Risk Factors and Prevention of Incisional Hernia

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Acknowledgements

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Risicofactoren en de preventie van littekenbreuken

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Introduction and outline of thesis

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Patients requiring abdominal surgery can be operated via open surgery, laparoscopic surgery or surgery through an natural orifice. In case of open surgery, the midline incision is the most frequently used incision for gaining access to the abdomen. At the end of surgery the abdominal wall will be sutured to ensure that abdominal contents remain in their original place. After closure of the abdomen the surgeon will sometimes opt to close the subcutaneous fat layer separately, after which the skin will be closed via suture or staples. In case of failure of the abdominal wall closure the contents of the abdomen may protrude through the defect causing a possible bulge and symptoms to occur. This failure or incisional hernia (IH) is defined by the European Hernia Society as an abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination and/or imaging (1).

Anatomy

The abdominal wall consists of a combination of skin, subcutaneous fat, muscles, fascia, blood and lymphatic vessels and nerves. Access to the abdominal cavity can (in most cases) only be achieved by cutting through these tissues. The midline incision, which cuts through the middle of the anterior abdominal wall, is frequently performed and generally preferred by surgeons because of its ease, speed and excellent exposure. The anterior abdominal wall consists of the abdominal rectus muscles, the external and internal oblique muscles, and the transverse abdominal muscle. The abdominal rectus muscles insert on the ribcage superiorly and on the pubic bone inferiorly. The external and internal oblique muscles and transverse abdominal muscles are situated lateral to abdominal rectus muscles. The fascia or aponeurosis of the external oblique muscle, internal oblique muscle and the transverse abdominal muscle surrounds the abdominal rectus muscle (anterior rectus fascia and posterior rectus fascia) and join together in the midline, forming the linea alba. However, below the arcuate or semicircular line, which is situated below the umbilicus, the fascia does not surround the rectus muscle, but instead is situated ventrally to the abdominal rectus muscles (Figure 1). Blood supply to the rectus muscles is provided by the superior and inferior epigastric
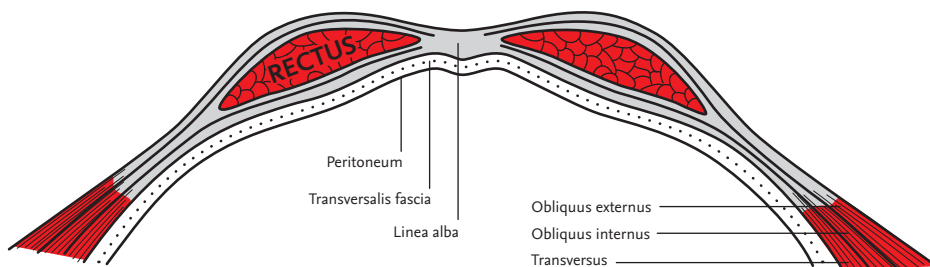

Figure 1   Abdominal wall musculature

arteries, which arise from the internal thoracic artery and external ileac artery. The epigastric arteries are situated between the abdominal rectus muscle and the posterior rectus fascia. The abdominal rectus muscles are innervated through the intercostal nerves that move from the thoracic spinal column (T1-T12) through the neurovascular plane between the internal oblique and the transverse abdominal muscles around the abdominal cavity.

History

Ever since man has been standing in the erect position, probably abdominal wall hernias have existed. The earliest findings of hernias date back to ancient Egypt where tomb paintings show servants and workmen with protuberances near or above the umbilicus. Other references to hernia include: the Ebers Papyrus (one of the most complete medical texts dating to ancient Egypt), the Corpus Hippocrates (the collected writings of Hippocrates and his followers) and Celsus who was the first to advocate a layered closure of the abdominal wall to prevent IH (2, 3). It was not until 1827 when Sir Astley Cooper gave the first description of incisional hernia: "Wounds of the abdominal wall in the healing of which the muscles fail to unite, and a laceration of some of the fibers of the abdominal muscles under violent exertions or blows, which allows the peritoneum to pass between them" (4). Still, the treatment of IH remained limited to trusses, herniotomy, cautery and exsanguination, which had very high morbidity and mortality rates. This however changed after the introduction of general anesthesia by means of chloroform and ether in the beginning of the nineteenth century (5, 6). In addition later that century aseptic techniques were introduced by Joseph Lister in 1865, rapidly increasing the number of surgical interventions and creating the possibility of intra-abdominal surgery (7). As abdominal surgery became more common, the incidence of IH also increased. In 1901 Eads recognized the high frequency of incisional hernia, stating: "The occurrence of ventral hernia as a sequence of abdominal section is so common that it should command our thoughtful consideration" (8). More than a century later this statement still holds true.

Incidence and risk factors

IH is one of the most frequent postoperative complications after abdominal surgery. After a 10 year follow-up 10-20% of patients in the general population will have developed IH after abdominal surgery (9-11). Certain factors, however, can increase the risk of developing IH. These factors can generally be divided into two groups, mechanical factors and wound healing factors.

Mechanical factors

A common physics law is that energy or pressure prefers the path of least resistance. This principle also applies to the human body. Weak areas such as the inguinal region can fail in case of increased pressure.

The same holds true in case of laparotomy wounds. Recent laparotomy wounds are in a process of healing and susceptible to pressure increasing the risk of wound breakdown. In addition, completely healed laparotomy wound only regain up to 80% of their original strength and increased intra-abdominal pressure can also increase the risk of failure (12). Today's most frequently serious risk factor causing increased intra-abdominal pressure is represented by obesity. The overabundance of intra-abdominal fat, which is frequent in patients with obesity, will increase IH incidence over 30%(13, 14). Other factors that increase the intra-abdominal pressure are chronic obstructive pulmonary disease, prostatism, ascites, obstipation, ileus and pregnancy (15-17).

Besides increased intra-abdominal pressure other mechanical factors play an important role in the development of IH. During the closure of the abdomen the different incised layers will be sutured together, however the technique of this closure is of utmost importance. Suture techniques have been subject of research ever since abdominal surgery became common practice. The period in which a suture holds its initial strength is relevant as a surgeon would want a suture to hold its strength at least until wound healing has been largely completed. For this reason different types of absorbable and non-absorbable suture material have been developed. Previous studies have demonstrated that one should use slowly absorbable sutures for closure of the abdominal wall. This type of suture is equal with regard to IH incidence compared to non-absorbable sutures but inflicts less pain (18).

In addition to the type of suture research has shown that we should use a continuous mass closure technique when closing the abdominal wall (18-20). When performing the continuous closure, research has suggested to use a 4:1 suture length to wound length ratio (SL:WL). This increased length of suture would counter the effect of abdominal distention after surgery caused by regular inspiration, coughing and postoperative complications such as ileus (21-23). In addition to the SL:WL principle recent studies have demonstrated that small suture bites also yield a higher tensile strength compared to large bites reducing IH formation (24, 25).

Wound healing factors

After closure of the abdominal wall wound, the regular wound healing process will start. Normal wound healing consists out of three overlapping major phases: inflammation (24 – 72 hours), regeneration (days – weeks) and maturation (months). The wound healing process is complex and involves many interacting cells, cytokines and growth factors, carbohydrates and proteins, all of which cascade into and act within the wound margins. However, the healing of the wound can become compromised due to postoperative complications or factors already present preoperatively. The most profound postoperative factor for impaired wound healing is wound infection or surgical site infection (SSI). Five percent of all surgical procedures will develop SSI (26). During the inflammation phase bacteria will be removed from the wound area by

monocytes and polymorphonucleocytes. However, in some cases (for instance in avascular areas) the human body is unable to clear the bacterial load, increasing the risk of SSI. In other instances the bacterial load might be too high (for instance after surgery of the colon) which also increases the risk of SSI. Due to colonization of bacteria the inflammation period will be prolonged and wound healing will be become compromised (27).

Preoperative factors that can effect wound healing but also enhance SSI development are increased age, use of corticoid steroids, diabetes and obesity (28-34). In addition to preoperative factors that impair wound healing, there are also pre-operative factors that have an effect of the strength of the wound. The failure of several surgical techniques to provide durable results has prompted investigators towards the research of the pathophysiology. Research demonstrated that collagen metabolism disorders, such as Ehlers Danlos and Marfan, are strongly associated with hernia and high recurrence rates, supporting the hypothesis that abdominal hernia represents a disease of the extracellular matrix (35, 36). The extracellular matrix consists mainly out of collagen and is responsible for the most part for its tensile strength. The ratio of mature collagen (type 1) and immature collagen (type 3) is in dysbalance in aortic abdominal aneurysm patients (37). Patients with an abdominal aortic aneurysm are more susceptible to herniation due to this dysbalance and have higher risk of IH formation of 30% (38-42). In addition, matrix metalloproteinases (MMP), which are partly responsible for collagen degeneration and tissue inhibitors of MMPs (TIMP), have been implicated as another possible balance that is deregulated in these compromised patients causing weaker connective tissues.

Treatment

Besides the high frequency of IH after abdominal surgery IH is also a complication with a high impact on quality of life. Recent research showed that of all patients with IH, the majority had symptomatic hernia. In addition, patients quality of life and body image was negatively affected by IH (43). Due to symptoms and negative impact on quality of life, surgeons frequently opt to perform repair of IH. It has been investigated that the use of a mesh compared to primary suture will significantly improve the results of IH repair (16). The long-term follow-up of the referred study displayed remarkable results with a 10-year cumulative recurrence rate of 32% for mesh repair compared to 63% for suture repair (44). Based on this article IH repair with suture should be abandoned. In this trial the open sublay technique (mesh on posterior rectus fascia) was used but other techniques such as the onlay repair (mesh on anterior rectus fascia) can also be applied. However, currently no evidence exists regarding which IH repair technique is preferable (45, 46). Besides open techniques, the use of laparoscopic IH repair has been gaining popularity. Laparoscopic hernia repair has shown to be equal with regard to IH recurrence but increases the change of peri-operative complications such as bowel injury (47, 48). Despite better results after mesh repair and the introduction of laparo-

scopic techniques, the recurrence rates remain unacceptably high and should not be accepted as optimal treatment. In addition, mesh repair also facilitates mesh related complications, such as infection, seroma, hematoma and fistulas resulting in possible removal of the mesh and/or complex abdominal wall wounds (44, 49, 50). Furthermore, patients previously treated for a hernia with mesh repair are associated with an increase in intraoperative and postoperative complications in case of relaparotomy (51, 52).

For this reason physicians might be tempted to opt for a conservative approach in case of asymptomatic hernias or in patients with severe comorbidities. This watchful waiting approach has already been investigated in inguinal hernia patients but no evidence with regard to IH exists (53, 54). However, considering the reduced quality of life, recurrence rate, and hernia repair related complications, it would be better to prevent IH formation altogether.

Prevention

In the last decade scientists have increased their efforts in order to prevent IH from occurring. Earlier mentioned suture techniques have improved incidence rates but IH remains the most frequent postoperative complication after abdominal surgery. Patients with risk factors such as obesity and aortic aneurysm are too compromised and will in most cases develop IH regardless of suture technique. In these compromised cases it may be possible to prevent IH by implementing prophylactic or primary mesh augmentation (PMA). In case of PMA a mesh is placed during closure at the end of the surgery in order to strengthen the abdominal wall. Recently a few trials have been published focusing on PMA, however questions remain as to the effectiveness of PMA, the best technique for PMA and the possible postoperative complications.

Outline of thesis

Chapter 2 presents a cost analysis of incisional hernia repair. In this study patients with IH repair are divided into 2 groups: patients with non-complex hernia repair and with complex hernia repair analyzing costs. In addition costs between an academic hospital and a community hospital are compared.

Chapter 3 presents a cross-sectional study of patients with an end-colostomy. In this study it is investigated if parastomal herniation is a risk factor for IH formation.

Chapter 4 presents a radiological study of patients with an end-colostomy. In this study it is investigated whether placement of a colostomy and possible parastomal hernia would alter the abdominal wall.

Chapter 5 presents a meta-analysis of studies describing results of onlay mesh repair and sublay mesh repair. In this review it is investigated which of the two techniques is preferable.

Chapter 6 presents a retrospective study in which patients with IH are included. In this study it is noted whether patients were treated operatively or conservatively. In addition it is evaluated if patients cross-over from one group to the other and what the results of the chosen treatment are.

Chapter 7 presents a meta-analysis of studies describing results of primary mesh augmentation and primary suture after abdominal surgery. In this review it is investigated if primary mesh augmentation reduces incisional hernia formation

Chapter 8 presents a study protocol a randomized controlled study (PRIMA trial). In this trial primary suture is compared to onlay mesh and sublay mesh augmentation.

Chapter 9 presents the short term results of a randomized controlled study (PRIMA trial). In this trial it is investigated if primary mesh augmentation causes an increase in postoperative complications.

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COST AND RISK FACTORS

Complex abdominal wall hernia: an analysis of costs

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Abstract

Introduction: Incisional hernia (IH) is the most frequent complication after abdominal surgery and can become a complex abdominal wall hernia (CAWH). Patients with CAWH need specialized care. This retrospective cohort study investigates what the true costs are for IH patients with non-CAWH and CAWH determining the difference in costs for patients treated in an academic centre and a community hospital.

Methods: Patients diagnosed with primary IH between 2003 and 2012 in an academic hospital and community hospital were included. IHs were divided into a non-CAWH and a CAWH group. Patients with CAWH were classified into 3 groups; minor, moderate and major. Cost comparison included comprehensive data of direct medical costs.

Results: Of the total number of 473 IH patients, 157 (33%) patients had non-CAWH and 316 (67%) patients had CAWH. In general the costs for a patient with non-CAWH (€5303) were comparable to a patient with CAWH (€5921) (p=0.853). The costs for a patient with minor (€5304) and moderate CAWH (€5719) were significant lower, compared to patients with major CAWH (€7910) (p=0.009). The costs of non-CAWH and moderate CAWH were higher in an academic hospital compared to a community hospital. In the major CAWH group a trend for lower costs was observed in favour of the academic centre (€6002), compared to the community hospital (€8920) (P=0.073).

Conclusion: From a cost perspective patients with non-CAWH minor and moderate CAWH should be referred to community hospitals. Major CAWH are significantly more costly compared to non-complex and other types of CAWH. Patients with major CAWH should be centralized and referred to an experienced (high volume) center capable to treat these technically challenging patients. Centralization of major complex cases will increase experience, improve postoperative outcome and possibly result in lower healthcare costs.

Introduction

Incisional hernia (IH) is the most frequent complication after surgery of the abdomen (1). Surgical correction of IH is required if patients have complaints of pain or discomfort (2). Emergency surgery is needed if abdominal contents becomes incarcerated or strangulated (3, 4). Furthermore, the recurrence rate is still highly present, which may lead to multiple repairs or re-operations (2, 5-12).

IH's can become complex IH's, due to fistulas, burst abdomen, infection of the wound and mesh and a disturbed anatomy. The exact definition of a complex IH remains unclear. It is agreed that a more detailed description of the term 'complex abdominal wall hernia (CAWH)' is needed, since patients who suffer from it need specialized care. Therefore, the European Hernia Society organized several meetings and identified common criteria used for CAWH dividing it in severity classes (13, 14). CAWH can lead to complicated abdominal wall defects with a high risk of morbidity of 10.7% (12). These CAWH's will lead to extensive costs: outpatient clinic visits, re-operations, radiological examinations, alternative operation materials like biologicals and longer stay or duration at day-care or at the intensive care unit.

To perform a good and complete health economic analysis a comparison of costs and outcomes should be made as well as a comparison of different treatments (3, 4). In this retrospective study a cost analysis was applied in which the costs of two different types of IH repair (non-CAWH and CAWH) were compared. In addition the difference in costs was determined between an academic centre and a community hospital.

Methods

A multicentre retrospective cohort study was performed. All patients diagnosed with primary IH between 2003 and 2012 at the Erasmus University Medical Center in Rotterdam (academic centre) and at the Reinier de Graaf Hospital in Delft (community centre) were included.

Patients diagnosed with IH were identified by using the electronic hospital database. Patient and healthcare resource data were retrospectively collected from medical records. This includes pre-operative patient characteristics: age, body mass index (BMI), gender, corticosteroid use, chronic obstructive pulmonary disease (COPD) and diabetes mellitus. Post-operative risk factors were identified as well: fascial dehiscence, open abdomen, fistulas and surgical site infections. For health care resources the following items were collected: duration of hospital admission, duration of surgery, radiological examinations, number of outpatient clinical visits, mesh type, physician fees, type of operation (open versus laparoscopic operation) and number of re-operations.

Patients from both hospitals were divided in patients with CAWH and non-CAWH. Furthermore patients with CAWH were classified into 3 groups; minor, moderate and major. Classification was done according to criteria for the definition of CAWH, set up by the European Hernia Society (13).

Cost calculation

Real medical costs were calculated from a healthcare perspective by multiplying the volumes of health care use with the corresponding unit prices. For the calculation of the total medical costs per patient we distinguished all intramural medical costs (e.g. inpatient days, health practitioner care, full cost prices of medical treatment, hours' work of the surgeon). For the most important cost items unit prices were determined by following the micro-costing method, which is based on a detailed inventory and measurement of all resources used (3, 15, 16). For these we used charges as a proxy of real costs. In the Netherlands a detailed 'fee for service' system is used for the remuneration of medical interventions and diagnostic procedures. A distinction was made between costs of the university and the community hospital.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 21.0). Groups (baseline characteristics) were compared by using the Chi-squared test or the Mann-Whitney U test. Since cost data per patient (but not per day care) are typically highly skewed, nonparametric bootstrap techniques were used to compare direct medical costs. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Between 2003 and 2012 a total of 473 patients with a median age of 65 years (SD 14) were included. In general 231 (49%) of the patients were male with a mean BMI of 28 (SD 5). Of all patients 135 (29%) suffered from diabetes. The remaining baseline characteristics are presented in Table 1. Of all CAWH patients 168 (53%) patients had minor CAWH, 87 (28%) patients had moderate CAWH and 61 (19%) patients had major CAWH.

Table 1 Baseline characteristics

	General	Non-CAWH	CAWH	p-value	Academic	Community	p-value
	473	157	316	-	203	270	-
Age (SD)	65 (14)	65 (14)	65 (14)	0.995	61 (14)	68 (14)	0.000
Male (%)	231 (49)	77 (49)	154 (49)	1.000	98 (48)	133 (49)	0.842
BMI (SD)	28 (5)	25 (3)	30 (6)	0.000	28 (5)	28 (5)	0.053
DM (%)	135 (29)	45 (29)	90 (29)	0.287	59 (29)	76 (28)	0.974
COPD (%)	98 (21)	26 (17)	72 (23)	0.115	22 (11)	76 (28)	0.000
Fistulas (%)	7 (2.2)	0	7 (2.2)	0.136	5 (2.5)	2 (1)	0.000
Open abdomen (%)	26 (8.2)	0	26 (8.2)	0.000	17 (8)	9 (3)	0.003
Fascial dehiscence (%)	6 (1.9)	0	6 (1.9)	0.088	4 (2)	2 (1)	0.486

Costs of non-CAWH versus CAWH

Of the total number of 473 patients there were 157 (33%) patients with non-CAWH and 316 (67%) with a CAWH.

The mean costs of a patient with IH were €5716 (SD: €4977; Table 2). The mean costs for a patient with non-CAWH (€5305,SD €4304) did not differ significantly from a patient with CAWH (€5921,SD: €5275; p= 0.853).

For patients with minor CAWH costs were €5304 (SD: €4329). For patients with moderate CAWH the costs were €5719 (SD: €5392) and for patients with major CAWH this was €7910 (SD: €6864). This implies that there is a maximum difference of €2606 between the minor and major CAWH group (p = 0.009).

Table 2 Costs of non-CAWH and CAWH in general, in an academic hospital and in a community hospital

	General (€)	Academic (€)	Community (€)	p-value
	5716	6364	5240	0.022
Non-CAWH	5305	6466	4383	0.023
CAWH	5921	6311	5647	0.299
Minor	5304	6052	4859	0.104
Moderate	5719	6777	4378	0.035
Major	7910	6002	8920	0.073

Academic versus Community Hospital

Of the total number of 473 patients there were 203 (43%) patients treated in the academic hospital and 270 (57%) patients in the community hospital. In the academic hospital there were 70 (34%) non-CAWH patients , compared to 87 (32%) non-CAWH patients in the community hospital. There were 133 (66%) CAWH patients in the academic hospital compared to 183 (68%) patients in the community hospital. Of the CAWH group the number of patients with a mild CAWH was 63 (31%) in the academic hospital compared to 105 (39%) in the community hospital. The number of patients with moderate CAWH was 49 (24%) in the academic hospital and 38 (14%) in the community hospital and the number of patients with severe CAWH was 21 (10%) in the academic hospital and 40 (15%) in the community hospital. As mentioned earlier the mean costs for a patient who developed IH were €5716 (SD €4977). In general the costs for a patient with IH were significantly higher in an academic centre (€6364, SD: €5611) compared to patient in a community hospital (€5240, SD: €4397) (p=0.022).

In general the costs of patients with non-CAWH were significantly higher in the academic centre (€6466, SD: €6002) compared to the community hospital (€4384, SD: €1687). The costs of CAWH in academic centre were not significantly higher (€6311, SD: €5417) compared to a community hospital (€5647, SD: €5168; p=0.299).

The costs for a patient with minor CAWH were comparable for the academic hospital (€6052, SD: €5065) and the community hospital (€4859, SD: €3779). However, for patients with moderate CAWH costs were higher in the academic hospital (€6777, SD: €6503) compared to the community hospital (€4378, SD: €3076; p=0.035). In the major CAWH group a trend in costs in favour of the academic centre (€6002, SD: €3440) was found compared to the community hospital (€8920, SD: €7960; p=0.073). Figure 1 and 2 give an overview of the different costs aspects for CAWH and non CAWH in the academic and community hospital.

Discussion

This study evaluates the real costs of CAWH compared to non-CAWH. In general patients with non-CAWH and moderate CAWH were more costly if treated in the academic hospital. Patients with major CAWH were the most costly of all types of repairs. A trend was observed in the major CAWH group in favor of the academic hospital.

Costs of non-CAWH versus CAWH

As stated above there was not a significant difference in costs between non-CAWH and CAWH but there was a significant difference in costs between the classification of minor, moderate and major. This was due to more (laparoscopic) operations, a longer duration of stay at the hospital and more outpatient clinic visits for patients who developed major CAWH. With these data it can be concluded that patients with major CAWH tend to have more outpatient clinic visits part of these patients having been re-operated with a longer duration of stay at the hospital as a consequence. This is also stated by Helgstrand et al, who showed that major complications will lead to prolonged hospital stay (17). Those patients will exceed the standard price, which is set as compensation for every patient operated for IH. The estimated compensation a hospital receives for an IH-procedure ranges from €150 (open operation) to €6500 (laparoscopic operation). Patients with major CAWH will not measure up to this price and will exceed it, due to their patient related circumstances and patient characteristics (18). Hospitals are not stimulated to perform these complex repairs and as a results treatment can be delayed or not be performed at all. Currently in the Netherlands patients with CAWH are randomly treated in either a community hospital or an academic hospital. After evaluation of costs it seems appropriate to treat patients from the start in the most cost-saving hospital. In order to accomplish this, patients should be pre-operatively classified. This can only be achieved by taking all the risk factors into account for every patient validating a classification system. Furthermore this study also implies the huge impact of postoperative complications on healthcare costs, which is also stated by Vonlathen et al. Not only should effort be taken to identify patients who might develop postoperative complications, the most relevant part is to lower these postoperative complications for every patient, since this is the main cause of high healthcare costs (19).
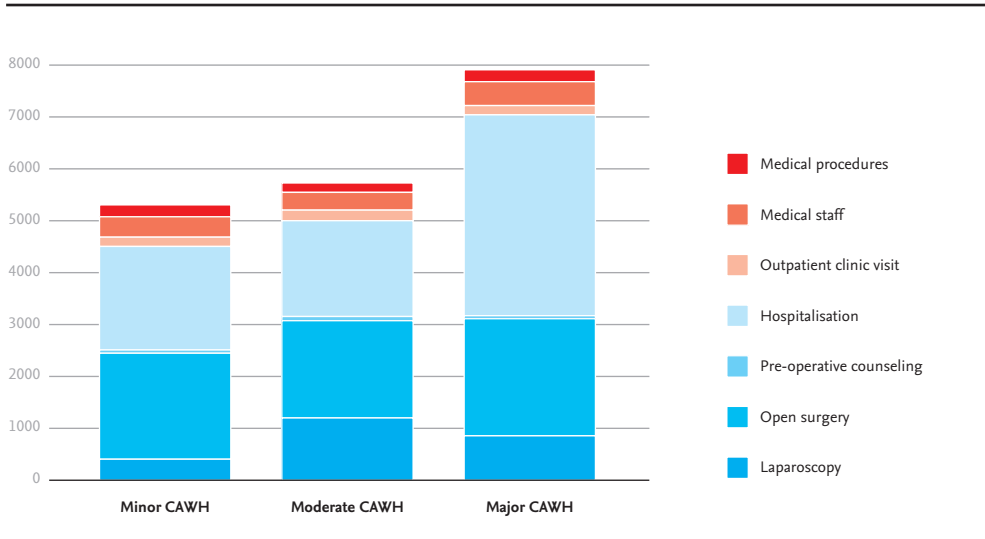
Figure 1 Overview of costs aspects contributing to the costs of a minor, moderate and major CAWH
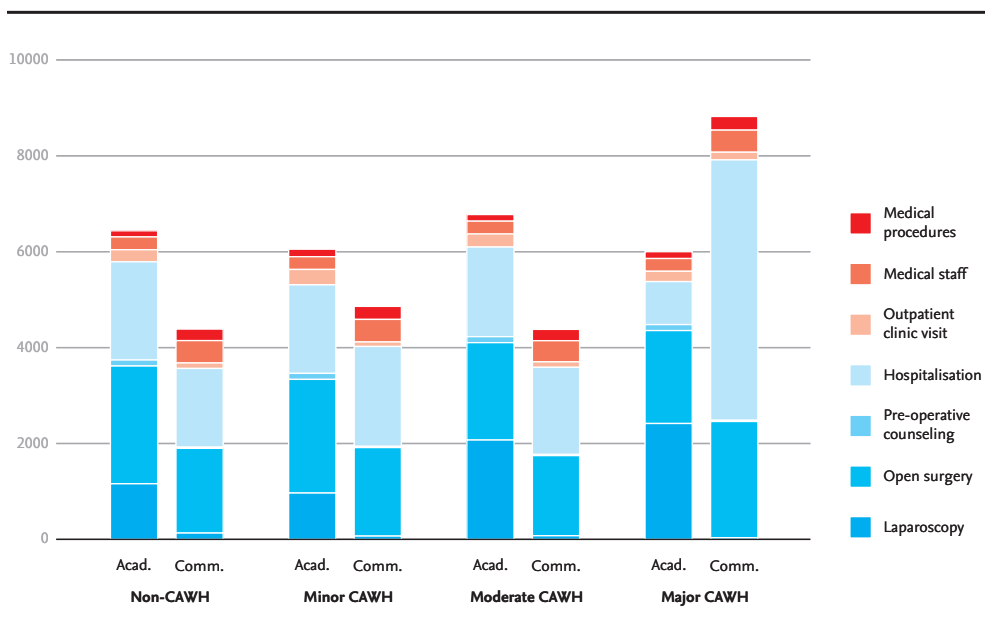

Figure 2 Overview of costs aspects contributing to the costs of a non-CAWH, minor, moderate and major CAWH compared in an academic and a community hospital

Academic versus community hospital

Our data show higher costs for non-CAWH and moderate CAWH repair at the academic hospital. However, a trend was observed in the major CAWH group in favor of the academic centre. There is a big difference in costs for this patient group between the academic and community hospital. The reason for this is mainly determined by the fact that patients in an academic hospital with major CAWH have a shorter duration of stay in the hospital. Even though there is a big difference in costs for CAWH patients between the academic and community hospital, only a trend was observed and results were not statistically significant. This can be explained by the fact that this study concerns a small sample size.

Furthermore, the difference in costs is also determined by the difference in costs of the different meshes. This depends on the price by which the hospital purchases the meshes. When the surgeon prefers a type of mesh and when using a specific mesh more often, the mesh company sells their meshes for a lower price. This will lead to different prices between an academic and community hospital for a type of mesh. For the surgical treatment of the patients in this study both the academic and community hospital did not use biological meshes.

According to the results it can be concluded that from a cost-analysis perspective patients with non-CAWH and moderate CAWH should be referred to a community hospital. Minor CAWH was not more costly in either type of hospital. Patients with major CAWH were significantly more expensive compared to patients with non-CAWH. A reduction of costs could be established by centralization of these complex patients. We recommend to perform these types of repairs only in an experienced (high volume) center considering the trend for lower costs in our study. Centralization and treatment of patients in the proper hospital will not only lead to lower healthcare costs but also to better specialized care. This may be due to the fact that in specialized academic centers surgeons are more experienced and well known with CAWH (20).

Limitations

There are several limitations to this study. First, this study only represents the costs to the payer and not the costs from societal perspective, such as loss of productivity. Secondly, we have taken into account the complications, risk factors and defect size of the patients but not all these data were available or documented in the database. This might lead to an underestimation of the true costs. Despite a few limitations we still think that with these results patients' care can be improved and health care costs can be reduced. Further research should be done to validate the definition of CAWH and to predict which patient will develop CAWH (13).

Conclusion

The data of this study provides new insights into the costs of non-CAWH and CAWH also suggesting that non-CAWH, minor and moderate CAWH should be referred to community hospitals. Major CAWH are the most costly type of repair. A reduction of costs could possibly be accomplished by centralization of major CAWH in experienced academic (high volume) centers for treatment of these technical challenging patients. In the future this might lead to less burden on healthcare costs, but more important: to high quality care.

A. Jairam and L. Timmermans contributed equally to this article.

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

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Abstract

Introduction: 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 (AAA) and obesity. Our hypothesis is that PH 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 PH. All possible risk factors for IH were scored. A physical examination was performed and, when available, CT scans were scored for IH and PH.

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 PH had a prevalence of 52.3% during physical examination. During CT scan examination prevalence was even higher, being 48.3% and 52.9%. IH and PH were both present in the same patient in 30% of all examined, and in 35.6% after CT-scan examination. PH 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 PH have a seven times higher chance of developing an IH compared to patients without PH.

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 (PH) is a frequent complication following stoma creation, with an incidence of up to 48% (7). Clinical findings in our center suggest that PH might be a risk factor for later IH. PH 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 PH and IH. We hypothesized that the presence of a PH 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 PH. 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). PH 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 PH 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, abdominal aorta aneurysm (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 PH. 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, Crohn's 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.

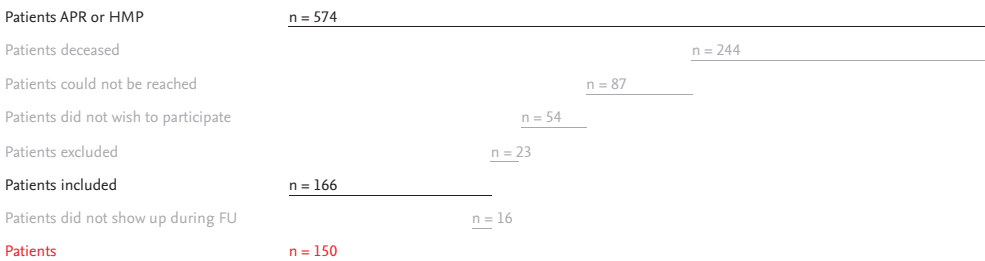|		
Patients APR or HMP	n = 574	
Patients deceased		n = 244
Patients could not be reached		n = 87
Patients did not wish to participate		n = 54
Patients excluded		n = 23
Patients included	n = 166	
Patients did not show up during FU		n = 16
Patients	n = 150	

Figure 1   Flow diagram depicting patient acquisition

Table 1 Risk factors

	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
PH	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.*

Risk factors

All possible risk factors were scored and the results are presented in Table 1. The presence of a PH 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 PH 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), PH 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.

Prevalence

During physical examination, out of the total of 150 patients, 56 IHs (37.3%) and 79 PHs (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 PHs (52.9%). Both were present in 31 of the CT scans (35.6%), which was also statistically significant (p < 0.001) (Figure 2). Physical examination for the diagnosis of IH reached a sensitivity of 0.79 and a specificity of 0.96. For PH a sensitivity of 0.87 was reached with a specificity of 0.95.

Table 2 Physical examination and CT-scan examination

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

Discussion

This study confirms our hypothesis that the presence of PH represents a risk factor for the occurrence of IH. Patients who acquire a PH had a seven times higher odds of developing an IH compared to patients without a PH.
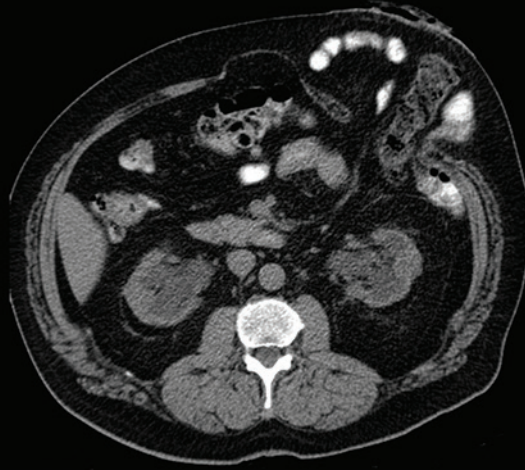
Figure 2 CT-scan displaying a combination of IH and PH

The prevalence of PH in our study was 52.7%, which corresponds with existing literature and in our previous experience with colostomies (7). The incidence of PH does not differ when open or laparoscopic colostomy creation are compared, suggesting that PH is not affected by midline incision or hernia (7, 19, 20). A number of potential theories explaining the high rate of PH have been suggested in the literature. Increased abdominal pressure can exit through the opening in the abdominal wall possibly promoting PH. According to Laplace's law, the tangential forces working on the colostomy may enlarge the fascial opening and cause PH (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 PH. These mechanisms can explain the high incidence of PH 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 PH. 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 3. 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 PH 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 PH and IH: Patients with a PH and/or IH did not have more inguinal, umbilical or other incisional hernias. One can also hypothesize that all patients with a PH have a form of herniosis in light of the fact that PH 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.
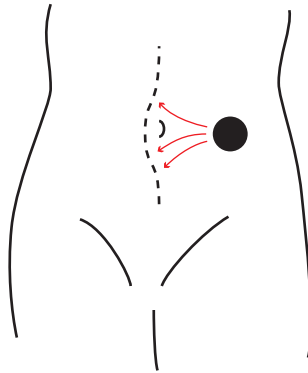
Figure 3   Midline shift after enterostomy creation

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. 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 con-tamination 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 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 PH could be found, it is unclear whether PH or IH occurred first. Nevertheless an assumption was made on the basis of the patients' anamneses that PH 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 examina-tion 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 PH increases the chances of IH occurrence by seven times. Fur-thermore, patients operated in an emergency setting also have a 5 times higher chance of IH, as shown in the multivariate analyses of variance. Thus, PH and — to a lesser extent — operation in an emergency set-ting 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 PH (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 PH formation. In case of PH correction, an effort should be made to correct both the IH and PH. Creating an mesh overlap over the midline, as demonstrat-ed by Berger et al, would reduce the chance of IH development and PH 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.
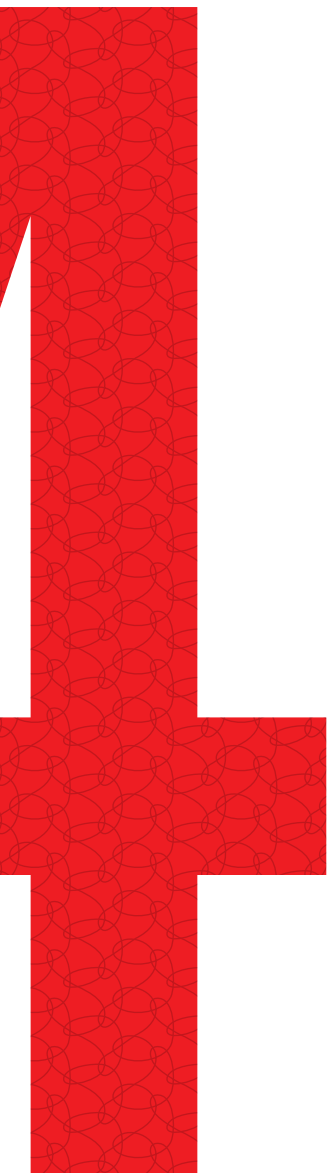
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Abdominal rectus muscle atrophy and midline shift after colostomy creation

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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 due to decreased restraining forces at the site of the colostomy, and left abdominal rectus muscle (ARM) atrophy due to intercostal nerve damage.

Methods: Patients were selected if they had received an end-colostomy via open surgery between 2004 and 2011. Patients were eligible if a CT had been performed postoperatively. If available, pre-operative CTs were collected for case-control analyses. Midline shift was measured using V-Scope application in the 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 CTs were available for 77 patients; of these patients, 30 also had received a preoperative CT. 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: Colostomy creation alters the abdominal wall. Atrophy of the left abdominal rectus muscle was seen caudal to the level of the colostomy, and a midline shift to the right side was evident on CT. 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 CTs 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 CTs were uploaded to the I-Space PACS, format converted, and then
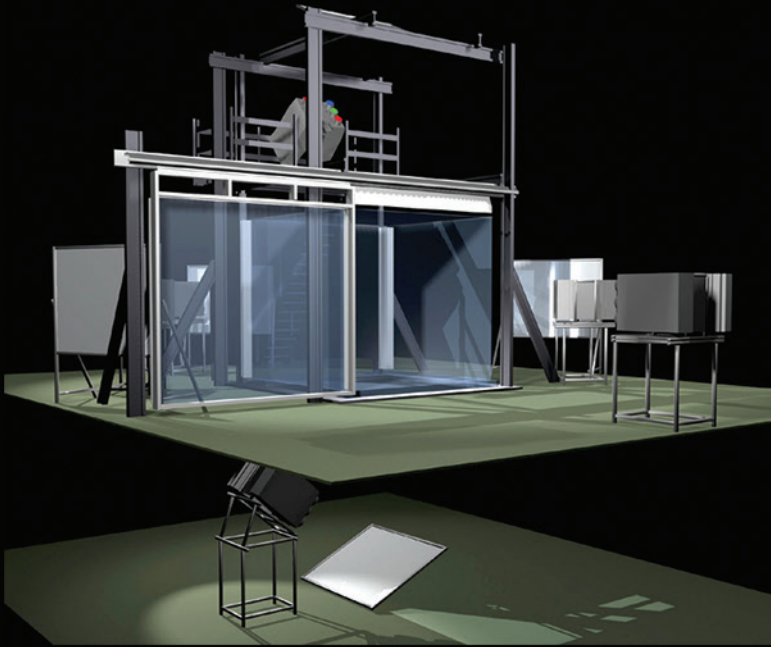
Figure 1 The I-space installed at the Erasmus is a CAVEtm-like virtual reality environment where images can be projected as 3-dimensional hologram.
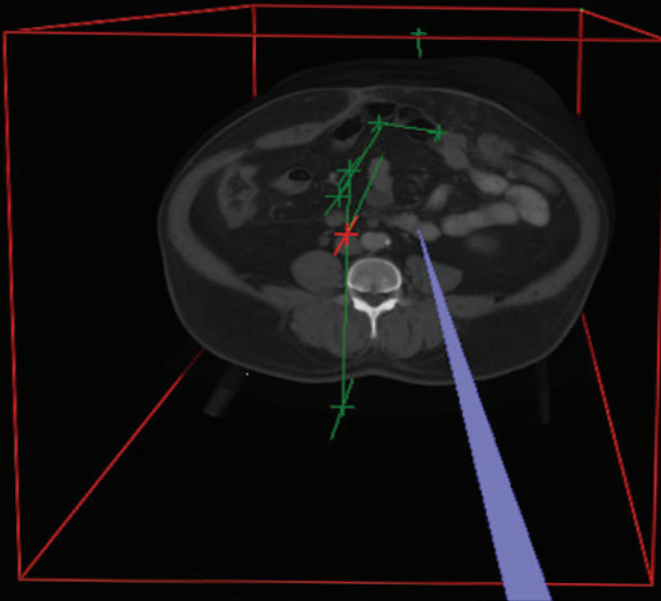
Figure 2 The distance between the ARM to the exact midline is being measured in a 3-dimensional hologram.

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 (Figure 3).

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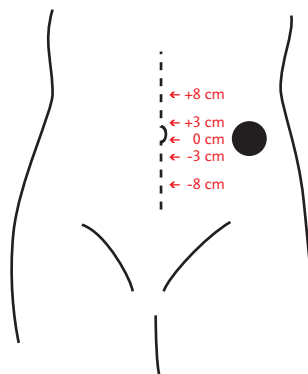
Figure 3   ARM thickness was measured at 8 centimetres (cm) above and below, 3 cm above and below and at colostomy level

Results

Inclusion and exclusion criteria

A total of 160 patients from the PACIFIC cohort who had given informed consent were screened if a post-operative 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 CTs 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 (rs= -0.28 preoperatively, rs= - 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 to 9.8) corresponding with a shift to the right. Comparing the preoperative CTs with the CTs 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 CTs with the postoperative CTs 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.

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.

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.

Table 1 Preoperative versus postoperative data

Left ARM (n = 30)				Right ARM (n = 30)		
Preoperative*	Postoperative*	p-Value**		Preoperative*	Postoperative*	p-Value**
8.1 (2.4)	8.5 (2.1)	0.203	+8 cm	8.3 (2.4)	8.5 (2.6)	0.609
8.8 (2.6)	9.8 (2.6)	0.010	+3 cm	8.9 (2.5)	9.6 (3.1)	0.081
9.1 (2.8)	10.2 (2.5)	0.024	0 cm	9.3 (2.7)	9.6 (2.7)	0.448
9.6 (2.7)	10.3 (2.7)	0.086	-3 cm	9.9 (2.7)	10.5 (3.3)	0.178
10.8 (3.2)	10.4 (3.2)	0.466	-8 cm	10.9 (3.1)	11.1 (3.5)	0.609

Midline shift at stoma		
Preoperative*	Postoperative*	p-Value**
-1.3 (4.6)	2.1 (9.3)	0.043

*Values represent the means and standard deviation in mm
** p-values are two-sided. For continuous variables the paired student t-test was used.

Table 2 Left ARM vs. right ARM data

No PH (n = 33)					PH (n = 44)		
	Left ARM*	Right ARM*	p-value**			Left ARM*	Right ARM*	p-value**
+8	9.3 (2.1)	9.1 (2.3)	0.440		+8	7.9 (2.3)	7.4 (2.3)	0.036
+3	10.1 (3.3)	9.5 (3.2)	0.137		+3	9.6 (2.4)	8.8 (2.9)	0.024
0	10.8 (3.1)	10.7 (3.4)	0.797		0	10.2 (3.0)	9.3 (2.5)	0.004
-3	10.7 (2.8)	11.7 (3.6)	0.044		-3	10.2 (2.8)	10.1 (3.6)	0.677
-8	11.1 (3.6)	12 (3.7)	0.017		-8	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.

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 CTs 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 CTs, 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 CTs 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 of all patients and standard follow-up CTS 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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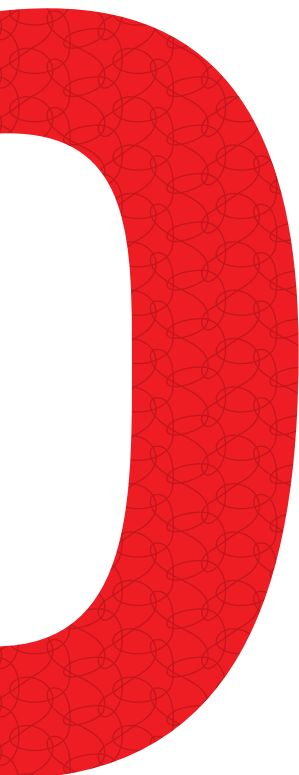
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2

TREATMENT
OPTIONS

Meta-analysis of sublay versus onlay mesh repair in incisional hernia surgery

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Abstract

Introduction: Incisional hernia (IH) remains a very frequent postoperative complication. The two techniques most frequently used are the onlay repair (OR) and sublay repair (SR). However it remains unclear which is superior.

Methods: A meta-analysis was conducted according to the PRISMA guidelines. The quality of the non-randomized studies was assessed using the Newcastle-Ottawa-scale (NOS).

Results: Out of 178 papers, 10 studies were selected comprising 1948 patients. Two of the studies scored below 5 points on the NOS and were not selected. A trend was observed for IH recurrence in favour of SR (OR 2.41, 95%CI 0.99 to 5.88, I2 70%, p = 0.05). Surgical site infection occurred significantly less after SR (OR 2.42, 95%CI 1.02 to 5.74, I2 16%, p = 0.05). No difference with regards to seroma and hematoma could be discovered.

Conclusions: Although the majority of included studies were retrospective studies, SR seems the preferred technique for IH repair.

Introduction

Incisional hernia (IH) remains one of the most frequent postoperative complications after abdominal surgery, with incidences ranging from 11 to 20% (1, 2). The incidence of IH is even higher in patients with risk factors such as obesity and abdominal aortic aneurysms (AAA) (3, 4). Each year around 200.000 IH are treated in the United States. The treatment of choice for IH should be mesh repair (5, 6). Mesh repair results in lower recurrence rates compared with primary suture as was demonstrated by Luijendijk et al (3 year cumulative recurrence rate of 24% compared to 43%) and Burger et al (10 year cumulative recurrence rate of 32% compared to 63%) (5, 6). In the before mentioned studies performed by Luijendijk and Burger, the Rives-Stoppa sublay repair (SR) technique was used (7, 8). With this technique the mesh is placed on the posterior rectus fascia after dissection of the fascia from the rectus muscle and approximation of the edges of the two fascia. Another frequently used technique for IH is the Chevrel or onlay repair (OR) technique (9). With this technique the mesh is placed on the anterior rectus fascia after dissection of the fascia from the subcutis and approximation of the edges of the two fascia. However, no consensus has been reached as to which technique is preferable. The anatomical position of the mesh placement has an impact on tissue incorporation, tissue reaction and the tensile strength of the abdominal wall (10-12). These factors are important with regards to IH recurrence and postoperative complications.

A systematic review of the literature and meta-analysis were performed in order to discover which of the two techniques has better results with regards to IH recurrence, operation time, and postoperative complications such as surgical site infection (SSI), seroma, hematoma and fistula.

Methods

A systematic search of MEDLINE, Embase, Web of Science, Scopus, PubMed publisher and the Cochrane library was performed. All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement were followed (13). Manual reference checks (BG) of accepted papers in recent reviews and papers included were performed to supplement the electronic searches. Details of the search syntax are listed in the Appendix. Studies were evaluated for inclusion independently by two reviewers (LT, BG) based on title and abstract and finally were evaluated independently based on the full text. Studies were included if they met the following criteria: 1) participants: adult patients who underwent elective IH repair; 2) interventions: onlay and sublay mesh repair as described by European Hernia Society (EHS) 3) outcome measures: IH recurrence, 4) secondary outcome measures: SSI, seroma, hematoma, fistula, operation time, period of hospitalisation. A random check was performed by the senior author (JFL) (14). Papers in which additional dissections had been implemented were excluded in order to reduce heterogeneity as this review was strictly interested in comparing OR and SR. Any discrepancies in inclusion were resolved by discussion between the reviewers and the senior author (JFL).

All required data from each study included were extracted using a standardized form which covered: 1) study characteristics (study design, year of publication, study period) 2) type of intervention (onlay and sublay) 3) peri-operative information (operation time, period of hospitalisation) 4) postoperative complications (IH recurrence, SSI, seroma, hematoma, fistula).

Assessment of study quality

The methodological quality of the included non-randomized studies was assessed according to the Newcastle Ottawa Scale (NOS) criteria (15).

Data analysis

It was estimated that the majority of papers would be non-randomized studies. Therefore it was decided to implement a quality assessment before including studies for meta-analysis. Non-randomized studies were deemed eligible if a NOS score of 5 (out of 9) or higher was established.

To pool data and calculate a pooled mean for each patient level outcome, a random effects model was used, which takes into account both the variance between studies and the variance within a study (16). Odds ratios or mean differences with 95% confidence intervals were calculated to evaluate the statistical difference between outcomes following OR and SR. Statistical heterogeneity was assessed for IH recurrence, SSI, seroma, hematoma and fistula, by calculating the Q statistics and the I^2 statistic.

Selective dissemination of evidence was assessed by plotting each outcome measure of each study against precision (1/standard error) in a plot with p-value contours. Funnel plot asymmetry, specifically with an apparent lack of studies in high p-value areas of the plot, can be indicative of publication bias (17). Individual study effects on the results were examined by removing studies one at a time to determine whether removing a particular study would change the significance of the pooled effect. Two-sided $p \leq 0.05$ was considered statistically significant. Analyses were performed using Review Manager software (RevMan, 5.0.25; The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search and study characteristics

A total of 178 papers were identified after removal of duplicates. Of these 178, 153 were excluded on basis of title and abstract. After full-text assessment, 21 papers were excluded due to the paper being an abstract or letter to the editor, the paper could not be obtained, the paper had been published in two different journals with similar results and if the paper did not fulfill the inclusion criterium that information needed to be available for distinguishing results for both techniques.

A total of 10 papers (2 randomized controlled trials (RCTs) (18, 19), 1 prospective study (20), 7 retrospective studies (21-27)), compromising a total of 1948 patients (775 onlay operations and 1173 sublay operations), did meet the inclusion criteria. The PRISMA flow diagram for systematic reviews is presented in Figure 1. The non-randomized studies were assessed on quality using the NOS criteria. Two studies did not meet the criteria for inclusion in the meta-analysis, as they scored lower than 5 points (out of 9) (Table 1).

Table 1 Study characteristics

Reference	NOS	Study Type	Year	Hernia size	# OR	# SR	Outcome measures	Follow-up
Kumar et al (19)	7	Prospective	2012	3cm to 12cm*	45	18	IH recurrence, SSI, seroma, postoperative pain	60 months **
Forte et al (22)	4	Retrospective	2011	-	9	207	IH recurrence, SSI, seroma	12 months **
Abdollahi et al (23)	6	Retrospective	2010	-	312	32	IH recurrence, SSI, seroma, intestinal fistula,	98 months **
Venclauskas et al (17)	(2b***)	RCT	2010	11.5cm (OR)** – 11cm (SR)**	57	50	IH recurrence, SSI, seroma, hematoma, ligature fistula, operative time, postoperative pain,	12 months **
Weber et al (18)	(2b***)	RCT	2010	>25cm² **	235	224	IH recurrence, operative time	60 months **
Coskun et al (26)	6	Retrospective	2009	-	22	23	IH recurrence, SSI, seroma, hematoma, fistula	54 months **
Gleysteen et al (21)	7	Retrospective	2009	10cm **	75	50	IH recurrence, SSI, seroma, hematoma,	64 months **
Israelsson et al (20)	5	Retrospective	2006	-	281	228	IH recurrence, operative time	12 months **
de Vries et al (25)	6	Retrospective	2004	"large"			IH recurrence, SSI, seroma, enterocutaneous fistula, hematoma	30 months **
Kingsnorth et al (24)	3	Retrospective	2004	"loss of domain"	16	33	IH recurrence	-

NOS = Newcastle-Ottowa Score, OR = onlay repair, SR = sublay repair, * = range, ** = mean, *** = Oxford level of evidence, RCT = randomized controlled trial, IH = incisional hernia, SSI = surgical site infection

Incisional hernia recurrence

Eight studies (18, 20-22, 24, 26-28), comprising a total of 1359 patients, reported data regarding IH recurrence and were included into meta-analysis (Figure 2 and 3) 20-22, 24, 26-29. A trend in favour of SR was observed (OR 2.41, 95% CI 0.99 to 5.88, I2 70%, p = 0.05). During sensitivity analysis results proved to be unstable and heterogeneity remained high. However, after exclusion of the study by Weber heterogeneity
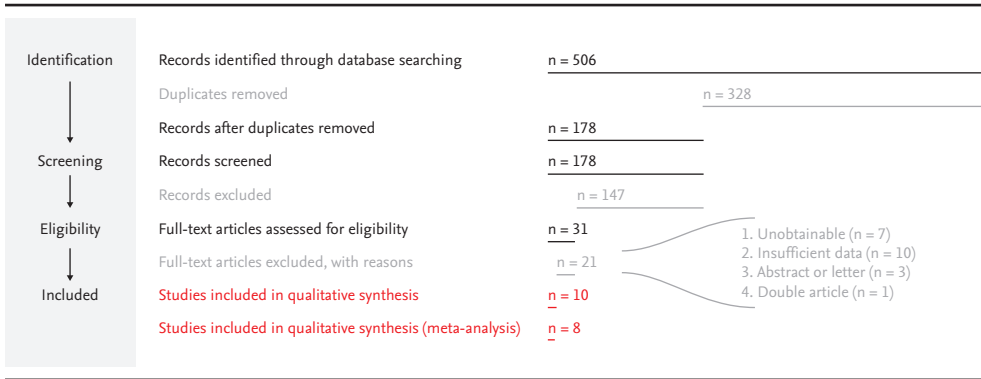
Figure 1   PRISMA, study flow diagram
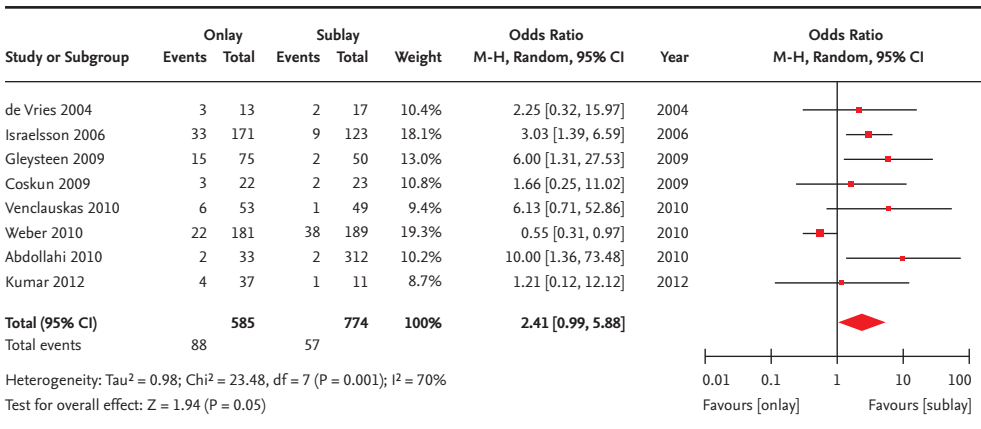
Figure 2   Incisional hernia recurrence
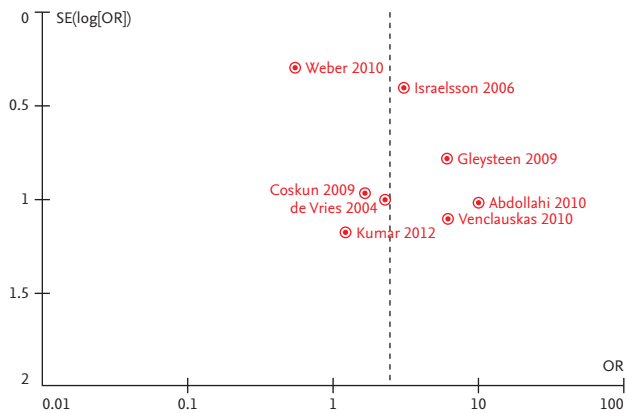
Figure 3   Funnel plot of incisional hernia results

was reduced to 0 and results became statistically significant (OR 3.35, CI 95% CI 1.93 to 5.82, I2 0%, p < 0.001).

The two studies not included in the meta-analysis also reported on IH recurrence (23, 25). In one study the recurrence rate for OR was 33% (3 out 9) compared with 0.48% (1 out of 207) in the SR group. In the other study the recurrence rate in the OR was 12.5% (2 out 16) compared with 3% (1 out 33) in the SR group.

SSI

Six studies, comprising a total of 747 patients, reported data regarding SSI and were included into meta-analysis (18, 20, 22, 24, 26, 27). SSI occurred significantly less in the SR group (OR 2.42, 95% CI 1.02 to 5.74, I2 16%, p = 0.05). During sensitivity analysis the results proved to be unstable with acceptable heterogeneity scores.

One study, not included in the meta-analysis, reported data regarding SSI (23). The SSI rate in the OR group was 11.1% (1 out 9) compared with 3.4% (7 out 207) in the SR group.

Study or Subgroup	Onlay Events	Onlay Total	Sublay Events	Sublay Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de Vries 2004	3	13	0	17	7.4%	11.67 [0.55, 248.91]	2004
Gleysteen 2009	9	75	4	50	32.9%	1.57 [0.46, 5.40]	2009
Coskun 2009	2	22	3	23	17.3%	0.67 [0.10, 4.43]	2009
Venclauskas 2010	8	57	1	50	14.3%	8.00 [0.96, 66.40]	2010
Abdollahi 2010	1	33	7	312	14.2%	1.36 [0.16, 11.42]	2010
Kumar 2012	6	45	1	50	13.9%	7.54 [0.87, 65.26]	2012
Total (95% CI)		245		502	100%	2.42 [1.02, 5.74]	
Total events	29		16				

Heterogeneity: Tau² = 0.20; Chi² = 5.98, df = 5 (P = 0.31); I² = 16%
Test for overall effect: Z = 2.00 (P = 0.05)

Favours [onlay] — Favours [sublay]

Figure 4   Surgical site infection

Seroma

Six studies, comprising a total of 715 patients, reported data regarding seroma and were included into meta-analysis (18, 20, 22, 24, 26, 27). No statistical significant results were achieved (OR 1.06, 95% CI 0.38 to 2.95, I2 48%, p = 0.89). During sensitivity analysis the results proved to be stable with fluctuating heterogeneity scores.

One study, not included in the meta-analysis, reported data regarding seroma (23). The seroma rate in the OR was 11.1% (1 out 9) compared with 1.9% (4 out 207) in the SR group.

Study or Subgroup	Onlay Events	Onlay Total	Sublay Events	Sublay Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
de Vries 2004	0	13	0	17		Not estimable	2004	
Gleysteen 2009	8	75	8	50	35.3%	0.63 [0.22, 1.80]	2009	
Coskun 2009	1	22	2	23	13.1%	0.50 [0.04, 5.94]	2009	
Abdollahi 2010	0	33	10	312	10.4%	0.43 [0.02, 7.50]	2010	
Venclauskas 2010	26	57	12	50	41.1%	2.66 [1.16, 6.11]	2010	
Kumar 2012	0	45	0	18		Not estimable	2012	
Total (95% CI)		245		470	100%	1.06 [0.38, 2.95]		
Total events	35		32					

Heterogeneity: Tau² = 0.48; Chi² = 5.81, df = 3 (P = 0.12); I² = 48%
Test for overall effect: Z = 0.11 (P = 0.91)

0.01   0.1   1   10   100
Favours [onlay]   Favours [sublay]

Figure 5   Seroma
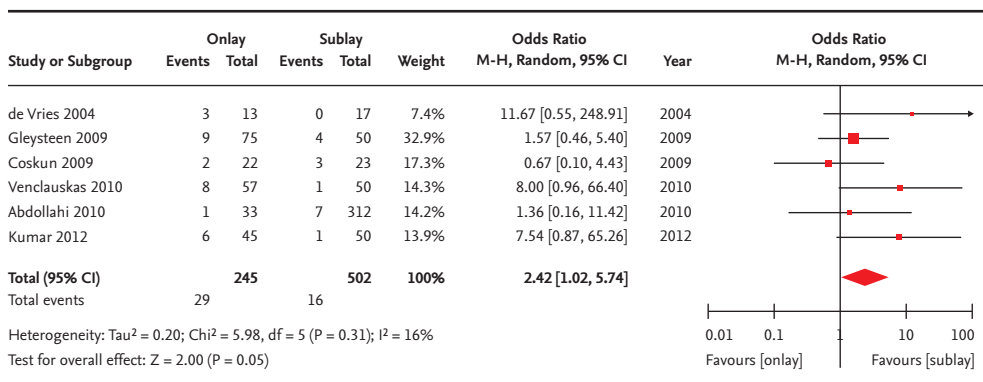
Hematoma

Four studies, comprising a total of 307 patients, reported data regarding hematoma and were included into meta-analysis (18, 22, 26, 27). No statistical significant results were achieved (OR 0.54, 95% CI 0.21 to 1.38, I2 0%, p = 0.19). During sensitivity analysis the results and heterogeneity proved to be stable.

Study or Subgroup	Onlay Events	Onlay Total	Sublay Events	Sublay Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
de Vries 2004	2	13	1	17	13.8%	2.91 [0.23, 36.16]	2004	
Coskun 2009	2	22	5	23	28.0%	0.36 [0.06, 2.09]	2009	
Gleysteen 2009	5	75	7	50	58.2%	0.44 [0.13, 1.47]	2009	
Venclauskas 2010	0	57	0	50		Not estimable	2010	
Total (95% CI)		167		140	100%	0.54 [0.21, 1.38]		
Total events	9		13					

Heterogeneity: Tau² = 0.01; Chi² = 2.04, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 1.29 (P = 0.20)

0.01   0.1   1   10   100
Favours [onlay]   Favours [sublay]

Figure 6   Hematoma

Fistula

Four studies (24, 26, 27, 29) reported data regarding fistula (17, 23, 25, 26). However, the definition of fistula (enterocutaneous, ligature or intestinal) differed in three studies and was not reported in one. In two studies no cases of postoperative fistula were reported (26, 27). In the RCT by Venclauskas, ligature fistula was reported in 14% (8 out 57) after OR and in 4% (2 out 50) after SR, this was not statistically significant. In the study by Abdollahi, intestinal fistula was reported in 3% (1 out 33) after OR and in 0.3% (1 out 312) after SR, no statistics were performed.

Operation time

Three studies reported data regarding operating time (18, 21, 28). However, not all studies reported standard deviations making pooling of the results impossible. All three studies reported lower mean operating times for OR. The study by Israelsson reported a mean OR operation time of 92 minutes (95% CI 88-97) compared with 102 minutes (95% CI 96-108) in the SR group, no statistics were performed (21). The RCT by Venclauskas reported a significantly lower (p = 0.001) operation time for the OR group (135 minutes, CI 95% 87.5 – 182.5) compared with the SR group (168.4 CI 95% 114.4 – 222.4) (18). The RCT of Weber reported a mean OR operation time of 75 minutes (range 30 – 210) compared with 77 minutes (range 25-220) in the SR group, this was not statistically significant (28).

Postoperative pain

Two studies reported data regarding postoperative pain (18, 20). However, the two studies reported pain in a different manner and thus could not be pooled for meta-analysis. In the RCT by Venclauskas a visual analogue scale (VAS) was used to asses pain during the stay of the patient and an average was presented in their data (18). The mean VAS score for OR was not statistically different compared to SR during rest (3.96, 95% CI 2.40 – 4.52 vs 3.78, 95% CI1.82 – 5.75; p = 0.607) and during activity (5.48, 95% CI 3.82 – 7.14 vs 5.2, 95% CI 2.89 – 7.5; p = 0.607). In the prospective study by Kumar, postoperative pain was also measured by means of VAS (20). However, they opted to group their results in a significant pain group (VAS >5) and non-significant pain (VAS <5) group. Patients in the SR group patients had significant more pain (33.3% vs 61.1%), however no p-value was provided.

Discussion

SR seems the preferred technique compared to OR for IH repair as it results in lower SSI rates. In addition a trend towards lower recurrence rates was observed when using SR. The two techniques did not differ with regards to seroma formation or hematoma. Although results regarding operation time could not be pooled, OR seemed to take up less time then SR. No definitive conclusions could be drawn from results regarding postoperative pain and fistula.

Recurrence

IH repair is a frequently performed surgery all over the globe. The OR and SR are well known techniques for IH repair, both with advantages and disadvantages. The OR is assumed to be easier to perform and less time consuming. The dissection of the posterior rectus fascia from the rectus muscle during SR can be challenging, especially in cases of previous infection and adhesions. However, SR is assumed by many to reduce IH recurrence, although not directly confirmed in this study. This reduction of IH recurrence might

be caused by a higher tensile strength of the abdominal wall after SR. The intra-abdominal pressure would fix the mesh between the posterior fascia and the abdominal muscle. However, experimental studies focussing on abdominal wall strength have reported inconsistent results. Binnebösel et al described less stability of the mesh with regard to OR in their hernia model (30). But Ko et al discovered no significant differences in tensile strength between OR and SR in their study (12).

Furthermore, the SR mesh position seems favourable with regards to tissue incorporation. Binnebösel et al described significant ingrowth and lower collagen type 1:3 ratio after OR in an animal model (10). These factors are known to promote IH formation. In addition, in an experimental study by Garcia-Urena et al, an increase of mesh shrinkage after OR (31) was described. Mesh shrinkage may reduce this overlap and promote IH recurrence.

Postoperative complications

Although OR is thought to be easier and quicker to perform, it has been suggested that the dissection of the suprafascial space would promote seroma formation and SSI (32). With regard to seroma formation we could not detect any difference in this study. However, of all studies that reported data on seroma only half of them provided information regarding drain placement (18, 22).

SR was superior to OR with regards to SSI. This could be explained by the more superficial position of OR making it easier for bacterial colonisation. Additionally, mesh positioning on the posterior rectus fascia would benefit from are more vascularised area compared to the OR position.

Dissection of the SR space could be troubled by the higher grade of vascularisation and the presence of the inferior and superior epigastric arteries which could increase the amount of hematoma formation after SR. However this was not observed during meta-analysis.

Information regarding postoperative pain and fistula could not be pooled in this meta-analysis. Definitions of the postoperative complications varied and/or were reported in such a manner that making assumptions regarding these topics was not possible. However it seems plausible that the dissection of the space between the posterior rectus fascia and rectus muscle is a more elaborate procedure and with more possibilities to damage, ligate or cut nerves and thus induce (chronic) pain. The experience of the surgeon in these cases is also of utmost importance and could make a large difference with regards to postoperative pain.

Limitations

Performing a good meta-analysis can be challenging and a number of aspects should be kept in mind during the process. Ideally, a meta-analysis should consist of a number of high quality studies, preferably RCTs, with comparable study populations and interventions. The results of the individual studies should

be homogeneous and have a common dependent variable, or end point. Also, the quality of the data being combined should be similar among studies. This limits the possibility of bias and heterogeneity between studies (33).

In this meta-analysis only two RCTs were included and the vast majority of studies were of retrospective nature. However, all of the included studies had comparable study populations, similar interventions, a common endpoint (incisional hernia recurrence). Additionally, a quality assessment was performed to make sure that non-randomized trials were of decent quality before including them in the meta-analysis. Excluding trials however might also facilitate publication bias. All data from the excluded studies regarding IH recurrence, SSI and seroma displayed comparable results as calculated in this meta-analysis.

The results regarding IH recurrence, the main outcome of this study, were subject to a high level of heterogeneity. When looking at the funnel plot for this analysis, the study by Weber et al in particular is the source of asymmetry (28). Removal of this study reduced the heterogeneity to zero and results remained statistically significant. Furthermore, the RCT by Weber et al was of mediocre quality and might be subject to location bias. Additionally, this study did differ somewhat compared with other studies as Weber et al only included larger hernia, which could attribute to heterogeneity.

Although the included studies were all assessed regarding quality, the retrospective nature of most studies still is a limitation to this meta-analysis. The number of IH recurrence and postoperative complications are likely to be underreported. In addition, a lot of variables such as the amount of mesh overlap, experience of the surgeon, number of stitches and time to recurrence, remain unclear or differed between studies. These inconsistencies and the instability of this meta-analysis make it difficult to allow for solid conclusions.

Conclusion

Although the majority of included studies were of retrospective nature, SR seems the preferred technique for IH repair compared to OR

Acknowledgements

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     Hasfali servek muteti kezelesenek eredmenyei: varrattal, illetve halo beultetessel (onlay vs sublay) torteno nyitott es laparoszkopos hasfal rekonstrukcio eredmenyeinek osszehasonlitasa (prospektiv, randomizalt, multicentrikus vizsgalat). Magy Seb. 2002 Oct;55(5):285-9.

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Appendix

Embase 144

(hernia/exp OR scar/exp OR 'postoperative complication'/exp OR (herni* OR scar* OR cicatr* OR postoperat* OR (post NEXT/1 operat*)):ab,ti) AND (onlay OR chevrel OR prefascial OR 'pre fascial'):ab,ti AND (sublay OR (rives NEAR/1 stoppa) OR underlay OR 'under lay' OR subfascial OR 'sub fascial' OR preperitoneal OR 'pre peritoneal' OR retrorect* OR (retro NEXT/1 rect*)):ab,ti

Medline ovidsp 106

(exp hernia/ OR exp Cicatrix/ OR exp "Postoperative Complications"/ OR (herni* OR scar* OR postoperat* OR post-operat*).ab,ti.) AND (onlay OR chevrel OR prefascial* OR pre fascial*).ab,ti. AND (sublay OR (rives ADJ1 stoppa) OR underlay* OR under lay* OR subfascial* OR sub-fascial* OR preperitoneal* OR pre peri-toneal* OR retrorect* OR (retro ADJ rect*)).ab,ti.

Cochrane central 3

((herni* OR scar* OR cicatr* OR postoperat* OR (post NEXT/1 operat*)):ab,ti) AND (onlay OR chevrel OR prefascial OR 'pre fascial'):ab,ti AND (sublay OR (rives NEAR/1 stoppa) OR underlay OR 'under lay' OR subfascial OR 'sub fascial' OR preperitoneal OR 'pre peritoneal' OR retrorect* OR (retro NEXT/1 rect*)):ab,ti

Web of science 104

TS=(((herni* OR scar* OR cicatr* OR postoperat* OR (post NEXT/1 operat*))) AND (onlay OR chevrel OR prefascial OR 'pre fascial') AND (sublay OR (rives NEAR/1 stoppa) OR underlay OR 'under lay' OR subfascial OR 'sub fascial' OR preperitoneal OR 'pre peritoneal' OR retrorect* OR (retro NEXT/1 rect*)))

Scopus 143

TITLE-ABS-KEY((herni* OR scar* OR cicatr* OR postoperat*) AND (onlay OR chevrel OR prefascial OR "pre fascial") AND (sublay OR (rives W/1 stoppa) OR underlay OR "under lay" OR subfascial OR "sub fascial" OR preperitoneal OR "pre peritoneal" OR retrorect* OR (retro-rect*)))

PubMed publisher 6

((herni*[tiab] OR scar*[tiab] OR postoperat*[tiab] OR post-operat*[tiab])) AND (onlay[tiab] OR chevrel[tiab] OR prefascial*[tiab] OR pre fascial*[tiab]) AND (sublay[tiab] OR rives stoppa[tiab] OR underlay*[tiab] OR under lay*[tiab] OR subfascial*[tiab] OR sub-fascial*[tiab] OR preperitoneal*[tiab] OR pre peritoneal*[tiab] OR retrorect*[tiab] OR retro rect*[tiab]) AND publisher[sb]

6

Watchful waiting in incisional hernia; is it safe?

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Abstract

Introduction: Incisional hernia (IH) is one of the most common postoperative complications after abdominal surgery. Operative treatment (OT) using mesh is still the treatment of choice. However, a watchful waiting (WW) strategy might be a considered for the treatment in some cases. This retrospective study compares the outcomes of WW and OT

Methods: Patients presenting with IH in an academic surgical department between January 2004 and December 2009, were included and divided into WW and OT. Crossovers between both groups were also analysed. Patients' characteristics, information about the initial abdominal surgical procedure, symptoms at presentation, and hernia characteristics were collected retrospectively. In case of OT, postoperative complications were analysed.

Result: In total 255 patients were selected of which 151 patients (59%) were included in the OT group and 104 patients (41%) in WW group. The reasons for WW were the absence of symptoms in 34 patients (33%), comorbidities in 24 (23%), and obesity in 23 (22%). During follow-up 34 patients (33%) crossed-over from WW to OT. Eight of the crossovers (24%) were emergency repairs due to incarceration. The incidence of unexpected preoperative intestinal perforation was significantly higher in the crossover group (13%) compared to the OT group (2%) (p=.002). Postoperative fistulas were seen in 7% of patients who crossed over from watchful waiting to OT versus 0% in primary OT (p=.002). Postoperatively three patients died, two of these patients were surgically treated after initially belonging to the WW group.

Conclusion: WW for IH leads to high crossover rates with significant higher incidence of peroperative perforations, fistulas, and mortality in this selected patients group, particularly in patients who underwent emergency repair of IH due to incarceration.

Introduction

Incisional Hernia (IH) is one of the most common postoperative complications after abdominal surgery. Incidences of IH are ranging from 11-20% and even higher in risk groups (1-3). In the United States alone about 100.000 IH are surgically treated each year (4). After many years of research the treatment of choice is mesh repair (5). However, recurrence rates after mesh repair are still unacceptable high, with a 10 year cumulative incidence rate up to 32% (6). The use of mesh facilitates the possibility of mesh-related complications, such as wound infection (6%-10%), mesh infection (1-4%), formation of seroma (30%), hematoma (7.5%), and fistulas (0.5%-3,5%) resulting in potentially need for mesh explantation (5.1%) and/or complex abdominal wall wounds (6-13).

Recently, operative treatment (OT) of patients with oligosymptomatic IH has been questioned (14). Patients who were treated for IH and pre-operatively did not have symptoms or mild symptoms, suffered from relevant pain after short- and long term follow-up. Another option in IH patients is conservative treatment or watchful waiting (WW). WW for IH is an option but has never been properly investigated and outcomes are unknown. Various symptoms and indications regarding IH repair and its natural course are mentioned in literature. Nevertheless, published data accurately describing these symptoms, indications and outcomes of WW in IH is lacking (15). Cost-effectiveness and safety have already leaded to implementation of WW in inguinal hernia practice (16-18).

We conducted a retrospective study to evaluate the incentives for OT or WW, outcome of these approaches, and potential crossovers between the groups. The aim of the study was to compare the outcomes of WW and OT on patients with IH.

Methods

A single (academic) centre retrospective study was performed. All patients who presented with IH between January 2004 and December 2009 at the Erasmus University Medical Center Rotterdam were included. The study cohort was retrieved with a medical chart review. The electronic hospital data systems and patient records were reviewed. All patients were identified by searching the electronic hospital database for DBC Codes (Diagnose Behandel Combinatie; Diagnosis Related Groups [DRGs]) and followed until a minimum follow-up of three years was reached.

According to the primary hernia management patients were divided into two groups: patients who were managed with WW and a group of patients who were planned for OT. However, some of the patients in the initial WW group underwent surgical repair during follow-up. In addition, for some of the patients in the OT group it was decided to cancel the operation and switch to WW. These crossovers between both groups were analysed individually. Patients whose wounds after initial abdominal surgery did not heal 'per primam' were excluded. Moreover, patients who presented with incarcerated IH and needed emergency surgery were excluded because WW had never been an option.

The following data were collected retrospectively through patient records review: patient characteristics, (i.e. gender, age at diagnosis, Body Mass Index (BMI), smoking, medical history). Information about the initial abdominal surgical procedure was collected and analysed for type of surgery (i.e. gastro-intestinal, gynaecological, vascular, urological, trauma, and others), admission to Intensive Care Unit (ICU), and postoperative complications.

The symptoms at presentation were divided into categories (i.e. pain, signs of incarceration, nausea, cosmetic complaints, difficulties with defecation, inconvenience during daily activities, absence of symptoms). The hernia size was collected if an absolute number was available in the medical records.

In case of OT of IH, postoperative complications (i.e. Surgical Site Infection (SSI), other infections, abscesses, postoperative ileus, perforations, fistulas,were scored. In case of watchful waiting the motives were divided into categories (i.e. absence of symptoms, comorbidity, obesity, large hernia size, and patient's preferences)

Statistical analyses were performed with the SPSS statistical software package (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Levene's test for equality of variances was used to assess normality of continuous data. Continuous variables are presented as means or medians. Medians with Inter Quartile Range (IQR) between brackets and means with Standard Deviations (SD) between brackets. Categorical variables are presented as numbers with percentages between brackets. Differences between the two groups were compared using a Mann-Whitney-U test (continuous data) or a Chi-square test (categorical data). Time to crossover was calculated using life-table methods. A p-value <0.05 was considered statistically significant.

Results

A total of 255 eligible patients with IH were identified in the hospital database. Seven patients (3%) were excluded from analysis because they presented with incarcerated IH and needed emergency surgical treatment. At presentation with IH, 151 patients (59%) were planned for elective surgical repair. In 104 patients (41%) WW was chosen. However, 34 patients (33%) of the WW group were eventually operated during follow up; eight of these crossovers (24%) were emergency repairs due to incarceration. Furthermore, 11 patients (7%) withdrew from OT and switched to the WW group (Figure 1).

Patient characteristics

Baseline demographic characteristics of the initial WW and OT groups are given in Table 1. At the time of diagnosis the mean age was 58 years (SD 13) in the WW group and 53 years (SD 13.1) in the OT group (p=0.003). In the OT 48% were males and in the WW group 51% were males (p=0.607). The mean Body Mass Index (BMI) was 28.5 kg/m2 (SD 6.5) in the WW group and 27.7 kg/m2 (SD5.6) in the OT group (p=0.301). At
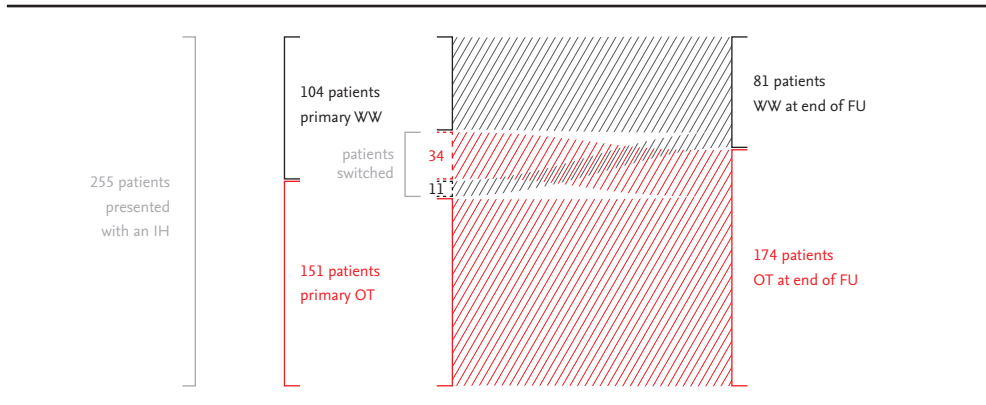
Figure 1 Flow diagram

Table 1 Patient characteristics

	Watchful Waiting (N=104)	Operative Treatment (N=151)	
Age (SD)	58 (13.0)	53 (13.2)	.009
Female (%)	53 (51)	72 (47.7)	.607
BMI (SD)	28.5 (6.5)	27.7 (5.6)	.424
Smoking (%)	17 (19.8)	51 (34)	.020
Death (%)	24 (23.1)	19 (12.6)	.028
Initial type of surgery			
Gastro Intestinal (%)	66 (64.1)	77 (51.0)	.034
Urology (%)	12 (11.7)	24 (15.9)	.268
Vascular (%)	6 (11.7)	16 (10.6)	.130
Gynecology (%)	9 (8.7)	18 (11.9)	.213
Trauma (%)	1 (1.0)	1 (0.7)	.650
Other (%)	9 (8.7)	15 (9.9)	.454
Medical history			
COPD (%)	17 (17.5)	20 (13.3)	.367
Malignancy (%)	33 (34.4)	44 (29.5)	.425
AAA (%)	6 (6.2)	11 (7.4)	.718
Corticosteroid use (%)	19 (19.8)	29 (19.3)	.929
Stoma (%)	14 (14.1)	13 (8.7)	.180
Inital admission data			
ICU admission (%)	19 (20.7)	37 (26.6)	.300
SSI (%)	19 (20.7)	21 (15.1)	.276
Post-op fistula (%)	0 (0)	3 (2.2)	.156
Abscess (%)	8 (8.7)	13 (9.4)	.524
Ileus (%)	4 (4.3)	5 (3.6)	.773
Pneumonia (%)	2 (2.2)	11 (8.0)	.062
Anastomotic leakage (%)	6 (6.5)	6 (4.3)	.460

BMI, Body Mass Index; COPD, Chronic Pulmonary Obstructive Disease; AAA, Aneurysm Abdominal Aorta; ICU, Intensive Care Unit; SSI, Surgical Site Infection

the time of presentation 20% of the patients reported smoking in the WW group and 34% in the OT group (p=0.020). Gastrointestinal surgery was the initial type of surgery in 64% in the WW group versus 51% in the OT group (p=.035). There were no significant differences in the other different categories of initial surgery. Other medical history, comorbidities, and complications after initial surgery (i.e. ICU admission, SSI, postoperative fistula, abscesses, ileus, pneumonia, and anastomotic leakage) were not significantly different between both groups.

Hernia characteristics

The hernia characteristics are outlined in Table 2. The median time between initial abdominal surgery and the presentation with IH was 15 months (IQR 7-39). The mean hernia size was 7.0 cm (SD 5.7) in the WW group and 6.4 cm (SD 4.7) in the OT group (p =.625). Patients who presented with asymptomatic IH were more often assigned to the WW group: 23.2% versus 1.4% (p=.001).

Table 2 Hernia characteristics

	Watchful Waiting (N=104)	Operative Treatment (N=151)	p-value
Size in cm (SD)	7.0 (5.7)	6.4 (4.7)	.652
Symptoms at presentation			
No symptoms (%)	23 (23.2)	2 (1.4)	.000
Pain (%)	38 (38.4)	73 (49.3)	.090
Signs of incarceration (%)	2 (2.0)	3 (2.0)	.997
Nausea (%)	1 (1.0)	4 (2.7)	.355
Cosmesis (%)	14 (14.1)	28 (18.9)	.327
Defecation difficulties (%)	23 (23.2)	40 (27.0)	.503
Limitations daily activity (%)	5 (5.1)	8 (5.4)	.573

Watchful waiting group

In total 104 patients were assigned to the WW group. In 34 patients (33%) the absence of symptoms was a reason to choose for WW. Comorbidities and obesity were reasons for WW strategy in 24 (23%) and 23 (22%) patients respectively. Eleven patients (11%) refused OT and in four (4%) cases the large size of the hernia was decisive.

During follow-up 34 patients (33%) crossed over to the OT group. The median time to crossover from the WW group to the OT group was 21 weeks (IQR 2-53). The majority of the patients (94%) crossed-over from WW to OT in the first 24 months after diagnosis (Figure 2). Eight patients (24%) were operated in an emergency setting with incarceration of the hernia and 13 patients (38%) crossed to operative treatment because they suffered from increased abdominal pain without signs of incarceration. Six patients (18%) were not satisfied with WW, three (9%) lost weight preoperatively, four (12%) had an increase of hernia size or cosmetic complaints.
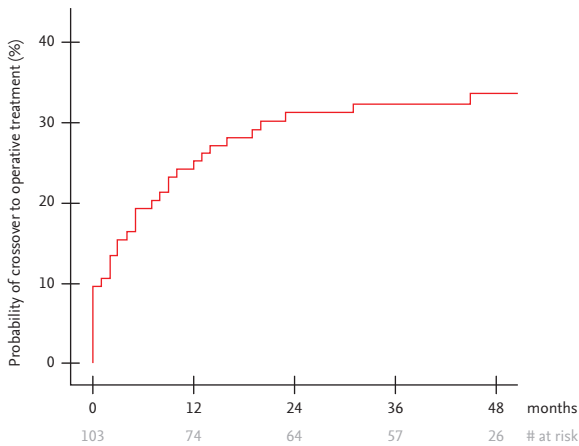
Figure 2 Probability to crossover from watchful waiting to operative treatment

Operative treatment group

In total 151 patients were planned for OT of which 140 patients underwent the surgical procedure after a median of 14 weeks (IQR 8-22). The remaining 11 (7%) patients crossed over to WW. Six (55%) patients crossed over because their IH became of inferior importance with regard to their comorbidities, four (36%) patients decided to refrain from surgery, and one (9%) patient was cancelled because of increased operation risk due to obesity.

Morbidity and mortality

The complications are summarised in Table 3. The incidence of unexpected peroperative intestinal perforations was 13% in the crossover group compared versus 2% in the OT group (p=.002). The incidence of postoperative fistulas was 7% in patients who crossed over from WW to OT versus 0% in the OT group (p=.003). During follow up 19patients (13%) died in the OT group and 24 (23%) in the WW group (p=.003). Postoperatively three patients died. Two patients were initially conservatively treated patients who needed emergency surgical repair due to incarceration of the hernia. One patient died during admission after elective hernia repair (p=0.035). The death of the other 40 patients during follow up was not related to IH.

Discussion

This is the first study that offers a closer look into conservative treatment of IH: the WW approach. The study describes the incentives to choose between OT and the natural course of WW. In this selected patient category we found a high crossover rate from WW to OT, and higher morbidity and mortality. Eight (8%) of the patients in the WW group needed emergency treatment.

Table 3 Morbidity and mortality after IH repair

	WW > OT	OT	p-value
Overall Morbidity (%)	9 (29)	22 (17)	.141
SSI (%)	0 (0)	7 (5)	.192
Fistula (%)	2 (6.5)	0 (0)	.003
Abscess (%)	0 (0)	4 (3)	.328
Perop. Perforation (%)	4 (13)	2 (2)	.002
Postop. Ileus (%)	0 (0)	3 (2)	.397
Infection (%)	2 (6)	4 (3)	.358
IH related Mortality (%)	2 (6.1)	1 (0.7)	.035

OT, Operative Treatment, WW, Watchful Waiting; SSI, Surgical Site Infection; IH, Incisional Hernia

The decision for OT or WW was made by individual surgeons in the hospital. According to the medical charts the decisions whether to operate or not were based on patient's medical history, characteristics, and symptoms at presentation. A questionnaire sent among renowned surgeons in IH repair demonstrated that pain and limitations during daily activities were considered the most important indications for repair. Cosmetic complaints were considered least important (19). In our study the absence of symptoms is significantly higher in the WW group. Patients with episodes of pain tend to be planned more frequently for surgical treatment although this difference was not significant in our study.

During the study 43 patients died between diagnose and follow up. We presume that the significant higher number of patients in the WW group that deceased during the follow-up period is a reflection of a worse general health status of these patients. Also the higher age of the patient in the WW group is likely to contribute to a higher mortality in the WW group.

In the present study 33% of the WW patients switched to OT. Eight of these initial conservative patients were treated in an emergency setting leading to significantly more postoperative complications (i.e. bowel perforations and postoperative fistulas). Two out of 8 (25%) emergency operations in the cross-over group died during hospital admission. The risks for poor early outcomes after emergency repair, such as postoperative mortality, recurrence, and readmissions, have already been described (20-22). A large nationwide prospective cohort comparing emergency and elective incisional hernia repair showed a 30-day mortality of 6.4% (20). An explanation for the higher 30-day mortality in our group may be that a number of these patients were assigned to WW due to comorbidity (23%) and obesity (22%). Furthermore, patients who presented with incarcerated IH were excluded in our study. In case of emergency repair it is likely that these crossover patients have a higher risk of morbidity and mortality than relatively healthy patients. Therefore controlled elective treatment of complex and compromised patients should be considered to prevent emergency repair. Although smoking is an independent risk factor readmission and complications after IH repair, there were significantly more patients who smoked in the initial OT group (23). This indicates that

smoking does not contribute to the decision whether or not to operate.

The majority of patients who switched from WW to OT did so during the first 24 months after diagnosis of IH. Because it is unlikely that patients need surgical repair after the first two years, there seems to be no need for longer follow-up.

Obviously our study has some limitations and most can be attributed to the retrospective design of the study. Possibly patients of the WW group had OT elsewhere. This might contribute to a selection bias and lead to underestimation of crossovers and hernia related morbidity and mortality. This study does not provide any data regarding quality of life and long term follow up. Standard follow-up which includes long term follow-up of both groups and data about quality of life might strengthen the results of further studies and provides more insight into safety and cost-effectiveness of WW in IH. We have to be careful to draw general conclusions from the patient's characteristics because of the heterogeneity of the selected patient groups and the absence of decision making tools (i.e. guidelines or protocols for the treatment of IH). A current randomised prospective trial comparing OT with WW in oligo- and asymptomatic IH should be awaited before abandoning WW strategy in standard practice (24). Patients who are treated conservatively should be informed and aware of potential risks of emergency repair, resulting in higher morbidity and mortality.

In conclusion, WW strategy in IH leads to high crossover rates with significant higher morbidity and mortality, especially in patients who underwent emergency repair of IH. Controlled elective treatment of IH should be considered to prevent emergency repair.

J. Verhelst and L. Timmermans contributed equally to this manuscript.

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3 PREVENTION

Meta-analysis of primary mesh augmentation as prophylactic measure to prevent incisional hernia

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Abstract

Introduction: Incisional hernia (IH) remains one of the most frequent postoperative complications after abdominal surgery. As a consequence, primary mesh augmentation, a technique to strengthen the abdominal wall, has been gaining popularity in the last decade. This meta-analysis was conducted to evaluate the prophylactic effect of primary mesh augmentation on the incidence of IH compared to primary suture.

Methods: A meta-analysis was conducted according to the PRISMA guidelines. Articles, published between January 1990 and March 2013, were searched for in Medline, Embase, Web of Science and the Cochrane Library. Randomized controlled trials comparing primary mesh augmentation and primary suture for closing the abdominal wall after surgery were included. The quality of the randomized controlled trials was assessed using the Oxford level of evidence scale and the criteria specified by the Cochrane Collaboration.

Results: Out of 576 papers, 5 randomized controlled trials were selected comprising 346 patients. IH occurred significantly less in the primary mesh augmentation group (RR 0.25, 95% CI 0.12 to 0.52, I2 0%; P <0.001). No difference could be observed with regards to wound infection (RR 0.86, 95% CI 0.39 to 1.91, I2 0%; P=0.71) or seroma (RR 1.22, 95% CI 0.64 to 2.33, I2 0%; P=0.55). A trend was observed for chronic pain in favour of the primary suture group (RR 5.95, 95% CI 0.74 to 48.03, I2 0%; P=0.09).

Conclusion: The use of primary mesh augmentation for abdominal wall closure is associated with significantly lower incidence of IH compared to primary suture. No significant differences could be observed for postoperative complications, such as infections and seroma.

Introduction

Since the beginning of the surgical profession, the optimal technique for abdominal wall closure has been investigated in many studies in an attempt to prevent incisional hernia (IH) and fascial dehiscence. Unfortunately, the introduction of the mass closure technique, continuous sutures, slowly absorbable sutures, suture length to wound length ratio (SL:WL) of 4:1 and small stitch length have not resulted in acceptable IH rates (1-5). On the contrary, IH remains one of the most frequent postoperative complications after abdominal surgery with incidences in the general population of 5.2% to 20% (1, 6, 7).

Risk factors for the development of IH, such as abdominal aortic aneurysm (AAA) and obesity, can increase the incidence of IH up to 35% (8-12). It is generally thought that patients with AAA are suffering from a connective tissue disorder, and are more prone to develop IH and inguinal hernia (13-15). It is also believed that obese patients have a higher intra-abdominal pressure causing higher tension on the abdominal wall suture closure compared to patients without obesity. High tension on the suture should be avoided, as it weakens the wound, impairs collagen synthesis and increases the rate of infection and the incidence of IH (16-19). Other factors that influence wound healing negatively are malignancy, diabetes, steroid use, surgical site infection, smoking and malnutrition (20-23).

It has been shown that IH has a negative effect on patient's quality of life and reduces the body image (24). In the United States a total of 400.000 patients are treated for IH each year (25). Mesh repair can significantly reduce the risk of IH recurrence. However, IH mesh repair still has a 10 year cumulative recurrence rate of 32%, and cumulative re-operation rates have been reported as high as 23% (25). Considering the impact of IH on patient's quality of life and body image in addition to the high recurrence rates, research should therefore focus on prevention of IH.

In 1995 a Belgian research group was the first to publish results focussing on primary mesh augmentation (PMA) as a means to reduce the incidence of IH (26). Since 1995 a number of articles, including randomized controlled trials (RCT), have been published on this subject. However, in these trials a variation of different patients groups, meshes and augmentation techniques are used. Therefore, a systematic review and meta-analysis of RCTs were conducted to evaluate the effectiveness of PMA on IH incidence, the operation time, length of hospital stay and rate of postoperative complications such as infection, seroma, hematoma and chronic pain.

Methods

Data sources, searches and selection criteria

A systematic search of MEDLINE, Embase, Web of Science and the Cochrane library was performed for articles published between January 1990 and October 2012. All aspects of the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) statement were followed (27).

No formal protocol was created for this meta-analysis; however the actions undertaken during the review process are described in this section. Manual reference checks of accepted papers in recent reviews and papers included were performed to supplement the electronic searches. The search syntax included keywords corresponding to the target population (adults), interventions (elective abdominal surgery) and target condition (IH). Details of the search syntax are listed in the Appendix. Language restrictions were not used for the initial search in order to investigate potential language bias as demonstrated in the flow diagram (Figure 1). Subsequently, the exclusion criteria of article type (non-randomized) and non-adult participants were applied and duplicates were removed. Studies were evaluated for inclusion independently by two reviewers (BG, LT) based on title and abstract and finally were evaluated independently based on the full text.

Studies were included if they met the following criteria: 1) participants: adult patients who underwent elective abdominal wall surgery; 2) interventions: Abdominal wall closure with primary suture (PS) or non-absorbable PMA; 3) outcome measures: IH 4) types of studies: RCTs. A random check was performed by the senior author (JFL). Any discrepancies in inclusion were resolved by discussion between the reviewers and the senior author (JFL).

Identification	Records identified through database searching	n = 1032
	Duplicates removed	n = 456
	Records after duplicates removed	n = 576
Screening	Records screened	n = 576
	Records excluded	n = 559
Eligibility	Full-text articles assessed for eligibility	n = 17
	Full-text articles excluded, with reasons	n = 12 — 1. Not available (n = 4) 2. No RCT (n = 7) 3. Absorbable mesh (n = 1)
Included	Studies included in qualitative synthesis	n = 5
	Studies included in qualitative synthesis (meta-analysis)	n = 5

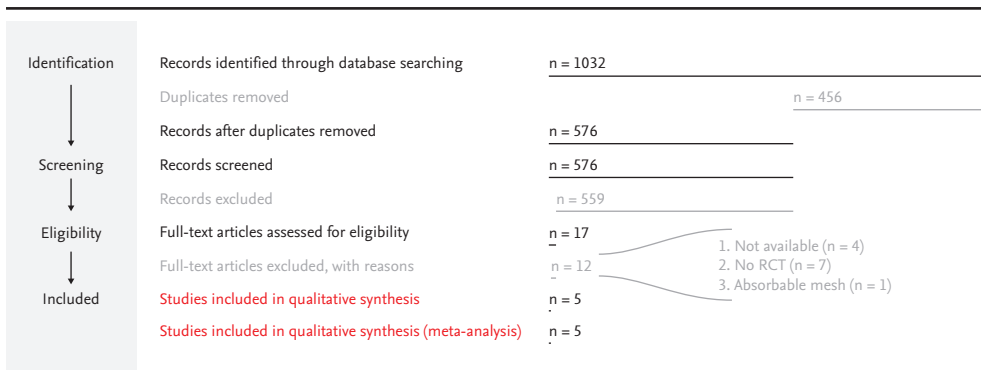**Figure 1** PRISMA 2009 Flow Diagram

Data extraction and management

Two reviewers (BG, LT) extracted all required data from each study included independently using a standardized form which covered: 1) study characteristics (study design, year of publication, study location, study period, level of evidence and risks of bias; 2) baseline characteristics of each study (type of intervention,

number of patients, age, sex, body-mass index (BMI), type of sutures, type of mesh, mesh location, and duration of follow-up); 3) type of intervention (abdominal wall surgery: PS vs non-absorbable PMA); and 4) surgery-related factors (reported incidence of IH and postoperative complications). Disagreements were resolved by consensus.

Assessment of study quality

The level of evidence of each paper was established according to the Oxford Centre for Evidence-Based Medicine Level of Evidence scale (28). The methodological quality of the included studies was assessed according to the criteria specified by the Cochrane Collaboration and risks of bias summary figures were generated (29).

Data analysis

To pool data and calculate a pooled mean for each patient level outcome, a random effects model was used, which takes into account both the variance between studies and the variance within a study (30). Risk ratios or mean differences with 95% confidence intervals were calculated to evaluate the statistical difference between outcomes following PS or PMA. Statistical heterogeneity was assessed for incidence of IH, mesh infection, wound infection, seroma, operation time and hematoma by calculating the Q statistics and the I^2 statistic.

Selective dissemination of evidence was assessed by plotting each outcome measure of each study against precision (1/standard error) in a plot with p-value contours. Funnel plot asymmetry, specifically with an apparent lack of studies in high p-value areas of the plot, can be indicative of publication bias (31). In addition, the individual study effects on the results were examined by removing each study one at a time to determine whether removing a particular study would change the significance of the pooled effect. Two-sided P ≤ 0.05 was considered statistically significant. Analyses were performed using Review Manager software (RevMan, 5.0.25; The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search and study characteristics

Of 576 papers found after the initial search, 5 fell within the scope of the study; i.e. 5 RCTs comparing abdominal wall closure with non-absorbable PMA and with PS in patients who underwent elective abdominal surgery. The PRISMA flow diagram for systematic reviews is presented in Figure 1. Two studies included provided level 1b evidence and 3 studies provided level 2b evidence on the Oxford Level of Evidence Scale. The evaluation of risks of bias is demonstrated in Figure 2. No studies were excluded after assessing the quality of the papers included.

	Abo-Ryia 2013	Bevis 2011	El-Khadrawy 2009	Strezekczyk 2006	Gutiérrez de la Peña 2003
Random sequence generation (selection bias)		+		+	
Allocation concealment (selection bias)		+		+	
Blinding of participants and personnel (performance bias)		+		+	
Blinding of outcome assessment (detection bias)		−		+	
Incomplete outcome data (attrition bias)	+	+	+		+
Selective reporting (reporting bias)	+	−	−	−	−
Other bias	+	+	−		−

Figure 2 Summary of risk of bias assessment.

The meta-analysis was performed using these 5 RCTs comprising 346 patients. Three techniques often used in IH repair (onlay, sublay and pre-peritoneal) were used for PMA in the included RCTs. None of the deaths reported in the studies included were related to the mesh placement. Study characteristics and baseline characteristics of patients are given in Table 1. The total number of complications per treatment group reported in each study is presented in Table 2.

Outcome parameters

Five studies (n=346 patients) investigated pooled occurrence of IH and were included in the meta-analysis (32-36). IH occurred significantly less in the PMA group (RR 0.25, 95% CI 0.12 to 0.52, I2 0%; P < 0.001) (Figure 3).

Study or Subgroup	PMA Events	PMA Total	PS Events	PS Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Gutiérrez de la Peña	0	44	5	44	6.3%	0.09 [0.01, 1.60]	2003	
Strezekczyk	0	36	8	38	6.5%	0.06 [0.00, 1.04]	2006	
El-Khadrawy	1	20	3	20	10.9%	0.33 [0.04, 2.94]	2009	
Bevis	5	37	16	43	63.4%	0.36 [0.15, 0.90]	2011	
Abo-Ryia	1	32	9	32	12.8%	0.11 [0.01, 0.83]	2013	
Total (95% CI)		**169**		**177**	**100%**	**0.25 [0.12, 0.52]**		
Total events	7		41					

Heterogeneity: Tau² = 0.00; Chi² = 3.07, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.75 (P = 0.0002)

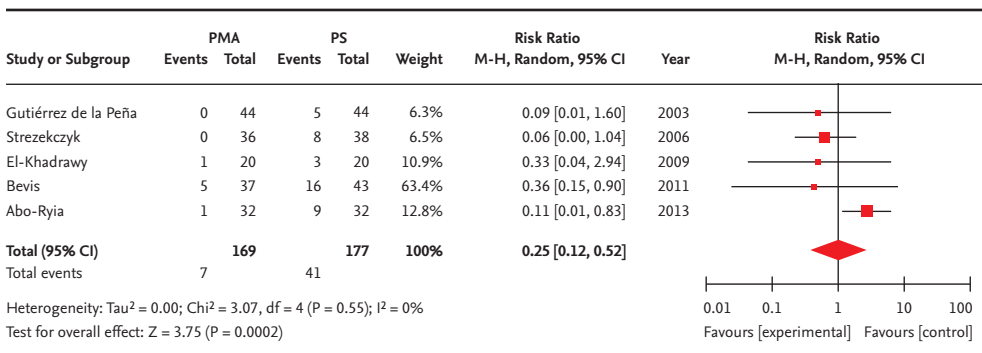Favours [experimental]   Favours [control]

Figure 3 Incisional hernia

Table 1 Study & Baseline characteristics

Study and Reference	Study Period	Ox LoE	N	Suture : PMA	Age*/**	Male (%)	BMI* (kg/m2)	SL / WL ratio	Type of mesh	Mesh position	Mesh (overlap)	Type of surgery	Length of FU*
Bevis (35).	2003 - 2007	1b	80	43 / 37	73 (59 - 89)	77 (96)	-	4:1	PP	Sublay	7,5 x 30 cm mesh	AAA	25.4 months
Abo-Ryia (34).	2004 - 2006	2b	64	32 / 32	36.9 (11.3) / 38.5 (10.8)	7 (21.8) / 6 (18.8)	51.4 (10.5) / 52.2 (9.1)	-	PP	Pre-peritoneal	5 cm x 4 cm overlap	RYGB / VBG / VSG	48 months
Strzelczyk (33).	2002 - 2005	1b	74	38 / 36	38.9 (11.8) / 39.4 (12.3)	47 (64)	46.8 (7.6) / 46.2 (7.1)	-	PP	Sublay	4 cm x 2 cm overlap	RYGB	28 months
El-Khadrawy (34).	2000 - 2002	2b	40	20 / 20	47.7 (14.8)	18 (45)	.	4:1	PP	Pre-peritoneal	2 cm x ? overlap	Misc	36 months
Gutiérrez de la Pena (32).	-	2b	88	44 / 44	64.3 (42 - 83)	67 (59)	-	-	PP	Onlay	3 cm x 3 cm overlap	Misc	36 months

*Mean (SD), SD = standard deviation, **Median (range), ***Median (IQR1 ; IQR3), Ox LoE = Oxford Level of Evidence, PMA = Prophylactic Mesh Augmentation, IQR = interquartile range, SL/WL ratio = Suture length to Wound length ratio, PP = Polypropylene, l = lateral c = caudal and cranial AAA = Abdominal Aortic Aneurysm, RYGB = Roux-en-Y Gastric Bypass, VBG = vertical banded gastroplasty, VSG = vertical sleeve gastrectomy, Misc = Miscellaneous.*

Table 2 Classification of wound-related complications

Study and Reference	Type of intervention	Total # of complications	Haematoma	Seroma	Incisional hernia	Wound infection	Mesh infection	Complete dehiscence	Reoperation	Mesh removal
Bevis (35).	PS	20	-	0	16	2	-	-	2	-
	PMA	12	-	2	5	2	0	-	2	1
Abo-Ryia (34).	PS	12	-	5	9	5	-	0	-	-
	PMA	12	-	6	1	5	-	0	-	-
Strzelczyk (33).	PS	13	-	3	3	4	-	1	-	-
	PMA	8	-	4	1	2	-	0	-	-
El-Khadrawy (34).	PS	12	-	4	8	0	-	0	-	-
	PMA	5	-	5	0	0	-	0	-	-
Gutiérrez de la Pena (32).	PS	11	2	3	5	1	-	0	-	-
	PMA	5	3	1	0	1	-	0	-	0

PS = primary suture, PMA = Prophylactic Mesh Augmentation

Five studies (n=346 patients) investigated pooled occurrence of wound infection and those were included in the meta-analysis (32-35). There was no statistically significant difference in the occurrence of wound infection between the PMA group and the PS group (RR 0.86, 95% CI 0.39 to 1.91, I2 0%; P=0.71) (Figure 4).

Five studies (n=346 patients) investigating pooled occurrence of seroma were included in the meta-analysis (32-35). There was no statistically significant difference in the occurrence of seroma between PMA and PS group (RR 1.22, 95% CI 0.64 to 2.33, I2 0%; P=0.55) (Figure 5).

Two studies (n=128 patients) investigated pooled chronic pain and were included in the meta-analysis (32, 34). There was no statistically significant difference in chronic pain between PMA and sutured abdominal closure, however a trend was visible (RR 5.95, 95% CI 0.74 to 48.03, I2 0%; P=0.09) (Figure 6).
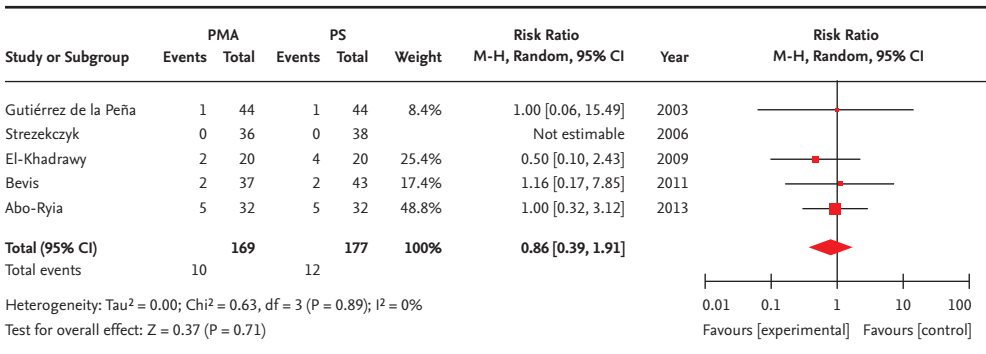
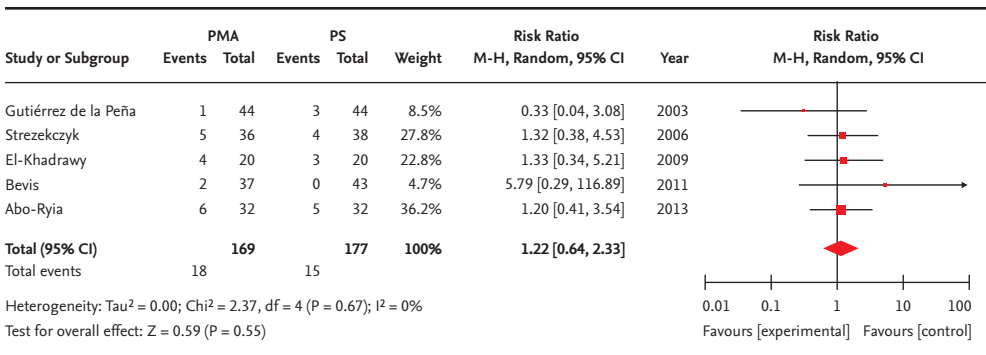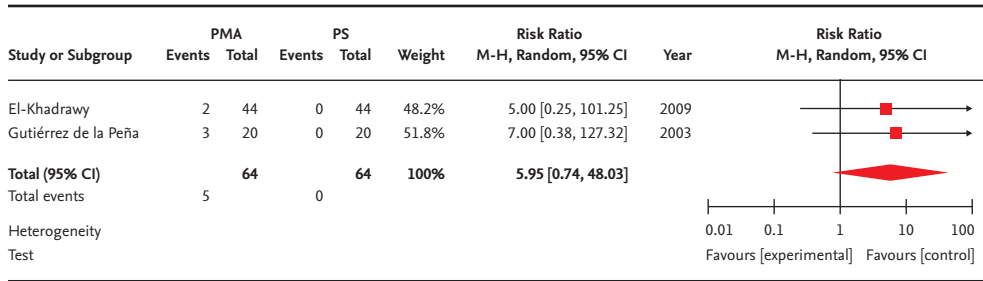| Study or Subgroup	PMA Events	PMA Total	PS Events	PS Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gutiérrez de la Peña	1	44	1	44	8.4%	1.00 [0.06, 15.49]	2003
Strezekczyk	0	36	0	38		Not estimable	2006
El-Khadrawy	2	20	4	20	25.4%	0.50 [0.10, 2.43]	2009
Bevis	2	37	2	43	17.4%	1.16 [0.17, 7.85]	2011
Abo-Ryia	5	32	5	32	48.8%	1.00 [0.32, 3.12]	2013
Total (95% CI)		169		177	100%	0.86 [0.39, 1.91]	
Total events	10		12				
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 3 (P = 0.89); I² = 0%							
Test for overall effect: Z = 0.37 (P = 0.71)							

0.01 0.1 1 10 100
Favours [experimental]   Favours [control]

Figure 4   Infection

Study or Subgroup	PMA Events	PMA Total	PS Events	PS Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gutiérrez de la Peña	1	44	3	44	8.5%	0.33 [0.04, 3.08]	2003
Strezekczyk	5	36	4	38	27.8%	1.32 [0.38, 4.53]	2006
El-Khadrawy	4	20	3	20	22.8%	1.33 [0.34, 5.21]	2009
Bevis	2	37	0	43	4.7%	5.79 [0.29, 116.89]	2011
Abo-Ryia	6	32	5	32	36.2%	1.20 [0.41, 3.54]	2013
Total (95% CI)		169		177	100%	1.22 [0.64, 2.33]	
Total events	18		15				
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 4 (P = 0.67); I² = 0%							
Test for overall effect: Z = 0.59 (P = 0.55)							

0.01 0.1 1 10 100
Favours [experimental]   Favours [control]

Figure 5   Seroma

Study or Subgroup	PMA Events	PMA Total	PS Events	PS Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
El-Khadrawy	2	44	0	44	48.2%	5.00 [0.25, 101.25]	2009	
Gutiérrez de la Peña	3	20	0	20	51.8%	7.00 [0.38, 127.32]	2003	
Total (95% CI)		**64**		**64**	**100%**	**5.95 [0.74, 48.03]**		
Total events	5		0					
Heterogeneity								
Test								

Figure 6 Chronic pain

Four studies reported data regarding fascial dehiscence, however numbers were so low and definitions differed throughout most studies that these results could not be pooled. Gutiérrez de la Peña and Strzelczyk describe that no eviscerations or wound dehiscence were observed in their study. El-Khadrawy et al describes that 1 (5%) complete wound disruption was observed in the PS compared to none in the PMA, and 2 (10%) partial wound disruptions were observed in the PS group compared to 1 (5%) in the PMA group. Abo-Ryia et al describe 2 partial dehiscences in the PS group compared to 1 in the PMA group, this was not statistically significant.

Two studies reported data on operation time, however as the study by Bevis did not report standard deviations these results could not be pooled (35, 36). Bevis et al reported no statistically significant difference in median duration of operation (min) between the PMA group and the PS group (150 min, range 90 - 225 vs 140 min, range 90 – 300; P = 0.59). Abo-Ryia et al also discovered no statistically significant difference in mean duration of their operations between the PMA group and the PS group (vertical banded gastroplasty: 81.2 min, SD 7 vs 76.2 min, SD 9; roux-and-y gastric bypass: 151 min, SD 9 vs 144.9 min, SD 9; vertical sleeve gastrectomy: 123.5 min, SD 8 vs 115.1 min, SD 5)

One study reported data regarding operating time and thus no pooled assessment could be calculated. Strzelczyk et al (33) reported no statistically significant difference in mean duration of hospitalization (days) between the PMA group and the PS group (8.4 days, SD 3.2 vs 10.3 days, SD 5.9; P = 0.09).

Inspection of funnel plots revealed no indications for publication bias. However, due to the limited number of studies no formal tests of funnel plot asymmetry were performed. Further sensitivity analyses were performed for all outcomes by removing each study with Oxford level of evidence scale lower then 1b and each study which scored mediocre on the evaluation of risk of bias; this did not change the significance-level of any of the risk ratios.

During the analysis we observed no statistical heterogeneity, however it was already decided to use a random effects models beforehand due to the clinical diversity of the included trials.

Discussion

This meta-analysis shows that the use of PMA for abdominal wall closure is associated with significantly lower incidence of IH compared to PS. No significant differences could be observed for postoperative complications, such as infections and seroma, between the two groups. However, this study did observe a trend of increased chronic pain in favour of the PS group. Furthermore, data regarding postoperative hematoma formation, duration of hospital stay and operation time could not be pooled, because it was reported only once in the studies included.

Study characteristics

All studies included had a relatively long follow-up period which is essential for investigating IH, as it is known that IH can still occur after 10 years (6, 7, 25). Other characteristics of the studies included differed in some aspects. In three studies (Abo-Ryia, El-Khadrawy and Gutiérrez de la Peña) no description of blinding was described and it is likely that personal were not blinded during follow-up (32, 34). Bevis describes that patients were blinded but that surgeons at during follow-up had access to the full patient notes (35). All three studies are at risk for detection bias. Only in the study of Strzelczyk were the surgeons blinded for the randomization results during follow-up (33).

The study by Bevis et al. was the only study that performed a power analysis prior to the start of trial (35). Unfortunately, they were not able to reach the number of patients calculated and thus were underpowered.

Patient characteristics

Three of the included studies (Abo-Ryia, Bevis and Strzelczyk) had clearly defined study groups, only including patients with AAA or morbid obesity (33, 35). Both risk factors increase the risk of IH significantly and have an incidence rate of over 30%. The other two (El-Khadrawy and Gutiérrez de la Peña) studies included patients according to a predefined list of risk factors (hepatic cirrhosis, jaundice, renal impairment, malignancy, cardiac disease, chest problems, previous abdominal incisions, steroid therapy, old age, respiratory failure, clear malnutrition, obesity, habitual smoker) (32, 34). Patients needed one or more of these risk factors in order to be eligible for inclusion. Although these characteristics are known risk factors for the development of IH or impaired wound healing, the actual increase in risk by these factors is often not known.

All studies focussed on the use of PMA in midline laparotomy patients. However, the study of Gutiérrez de la Peña included more than one type of incision (32). Except for midline laparotomy, this study also included some paramedian incisions. Paramedian incisions, however, are known to have a lower incidence of IH compared to the traditional midline laparotomy (37).

It has been demonstrated that the use of ultrasonography or other additional radiological tests will

yield a higher number of IH diagnosis (38). Only one study (Strzelczyk) performed standard ultrasonography during follow-up (33). Three studies (Abo-Ryia, Bevis and Gutiérrez de la Peña) performed additional radiological testing in cases of doubt after physical examination (32, 35). El-Khadrawy did not perform additional testing (38). The combination of not regular use of ultrasound, the patient study groups, and inclusion of paramedian incisions might explain the relatively low incidence of IH found in the two studies (Gutiérrez de la Peña and El-Khadrawy).

PMA techniques

One RCT was not included in the meta-analysis (39). In this study an absorbable mesh (Vicryl) was used for PMA and as we were interested in long term protection, this study was excluded.

Not all studies used the same type of PMA. The studies included used the onlay (32), sublay (33, 35) or pre-peritoneal techniques (34, 40). The onlay technique (mesh placed on the anterior rectus fascia) is somewhat different compared with the sublay (mesh placed on the posterior rectus fascia and peritoneum) and pre-peritoneal (mesh placed on the peritoneum) mesh positions. The onlay technique is generally easier, quicker to perform but might also facilitate seroma formation (41, 42). This was, however, not observed in the study by Gutiérrez de la Pena. In this study no evaluation regarding superiority of the different techniques could be calculated. In addition, current literature on incisional hernia repair is still indecisive as to which of the techniques is superior (41, 42). Ideally a meta-analysis of exactly the same types of surgery is preferable, reducing intervention heterogeneity. However, we hypothesize that the concept of PMA is similar with regards to the different techniques and thus a meta-analysis can be performed. In addition, removing the study using the onlay technique did not alter the results of the meta-analysis.

Postoperative complications

In all studies included the postoperative complications which were routinely described were represented by IH, infection and seroma. However, three studies did not mention hematoma (33-35), one did not mention fascial dehiscence35, and three did not mention possible mesh explantation (33, 34, 40). It seems strange not mentioning mesh removal, considering 25% meshes had to be extracted in a previous PMA cohort study (43). Two studies reported data on chronic pain in favour of the PS group; however, this was not statistically significant (32, 34). In addition, these studies lacked information on how the chronic pain was assessed and which scale was used. Therefore, a good interpretation of the intensity of the pain was not possible. Furthermore, no clear definitions were described for any of the postoperative complications.

In addition to all postoperative complications it will be interesting to get more insight in long term mesh related complications such as fistula and late infection. These complications are not discussed in the included papers but are known to occur in incisional hernia surgery. Also, in cases of re-laparotomies the

question if PMA will make getting access to the abdomen more difficult, increasing the chance of enterotomy, is very important and needs to addressed in other trials (44, 45).

Conclusion

Despite continuous research regarding abdominal wall closure, the incidence of IH remains unacceptably high, especially in patients who have one or more risk factors for the development of IH. However, in an attempt to reduce this incidence new surgical techniques were developed to reduce the incidence of IH to an acceptable proportion. This study shows that the use of PMA for abdominal wall closure is associated with significantly lower incidence of IH compared to PS. No significant differences could be observed for postoperative complications, such as infections and seroma, Thus PMA seems an effective and save method for the prevention of IH in high risk groups. However, the quality of the available RCTs was in some cases low and important outcome measures, such as mesh removal, hematoma, fistula, postoperative pain, operation duration, hospital stay, enterotomy during relaparotomy, quality of life, and cost-effectiveness were not reported in all studies included. Other large high quality RCTs should be performed to evaluate these shortcomings.

Acknowledgments

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Kedvezobb muteti eredmenyek "onlay" haloval, mint "sublay" helyzetben beultetettel. Varrattal, illetve halobeultetessel torteno hasfal-rekonstrukcio prospektiv, randomizalt, multicentrikus vizsgalata--oteves utankovetes eredemenyei. Magy Seb. 2010 Oct;63(5):302-11.

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Appendix

Embase

('surgical mesh'/de OR prosthesis/de OR (mesh OR prosthe* OR implant*):ab,ti) AND (prophylaxis/de OR prevention/de OR (prophyla* OR prevent*):ab,ti) AND ('incisional hernia'/de OR 'abdominal wall hernia'/ de OR ((incision* OR scar* OR cicatri* OR postoperat* OR surg* OR operat* OR ventral* OR abdom*) NEAR/3 (herni*)):ab,ti)

Medline in OvidSP

("surgical mesh"/ OR "Prostheses and Implants"/ OR (mesh OR prosthe* OR implant*).ab,ti.) AND ("prevention and control".xs. OR "Primary Prevention"/ OR (prophyla* OR prevent*).ab,ti.) AND ("Hernia, Ventral"/ OR ((incision* OR scar* OR cicatri* OR postoperat* OR surg* OR operat* OR ventral* OR abdom*) ADJ3 (herni*)).ab,ti.)

Cochrane Central

((mesh OR prosthe* OR implant*):ab,ti) AND ((prophyla* OR prevent*):ab,ti) AND (((incision* OR scar* OR cicatri* OR postoperat* OR surg* OR operat* OR ventral* OR abdom*) NEAR/3 (herni*)):ab,ti)

WoS

TS=(((mesh OR prosthe* OR implant*) NEAR/3 (prophyla* OR prevent*)) AND (((incision* OR scar* OR cicatri* OR postoperat* OR surg* OR operat* OR ventral* OR abdom*) NEAR/3 (herni*))))

PubMed

((mesh[tiab] OR prosthe*[tiab] OR implant*[tiab])) AND ((prophyla*[tiab] OR prevent*[tiab])) AND (((incision*[tiab] OR scar*[tiab] OR cicatri*[tiab] OR postoperat*[tiab] OR surger*[tiab] OR surgic*[tiab] OR operation*[tiab] OR operative*[tiab] OR ventral*[tiab] OR abdom*[tiab]) AND (herni*[tiab]))) AND publisher[sb]
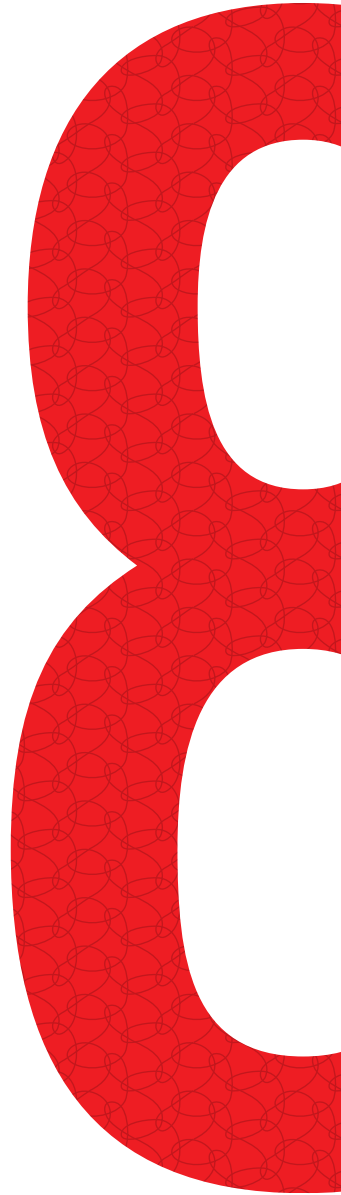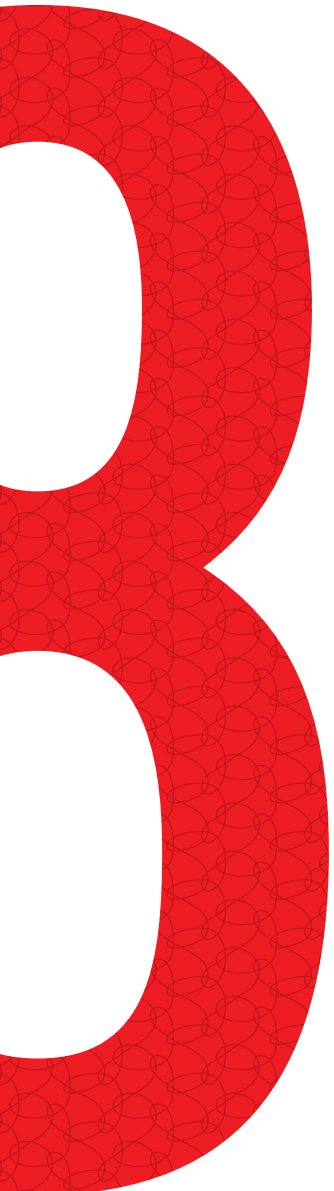
A double blind randomized controlled trial comparing primary suture closure with mesh augmented closure to reduce incisional hernia incidence

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Abstract

Introduction: Incisional hernia is the most frequently seen long term complication after laparotomy causing much morbidity and even mortality. The overall incidence remains 11-20%, despite studies attempting to optimize closing techniques. Two patient groups, patients with abdominal aortic aneurysm and obese patients, have a risk for incisional hernia after laparotomy of more than 30%. These patients might benefit from mesh augmented midline closure as a means to reduce incisional hernia incidence.

Methods/design: The PRImary Mesh Closure of Abdominal Midline Wound (PRIMA) trial is a double-blinded international multicenter randomized controlled trial comparing running slowly absorbable suture closure with the same closure augmented with a sublay or onlay mesh. Primary endpoint will be incisional hernia incidence 2 years postoperatively. Secondary outcomes will be postoperative complications, pain, quality of life and cost effectiveness.

A total of 460 patients will be included in three arms of the study and randomized between running suture closure, onlay mesh closure or sublay mesh closure. Follow-up will be at 1, 3, 12 and 24 months with ultrasound imaging performed at 6 and 24 months to objectify the presence of incisional hernia. Patients, investigators and radiologists will be blinded throughout the whole follow up.

Conclusion: The PRIMA trial will provide level 1b evidence whether mesh augmented midline abdominal closure reduces incisional hernia incidence in high risk groups.

Trial registration Clinical trial.gov NCT00761475

Introduction

Incisional hernia (IH) is the most frequently seen long term complication in surgery causing much morbidity and even mortality in patients (1-4). Despite studies on the optimal closing technique for laparotomies, the risk for IH after midline incision remains about 11-20% (5, 6). In the Netherlands alone about 4000 IH operations are performed each year. Incisional hernia surgery is, in fact, a re-operation to relieve symptoms caused by this common complication and the results of repair are often disappointing (7, 8).

Patient-related risk factors for incisional hernia after a laparotomy, like obesity, steroid use, malnutrition, smoking, abdominal aortic aneurysm (AAA), and connective tissue disorders are known (7, 9-13). Despite this knowledge a sufficient method for prevention, has not been developed yet. Most research in the field of incisional hernia surgery has been performed to prevent recurrence after repair. The closure technique of midline incisions has grosso modo remained unchanged since many decades and primarily consists of suturing the linea alba. Interest in prevention of incisional hernias with the aid of synthetic mesh is growing and small, yet promising studies have now been published (14-25).

One specific group of high-risk patients are patients with an AAA. Aortic aneurysm is considered to be related to a type of connective tissue disorder. The connective tissue in these patients is thought to be compromised, playing an important role in the pathogenesis of an aneurysmal distension of the aorta. Healing of the midline fascia after laparotomy may be compromised due to formation of collagen with insufficient strength. Sutures can tear through the fascia and defects can develop in the abdominal wall. The relationship between aortic aneurysm and other abdominal wall hernias, like inguinal hernias, has been reported (26-28). Retrospective and prospective studies have shown an average risk for incisional hernia after AAA repair of about 30 % (Table 1) (9, 26, 28-34).

Table 1 Publications concerning risk for incisional hernia after aortic aneurysm repair with midline incision with a minimum of 2 years follow-up.

Author	Year	Follow-up	Article Type	# Hernias	# AAA	%
Fassiadis et al	2005	50 months	RCT	20	22	90,9
Rodriguez et al	2004	36 months	Prospective	14	61	22,9
Liapis et al	2004	63 months	Prospective	32	197	16,2
Raffetto et al	2003	33 months	Prospective	50	177	28,2
Augestad et al	2002	42 months	Case series	49	140	35
Musella et al	2001	49 months	Prospective	16	51	31,4
Adye and Luna	1998	36 months	Retrospective	18	58	31,0
Holland et al	1996	24 months	Case series	13	34	38,2
Stevick et al	1988	38 months	Retrospective	10	27	37,0

NOS = Newcastle-Ottowa Score, OR = onlay repair, SR = sublay repair, * = range, ** = mean, *** = Oxford level of evidence, RCT = randomized controlled trial, IH = incisional hernia, SSI = surgical site infection

Another high risk group is the group of obese patients (35). Patients with a BMI of 30 or more have a high risk of developing an incisional hernia after midline incision, with an incidence of 22% after 12 months (13, 36). Most recent literature is showing us that even a BMI of more than 27 gives a 20% risk for developing an incisional hernia after midline laparotomy (37). Considering only 50% of incisional hernia will be clinically evident in the first 12 months, the total incidence is likely to be above 30%. It is known from the study of Burger et al. that an extensive follow up time of up to 10 years is needed to evaluate outcome in hernia surgery (7). A tailored approach might be necessary, since hernia formation is multifactorial. Thus, the above mentioned high-risk group of patients with obesity and aneurysmal disease can benefit most from prevention.

Some small studies have been performed to evaluate the effect and safety of primary laparotomy wound closure with the aid of prosthetic mesh (Table 2) (14-25). These studies show a very low risk for incisional hernia and a low infection rate, even when used in contaminated area's, as seen in colostomy surgery. However, no high quality and adequately powered randomized controlled trial has been performed to evaluate the impact of prophylactic mesh augmentation for prevention of incisional hernia in high risk patients. This is the reason that the PRImary Mesh Closure of Abdominal Midline Wound (PRIMA) trial is being conducted.

Table 2   Publications concerning incisional hernia prevention with the aid of prosthetic mesh.

Author	Year	Type Article	# Patients	Hernia primary	Hernia Mesh	Follow-up	Mesh Type	Mesh Position
G. Currò et al	2011	Prospective	95	15/50	2/45	24 months	Polypropylene	Sublay
O. H. Llaguna et al	2011	Prospective	134	11/62	1/44	17 months	Biological	Intraperitoneal
P. M. Bevis et al	2010	RCT	85	16/43	5/37	36 months	Polypropylene	Sublay
G. Currò et al	2010	Prospective	50	8/25	1/25	12 months	Polypropylene	Sublay
M. P. Hidalgo et al	2010	Cohort	72	-	0/72	46 months	Polypropylene	Onlay
O. H. El-Khadrawy et al	2009	RCT	40	1/20	3/20	36 months	Polypropylene	Preperitonial
G. Hebert et al	2009	Cohort	16	-	1/16	6 months	Mix	Sublay
J. Strzelczyk et al	2006	RCT	74	8/38	0/36	28 months	Polypropylene	Sublay
J.L. O'Hare et al	2007	Cohort	39	-	1/28	48 months	Polypropylene	Sublay
C. Gutierrez de la Pena et al	2003	RCT	88	5/44	0/44	36 months	Polypropylene	Onlay
J. Strzelczyk et al	2002	Prospective	60	9/48	0/12	12 months	Polypropylene	Sublay
A. Pans	1998	RCT	288	41/144	33/144	29 months	Vicryl	Intraperitoneal

Objective

The objective of this study is to evaluate the effectiveness of incisional hernia prevention in patients after laparotomy for aortic aneurysm and in obese patients with a BMI of more than 27. A double blind randomized controlled trial will compare the commonly used technique of running suture to closure with the aid of a prosthetic mesh.

- The primary outcome measure will be incisional hernia occurrence 2 years postoperatively.
- Secondary outcome measures will cover relevant postoperative complications, post-operative pain and quality of life.

Methods/Design

Trial design

The trial is a double blinded randomized controlled international multicenter trial comparing traditional closure with running slowly absorbable suture to closure with the aid of prosthetic mesh. A total of 11 centers have agreed to participate in the trial which are located in three different countries (The Netherlands, Germany and Austria). A total number of 460 patients will be included. Patients will be randomized in three groups per-operatively to either receive primary closure, or mesh supported closure either in a sublay or onlay position. Patients will be kept unaware of the procedure until the endpoint of the trial was assessed. Outpatient clinic controls will be done by surgeons or surgical residents blinded for the procedure. Results will be stratified by center and operation indication.

Participants

Patients meeting the inclusion criteria scheduled for elective laparotomy will be asked to participate in the study. After ample information has been given, patients will be asked for informed consent.

Inclusion criteria

- Every elective midline laparotomy for patients with Abdominal Aortic Aneurysm AND/OR patients with a BMI of more than 27*.
- Signed informed consent.

The initial inclusion criteria featured patients with a BMI of 30 or higher. However as stated before, a study was published during the enrollment of this trial demonstrating that patients with a BMI 27 or more could also be included (37). We amended our protocol to lower our inclusions criteria for BMI, from 30 to 27.

Exclusion criteria

- Age < 18 years
- Inclusion in other trials with interference of the primary endpoint
- Life expectancy less than 24 months (as estimated by the treating physician)
- Pregnant women
- Immune suppression therapy within 2 weeks before surgery
- Bovine allergy

Registration and randomization procedure

Patients who are scheduled for operation and who have given informed consent will be registered by contacting the trial coordinator using the telephone or using the online inclusion randomization system. Included patient are registered in an online data base (designed and managed by HOVON data center, Rotterdam, the Netherlands) called TOP (Trial Online Process; see http://www.primatrial.nl). The patient name code, 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 will take place at the end of the scheduled operation before closing the abdomen in the operating room by contacting the trial coordinator using the telephone or using the online inclusion randomization system. The patient will stay in the randomization group on an intention to treat principle.

Intervention

Patients will be randomized for three different closing techniques (1A: primary suture closure of the midline fascia, 2B onlay mesh supported closure and 3C sublay mesh supported closure). Both mesh techniques are extensively used in incisional hernia surgery. However, a powered randomized comparison of these two techniques has not been performed. Infection rates in these trials seem low, even in the presence of open bowel (38-43). Because the study population will not be operated for an incisional hernia, which necessitates extended dissection of the abdominal wall in a previously operated area, infection rates are expected to be lower than the rates mentioned in the literature. Intra-peritoneal placement has not been considered given the high risk for adhesions between viscera and mesh (44).

The mesh will be fixed to the fascia structures with fibrin sealant (Tissucol DUO 500 2,0ml (Baxter Deutschland GmbH, Unterschließheim, Germany) in order to avoid sutures subcutaneously, to prevent the production of seroma and to simplify the procedure (45). Nowadays fibrin sealants are occasionally used in inguinal hernia surgery (46-48). The mesh will be fixed adequately with fibrin sealant to the ventral part of linea alba and posterior rectus sheath. The Optilene Mesh LP, 6 x 35 cm, B. Braun Aesculap AG, Tuttlingen, Germany, will be used as it was shown to have an optimal fixation with fibrin sealant and to provide good tensile strength (49).

Only the first operations of each center will be supervised by one of the PRIMA trial research fellows. If during operation an incisional hernia was discovered the patient was excluded from the trial, as the interest of this study was incisional hernia prevention, not repair. All centers were familiar with the 4:1 suture length to wound length ratio concept although not measured. As the focus of the trial was on the effect of primary mesh augmentation versus common day practice closure, no measurements of the suture closure were done.

Group A. Primary closure of the midline

The midline fascia will be closed in all three groups with a running slowly absorbable suture (MonoPlus, USP 1 ,Needle HRT48, 150 cm loop, B.Braun Aesculap, Tuttlingen, Germany). The ratio of suture length to wound length of 4:1 is recommended (but not measured). Subcutaneous tissue and skin are closed in a fashion preferred by the surgeon.

Group B. Onlay mesh supported closure

First, the midline will be closed as indicated in group A.

The Optilene Mesh LP will be positioned on the primary closed midline fascia with an overlap of 3 cm at each side. The mesh will then be fixed with fibrin sealant (5ml). The fibrin sealant will be applied on the entire surface of the mesh, and in one shot having permanent contact between the mesh and the tip of the joining piece. Immediately after application of the fibrin sealant, the mesh will be smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface and especially on the suture line. If present, it is also possible to use spray fixation using the EASYSPRAY system, Deutschland GmbH, Unterschließheim, Germany. When laparotomy is larger then 25cm use 2 applicators of Tissucol (10ml). Subcutaneous tissue and skin are closed in a fashion preferred by the surgeon.

Group C. Sublay mesh supported closure

A space will be created between both posterior rectus sheaths and the rectus muscle. Both posterior rectus sheath edges are sutured using a running slowly absorbable suture,(Monoplus, USP1, Needle HRT48, 150 cm, B. Braun Aesculap AG, Tuttlingen, Germany). A suture length to wound length ratio of 4:1 was recommended (not measured). The Optilene Mesh LP will then placed between the posterior rectus sheath and the rectus muscle with an overlap of 3cm at each side and fixed with fibrin sealant (5ml). The fibrin sealant will be applied on the entire surface of the mesh, in one shot having permanent contact between the mesh and the tip of the joining piece. Immediately after application of the fibrin sealant, the mesh will be smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface and especially on the suture line. If present, it is also possible to use spray fixation using the EASYSPRAY sys-

tem, Deutschland GmbH, Unterschließheim, Germany. When laparotomy is >25cm use 2 applicators of Tissucol (10ml). The midline anterior rectus sheath will be closed using a running slowly absorbable suture (Monoplus, USP1, Needle HRT48, 150 cm, B. Braun Aesculap AG, Tuttlingen, Germany), covering the mesh. A suture length to wound length ratio of 4:1 was recommended (not measured). Subcutaneous tissue and skin will be closed in a fashion preferred by the surgeon.

Postoperative treatment:

Wound drainage will not be routinely applied. Seromas do not have to be punctured or drained, but can be left untreated to resolve spontaneously.

Implementation

Pre-operative data

- Date of birth
- Length and weight
- Smoking history (current smoker (Y or N)
- Medical history (COPD, diabetes, cardiac disease)
- Preoperative Radiotherapy or chemotherapy
- Preoperative corticosteroids
- Postoperative corticosteroids
- Previous abdominal operations
- Other abdominal hernias (inguinal, umbilical, epigastric hernias)
- ASA class
- Width of linea alba (when pre-operative CT imaging is available)
- Size of aneurysm and location
- Epidural catheter

Operation data

- Type of operation
- Type and length of prosthesis
- Volume of fibrin sealant applied
- Length of incision
- Blood loss
- Operation time

- Antibiotic prophylaxis
- Suture material
- Drains and location
- Thrombosis prophylaxis
- Pain medication
- Complications (intestinal lesions, bleeding, other)

Post-operative data

- Blood transfusion
- Postoperative ventilation and duration
- Postoperative ileus and duration
- Postoperative complications:
  - Surgical Site Infection, according to the guidelines proposed by Mangram in 1999(50). Definitions on page 23
  - Wound hematoma: accumulation of blood in the wound area, which warrants surgical exploration and intervention.
  - Seroma subcutaneously
  - Pulmonary infections
  - Ventilation problems
  - Re-intervention and difficulties caused by the mesh at re-entry
  - Re-admission and indication

Ultrasound examination

At 6 and 24 months ultrasound imaging will be performed to examine the midline for any asymptomatic clinically not detectable incisional hernias. This will provide valuable information about the onset of an incisional hernia. Size and location of all incisional hernias noted radiographically will be registered, as well as complaints presented by the patients. Endpoint of this study will be at 2 years follow up. At this follow-up the presence of a hernia will be investigated by physical examination and ultrasound imaging.

Outpatient follow-up

- Outpatient clinic visit at 1,3, 12 and 24 months
  - Incisional hernia
  - Wound infection
  - Seroma formation

- • Other wound problems
- • Inguinal hernia
- • Ultrasound at 6 and 24 months
- • VAS score at 1 month
- • VAS scores and Quality of Life forms preoperatively (day of operation or the day before) and at 3, 12 and 24 months

Evaluation moments	Pre-operative	Months →				
		1	3	6	12	24
MOS SF-36 (1)	✕		✕		✕	✕
EQ-5D (2)	✕		✕		✕	✕
VAS score (3)		✕	✕		✕	✕
Outpatient clinic	✕	✕	✕		✕	✕
Ultrasound				✕		✕
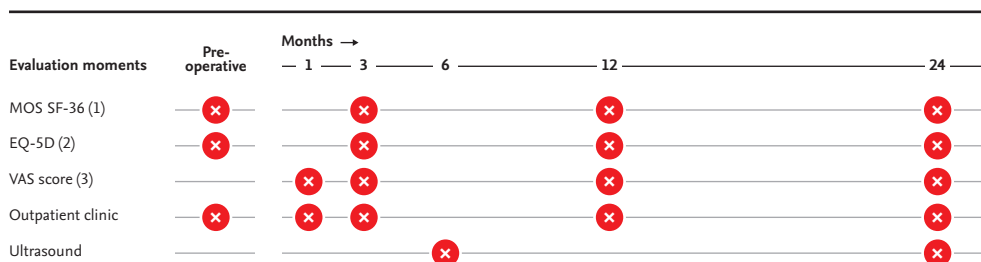
(1) MOS SF-36: Questionnaire concerning quality of life (SF-36 TM Health Survey, Medical outcomes Trust, Boston, Massachusetts 02116, USA)
(2) EQ-5D: Euro Qol Group quality of life questionnaire
(3) VAS score: Pain measurement tool on which patients can define their pain on a sliding scale

Table 3   Follow up schedule

Economical evaluation

Cost effectiveness will be calculated after 2 years. The direct costs, admissions, operation costs, costs of materials and treatment of complications and incisional hernias, will be calculated. Quality Adjusted Life Years will be calculated.

An incisional hernia correction costs €3777,-. When 100 patients are operated with the aid of a mesh insertion we estimate to prevent 15 incisional hernias (= €56.655,-). One hundred meshes cost approximately €30.000,-. We would save €26.655,- if all incisional hernias are repaired. We did not include all extra costs as for example visits to the general practitioner, but these will be included in our final analysis.

Statistical analysis

Three comparisons will be made leading to pair-wise comparison at alpha = 0.017 (=0.05/3) according to Bonferroni's correction for multiple testing. Assuming a 30% rate of incisional hernia in group A, and about 10% in both groups B and C, for a power of 90 % comparing group A versus group B and C, 92 patients are required in group A and 164 in groups B and C. Allowing for some dropouts, 100 will be included in the control group and 180 in each experimental group.

It is expected that differences between groups B and C can only be demonstrated with a very large number. Therefore it was decided to set the objective to showing "non inferiority" for onlay (group C) versus sublay (group B). Setting the non-inferiority margin at 10 %, the power to show non-inferiority regarding the incidence rate of incisional hernia will be greater than 80 %.

For the comparison of both experimental groups with the control group, Kaplan-Meier curves will be constructed and the log-rank tests will be performed. These logrank tests will be done with stratification by center and operation indication.

For the comparison of both experimental groups B and C, the cumulative 2-years probability will be calculated with the one-sided 98.3 % confidence interval for the difference. Analysis will be done according to the intention-to-treat principle in comparing group A with groups B and C. For the comparison of groups B and C a per-protocol analysis will be the primary analysis.

Comparison of VAS and QOL scales between groups will be done using Repeated Measures Anova (SAS PROC MIXED) with baseline value, age, gender, operation indication and center as covariates.

The following putative risk factors regarding incisional hernia (smoking, infection, diabetes, corticosteroids) will be evaluated using Cox-regression.

Serious Adverse Event (SAE) reporting & Monitoring

A SAE will be reported to the Dutch Department for Human Research (Centrale Commissie Mensgebonden Onderzoek), Baxter and Braun within 24 hours.

Requirements for SAE reporting will be:

1. (Prolonged) Hospitalisation (defined as a longer stay in the hospital than normally expected caused by a postoperative complication)
2. (Re-)operation
3. Death

Once a year, data from each center will be monitored. In compliance with GCP guidelines, monitors will verify data collected on data collection forms against source documents. Source documents are defined as any original records or data related to the trial or to subject treatment or medical history. Source documents include: original hospital, clinical, and office charts, laboratory notes, subject diaries or evaluation checklists, pharmacy records, recorded data from automated instruments, transcriptions (certified to be accurate after verification), magnetic media, or x-rays.

Ethics

Before centers could participate in this trial, approval was obtained from the local medical ethics committee (Medische Ethische Toetsings Commissie, Erasmus MC). Patients will be extensively informed about the

research project and can only participate after giving informed consent. Patients will always be permitted to withdraw from the study without providing further reasons. This will have no consequences for further treatment. Data of these patients will be evaluated in the final analysis. This trial was registered at Clinical trial.gov under NCT00761475.

History and current status

After Ethical approval was obtained the trial started including patients in the middle of 2009. Initially the intake of patients was rather slow. This was attributed to the the low number of participating hospitals, the continued increase of laparoscopy and endovascular treatment, and the inclusion criteria of BMI >30. After the publication of Seiler et al the BMI inclusion criteria were lowered from 30 to 27(37). The BMI amendment and the inclusion of additional participating hospitals made it possible to include more patients per month. Currently the trial is in the final stage of the inclusion of patients. It is estimated that the last patients will be seen in the outpatient clinic in the beginning of 2015. Around this time the final results will be subjected to peer-review for publication.

Discussion

Incisional hernia continues to be one of the most frequent complications after laparotomy. Up to this date no intervention strategy has led to a resolution to this problem. In high risk patients, with a risk for incisional hernia more than 30 %, an alternative technique with lower incisional hernia incidence would be highly desirable.

In daily practice almost all midline laparotomies are closed with slowly absorbable running sutures. This technique seems ample for low risk patients. Despite the high incidence of incisional hernia, this technique is still used in high risk patients. These patients are known to have altered collagen synthesis in wound repair or increased abdominal wall stress, leading to insufficient repair of the midline after operation.

In incisional hernia surgery the use of prosthetic mesh has proven its effectiveness and safety. For this reason a RCT investigating the effectiveness and safety of augmenting the closure of the midline with prosthetic mesh in high risk patients is being conducted. A high level of evidence will be obtained due to the design of the study, as it was a randomized, double blind, powered, multicenter study.

Conclusion

The PRIMA trial is a prospective international multicenter double blind randomized trial comparing primary suture closure of midline laparotomy to closure aided with a prosthetic mesh. This trial might provide the surgical society a technique to prevent incisional hernia in high risk patients.

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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 swell-

ing, 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 histopathologic 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.

Short term results of a randomized controlled trial comparing primary suture with primary glued mesh augmentation to prevent incisional hernia

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Abstract

Background: Incisional hernia (IH) is one of the most frequent postoperative complications after abdominal surgery. Patients with an abdominal aortic aneurysm (AAA) and patients with a BMI of 27 or higher have an increased risk to develop IH. Primary mesh augmentation (PMA) is a method in which the abdominal wall is strengthened to reduce IH incidence. This study focussed on the short-term results of the PRIMA trial, a multicentre double blind randomized controlled trial (RCT).

Methods: Between 2009 and 2012 patients were included if they were operated via midline laparotomy, and had an AAA or a BMI of 27 or higher. Patients were randomly assigned to either receive primary suture (PS), onlay glued mesh augmentation (OMA), or sublay glued mesh augmentation (SMA).

Results: Outcomes represent results after 1 month follow-up. A total of 480 patients were randomized. During analysis significantly ($p = 0.002$) more seromas were detected after OMA (n = 34, 18.1%) compared to PS (n = 5, 4.7%) and SMA (n = 13, 7%). No differences were discovered in any of the other outcomes such as surgical site infection (SSI), hematoma, reintervention or readmission. Multivariable analysis revealed an increase in seroma formation after OMA with an odds ratio (OR) of 4.3 ($p = 0.004$) compared to PS and an OR of 2.9 ($p = 0.003$) compared to SMA.

Conclusion: Based on these short-term results, PMA is a save procedure with only an increase in seroma formation after OMA , but without an increased risk of SSI.

Introduction

Incisional hernia (IH) is one of the most frequent postoperative complications after abdominal surgery. IH incidence ranges between 11% and 20% in the general population (1-3). However, risk factors for the development of IH, such as abdominal aortic aneurysm (AAA) and obesity, can increase the incidence of IH up to 35% (4-8). In AAA patients the connective tissue, especially the ratio between mature and immature collagen, is thought to be compromised (9, 10). The formation of collagen of insufficient strength plays an important role in the development of the distension of the aorta. But this loss of balance is also thought to be of key importance in the formation of IH after laparotomy (11, 12). In patients with obesity it is thought that the increase in intra-abdominal pressure induces stress on the suture line which promotes IH formation (7, 13).

IH can cause morbidity such as pain, reduced quality of life and poor body image, and in some cases can become incarcerated and even lead to mortality (3, 14). In the United States around 500.000 IH are surgically repaired annually (15). IH repair with mesh reinforcement has shown to produce lower recurrence rates compared with primary closure (16). However, recurrence rates for mesh repair are still unacceptably high, with a 10 year cumulative incidence rate of 32% (15). Considering the high incidence of IH, the unsatisfactory results of IH repair and the high impact on quality of life, research should be focusing on prevention rather than on treatment. In 2009 the PRIMA trial (PRImary Mesh Closure of Abdominal Midline Wounds), an international multicenter randomized controlled trial (RCT), was initiated to investigate primary mesh augmentation (PMA) as means to reduce IH incidence. Previously other RCTs and even meta-analyses focussing on IH prevention by means of PMA have been published (17-20). However, as pointed out in the most recent meta-analysis, the quality of the RCT's was generally low and short term results, such as hematoma, fascial dehiscence, mesh infection and mesh removal, were often not described (21).

This paper will focus on the short-term results (postoperatively up to 1 month) of the PRIMA trial. We hypothesize that PMA does not increase postoperative complications compared to primary suture (PS).

Methods

Study design

The PRIMA trial is a multicenter randomized controlled trial which included patients between 2009 and 2012 in 11 hospitals in the Netherlands, Germany and Austria and follow-up is currently being conducted. This trial was initially approved by the local Ethics Board in the Erasmus University Medical Center in Rotterdam and was later extended to all participating centers. The primary endpoint of this study was IH incidence after 2 years, and secondary endpoints were postoperative complications, postoperative pain, cost-effectiveness and quality of life. This study was registered in the clinicaltrials.gov database and was assigned ID number: NCT00761475.

Patient population and randomization

Patients were eligible for inclusion in case of: 1. midline laparotomy, 2. presence of an AAA and / or body mass index (BMI) equal to or higher than 27. Exclusion criteria were: 1. Age < 18 years, 2. Inclusion in other trials with interference of the primary endpoint, 3.Life expectancy less than 24 months (as estimated by the treating physician), 4.Pregnant women, 5.Immune suppression therapy within 2 weeks before surgery, 6.Bovine allergy, 7.presence of IH. After obtaining informed consent patients were included into the trial via the TOP system (Trial Online Process; see http://www.primatrial.nl), where data were securely stored. Patients were randomized into 3 groups also via the TOP system by means of the minimization method and stratified by centre and operation indication. Randomization was performed during the operation, securing optimal allocation concealment (22). Patients could be randomized for either primary suture (PS), onlay mesh augmentation (OMA) or sublay mesh augmentation (SMA).

The following data were prospectively gathered and collected: Pre-operative data (sex, age, length, weight, BMI, current smoking status, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), American Society of Anesthesiologists score (ASA), previous midline incision, other hernia) intra-operative data (type of operation, antibiotics used, length of incision, subcutis suture, wound drain, operation time, blood loss, intestinal lesion, bleeding, mesh placement not possible) and postoperative data (up until 1 month)(intensive care admission, ventilation, blood transfusion, admission days, SSI (CDC definitions of SSI), seroma (a collection of serous fluid in a dead space, which can either be in situ or leaking through a wound), hematoma, fascial dehiscence, mesh removal, ileus, reinterventions, readmissions, death). The doctors who performed the surgery did not perform the follow-up, as this could lead to bias. Patients and the research personnel that performed the follow-up-were kept unaware to which group patients were randomized, reducing possible bias.

Surgical Procedures

1. PS

PS consisted out of a running slowly absorbable suture (MonoPlus, USP 1 ,Needle HRT48, 150 cm loop, B.Braun Surgical Spain, Rubi, Spain) of the linea alba. A suture length to wound length (SL:WL) ratio of 4:1 was routinely applied in all centers, however the ratio was not measured in order to reproduce real world surgery.

2. OMA

OMA consisted of creating an anterior plane (between anterior rectus fascia and subcutis) and closing the midline with a running slowly absorbable suture (MonoPlus) (4:1 ratio recommended). Dissection of the anterior plane was in general considered to be easy to perform using proper traction and dissection meth-

ods, and tensionless closure was possible in all cases. A polypropylene light weight mesh (Optilene Mesh LP 6 x 35 cm, B. Braun Aesculap AG, Tuttlingen, Germany) was cut to fit the dissected space and placed on the anterior rectus fascia with an overlap of 3 cm at each side. The mesh size was specifically made for this trial, however cutting a regular Optilene or polypropylene mesh is also possible. In rare cases when the incision would be greater than 35cm, it was recommended to use another mesh and tie it to the original mesh, in order to obtain 3cm overlap. The mesh was then fixed with fibrin sealant (Tissucol DUO 500 2,0ml; Baxter Healthcare, Deerfield, IL, USA). The edges of the mesh were primarily glued, followed by center. The glued mesh was smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface. In case of an incision larger than 22cm, it was advised to use two vials of fibrin sealant. In some centers spray fixation was applied using the EASYspray system (Deutschland GmbH, Unterschließheim, German).

3. SMA

SMA consisted of creating a posterior plane (between posterior rectus fascia and rectus muscle, and below the arcuate line between the peritoneum and rectus muscle). Dissection of the posterior plane was in possible in almost all cases, however in some patients the fascia/peritoneum was very weak and dissection could be challenging. In most cases a anterior rectus fascia was already incised, during the initial median laparotomy, and dissection of this area was considered to be the easiest part of the dissection. If dissection was difficult, it was advised to create a plane on the cranial side of the wound and work caudally from there, considering the strength of the posterior wall. Using proper traction and (blunt) dissection methods, tensionless closure was possible in all cases. After dissection, the posterior plane (fascia and peritoneum) was closed with running slowly absorbable suture (MonoPlus) (4:1 ratio recommended). A polypropylene light weight mesh was cut to fit the dissected space and placed on the posterior plane with an overlap of 3 cm at each side. The mesh size was specifically made for this trial, however cutting a regular Optilene or polypropylene mesh is also possible. In rare cases when the incision would be greater then 35cm, it was recommended to use another mesh and tie it to the original mesh, in order to obtain 3cm overlap. The mesh was then fixed with fibrin sealant (Tissucol DUO 500 2,0ml; Baxter Healthcare, Deerfield, IL, USA). The edges of the mesh were primarily glued, followed by center. The glued mesh was smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface. In case of an incision larger than 22cm, it was advised to use two vials of fibrin sealant. Afterwards, closure of the midline/linea alba was established with running slowly absorbable suture (MonoPlus) (4:1 ratio recommended).

Statistical analysis

The sample size calculation was partially based on the data provided by the INSECT trial (23). In this study it was discovered that patients with a BMI over 27 have 20% chance of developing an IH within one year after

the initial operation. Considering that only 50 % of incisional hernia will be clinically evident in the first 12 months, the total incidence is likely to be above 30% after 2 years (2). In addition, patients were also eligible for inclusion if an AAA was diagnosed, as AAA patients also have an IH incidence of over 30%.

For the PRIMA trial, an IH rate of 30% for PS group was expected and of 10% for both PMA groups. The 3 comparisons lead to a pair-wise comparison of alpha = 0.017 (0.05/3) according to Bonferroni's correction for multiple testing. A superiority model for the comparison between PS vs OMA, and PS vs SMA was used with a power of 90%. A non-inferiority model for the comparison of OMA versus SMA was used, with the non-inferiority margin set at 10%, with a power of 80%. Allowing for some dropouts (5-10%), 100 patients were included in the control group and 180 patients in each experimental group. A total number of 460 patients were needed to detect a significant difference in IH incidence. During the course of the trial it was discovered that a larger number then initially anticipated dropped out of the study and thus 20 additional patients were included in agreement with the local Medical Ethics committee (24).

The one-way ANOVA, the Kruskal-Wallis test and the Pearson Chi-Square test were used for statistical analysis of demographic data, perioperative and postoperative data. Univariate and multivariate logistical regression analyses were conducted to predict Odds Ratios (OR) of potential risk factors. Risk factors discovered in this study or known in the literature will be added to the multivariate logistic regression analyses. The primary analysis was performed on an intention-to-treat (ITT) principle (patients remained in their assigned group even if for instance during the procedure placement of the mesh was not possible) and results are primarily presented and discussed using this principle. Per-protocol (PP) principle results are presented in the tables but not discussed in general. All statistical calculations were done using IBM SPSS© 17 Software (SPSS, Chicago, Illinois, USA). In accordance with Bonferroni´s correction for multiple testing, significance was assumed at P <0.017.

Results

Between March 2009 and December 2012, a total of 498 patients were selected for inclusion (Figure 1). Eighteen patients were not randomized due to withdrawal of informed consent, no midline incision used for access to the abdominal cavity, or a presence of an incisional hernia discovered during the operation. Of the 480 patients, 107 patients were randomized for PS, 188 patients were randomized for OMA, and 185 patients were randomized for SMA (Figure 1). Mesh augmentation was not applied in 18 cases (9.6%) in the OMA group, and 27 cases (14.6%) in the SMA group.

Patient characteristics

The majority of patients was male (60.8%) and the mean age of the included patients was 64.5 (SD 11.2) years. No differences were found between groups in preoperative data. The majority of patients were operated for either a vascular operation (33.1%) or lower gastro-intestinal (GI) operation (33.8%). The median
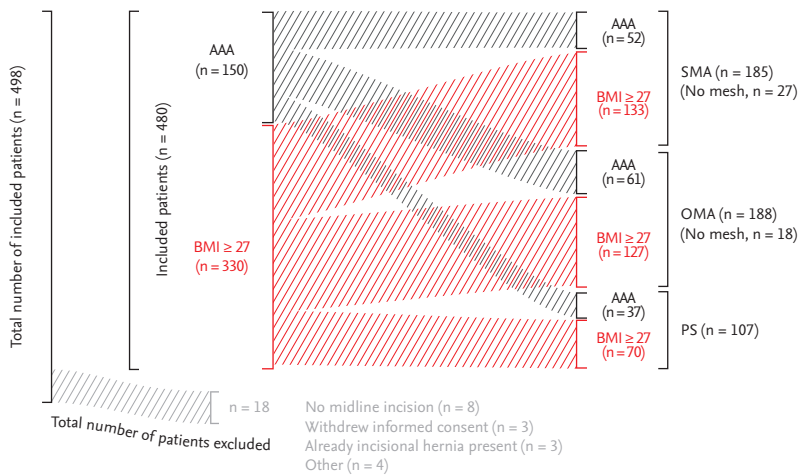
Figure 1 Study flow diagram

duration of the operation was 200 (IQR 150-253) minutes. Statistically (p<0.001) more patients received additional subcutaneous suturing in the OMA group (n = 70, 37.2%) compared to PS (n = 18, 16.8%) and SMA (n=34, 18.4%). No other differences were found in intraoperative and postoperative data (Table 1).

Outcome parameters

All outcomes are presented in Table 2. For all outcomes an intention-to-treat analysis was used. A total of 68 SSI (14.2%) were diagnosed postoperatively. According to CDC classifications SSIs were divided in to superficial infections (n =27, 5.6%), deep infections (n = 22, 4.6%) and intra-abdominal infections (n = 19, 3.9%). After stratifying for inclusion criteria, significantly (p = 0.006) more superficial SSIs were detected if a patient was included due to BMI ≥ 27 (n = 25, 7.6%) compared to patients included for an AAA (n = 2, 1.3%). Stratification with regards to type of operation (vascular, upper GI, lower GI, HPB, gynaecology or urology) was not possible due to low number of SSI making statistics unreliable. No significant differences were observed between intervention groups with regards to SSI.

A total of 52 seromas were observed postoperatively. Significantly (p = 0.002) more seromas were diagnosed after OMA (n = 34, 18.1%) compared to PS (n = 5, 4.7%) and SMA (n = 13, 7%). No significant difference was observed between PS and SMA.

A total of 21 hematomas were observed postoperatively that required a reintervention. Of all hematomas, only 1 (0.9%) was observed in the PS group, 11 (5.9%) in the OMA group and 9 (4.9%) in the SMA group. No significant differences were observed between groups.

Table 1   Patient characteristics

	General	PS	OMA	SMA	p-value
Total	480	107	188	185	
Preoperative					
Male (%)	292 (60.8)	68 (63.5)	116 (61.7)	108 (58.4)	NS
Age (SD)	64.5 (11.2)*	65.2 (10.5)*	64.2 (12.3)*	64.4 (10.4)	NS
Length (SD)	171.6 (9.6)	170.8 (9.5)	171.6 (10.2)	172.1 (9)	NS
Weight (SD)	90.1 (17.1)	86.9 (15.5)	90.7 (18.2)	91.3 (16.1)	NS
BMI (SD)	30.6 (5.3)*	29.8 (4.4)*	30.8 (5.9)*	30.8 (5.2)	NS
Smoking (%)	102 (21.3)	17 (15.9)	41 (21.8)	44 (23.8)	NS
DM (%)	94 (19.6)	19 (17.8)	36 (19.1)	39 (21.1)	NS
COPD (%)	52 (10.8)	9 (8.4)	24 (12.8)	19 (10.3)	NS
ASA (%)					NS
I	44 (9.2)	10 (9.3)	21 (11.2)	13 (7.0)	
II	234 (48.8)	55 (51.4)	90 (47.9)	89 (48.1)	
III	150 (31.3)	35 (32.7)	54 (28.7)	61 (33.0)	
IV	6 (1.3)	1 (0.9)	3 (1.6)	2 (1.1)	
unspecified	46	6	20	20	
Previous midline incision (%)	21 (4.4)	3 (2.8)	10 (5.3)	8 (4.3)	NS
Other hernia (%)	50 (10.4)	13 (12.1)	19 (10.1)	18 (9.7)	NS
Intraoperative					
Type operation (%)					NS
Vascular	159 (33.1)	39 (36.4)	64 (34)	56 (30.3)	
Upper GI	65 (13.5)	18 (16.8)	22 (11.7)	25 (13.5)	
Lower GI	162 (33.8)	29 (27.1)	67 (35.6)	66 (35.7)	
HPB	21 (4.4)	3 (2.8)	8 (4.3)	10 (5.4)	
Gynaecology	66 (13.8)	15 (14)	24 (12.8)	27 (14.6)	
Urology	7 (1.5)	3 (2.8)	3 (1.6)	1 (0.5)	
Antibiotics (%)	431 (89.8)	94 (87.9)	167 (88.8)	170 (91.9)	NS
Length incision (SD)	24.8 (9.6)	23.6 (10.5)	24.9 (9.3)	25.2 (9.5)	NS
Suture subcutis (%)	122 (25.4)	18 (16.8)	70 (37.2)	34 (18.4)	<0.001
Wound drain (%)	23 (4.8)	3 (2.8)	14 (7.4%)	6 (3.2%)	NS
Blood loss (IQR)	700 (300-1500)**	750 (300-1700)**	600 (300-1300)**	615 (300-1400)**	NS
Intraoperative complications (%)					
intestinal lesion	9 (1.9)	2 (1.9)	1 (0.5)	6 (3.2)	NS
bleeding	28 (5.8)	6 (5.6)	10 (5.3)	12 (6.5)	NS
no mesh placement	45 (12.1)	-	18 (9.6)	27 (14.6)	NS***
Duration operation (IQR)	200 (150-253)	180 (145-240)	200 (150-260)	212 (155-255)	NS
Postoperative					
Intensive care (%)	245 (51)	59 (55.1)	93 (49.5)	93 (50.3)	NS
Ventilation (%)	74 (15.4)	20 (18.7)	29 (15.4)	25 (13.5)	NS
Blood transfusion (%)	63 (13.1)	16 (15)	21 (11.2)	26 (14.1)	NS
Admission days (IQR)	10 (7-16)	10 (7-15)	11 (7-17)	10 (7-15)	NS

*Values are represented as mean and standard deviation

**Values represent the median and interquartile ranges.

***Only OMA and SMA groups are used for comparison

*** p-values are two-sided. For dichotomous variables Chi-square test was performed, for continuous variables the one-way ANOVA was use, in case of non-parametric continuous variables the Kruskal-Wallis test was used.

Table 2   Postoperative outcomes

	General	PS	OMA		SMA		p-value
			ITT	PP	ITT	PP	
Total	480	107	188	170	185	158	
SSI (%)							
superficial	27 (5.6)	4 (3.7)	14 (7.4)	13 (7.6)	9 (4.9)	8 (5.1)	NS
deep	22 (4.6)	2 (1.9)	13 (6.9)	12 (7.1)	7 (3.8)	6 (3.8)	NS
intra-abdominal	19 (3.9)	8 (7.5)	8 (4.3)	7 (4.1)	3 (1.6)	3 (1.9)	NS
Seroma (%)	52 (10.8)	5 (4.7)	34 (18.1)	32 (18.8)	13 (7)	13 (8.2)	0.002*, 0.002**
Hematoma (%)	21 (4.4)	1 (0.9)	11 (5.9)	11 (6.5)	9 (4.9)	9 (5.7)	NS
Fascial dehiscence (%)	16 (3.3)	1 (0.9)	6 (3.2)	6 (3.5)	9 (4.9)	5 (3.2)	NS
Mesh infection	6 (1.6)	-	5 (2.7)	4 (2.4%)	1 (0.5)	1 (0.6)	NS
Mesh removal (%)*							
complete	13 (3.5)	-	8 (4.3)	6 (3.5)	5 (2.7)	3 (1.9)	NS
partial	4 (1.1)	-	3 (1.6)	3 (1.8)	1 (0.5)	1 (0.6)	NS
reimplanted	8 (2.1)	-	3 (1.6)	3 (1.8)	5 (2.7)	3 (1.9)	NS
Ileus (%)	26 (5.4)	3 (2.8)	12 (6.4)	10 (5.9)	11 (5.9)	10 (6.3)	NS
Reintervention (%)	77 (16)	12 (11.2)	33 (17.6)	27 (15.9)	32 (17.3)	25 (15.8)	NS
Readmission (%)	76 (15.8)	12 (11.2)	37 (19.7)	31 (18.2)	27 (14.6)	22 (13.9)	NS
Death (%)	18 (3.8)	4 (3.7)	7 (3.7)	6 (3.5	7 (3.8)	5 (3.2)	NS

Chi-square test was performed with two-sided p-values

ITT = intention to treat analysis, PP = per protocol analysis

* Only OMA and SMA groups are used for comparison

p-values are based on the following comparisons: *PS vs OMA (ITT), **OMA vs SMA (ITT)

Table 3   Multivariable analysis

	PS vs OMA				PS vs SMA				SMA vs OMA			
	ITT		PP		ITT		PP		ITT		PP	
Seroma	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value
Multivariable*	4.3	0.004	4.7	0.002	1.5	0.451	1.8	0.281	2.9	0.003	2.6	0.007

Values are presented as Odds Ratios. Missing values were adjusted by multiple imputation method.

ITT = intention to treat analysis, PP = per protocol analysis, OR = odds ratio

* = adjusted for age, BMI, subcutaneous suture, wound drain, deep SSI

A total of 16 fascial dehiscences were observed postoperatively. Of all fascial dehiscences, 1 (0.9%) was observed in the PS group, 6 in the OMA group (3.2%), and 9 (4.9%) in the SMA group. No differences were observed between groups.

A total of 6 (1.6%) meshes got infected postoperatively and required reintervention. In 3 cases the mesh was removed completely. In 3 other cases the surgeons opted to perform only a partial mesh removal as only a part of the mesh was infected. In total 13 meshes were completely removed, 4 were partially removed, and 8 meshes were removed and reimplanted during the same operation. Besides before mentioned mesh infection, meshes were (partially) removed during reoperation for anastomotic leakage, intra-abdominal bleeding and fascial dehiscence. No differences were observed between groups.

A total of 26 (5.4%) postoperative ileus cases were observed. Of all ileus cases, 3 (2.8%) were observed in the PS group, 12 (6.4%) in the OMA group, and 11 (5.9%) in the SMA group. No differences were observed between groups.

With regards to postoperative reinterventions, readmissions or death within one month postoperatively, no differences were observed between groups. None of the deaths were related to dissection of the posterior or anterior plane, or the mesh or glue.

Multivariable analysis

Seroma was the only outcome which was significantly increased. It was opted to perform a multivariable analysis to ascertain the OR of seroma after OMA. We adjusted for a number of factors (BMI, subcutaneous suture, wound drain, deep SSI) which could be of influence on seroma formation. After correction, seroma formation in OMA had an OR of 4.3 (p = 0.004) compared with PS, and an OR of 2.9 (p = 0.003) compared with SMA.

Discussion

This RCT shows that apart from a significant increase in seroma formation, no differences were observed for other short-term complications after PMA. OMA increased the odds of developing seroma compared to PS and SMA. This increase in seroma and the use of prosthetic material did not significantly increase the rate of SSI, mesh infections or admission period.

Short term results

As stated before other RCTs and even meta-analyses exist regarding this topic, however this study is the first RCT that carefully documented all short-term results. Although these results are not the primary outcomes of this RCT, and power calculations were not based on these parameters, they are highly relevant. In this trial it was discovered that solely seroma was significantly increased after OMA. Seroma was diag-

nosed in most cases during physical examination. Only in cases of complaints possible radiologic studies would be used. It is possible asymptomatic seromas in patients with SMA were missed, this is a limitation. In most cases seroma was defined as a minor complication and no intervention was necessary. However, seroma can become infected but no increase in SSI was detected in this study. The anterior subcutaneous space created by dissection during OMA is prone for seroma formation and should be minimized if possible. In this trial an attempt was made to reduce this space by implementing fibrin glue. Mesh glue fixation is not new and has been in use in inguinal hernia repair and laparoscopic IH repair for some time (25). These studies have shown that the effectiveness dependent on the mesh/glue combination used, as not all meshes adhere well to all glues (26). However, the clinical use of glue for PMA has not yet been documented and studies comparing mesh suture fixation with mesh glue fixation are not available. Surgeons did like the quickness and technique of fixation of the mesh with fibrin glue. A recent meta-analysis focussing on seroma formation preventing by means of glue after breast surgery concluded that although data is scarce and not of high quality, currently no reduction could be observed (27). In another study by Lau et al that focussed on inguinal hernia repair it was suggested that the timing of glue application is also important (28). Once polymerization of the sealant has occurred before ventral layer closure, the dissected space will not have been reduced. In the study protocol, standard suturing of the subcutis was not implemented, neither was wound drainage. These are techniques which may reduce the incidence of seroma formation (29). For instance, none of the patients with a wound drain acquired a seroma. Future research regarding onlay or OMA should focus on reducing seroma formation.

PMA

This is the first trial which compares PS with OMA and SMA. Although in hernia surgery the sublay technique is assumed to be superior compared to the onlay technique with regards to IH recurrence, evidence is scarce In addition, prevention of IH is quite different compared to reducing recurrence. In this study the anatomical natural structure of the abdominal wall was still intact and it was not very difficult to acquire a tensionless closure. Furthermore it was opted to only use 3cm overlap on both sides, even though in hernia surgery 5cm is now recommended. We opted for a smaller overlap as the evidence for the 5cm overlap in hernia surgery is still insufficient, and further dissection of the wound could induce more morbidity and might thus not be necessary. Furthermore prevention of IH is quite different from reducing recurrence, due to the fact that there is no fascia defect and the mesh is positioned on a closed midline.

A goal of our study group is to prevent IH from occurring in general, not only in the surgical field but also in other specialities such as gynaecology and urology. However, some of the participants were not familiar with hernia techniques at the beginning of this trial but were required to perform both PMA techniques nonetheless. The learning curve might influence the results and could be a bias. However, doctors

inexperienced with the techniques were supervised by the study coordinator during the initial procedures, and both techniques were easily adapted by all doctors. Most of the doctors that were not familiar with hernia surgery preferred the OMA technique. A big advantage of OMA is that is far easier to explain and perform and the dissection doesn´t take as long as SMA. In this study we did not measure the time of the closure process but the time for the entire operation. It is evident that additional dissection will increase operating time, and the results resemble our own experiences. In general, dissection and closure in OMA took 15-20 minutes and in SMA took about 25-30 minutes. As in all studies, a number of patients did not receive the randomized treatment as was described in the study protocol. These cases did stay in their original randomization group as in accordance with the intention-to-treat principle. The reason for not applying OMA or SMA varied and include extensive blood loss, contaminated abdomen with an increased risk of SSI, fascia of insufficient strength to apply augmentation and time constraints.

Conclusion

Based on the short term results of this trial, OMA increased the amount of seroma but did not increase SSI or mesh infection. The true effectiveness of OMA will have to be evaluated during the long term results of this trial. During that time we will also be able to evaluate IH incidence, fistula formation, chronic pain, quality of life and cost-effectiveness.

Acknowledgements

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APPENDICES
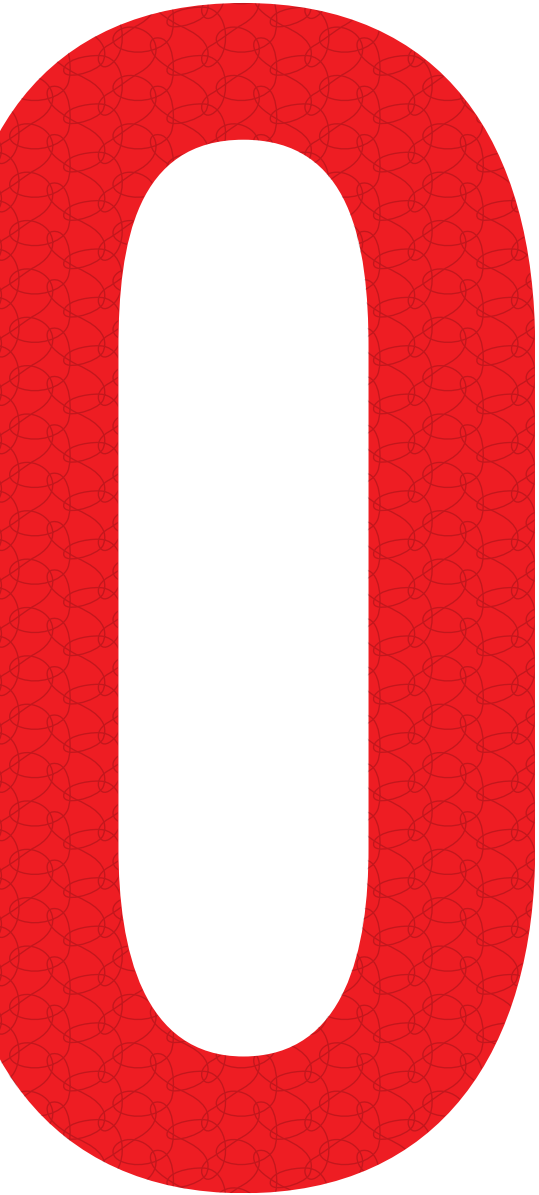
General discussion and future perspectives

L. Timmermans, J. Jeekel, J.F. Lange

As has been stated in this thesis many times before, incisional hernia (IH) is one if not the most frequent postoperative complication after abdominal surgery (1-3). The incidence of IH is partly dependent on incision site, suture technique and additional risk factors such as obesity and presence or history of abdominal aortic aneurysm. Its occurrence has great impact on lives of patients, as it reduces their quality of life and the image they have of their own body (4). IH repair is one of the most frequently performed operations for postoperative complications. In United States alone 200.000 IH repairs are performed annually, with a total cost of 3.2 billion dollars (5, 6). In this thesis we sought to discover risk factors for IH in order to better understand the pathogenesis, we sought to discover the best way to treat IH in order to reduce IH recurrence, and last we sought to prevent incisional hernia in order to reduce morbidity and mortality, improve patients quality of life and to reduce general health costs.

Cost perspective

As stated above, besides a significant impact on patients, IH is also a burden on the economy. In a study by Vonlanthen et al it was demonstrated that costs of surgery with complications are 2.3 times as high compared to surgery without complications. This number increased even further in case of more serious postoperative complications based on the Clavien-Dindo Classification (7). The same holds true in patients with IH.IH recurrence is acomplication which will obviously increase general costs after surgical repair even more. In previous studies performed by Luijendijk et al and Burger et al, it was demonstrated that mesh repair reduces IH recurrence(8, 9). In addition, a study from the Israelsson group demonstrated that mesh repair isnot only effective in reduction of recurrence but also cost-effective compared to suture repair (10). In this study the majority of reduced costs could be attributed to the reduction in IH recurrence. This reduction outweighed the additional costs of the mesh.

Currently, in the Netherlands a standard fee is being rewarded for every IH repair performed. However, complex cases (high body mass index (BMI), corticoid steroid use, fistula, contaminated abdomen, recurrent hernia, mesh infection and giant hernia) have an increased risk of postoperative complications and thus increased postoperative costs(11, 12). Hospitals are not stimulated to perform these complex repairs due to increased short term costs (additional materials such as biologic meshes) and possible increased long term costs (length of hospital stay, readmission and reoperations) and patients are often referred to other centers. In Chapter 2 a study was conducted to evaluate the costs of complex and non-complex IH repair as defined by the European Hernia Society to evaluate the additional costs of complex cases(11). Unexpectedly complex cases were not significantly more expensive compared to non-complex cases. However, complex IH repairs which were classified "major" were more expensive compared to non- and minor- and moderate complex hernias and responsible for a significant part of the total costs of complex cases. In this study comparison of costs was also performed between an academic hospital and acommunity hospital.

In general the community hospital had lower costs compared with the academic hospital. We concluded that from a costs perspective patients with a non-, minor- or moderate complex hernia should be referred to a community hospital. However, in major complex IHcases a trend for lower costs was observed in the academic hospital. This study focused on costs alone and a quality assessment of IH repairs was not performed, however we can assume that part of the reduced costs can be attributed to a reduction in post-operative complications. Patients with major CAWH should be centralized and referred to an experienced (high volume) center capable to treat these technically challenging patients. Centralization of major complex cases will increase experience, improve postoperative outcome and possibly result in lower healthcare costs. In addition, the fee for severe complex IH repair should be adjusted as to reduce patient delay.

Risk factors

An important step into IH prevention is to understand the pathogenesis and to identify potential risk factors. The search for risk factors for hernia development is not new and dates back to ancient Greece, where Hippocrates thought that: "hernia is more frequent in people consuming water from distant places and hernias may occur after distention of the abdomen". Since then we have come a long way into understanding the pathogenesis of (incisional) hernia. Since Hippocrates others have done extensive research regarding increased abdominal pressure as a risk factor for IH development (1, 13-16). The increase of intra-abdominal pressure induces increased tension on the sutured fascia which might promote herniation. Jenkins published an article in 1976 suggesting that the major cause of IH development is mechanical caused by suture breaking, knot slipping or the intact suture cutting through the fascia (17). He suggested to increase the length of suture material due to abdominal distention. Due to this increased length of suture material wound edge separation due to the suture cutting through the fascia would be reduced. Later studies by Pollock et al and Burger et al would further strengthen this hypothesis (18, 19). In a study by Burger et althe distance between rectus muscles was assessed using CT-scans within one month post-operatively and used as a predictor for IH development. Patients with a distance between rectus muscles of 25mm or more were more prone to develop an IH. Pollack et al performed a similar study using radiographs and discovered similar results. During closure stainless steel clips were placed lateral to each fascial suture making radiography assessment of wound edge separation possible. Of all patient with an increase in wound clip separation of 12mm or more, 94% did develop IH. BMI is used in most studies as a measure for increased intra-abdominal pressure.However, besides the increased tension on the sutures,obesity or a high BMI might also induce impaired wound healing. In a study by Xing et al it was observed that obese rats had impaired laparotomy wound healing, which they measured as a significant delay in the recovery of wound mechanical strength (20). This was attributed to abnormal collagen maturation and remodeling, which could be caused by a defect in fibroblast function. Also, in a study by Wagner et al it was discovered

that obesity impairs wound healing party due to a reduction in bone marrow-derived vasculogenic progenitor cells response to peripheral injury (21). Previously, it was demonstrated that adult endothelial progenitor cells will mobilize from the bone marrow to the site of tissue injuryand contribute to neovascularization during tissue repair (22). Impairment of these progenitor cells will impair wound healing and probably have an impact on IH development. The pathophysiology of obesity on IH is multifactorial and definitely complex. The incidence of IH in patients with obesity ranges over 30% in smaller studies (16, 23). However, in a recent large cohort study by Henriksen et al obesity and aortic abdominal aneurysm were identified as the main risk factors for IH development in 2597 patients (24).

Comparable to patients with obesity patients with an aortic aneurysm have an increased risk of IH, with an incidence of 30% or more (25-33). However, in contrast to obesity patients AAA patients are thought to be genetically more prone to hernia. The connective tissue in these patients is thought to be compromised, playing an important role in the pathogenesis of aneurysmal distension of the aorta (34-36). In 1980 Busuttil et al was the first to describe a collagen dysbalance in aortic aneurysm patients (37). This would later be further investigated by others such as Powell et al who discovered a dysbalance between collagen type I (stronger collagen) and type III (weak immature collagen) in aortic aneurysm patients (38). Similar results would later be discovered in inguinal hernia patients by Friedman et al (39). The genetics hypothesis would inspire a league of scientists to delve deeper into the hernia problem, calling it herniosis (40, 41). Herniosis would compromise the healing of the midline fascia after laparotomy due to formation of collagen with insufficient strength.

Currently, the world of hernia is divided into two camps, genetics versus mechanics. As often is the case, a combination of the two hypotheses will most likely prove to be true. In Chapter 3 a new mechanical risk factor for IH is described. Patients with a parastomal hernia were discovered to have a seven times increased risk to develop IHcompared to patients without a parastomal hernia. Most of these IHs developed next to the parastomal hernia. For this reason we hypothesized that due to colostomy formation the reduced forces of the abdominal wall on the midline would shift to the contralateral side. This shift would promote the earlier mentioned wound edge separation and increased tension on sutures, promoting IH. Furthermore, due to colostomy formation intercostal nerve damage could lead to atrophy of the ipsilateral rectus muscle, weakening the midline. In Chapter 4 we performed a radiological study to try to prove these hypotheses. CT-scans of patients with an end-colostomy were uploaded to the I-Space system and 3-dimensionally visualized and projected, after which multiple tests and measurements were performed. Atrophy of the left rectus muscle was seen caudally to the level of the colostomy and a midline shift to the right side was evident on CT. These results indicate that significant changes occur in the abdominal wall anatomy after end-colostomy formation and parastomal herniation.

Treatment options

IH is not only a very frequent postoperative complication but also one with a very high impact. It can cause morbidity such as pain, strangulation and incarceration and even mortality (42-45). In addition, even patients with an asymptomatic hernia can be affected in their daily lives due to a reduced quality of life and reduced body image. In aprospective study by van Ramshorst et al patients with IH scored lower mean scores in the short form 36 quality of life questionnaire and body image questionnaire (4). The golden standard for IH surgery remains operative treatment. In the randomized controlled study by Luijendijk et al it was discovered that patients treated for IH with mesh repair had significantly lower recurrences compared to patients with primary suture repair (9). Beside this trial only one other randomized controlled trial exists that compared suture repair with mesh repair (46). In this trial by Korenkov et al no difference between suture repair and mesh repair was discovered. The trial was discontinued due to a high rate of wound complications. However, the Luijendijk trial and the Korenkov trial differed substantially due to different techniques used. In the Luijendijk trial as a rule a sublay technique was attempted but this was not always possible and in some cases bridging or preperitoneal mesh placement was performed. In contrast, the Korenkov trial used an onlay technique, in which the mesh is placed on the anterior rectus fascia. Korenkov et al stated in their publication that therewas no randomized evidence that sublay repair was superior to onlay repair. However, since then a number of studies focusing on this dilemma have been published (47, 48). For this reason we performed a meta-analysis which is presented in Chapter 5 to evaluate if sublay repair is the preferred IH repair technique. In total eight studies could be selected of which the majority were retrospective studies and two were randomized controlled studies of low quality. After pooling all results a trend in favor of sublay repair was discovered with an odds ratio of 2.41. In addition, sublay repair had significantly lower infection rates compared to onlay repair with an odds ratio of 2.42. Sublay repair does seem to be the preferred technique in case of IH repair. Attention should be paid to the long term results of the Luijendijk trial, published by Burger et al (8). In this study mesh repair remained superior to suture repair, but with a 10 year cumulative recurrence rate of 32% after mesh repair, indicating that recurrence rates remain unacceptably high.

As stated before surgical repair is the golden standard for IH, however in a study by Nieuwenhuizen et al it was stated that 20% of all patients will not be operated (49). In this study hernia surgeons from Europe were asked for reasons to operate or implement a conservative policy in case of IH. The absence of symptoms was most often mentioned as a reason not to operate. This suggestion is collaborated by a study performed by Lauscher et al, who studied all IH repairs in their center and divided these into 2 groups (50). In the first group patients were included without pain or only mild pain (NRS 0-3, or oligosymptomatic hernia), the other group consisted of patients with relevant pain (NRS 4–10). The authors discovered that patients with relevant pain pre-operatively benefitted from the surgeryand a reduction in pain was ob-

served. However, patients with an oligosymptomatic hernia did often not benefit from surgery as 33.3% of patients developed pain after surgery. In this same paper it was suggested to apply a watchful waiting strategy for these types of hernia. Watchful waiting has already been shown to be safe and cost-effective in inguinal hernia patients (51-53). During long term follow-up however a significant part of watchful waiting patients did cross-over to the operative treatment group (31.9%) due to progression of symptoms. However, the watchful waiting strategy in IH patients has yet to be investigated and studies are lacking, although currently a trial is being conducted on this subject (54, 55). In Chapter 6 a retrospective cohort study is described and all patients diagnosed with IH between 2004 and 2009 in an academic hospital were included. We evaluated if patients were treated by operation or with a watchful waiting strategy and in how many cases patients crossed over from one group to the other. The main reasons for watchful waiting were asymptomatic hernia, increased operative risk due to obesity or co-morbidities. It was discovered that watchful waiting patients crossed over to the operative treatment group in 33% of cases. Of these crossovers, 24% crossed-over due to incarceration and had to be operated in an emergency setting.Patients that crossed over had higher morbidity and even mortality rates compared to primary operative treatment. Careful patient selectionand counseling should be implemented before applying a watchful waiting strategy.

Prevention

The focus of future research should be on the prevention of IH considering the high costs of IH, the numerous risk factors increasing the incidence of IH, the high impact on quality of life, the high recurrence rates after IH repair and unclear results of a watchful waiting strategy. The method of the best abdominal closure has been subject of investigation ever since abdominal surgery has become common practice. Child published his paper on abdominal wounds in 1918, stating that "in the closure of every abdominal incision, one immediate and most important indication must be met – the prevention of primary hernia" (6). In 1975 the first randomized controlled trial regarding abdominal closure was published pioneering proper research with as goal to minimize IH incidence (5). Since then we have come a long way in terms of adjusting our technique and performing adequate trials to investigate these techniques. These trials focused on continues suture vs interrupted suture, mass closure or layered closure and what type of suture to use, absorbable vs non-absorbable. The results of these studies would later be pooled in meta-analyses, providing us with an overall result of these pooled trials. Diener et al published a meta-analysis investigating continuous compared to interrupted sutures and included a total of 14 trials consisting out of 7711 patients (56). Patients undergoing an elective primary midline laparotomy with a continuous technique had a significantly lower chance of developing an IH, with an odds ratio of 0.59. Another factor influencing IH formation is the use of mass or layered closure. Weiland et al and Rucinski et al performed meta-analyses investigating these techniques and concluded that continuous closure results in a significant reduction of

IH (57, 58). With regard to suture type van 't Riet et al performed a meta-analysis concluding that slowly-absorbable and non-absorbable were equally better compared to absorbable sutures, but that slowly-absorbable sutures caused less pain compared to non-absorbable (59). These findings were later confirmed in the meta-analysis performed by Diener et al (56). So in general we may conclude that median laparotomies should be closed with slowly-absorbable continued mass suture. However, as stated before not only the type of suture is of importance but also the length of suture, firstly described by Jenkins et al (17). This technique would later be investigated and promoted in depth by Israelsson et al (23, 60, 61). In a prospective cohort a suture length to wound length ratio of less than 4:1 would significantly increase the incidence of IH (23% vs 9%). The same study group did publish several more articles on the effect of suture length to wound length ratio on IH rates and other wound complications (23, 61-63). All of these studies concluded that a suture length to wound length ratio of four or more reduces the incidence of IH. The same research group did later add totheir hypothesis by suggesting to use small stitches. In an experimental study by Cengiz et al it was discovered that rats in which the abdomen was closed with a smaller stitch from the wound edge had a higher abdominal bursting pressure (64). Millbourn et al did later publish a randomized controlled trial investigating the small bites technique. In this study patients closed with a small bites technique had significantly lower rate of IH (5.6%) compared to the long bites technique (18%) after one year. Deerenberg and Harlaar et al have performed a similar randomized controlled trial and discovered similar results with regard to IH development (65). All these suture techniques do give hope for improving the current high IH complication rate.

However, in patients with risk factors such as obesity and abdominal aortic aneurysm these techniques might not be sufficient to prevent IH and other techniques might be necessary. In 1995 Pans et al were the first to publish results focussing on primary mesh augmentation as a means to reduce the incidence of IH in obese patients (66). During closure of abdomen a mesh wasplaced in order to strengthen the abdominal wall. They did not discover a significant difference with regard to IH incidence. However, the investigators used a Vicryl mesh i.e. a rapidly absorbable mesh, as non-absorbable meshes were not commonly used during that time in fear of postoperative complications. This did change after the publication of the earlier mentioned trial by Luijendijk et al. A number of experimental studies were then performed to observe the effect of mesh on the strength and microscopic changes of the abdominal wall. All experimental studies displayed a clear increase in abdominal strength after primary mesh augmentation (67-69). Besides experimental studies in recent years also clinical studies have been performed with regards to primary mesh augmentation in patients with risk factors (70-73). However, the majority of the trials are generally lacking in quality and only two could be described as reasonable with regards to methodology and quality. The first randomized trial by Bevis et al, focussed on patients with an abdominal aortic aneurysm and patients were randomized to either receive primary suture (4:1 suture length to wound length ratio) or sublay mesh aug-

mentation (74). Patients with primary suture did develop IH significantly more often compared to the mesh group (37.2% vs 13.5%). Although not all postoperative complications were presented, they did not observe an increase in postoperative complications. In another randomized trial by Strzelczyk et al morbidly obese patients were randomized to either receiving primary suture or sublay mesh augmentation(75). No IHs were observed in the mesh group compared to 21% in the primary suture group. To obtain a proper overview and pooled results of the effect of primary mesh augmentation a meta-analysis was conducted which is described in Chapter 7. In total five studies could be included, consisting out of 346 patients. Primary mesh augmentation significantly reduced IH compared to primary suture with an odds ratio of 0.25. However, in general the quality of studies included was lacking and not all postoperative complications were described in the studies included. Furthermore, in this meta-analysis all types of primary mesh augmentation (onlay and sublay) were included and no subgroup analysis could be performed. For these reasons the PRIMA trial was initiated of which the protocol is described in Chapter 8. In this randomized controlled multicenter international trial the two primary mesh augmentation techniques, onlay and sublay, are compared to primary suture as a means to reduce IH. Patients were eligible for inclusion if they either had a BMI of 27 or higher or an abdominal aortic aneurysm. In Chapter 9 the short term results of this trial are presented. During the initiation of the trial surgeons questioned whether primary mesh augmentation would not lead to an increase in postoperative wound complications especially in patients with a potentially contaminated abdomen. A total of 480 patients could be included and no increase in postoperative wound infections could be observed between groups. The only postoperative complication that was increased was seroma formation after onlay mesh augmentationhoweverwithout an increase in infection. This leads to the conclusion that onlay and sublay primary mesh augmentation is a safe procedure. Whether both techniques are effective in prevention of IH in patients with risk factors is to be observed during long term follow-up.

Future Perspectives

As stated before, we have come a long way since the discovery of IH, however it remains the most frequent postoperative complication. The key of preventing a complication is to fully understand the pathology and currently we are making progress indeed but hernia experts are still divided between the mechanical and the herniosis theory. Interesting ideas have surfaced such as using growth factors (in combination with mesh) during abdominal closure in order to reduce IH formation (76-78). In addition, in the future wounds in general might be able to be closed with glue or adhesives (79).

Another possible prevention method reducing the size of the scar is represented by laparoscopic surgery. Since the introduction of laparoscopic surgery the number of midline abdominal incisions has been declining. Although laparoscopic surgery does produce trocar hernias, the incidence of these type of hernias does appear to be lower compared to the incidence of IH after midline laparotomy (80). Laparoscopic

surgery will not always be possible or yield enough exposure for abdominal surgery and in these cases patients still require midline laparotomy. In addition, laparoscopy has not yet been fully integrated in the daily surgical practice in many countries.

In contrast to laparoscopic surgery, abdominal wall closure is not a standard specific part of surgical training in the Netherlands. Proper teaching and instruction of the newest and best closure techniques could further improve the general skill of upcoming surgeons and reduce incidence rates. Implementation of new techniques of methods should always be accompanied with good monitoring to establish the effect of the intervention. Previous research has demonstrated the added value of monitoring devices and cohort databases. These systems give physicians a look into possible risk factors and items which could reduce postoperative complications and improve patients outcomes. One of these monitoring tools which has been implemented in the United States is the Surgical Care and Outcomes Assessment Program (SCOAP) (81). In this program hospitals in the state of Washington were asked to share their outcomes but also to comply to general protocol in order to reduce variance improving patient outcomes. For example participating hospitals were asked to perform pre-operative imaging by protocol in case of suspected appendicitis in order to reduce negative diagnostic laparoscopy rates. This simple change in hospital practice managed to reduce negative diagnostic laparoscopy rates from 12% to 6%. Comparable results with regard to incisional hernia incidence would not be unthinkable if abdominal closure would be done based on protocol (slowly absorbable continuous suture with 4:1 SL:WL using small bites). Furthermore, the use of protocol-based preoperative optimization could help us reduce postoperative complications. An increasing number surgeons in the United States are requiring patients to stop smoking before IH repair and will not operate in case patients fail urine smoke control tests. This may seem quite extreme but doctor and patients could come to a preoperative agreement to improve preoperative conditions reducing the risk of complications. Preoperative weight loss could be one of these factors.

In addition to research regarding surgical techniques and monitoring many studies have been performed in order to discover changes in connective tissues components, such as collagen, metalloproteinases and tissue inhibitors of metalloproteinases. Recently our research group has conducted a search for genetic mutations in the Rotterdam study, which consists out of roughly 15.000 people (82). However, the numbers are lacking for adequate analysis of this complex data and more cooperation between research groups is needed in order to obtain sufficient numbers. Recently in Germany a national study center has been initiated in which 80 centers are participating in numerous surgical trials (83). More of these collaborations should be created in search of improving surgical studies, increasing implementation, improving techniques and outcomes and reducing complications. Such a collaboration will help us to eliminate IH as one the most frequent complications after abdominal surgery reducing general health costs and last but not least: improving quality of life of patients.

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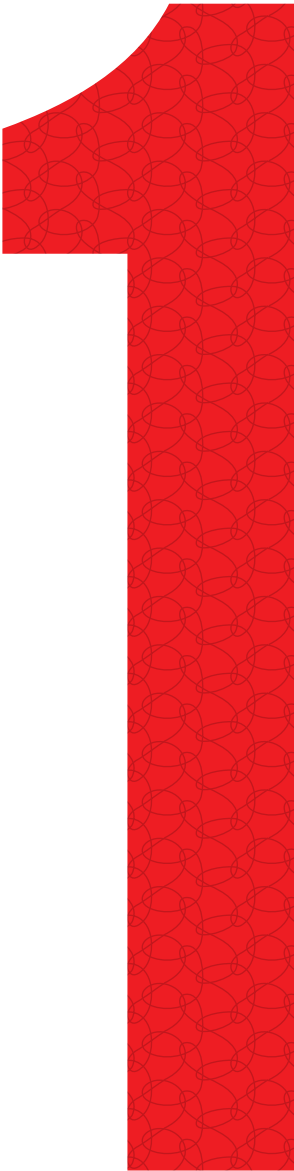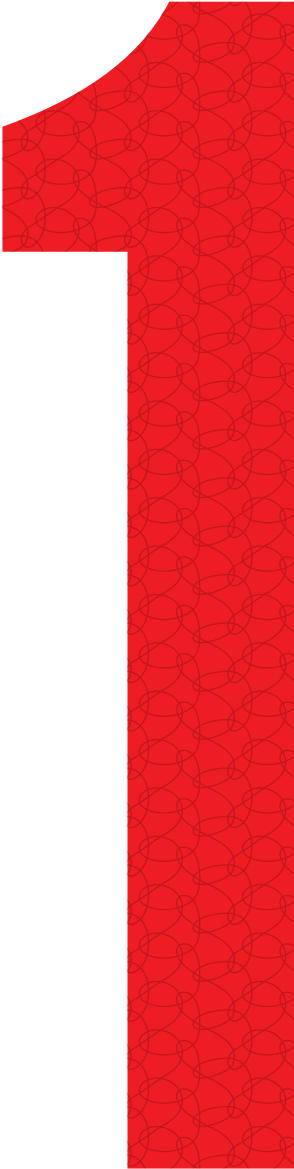
Nederlandse samenvatting

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In Hoofdstuk 1 wordt het onderwerp van dit proefschrift toegelicht: risicofactoren en preventie van de littekenbreuk. De littekenbreuk is de meest voorkomende postoperatieve complicatie na abdominale chirurgie. Het hebben van een hoog ´body mass index´ofwel BMI en van een abdominaal aneurysma van de aorta betekenen een hogere incidentie van littekenbreuken na abdominale chirurgie. Littekenbreuken hebben een significant negatieve invloed op de kwaliteit van leven van patiënten en op de manier waarop patiënten hun eigen lichaam beoordelen. Tegenwoordig is de gouden standaard voor de behandeling van de littekenbreuk operatieve behandeling met een kunststof mat (mesh). Helaas zijn de lange termijn resultaten teleurstellend.

In Hoofdstuk 2 wordt de impact van de complexiteit van littekenbreuken op de zorgkosten beschreven. Littekenbreuken kunnen in niet-complex en complexe littekenbreuken geclassificeerd worden. Daarbij kunnen complexe littekenbreuken worden ingedeeld in niet-, mild-,matig- en ernstig-complexe breuken. De operatieve behandeling van patiënten met een niet-complexe en matig complexe littekenbreuk bleek significant duurder in academische ziekenhuizen te zijn vergeleken met perifere ziekenhuizen. Daarbij bleek de operatieve behandeling van een ernstig-complexe littekenbreuk significant duurder te zijn vergeleken met die van een niet-, mild- of matig-complexe littekenbreuk. Vanuit een kosten perspectief dienen patiënten met een niet-, mild- en matig-complexe littekenbreuk te worden geopereerd in een perifeer ziekenhuis. Patienten met een ernstig-complexe littekenbreuk zouden moeten worden gecentraliseerd in een hoogvolume ziekenhuis met adequate faciliteiten om deze patiënten te behandelen. Dit zal de kwaliteit van zorg voor deze complexe patiëntengroep verhogen en mogelijk ook de kosten verlagen.

In Hoofdstuk 3 wordt een cross-sectionele studie beschreven waarin patiënten met een eindstandig colostoma op de polikliniek werden teruggezien. Patiënten werden onderzocht of zij een littekenbreuk en/of een parastomale hernia hadden ontwikkeld. Patiënten met een parastomal hernia hadden een zeven maal zo hoog risico op het ontwikkelen van een littekenbreuk. Een reden hiervoor zou kunnen zijn dat het plaatsen van een stoma zorgt voor verminderde innervatie van een deel van de buikwand, de musculus rectus abdominis, waardoor deze in dikte en sterkte vermindert. Een andere reden zou kunnen zijn dat de symmetrische krachten, die op de incisie midden in de buik (mediane incisie) inwerken, door het plaatsen van het stoma worden opgeheven. Hierdoor ontstaat een verhoogde trekkracht op delen van de mediane incisie welke kunnen zorgen voor een toename van de incidentie van littekenbreuken. Het hebben van een parastomale hernia zou volgens beide hypothesen de impact van deze veranderingen verergeren.

In Hoofdstuk 4 werden de in Hoofdstuk 3 voorgestelde hypothesen door middel van een retrospectieve radiologische studie getoetst. Van alle patiënten, die in Hoofdstuk 2 waren geïncludeerd, werd nagegaan of een CT scan van vóór en na de operatie voorhanden was. Deze scans werden in een computerprogramma geladen en in 3D weergegeven, waarna metingen konden worden verricht. Uit de resultaten bleek dat patiënten met een parastomale hernia een dunnere middelste buikwandspier, de musculus rectus abdominis,hadden vergeleken met patiënten zonder parastomale hernia. Daarnaast was bij patiënten met een parastomale hernia een shift van de mediane incisie ontstaan. Deze shift zou een verhoogde trekkracht op de middenlijn van de buikwand kunnen veroorzaken welke aan het ontstaan van een littekenbreuk kan bijdragen.

Hoofdstuk 5 betreft een systematic review en meta-analyse van de literatuur over de beste behandelmethode van littekenbreuken. Voor analyse geschikte artikelen, waarin onlay-herstel (plaatsing van de mat op het voorste fascieblad van de musculus rectus abdominis) met sublay-herstel (plaatsing van de mat boven op het achterste fascieblad van de musculus rectus abdominis) vergeleken werd, werden geïncludeerd. In totaal werden acht artikelen in de meta-analyse geïncludeerd met in totaal 1359 patiënten, die of sublay-herstel of onlay-herstel ondergaan hadden. Sublay-herstel leek een trend voor een verminderde recidief kans te vertonen ten opzichte van onlay-herstel. Bovendien werden er meer dan twee keer zo veel wondinfecties gezien na onlay-herstel. Ondanks dat een groot deel van de geïncludeerde artikelen retrospectieve studies waren lijkt sublay-herstel de te prefereren methode voor littekenbreukherstel.

In Hoofdstuk 6 wordt een retrospectieve serie patiënten beschreven,die conservatief zijn behandeld. Alle patiënten, die in een academisch ziekenhuis met een littekenbreuk gediagnosticeerd waren, werden geïncludeerd. Alle geïncludeerde patiënten werden verdeeld in een groep waarbij de littekenbreuk operatief werd hersteld en in een groep welke conservatief werd gehandeld. Hierbij werd onderzocht hoe vaak een conservatieve patiënt alsnog werd geopereerd en wat de uitkomst van deze crossovers waren. Patiënten, die initieel conservatief werden behandeld, ondergingen in 33% van gevallen als nog operatie. Voor deze patiënten betrof dit in 24% een spoedoperatie in verband met beklemming van de littekenbreuk. Crossovers gingen gepaard met een verhoogde kans op per- en postoperatieve complicaties en zelfs overlijden. Ondanks dat dit een retrospectieve studie met geselecteerde patiëntengroepen betrof, zijn dit cijfers welke bijzondere aandacht behoeven. Heldere patiëntinformatie over mogelijke complicaties bij conservatieve behandeling is essentieel. Concluderend is een electieve ingreep bij deze patiënten mogelijk een betere optie dan conservatieve behandeling.

In Hoofdstuk 7 worden een systematic review en meta-analyse beschreven over het gebruik van primaire

mesh augmentatie ter voorkoming van een littekenbreuk na mediane laparotomie. In totaal werden vijf artikelen geïncludeerd waarbij primair sluiten met primaire mesh augmentatie werd vergeleken. Uit deze meta-analyse bleek dat de incidentie van littekenbreuk met 75% na primaire mesh augmentatie verlaagd werd. Daarbij werd geen toename van postoperatieve complicaties gezien. Helaas waren de geïncludeerde studies in het algemeen van lage kwaliteit, werden niet alle postoperatieve complicaties besproken en was onduidelijk welke primaire mesh augmentatie techniek de beste is.

In Hoofdstuk 8 wordt het studieprotocol van de PRIMA-trial beschreven. Risicopatiënten voor een littekenbreuk werden geïncludeerd, indien zij een aneurysma van de abdominale aorta of een verhoogd BMI hadden en een mediane laparotomie moesten ondergaan. De patiënten werden in drie groepen gerandomiseerd: primair sluiten, onlay mesh augmentatie en sublay mesh augmentatie.

In Hoofdstuk 9 worden de korte termijn resultaten van de PRIMA-trial beschreven. Onlay mesh augmentatie ging met een toename van seroomvorming gepaard. Primaire mesh augmentatie ging niet met een toename van wondinfecties of andere postoperatieve complicaties gepaard.

List of publications

Accepted

Short term results of a randomized controlled trial comparing primary suture with primary glued mesh augmentation to prevent incisional hernia.
Timmermans L, Eker HH, Steyerberg EW, Jairam A, Pierik EGJM, Lases SS, de Jong D, van der Ham AC, Dawson I, Charbon J, Schuhmacher C, Izbicki JR, Neuhaus P, Knebel P, Fortelny R, Kleinrensink GJ, Jeekel J, Lange JF; Ann Surg 2014

Abdominal rectus muscle atrophy and midline shift after colostomy creation.
Timmermans L, Deerenberg EB, van Dijk SM, Lamme B, Koning AH, Kleinrensink G-J, Jeekel J, Lange JF; Surgery 2014

Meta-analysis of primary mesh augmentation as prophylactic measure to prevent incisional hernia.
Timmermans L, de Goede B, van Kempen BJH, Kazemier G, Jeekel J, Lange JF; Dig Surg 2013

A double blind randomized controlled trial comparing primary suture closure with mesh augmented closure to reduce incisional hernia incidence.
Nieuwenhuizen J, Eker HH, Timmermans L, Hop WCJ, Kleinrensink GJ, Jeekel J, Lange JF, PRIMA Trialist group; BMC Surg 2013

Meta-analysis of sublay versus onlay mesh repair in incisional hernia surgery.
Timmermans L, de Goede B, van Dijk SM, Kleinrensink GJ, Jeekel J, Lange JF; Am J Surg 2013

Parastomal hernia is an independent risk factor for incisional hernia in patients with end colostomy: a cross-sectional study.
Timmermans L, Deerenberg EB, Lamme B, Jeekel J, Lange JF; Surgery 2013

The principles of abdominal wound closure.
Meijer EJ, Timmermans L, Jeekel J, Lange JF, Muysoms FE; Acta Chir Belg 2013

Meta-analysis of glue versus sutured mesh fixation for Lichtenstein inguinal hernia repair.
de Goede B, Klitsie PJ, van Kempen BJH, Timmermans L, Jeekel K, Kazemier G, Lange JF; Br J Surg 2013

Reduce variation and improve quality in meta-analyses.

Timmermans L, de Goede B, Lange JF, Jeekel J; Ann Surg 2013

Chapter: The natural history of abdominal wall defects.

Deerenberg EB, Timmermans L, Jeekel J, Lange JF; Abdominal Wall Reconstruction by Nahabedian M, Bhanot P, 2013

Sealants in gastrointestinal anastomosis: a systematic review.

Vakalopoulos KA, Daams F, Wu Z, Timmermans L, Jeekel J, Kleinrensink GJ, van der Ham AC, Lange JF; J Surg Res 2012

Rectus muscle bulging after thoracic surgery: an unknown complication.

Timmermans L, Klitsie PJ, Maat APWM, de Goede B, Kleinrensink GJ, Lange JF; Hernia 2012

Medieval times in surgery.

Timmermans L, Deerenberg EB, Kleinrensink GJ, Lange JF, Jeekel J; Surgery 2012

Roux-en-Y Gastric Bypass as a Revisional Procedure after Gastric Banding: Leaving the Band in Place.

Meesters B, Latten G, Timmermans L, Schouten R, Greve JW; Surg Obes Rel Dis 2012

Roux-en-Y Gastric Bypass After Roux-en-Y Pancreaticojejunostomy.

Timmermans L, Schouten R, Meesters B, Greve JW; Surg Obes Rel Dis 2010

Submitted

Watchful waiting in incisional hernia; is it safe?

Timmermans L en Verhelst J, van der Velde M, Jairam A, Vakalopoulos KA, Jeekel J, Lange JF

Repair of complex abdominal wall hernias with Permacol mesh, a cross-linked porcine acellular matrix: results of the Dutch cohort study

Timmermans L en Kaufmann R, van Loon Y, Vroemen JPAM, Jeekel J, Lange JF

Parastomal hernia reduces the quality of life in patients with end colostomy

van Dijk SM, Timmermans L, Deerenberg EB, Lamme B, Kleinrensink GJ, Jeekel J, Lange JF

Surgical treatment of giant incisional hernia: a systematic review.

Deerenberg EB, Timmermans L, Hogerzeil DP, Slieker JC, Jeekel J, Lange JF

Risk factors for inguinal hernia in middle-aged and elderly men: Results from the Rotterdam Study.

de Goede B, Timmermans L, van Kempen BJH, van Rooij FJA, Hofman A, Kazemier G, Lange JF, Jeekel J

The effect of Triclosan-coated sutures on surgical site infections: a systematic review and meta-analysis.

Timmermans L, Meijer EJ, de Goede B, Jeekel J, Muysoms FE, Lange JF

Complex abdominal wall pathology: an analysis of costs.

Timmermans L en Jairam A, van der Velde M, van 't Riet, Polinder S, Jeekel J, Lange JF

Dankwoord

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Beste Marijke, liefje, we zijn nu al een aantal jaren samen en toch voelt dat niet zo. Als niet medicus is het fijn om thuis te komen en je te horen praten over streekproducten, en je laparoscopie uitdrukt als `met van die stokjes`. Ik ben je dankbaar dat je het nooit vervelend vond (of in ieder geval zo hebt geuit) als ik mijn weekenden, compensatie weken of de avonden gebruikte voor het onderzoek. Ik houd extreem veel van je, we gaan samen een moeie tijd tegemoed!

Curriculum vitae

Lucas Timmermans werd op 29 mei 1984 te Nijmegen geboren. In 2002 slaagde hij voor zijn eindexamen aan het Stedelijk Gymnasium te Nijmegen (profiel: Natuur en Gezondheid). Hij werd uitgeloot voor Geneeskunde en besloot Industrial Design te gaan studeren aan de Technische Universiteit van Eindhoven. In 2003 werd hij alsnog ingeloot voor Geneeskunde aan de Universiteit van Maastricht. Tijdens zijn laatste jaar van zijn studie liep hij zijn semi-arts stage in het Atrium Medisch Centrum te Heerlen en verrichte hij onderzoek naar morbide obesitas en hernia diafragmatica onder begeleiding van dr. J.W. Greve en drs. B. Meesters. In 2010 werd zijn artsdiploma behaald waarna hij werd aangenomen als arts-onderzoeker in het Erasmus Medisch Centrum te Rotterdam, onder begeleiding van prof.dr. J. Jeekel en prof.dr. J.F. Lange. Het wetenschappelijk onderzoek naar de risicofactoren en preventie van littekenbreuken heeft uiteindelijk geleid tot dit proefschrift. Na zijn tijd als fulltime onderzoeker, heeft hij een half jaar gewerkt als arts niet in opleiding tot medische specialist (ANIOS) chirurgie in het Reinier de Graaf ziekenhuis te Delft (opleider dr. M. van der Elst). Momenteel is hij werkzaam als ANIOS in het Amphia ziekenhuis te Breda (opleider dr. L. van der Laan).

PhD portfolio

Summary of PhD training and teaching

Name PhD student: Lucas Timmermans	PhD period: 2010 - 2014
Erasmus MC Department: Surgery	Promotor(s): Prof.dr. J. F. Lange
	Supervisor: Prof.dr. J. Jeekel

1. PhD training	Year	Workload (Hours/ECTS)
General courses		
NIHES – statistics and epidemiology courses	2011	3
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.5
CPO minicursus	2013	1.0
Specific courses (e.g. Research school, Medical Training)		
Scientific writing	2012	2.0
Seminars and workshops		
Principles of abdominal wall closure workshop	2012	1.0
Presentations		
International	2014	2
National	2014	1
International	2013	7
International	2012	1
National	2012	4
International	2011	1
(Inter)national conferences		
European Hernia Society, Gent	2011	1.0
Chirurgendagen 2011, Veldhoven	2011	1.0
Other		

2. Teaching	Year	Workload (Hours/ECTS)
Lecturing		
Supervising practicals and excursions, Tutoring		
Tutoring first year medical students	2011	1.5
Teaching of first year students	2010-2011	1.5
Supervising		
M. van de Velde	2011-2012	2.0
S. van Dijk	2012-2013	2.0