve injury, and the development of an incisional hernia, or so-called trocar site hernia – especially

when the closure is with quickly absorbable sutures and trocars exceeding 5 mm in diameter(84, 85). To further prevent IH in high-risk patients, a prophylactic mesh seems a useful option. Ongoing research on the use of prophylactic mesh augmentation of the abdominal wall in high-risk patients is likely to provide high quality evidence regarding the best position of the mesh in the abdominal wall(11). Additionally, research on the improvement of fascial wound healing to prevent IH should be performed. Interesting ideas about the use of stem cells and growth factors are currently being investigated(86-88).

The surgical treatment of IH is complex, and individual patient-, surgical technique-, and mesh-related issues should be addressed for each patient. Every incisional hernia is different, and a CT-scan should be used to preoperatively evaluate the dimensions of the hernia, loss of domain, and quality of remaining abdominal wall muscles and tissues. The complexity of hernia repair necessitates a dedicated and certified abdominal wall surgeon and surgical team. Many incisional hernia repairs benefit from techniques where planes in the abdominal wall are used or mobilized, which requires in-depth knowledge of the abdominal wall and experience in abdominal wall surgery. To improve evidence-based surgery in hernia repair, an international collaboration should be established, with the involvement of dedicated hernia surgeons in international studies. Only in this manner can high-quality research, with adequate patients numbers, be accomplished. A very important parameter in hernia research is the length and method of follow-up. Patient follow-up should exceed one year, and radiological imaging is essential in establishing recurrence rates. A national, or (preferably) international, registry of hernia patients would be helpful. EuraHS and the Danish Hernia Registry are excellent examples of this, and are used to answer various research questions that require large cohort studies of patients(89-92).

Even for dedicated IH surgeons, it is almost impossible to make an educated selection of a mesh from the hundreds of available types and brands on the market. It is therefore advised that the positive and negative experiences of hernia surgeons should be 'bundled' through international collaboration. Research should not be performed on specific brands of meshes, but rather on generic characteristics of each type of mesh. The initiative of the research group Matthews and Deeken on this subject should be applauded. An interesting concept might be some sort of 'certificate of approval' for a mesh, granted by an international committee of experts from the scientific societies

of hernia surgery. Combining the results of biomechanical studies, animal experiments, and clinical data, this committee could hand out such a certificate to certain meshes, and help other surgeons make an educated selection of mesh prostheses.

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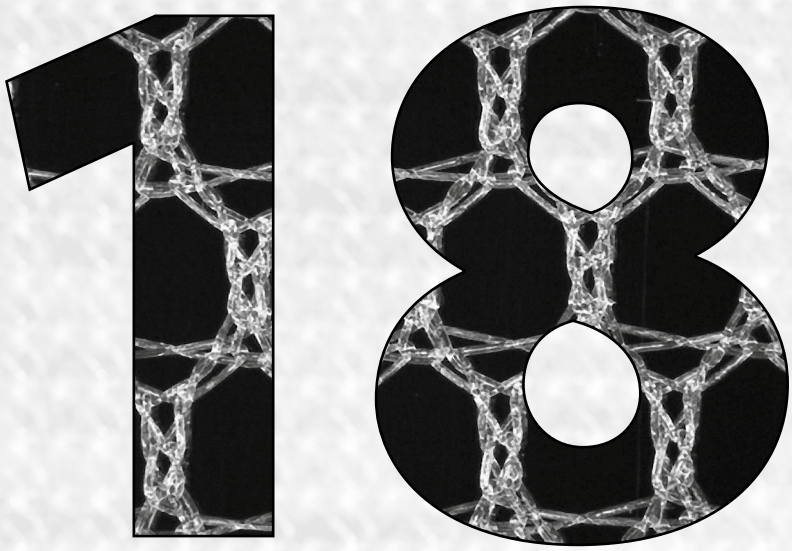
Chapter



Summary

In **Chapter 1** the subject of this thesis, incisional hernia (IH), is introduced. IH is the most frequent complication following abdominal surgery, and has great impact on patients' lives, as well as being a burden in terms of healthcare costs. Several patient factors and technical aspects play a role in the development of IH. As stated back in 1914 by Sir Victor Horsley, the radical cure of a hernia is best represented by its prevention.

Part 1. Prevention and incidence of incisional hernia

In the **first part** of the thesis, research is presented which determines the technical aspects of surgery that influence the development of IH.

Chapter 2 describes the design of a multicentre randomized controlled trial (RCT) – the STITCH trial – to compare the upcoming 'small bites' suture technique to the generally performed 'large bites' suture technique of the midline fascia after laparotomy. Across 10 participating hospitals, 560 patients were randomly allocated to these two techniques. The 'small bites' technique consisted of a running suture with small tissue bites of 5 mm and a stitch every 5 mm, performed with a 2-0 polydioxanone (PDS®) suture, with a 31 mm needle. The 'large bites' technique consisted of a running suture with large tissue bites of 1 cm and a stitch every 1 cm, performed with a 1 double loop PDS® suture, with a 48 mm needle.

In **Chapter 3,** the results of the STITCH trial are presented. Patients in the small bites group had fascial closures sutured with significantly more stitches than those in the large bites group (mean number of stitches 45 [SD 12] *vs* 25 [10]); a significantly higher ratio of suture length to wound length (5.0 [1.5] *vs* 4.3 [1.4]); and a significantly longer closure time (14 [6] *vs* 10 [4] min). During follow-up, radiological imaging of the abdominal wall was performed in 76% of patients. At 1-year follow-up, 57 (21%) of the 277 patients in the large bites group, and 35 (13%) of the 268 patients in the small bites group, had developed IH (p=0.0220, covariate adjusted odds ratio 0.52, 95% Confidence Interval 0.31–0.87; p=0.0131). Rates of adverse events did not differ significantly between the two groups.

Chapter 4 presents the findings of a systematic review and meta-analysis performed to analyze the evidence from RCTs on the optimal method or suture material for closing the midline fascia. When using the same suture technique,

no significant differences between suture materials regarding the incidence of IH were found. When using the same suture material, the 'small bites' technique had a significantly lower rate of IH than the 'large bites' technique. No significant differences were found between the continuous 'large bites' technique and a technique with interrupted sutures.

In **Chapter 5,** the European Hernia Society (EHS) guidelines on the closure of abdominal wall incisions are reported on. In these guidelines, it is recommended to close a midline incision with a continuous suture technique; to avoid fast-absorbable sutures; to perform fascial closure in one layer; and to not close the peritoneum separately. It is advised to use a slowly-absorbable suture and a 'small bites' technique, with a suture to wound length ratio of at least 4:1.

In **Chapter 6,** the incidence of IHs, and their correlation with parastomal hernias (PSH), is explored through examination of a cross-sectional study of 150 patients with left-sided colostomies. Patients with a PSH were found to have a 7-times greater occurrence of midline IH. Most of the IHs developed at the level of the colostomy.

In **Chapter 7,** the possible causes of the increased incidence of IH reported in Chapter 6 are further investigated. Seventy-seven patients with both a preoperative and postoperative abdominal CT-scan were selected from the cross-sectional study. The CT-scans of these patients were uploaded to the I-Space® system and three-dimensionally visualized and projected using V-scope® software. In the I-Space®, shift in the linea alba and thickness of the abdominal rectus muscles were measured. A thinner abdominal rectus muscle was found in patients with PSH, compared to those without. Furthermore, a shift of the midline to the right was found after colostomy creation. Both observations change the forces on the healing linea alba and likely contribute to the development of IH.

Part 2. Surgical treatment of incisional hernia

In the **second part** of this thesis, research on the surgical treatment of IH is presented.

In **Chapter 8,** the results of a systematic review on the surgical repair of IH are presented. Since evidence from RCTs was scarce, a meta-analysis

could not be performed. The results of cohort studies and non-randomized trials are compared with a generalized linear model, to determine the yearly recurrence risk for every technique. The surgical treatment options could broadly be divided into: open techniques without mesh; open techniques with mesh; and laparoscopic techniques with mesh. The open techniques with mesh augmentation performed best in terms of recurrence rates. Comparing individual techniques on yearly recurrence risk showed the best results for open repair with mesh in the sublay position.

In **Chapter 9,** the recommendations of the EHS for reporting outcomes of abdominal wall surgery can be found. It is recommended to use existing standards and statements available for the type of study that is being reported, i.e. the CONSORT, TREND, STROBE and PRISMA statements. Furthermore, recommendations are made to use standard definitions and classifications relating to hernia variables and treatment, and clear terminology proposed by the EHS and EuraHS. Likewise, the use of the validated Clavien-Dindo classification to report complications is recommended. An important proposal is to use 'time-to-event analysis' to report data on 'freedom-of-recurrence' rather than the use of recurrence rates, since this is more sensitive and accounts for patients lost to follow-up.

In **Chapter 10,** synthetic, composite, and biological meshes are compared in terms of adhesion formation and incorporation after 90 days in an animal model. The polyester composite mesh (Parietex composite®) demonstrated the best long-term results, with good incorporation and very little adhesion formation. The best performing biological mesh was non-crosslinked Strattice®, with very little adhesion formation, but only moderate incorporation.

Chapter 11 describes the implanting and comparing of several synthetic, composite, and biological meshes in a contaminated environment animal model. Polypropylene-based (Parietene®, Parietene composite® and Sepramesh®), condensed polytetrafluoroethylene (c-PTFE, Omyramesh®) synthetic and non-crosslinked biological (Strattice®) meshes developed none or very few mesh infections. Adhesion formation after 90 days was very slight with the biological mesh Strattice®, followed by the synthetic meshes Parietene composite® and Omyramesh®. However, incorporation of the biological mesh Strattice® was very poor after 90 days.

In **Chapter 12,** the cellular immune responses to the synthetic meshes investigated in Chapter 11 are examined. All meshes induced the influx of

T-cells and macrophages, and these cells were still found after 90 days. Both PTFE-based meshes (Omyramesh® and Dualmesh®) were mostly surrounded by T-cells, indicative of a chronic inflammatory reaction. Polypropylene meshes (Parietene® and Parietene composite®) had the lowest number of T-cells, indicative of resolution of the inflammatory reaction.

In **Chapter 13,** an in vitro model to study the biomaterial-dependent reaction of macrophages in an inflammatory environment is presented. The results are compared to an in vivo experiment with polypropylene mesh implantation in a contaminated environment. Macrophages were found to react in a similar biomaterial-dependent manner in the in vitro model as in the in vivo model.

In **Chapter 14,** the investigation of several biological meshes for infection susceptibility in a contaminated environment animal model, is presented. Crosslinked biological meshes (Permacol® and CollaMendFM®) demonstrated an infection rate of 70% compared to 4% in non-crosslinked biological meshes (Strattice® and Surgisis®). Incorporation in the abdominal wall after 180 days was poor in all meshes, and no residue of non-crosslinked Surgisis® could be found.

In **Chapter 15,** the study of long-term incorporation of biological meshes in a clean environment is presented. Even in this clean environment, cross-linked CollaMendFM® demonstrated a high infection rate, and only non-crosslinked Strattice® did not show any mesh infection. Incorporation of the non-infected meshes into the abdominal wall after 180 days was poor: 14% in Strattice® and 21% in Permacol®. No residue of any Surgisis® meshes could be identified at 180 days.

Chapter 16 of this thesis describes the relatively new phenomenon of mesh-bulging. A clinical case is presented in which a bulging Parietex composite® mesh was explanted and measured, and compared to the original implanted mesh. A striking expansion of the pores as the cause of bulging is demonstrated.

Conclusion

To prevent the development of IH, the abdominal wall can best be closed with a continuous 'small bites' suture technique, using a slowly-absorbable suture. Reducing the rates of PSH will likely reduce the incidence of IH. When

performing large hernia repair, mesh augmentation reduces recurrence rates. Several intraperitoneal-implanted synthetic composite meshes showed good incorporation and low adhesion formation. Even in the contaminated environment, some synthetic composite meshes did not show any mesh infection. Between clean and contaminated environments, the various brands of biological meshes behave very differently. Infection susceptibility and poor incorporation remain problematic with the majority of biological meshes. Only one non-crosslinked biological mesh was found to have no mesh infections and very little adhesion formation, but incorporation into the abdominal wall was insufficient for an intraperitoneal position.

Nederlandse samenvatting

Hoofdstuk 1 beschrijft het onderwerp van dit proefschrift: de preventie en behandeling van littekenbreuken. Na de ontdekking en introductie van asepsis en anesthesie in de 19e eeuw nam de abdominale chirurgie een grote vlucht. Met de toename van het aantal abdominale ingrepen werd de littekenbreuk een veel voorkomende complicatie en de incidentie is tot op de dag van vandaag onaanvaardbaar hoog. Littekenbreuken hebben een negatieve invloed op de kwaliteit van leven van patiënten en de manier waarop zij hun eigen lichaam boordelen. Het chirurgisch herstel brengt hoge kosten met zich mee en gaat gepaard met complicaties en recidieven. Het voorkomen van het ontstaan van een littekenbreuk is daarom ook van essentieel belang. Wanneer een littekenbreuk zich na abdominale chirurgie ontwikkelt wordt deze meestal symptomatisch en behoeft herstel. De chirurgische behandeling van een littekenbreuk heeft een hoog recidief percentage als er geen mat gebruikt wordt. De laatste jaren zijn er nieuwe synthetisch en biologische matten ontwikkeld voor het herstel van littekenbreuken. Voor kleine en middelgrote breuken is herstel met een mat eerste keus. Voor grote ('giant') littekenbreuken, met een defect van 10 centimeter of meer, bestaat nog geen consensus over de optimale manier van herstel.

Deel 1. Preventie en incidentie van littekenbreuken

Het **eerste deel** van dit proefschrift richt zich op de preventie en incidentie van littekenbreuken.

In **Hoofdstuk 2** is de opzet van de STITCH-trial gedetailleerd beschreven. In deze multicentrische gerandomiseerde-gecontroleerde-studie (RCT) werd de beste methode voor het hechten van de fascie van de linea alba onderzocht. In beide groepen werd de fascie gesloten met een voortlopende hechting van poydioxanone (PDS®). De meest gebruikte "large bites'-hechttechniek van de fascie (per centimeter een hechting met 1cm afstand van de fascierand) met een PDS 1-loop werd vergeleken met de veelbelovende 'small bites'-hechttechniek (per 5mm een hechting met 5mm afstand van de fascierand) met PDS 2-0. Na 1 jaar werd door middel van lichamelijk onderzoek en radiologische beeldvorming geëvalueerd of er een littekenbreuk was ontstaan.

In Hoofdstuk 3 zijn de resultaten van de STITCH-trial gerapporteerd. In 10 deelnemende ziekenhuizen werden 560 patiënten die een laparotomie ondergingen, gerandomiseerd in twee groepen. Patiënten in de 'small bites'-groep werden gesloten met meer steken (gemiddeld 45 vs 25), een hogere 'suture length to wound length ratio' van 4:1 en het sluiten van de fascie duurde langer (14 vs 10 min). De 'small bites'-techniek blijkt een significante vermindering van het aantal littekenbreuken na 1 jaar te geven met een verschil in incidentie van 13 tegenover 21%. De 'small bites'-techniek zal de nieuwe gouden standaard voor het sluiten van de buik worden.

In **Hoofdstuk 4** zijn de uitkomsten van een systematisch review en meta-analyse beschreven van alle RCT's, waarin separaat hechttechnieken of hechtmaterialen zijn onderzocht op de incidentie van littekenbreuken. Het bleek dat bij dezelfde hechttechniek het soort hechtdraad dat gebruikt wordt geen significant verschil toonde met betrekking tot de incidentie van littekenbreuken. Bij het gebruik van dezelfde hechtdraad liet de 'small bites'-techniek een lagere incidentie littekenbreuken zien dan de 'large bites'-techniek, maar tussen de 'large bites'-techniek en een techniek met staande hechtingen werd geen significant verschil gevonden.

Hoofdstuk 5 betreft de richtlijn over de optimale manier van het sluiten van de buik van de European Hernia Society. Voor electieve mediane laparotomieën wordt geadviseerd om de fascie te sluiten met een voortlopende techniek, het gebruik van een snel-oplosbare hechting te vermijden, de fascie in één laag te sluiten zonder separate sluiting van het peritoneum en een 'small bites'-techniek te gebruiken met een minimaal 4 maal zo lange hechting als de wond lang is (suture length to wound length ratio > 4:1).

In **Hoofdstuk 6** is de incidentie van littekenbreuken en parastomale hernia's (PSH) en hun correlatie onderzocht in een cross-sectionele studie. In deze studie van 150 patiënten met een eindstandig linkszijdig stoma, bleken patienten met een PSH een 7 maal zo hoog risico te hebben op een littekenbreuk. De meeste littekenbreuken ontwikkelen zich in de linea alba op het niveau van het stoma. Een reden hiervoor zou kunnen zijn dat het plaatsen van een stoma voor verminderde innervatie van de buikwand zorgt, waardoor atrofie van de m. rectus abdominis (MRA) op kan treden. Tevens ontstaat een niet-symmetrische krachtverdeling op het mediane laparotomielitteken als gevolg van het aanleggen van het stoma door de linker zijde van de buikwand heen.

In **Hoofdstuk 7** zijn 77 patiënten met een preoperatieve en postoperatieve CT-scan van de buik uit de cross-sectionele studie geselecteerd om deze werkingsmechanismen verder te onderzoeken. De CT-scans van deze patiënten werden onderzocht in de I-Space® door middel van V-scope® software. Hiermee konden de CT-scans als 3D-hologrammen worden geprojecteerd en verschuiving van de linea alba en de dikte van de MRA gemeten worden. Uit de resultaten bleek dat patiënten met een PSH een dunnere MRA hebben vergeleken met patiënten zonder PSH. Daarnaast ontstaat er bij de aanleg van een stoma een verschuiving van de linea alba naar rechts. Beide bevindingen veranderen de kracht op de genezende linea alba en dragen waarschijnlijk bij aan het ontstaan van littekenbreuken.

Deel 2. Chirurgische behandeling van littekenbreuken

Het **tweede deel** van dit proefschrift richt zich op de chirurgische behandeling van littekenbreuken.

In **Hoofdstuk 8** wordt een systematisch review van de literatuur beschreven, gericht op de beste techniek om een grote littekenbreuk te herstellen. Helaas waren er weinig gerandomiseerde prospectieve studies beschikbaar en was een meta-analyse van de data niet mogelijk. Om de verschillende technieken vergelijkbaar te maken voor recidieven werd een gegeneraliseerd lineair model gebruikt om het jaarlijks recidief risico voor alle technieken te berekenen. De beschreven chirurgische technieken werden onderverdeeld in open herstel zonder mat, open herstel met mat en laparoscopisch herstel met mat. De open technieken zonder mat hadden de hoogste recidief percentages. De open technieken, met matten in verschillende posities ten opzichte van de buikwand, lieten de beste resultaten zien. De geadviseerde positie voor de mat in de buikwand is de sublay positie gezien de lage recidiefkans op lange termijn en het lage jaarlijkse recidiefrisico.

In **Hoofdstuk 9** staan de aanbevelingen van de European Hernia Society ten aanzien van het rapporteren van uitkomsten van buikwandchirurgie. Er wordt geadviseerd om de bestaande richtlijnen en statements te gebruiken bij het rapporteren van de studie karakteristieken, zoals de CONSORT, STROBE en PRISMA statements. Verder wordt aanbevolen om de EHS-definities en classificaties voor buikwandbreuken en de Clavien-Dindo classificatie voor

het rapporteren van complicaties te gebruiken. Verder wordt voorgesteld om als uitkomstmaat 'afwezigheid-van-recidief' te gebruiken in plaats van het recidiefpercentage, omdat dit een meer gevoelige uitkomstmaat is en ook rekening houdt met patiënten, die 'lost to follow-up' zijn.

Hoofdstuk 10 beschrijft het vergelijk van synthetische en biologische matten met betrekking tot ingroei en adhesievorming na 90 dagen in een diermodel. De synthetische matten van polyester en polypropyleen lieten, in tegenstelling tot de biologische matten, goede ingroei zien. Synthetische composite mat Parietex composite® en biologische mat Strattice® gaven bijna geen aanleiding tot adhesievorming.

In **Hoofdstuk 11** rapporteren we de eigenschappen van synthetische en biologische matten in een gecontamineerd milieu in een diermodel. Zowel enkele synthetische (Parietene®, Parietene composite®, Sepramesh® en Omyramesh®) als biologische matten (Strattice®) bleken bestand tegen infectie. Na 90 dagen was de mate van adhesievorming op biologische mat Strattice® het laagst, gevolgd door synthetische matten Parietene composite® en Omyramesh®, maar waren de synthetische matten beter ingegroeid.

In **Hoofdstuk 12** werden de matten uit het gecontamineerde milieu aanvullend onderzocht op vreemdlichaamreactie. Bij alle matten werd na 90 dagen nog een influx van T-cellen en macrofagen gezien, indicatief voor een chronisch inflammatoire reactie. Wel waren er duidelijk verschillen tussen de matten te zien. Beide matten van PTFE (Omyramesh® en Dualmesh®) waren het meest omgeven door T-cellen. Bij de polypropyleen-matten (Parietene® en Parietene composite®) werden de laagste aantallen T-cellen gevonden, wat duidt op het uitdoven van deze reactie.

In **Hoofdstuk 13** presenteren we een nieuw in vitro model waarin de eigenschappen van synthetische matten kunnen worden vergeleken. De resultaten van het in vivo experiment met polypropyleen-matten in gecontamineerd milieu uit hoofdstuk 12 werden vergeleken het nieuwe in vitro model. De macrofagen in het in vitro model bleken op een vergelijkbare manier te reageren op verschillende biomaterialen als in vivo.

In **Hoofdstuk 14** onderzochten we de infectiegevoeligheid van verschillende biologische matten in een diermodel. Na implantatie in een gecontamineerd milieu trad bij 70% van de gecrosslinkte matten (Permacol® en CollaMendFM®) een matinfectie op, tegenover 4% van de niet-gecrosslinkte matten (Strattice® and Surgisis®). Na 180 dagen bleek niet-gecrosslinkt Surgisis®

volledig verdwenen te zijn en was de ingroei in de buikwand van de andere matten slecht tot matig.

In **Hoofdstuk 15** richten we ons op de ingroei van biologische matten in de buikwand. Dezelfde collageen matten werden geïmplanteerd in een schoon milieu. Zelfs in het schone milieu werd bij CollaMendFM® een hoog infectiepercentage gevonden en werd alleen bij Strattice® geen enkele matinfectie gevonden. Na 180-dagen werd bij alle collageen matten opnieuw een matige ingroei in de buikwand gevonden (Strattice® 14% en Permacol® 21%) en was niet-gecrosslinkt Surgisis® volledig verdwenen.

In **Hoofdstuk 16** beschrijven we een 'bulging mesh', een recent bekend geworden complicatie na littekenbreukherstel. Hierbij is er wel zwelling van de buikwand, maar geen sprake van een waar recidief en dekt de mat nog steeds het buikwanddefect af, echter hernieert de mat mee door het defect naar buiten. In deze casus wordt voor het eerst het uitrekken van de poriën van een polyester mat bewezen bij een patiënt als oorzaak van deze complicatie.

Conclusie

Om het ontwikkelen van een littekenbreuk te voorkomen kan het beste de fascie gesloten worden met een voortlopende langzaam oplosbare hechting in een 'small bites' techniek. Het aanwezig zijn van PSH geeft een hogere kans op een littekenbreuk. Indien een grote littekenbreuk hersteld wordt kan het beste een mat gebruikt worden om het recidief percentage te verlagen. Enkele synthetische matten laten een goede ingroei en lage adhesievorming zien indien ze geïmplanteerd worden in een intraperitoneale positie. Zelfs in het geïnfecteerde milieu blijken sommige synthetische matten infectieresistent. Het gedrag van verschillende biologische matten in zowel schoon als geïnfecteerd milieu is uiteenlopend. Slechte ingroei in de buikwand en matinfecties blijken problematisch bij de meeste soorten biologische matten. Slechts één soort niet-gecrosslinkte biologische mat liet geen matinfecties en een lage adhesiegevoeligheid zien, maar ook deze mat vertoonde een matige ingroei in de buikwand wanneer hij werd geïmplanteerd in een intraperitoneale positie.

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Henriksen NA, **Deerenberg EB**, Venclauskas L, Fortelny RH, Miserez M, Muysoms F. Triclosan-coated sutures and surgical site infection in abdominal surgery: the TRISTAN review and meta-analysis. *Submitted*

PhD Portfolio

Summary of PhD training and teaching

Name PhD student:	Eva Deerenberg	PhD period:	2010-2016
Erasmus MC Department:	Surgery	Promotor:	prof.dr. J.F. Lange
		Co-promotor:	prof.dr. J. Jeekel

1. PhD training

	Year	Workload
General courses		
- Laboratory animal science	2010	3 ECTS
- Statistics NIHES 'Biostatistics for clinicians' and 'Regression analysis for clinicians'	2011	2 ECTS
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2009	1 ECTS
Specific courses (e.g. Research school, Medical Training)		
- Advanced Suturing Course, VUMC	2015	1 ECTS
- Precourse EHS 2016	2016	1 ECTS
(Inter)national conferences (oral presentations)		
- European Hernia Society, Rotterdam (1)	2016	1 ECTS
- World Conference on Abdominal Wall hernia Surgery, Milan, Italy (1)	2015	1 ECTS
- American Hernia Society 2014, Las Vegas, USA (1)	2014	1 ECTS
- Rotterdam Interactive Congres on Hernia (1)	2014	1 ECTS
- Nederlandse Vereniging voor Heelkunde (2)	2013	2 ECTS
- American Hernia Society 2012, New York, USA (3)	2012	3 ECTS
- EuraHS symposium, Brussel, Belgium (1)	2012	1 ECTS
- Abdominal Wall reconstruction Conference, Washington, USA (2)	2011	2 ECTS
- European Society of Surgical Research, Achen, Germany (3)	2011	3 ECTS
- Nederlandse Vereniging van Heelkunde (1)	2011	1 ECTS
- Symposium Experimenteel Onderzoek Heelkunde, Amsterdam (1)	2011	1 ECTS
- Bomedical Engineering (BME), Katwijk aan Zee (1)	2011	1 ECTS
Other		
- Organiser Rotterdam Interactive Congress on Hernia (RICH) and pre-course 12 & 13 Januari 2012	2012	2 ECTS
- Member group developing 'European Hernia Society guidelines on closure of abdominal wall incisions'	2015	2 ECTS

2. Teaching

	Year	Workload
Lecturing		
- College 'Applied anatomy' 1st year medicine	2010	1 ECTS
Supervising practicals and excursions, Tutoring		
- Practical 'local anesthesia and intracutaneous suturing' 4th year medicine	2011	1 ECTS
Supervising Master's theses		
- S. Smith & T. Ruby (Industrial Design, TU Delft)	2010	2 ECTS
- E. Emirdag (Mechanical Engineering, TU Delft)	2011	1 ECTS
- S. van Welsenes & W. Kroesbeek (Mechanical Engineering, HRO)	2010	2 ECTS
- T. Vos (Mechanical Engineering, HRO)	2011	1 ECTS
- M. Roer, D. Hogerzijl en K. Vakalopoulos (research master, ErasmusMC)	2011	3 ECTS
Other		
- Six lectures on pathology in 'Thanatopraxy course', Skillslab ErasmusMC	2010	3 ECTS
Total		44 ECTS

Dankwoord

Er is een positieve bijdrage geleverd aan mijn wetenschappelijk onderzoek en onderzoekstijd door een groot aantal mensen mensen en hen bedank ik graag persoonlijk. Enkelen verdienen echter een publiekelijk dankwoord:

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beroepsmatig elkaars klankbord zullen blijven. Bedankt dat je vandaag aan mijn zijde staat als paranimf.

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Lieve Patrick, bedankt voor je eindeloze steun en motivatie als ik het promoveren even niet meer zag zitten. Ik hou van je.

Curriculum Vitae of Eva Barbara Deerenberg

Eva Barbara Deerenberg was born on March 2nd, 1982 in Den Helder, the Netherlands. She graduated from Erasmiaans Gymnasium Rotterdam in 2000, before commencing the study of Health Sciences at the University of Maastricht. Her interest in the pathophysiology and treatment of diseases convinced her to start a second study in 2001, adding Medical School to her study of Health Sciences. In 2004, Eva obtained her Master's degree in Health Sciences. During Medical School she undertook an internship in the department of Internal Medicine at St. Maarten Medical Center in Sint Maarten, Dutch-Antilles.

After obtaining her medical degree at the University of Maatricht in January 2008, she worked as a resident in the Department of Surgery at Erasmus University Medical Center and Maasstad Hospital. In 2010, she became research fellow to Prof. Dr J.F. Lange, Prof. Dr J. Jeekel and Prof. Dr G-J. Kleinrensink at the Department of Surgery of Erasmus University Medical Center. Her clinical and experimental work has culminated in the writing of this thesis.

She commenced her training in General Surgery in July 2012 at St. Franciscus Gasthuis (Dr G.H.H. Mannaerts and Dr T.M.A.L. Klem) and Erasmus University Medical Center (Dr B.P.L. Wijnhoven), Rotterdam. Her surgical training continued in January 2017 at Maasstad Hospital (Dr R.A. Klaassen), Rotterdam, with an ongoing focus on gastro-intestinal surgery and of course, abdominal hernia surgery.

She is happily married to Patrick Sem Treffers and together, they have a son Max.