UNIVERSITEIT GENT

Faculty of Medicine and Health Sciences

Department of General and Hepatobiliary Surgery and Liver Transplantation

Mesh fixation techniques in laparoscopic ventral hernia repair.

Emmelie Reynvoet

Promotor: Prof. Dr. F. Berrevoet

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If a man does not know to which port one is sailing, no wind is favorable.
Lucius Annaeus Seneca
cited by Herman Van Rompuy, Former President of the European Council

Promotor:

Prof. Dr. F. Berrevoet, Faculteit Geneeskunde, vakgroep Heelkunde, Dienst Algemene en Hepatobiliaire Heelkunde, Universiteit Gent

Members of the examination committee:

Prof. Dr. M. Miserez, Faculteit Geneeskunde, Departement Abdominale Heelkunde, Katholieke Universiteit Leuven

Prof. Dr. A. De Backer, Faculteit Geneeskunde, Dienst Abdominale Heelkunde, Vrije Universiteit Brussel

Prof. Dr. W. Ceelen, Faculteit Geneeskunde, vakgroep Heelkunde, Dienst Gastro-intestinale Heelkunde, Universiteit Gent

Prof. Dr. F. De Somer, Faculteit Geneeskunde, vakgroep Heelkunde, Dienst Hartheelkunde, Universiteit Gent

Prof. Dr. K. D'Herde, Faculteit Geneeskunde, vakgroep Medische Basiswetenschappen, Dienst Anatomie en Embryologie, Universiteit Gent

Prof. Dr. R. Ducatelle, Faculteit Dierengeneeskunde, vakgroep Pathologie, Bacteriologie en Pluimveeziekten, Universiteit Gent

Prof. Dr. S. Monstrey, Faculteit Geneeskunde, vakgroep Heelkunde, Dienst Plastische Heelkunde, Universiteit Gent

This thesis is based on the following papers which will be subsequently reported in part 3:

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2. Reynvoet E, Berrevoet F (2014) Pros and cons of tacking in laparoscopic hernia repair. Surg. Technol. Int. 25:136-140
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4. Reynvoet E, Van Cleven S, Van Overbeke I, Chiers K, De Baets P, Troisi R, Berrevoet F (2015) The use of cyanoacrylate sealant as single mesh fixation in laparoscopic ventral hernia repair : a large animal evaluation. Hernia *Epub ahead of print.*

Paper related to the subject of this thesis (added as addendum in part 6):

5. Reynvoet E, Chiers K, Van Overbeke I, Troisi R, Berrevoet F (2015) Intraperitoneal mesh devices for small midline hernias. Mesh behavior in a porcine model. Hernia *Epub ahead of print.*

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List of Abbreviations

BMI	Body Mass Index
CA	Cyanoacrylate (glue)
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
df	degrees of freedom
ECG	Electrocardiography
ECM	Extracellular Matrix
EHS	European Hernia Society
EMS	Endoscopic Multifeed Stapler
ePTFE	expanded Polytetrafluoroethylene
FBR	Foreign Body Reaction
FU	Follow-Up
H&E	Haematoxylin & Eosin
HR	Hazard Ratio
IM	Intramuscular
IPOM	Intraperitoneal Onlay Mesh
IV	Intravenous
LVHR	Laparoscopic Ventral Hernia Repair
mmHg	Millimeter of Mercury
mm/min	Millimeter per Minute
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
M	Months
N	Newton
N	Number
N/cm²	Newton per square centimeter
OR	Odds Ratio
ORC	Oxidized Regenerated Cellulose
P	Prospective
PDGF	Platelet-Derived Growth Factor
PDS	Polydioxanone
PE	Polyester
PET	Polyethylene Terephthalate

PP	Polypropylene
PTFE	Polytetrafluoroethylene
PVDF	Polyvinyldenefluoride
R	Retrospective
RE	Random Effect
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TAPP	Transabdominal Pre-Peritoneal
TGF-β	Transforming Growth Factor β
VAS	Visual Analogue Score
WoW	With or Without

PART 1

GENERAL INTRODUCTION

PART 1. GENERAL INTRODUCTION

1. Abdominal wall hernias: Basic principles.

1.1 Definition

"A hernia is a defect in supporting structures through which a contained organ or tissue *may* protrude. Hernias of the abdominal wall, or ventral hernias, occur at defects in the parietal fascia and muscle through which intra-abdominal or preperitoneal contents can protrude, at either congenital or acquired weaknesses in the abdominal wall. Acquired hernias may develop after an incision when tissue healing fails (incisional hernias) or through slow architectural deterioration of the muscular aponeuroses (primary hernias)."[1]

From a physical examination, a hernia presents as a mass or bulge at the abdominal wall that increases in size with a Valsalva maneuver. Ventral hernias may be asymptomatic or cause considerable discomfort, and can gradually enlarge over time. The hernia orifice or neck can be distinguished at the deepest musculo-aponeurotic layer, and the hernia sac with the hernia content is lined by the peritoneum and protrudes out of the neck. If the content can be repositioned within the surrounding musculature, a hernia is *reducible*, if the mass cannot be reduced, a hernia is irreducible or *incarcerated*. Incarceration of an intestinal segment can be associated with nausea, vomiting and severe pain, and then needs urgent surgical repositioning. If the blood supply to the intestinal segment is compromised, a hernia is *strangulated,* in which case local ischemia can lead to intestinal infarction and perforation. Strangulation is a serious and potentially fatal complication and is more frequent in hernias with large contents and a small neck.[1]
Hernias of the abdominal wall are very common: an estimated 5% of the total population will develop a hernia throughout lifetime.[2]

Four types of abdominal wall hernias can be defined: (Table 1.1.)

- **Inguinal hernias.** Although much more frequent in males, inguinal hernias are the most common hernias in both males and females, accounting for 78% of all abdominal wall hernias. An inguinal hernia presents as a groin mass that can enlarge through time and become symptomatic. An inguinal hernia can present as either direct or indirect. Direct hernias present as a bulging medial

of the internal inguinal ring and the inferior epigastric vessels, while indirect hernias occur lateral of the epigastric vessels and pass from the internal inguinal ring towards the external inguinal ring.

- **Femoral hernias** are defined as a protrusion of the peritoneum into the femoral canal and present as a bulge below the inguinal ligament. They account for 7% of all hernias and are four times more common in women than in men.

  Inguinal and femoral hernias will not be discussed in this work.

- **Primary ventral hernias**, or non-incisional hernias, also known as 'true ventral hernias', appear at anatomical weaknesses of the abdominal wall, with umbilical and epigastric hernias being the most common.
- **Incisional hernias** represent the last 10% and occur in the area of a former incision when tissue healing fails.[3]

Type of hernia	*Incidence (%)*
Inguinal	78
Incisional	10
Femoral	7
Umbilical	3
Epigastric	1
Other (rare)	1

Table 1.1. Different types of hernias with their incidences.[3]

1.2. The abdominal wall

The ventral abdominal wall extends from the xiphoid process and the costal arches to the pelvis (the iliac crest, the anterior superior iliac spine, the inguinal ligament of Poupart, the pubic tubercle, and the symphysis). Looking transversely, the ventral abdominal wall consists of skin, subcutaneous tissue, superficial fascia, muscles, transversalis fascia, extra-peritoneal fat and parietal peritoneum.

The superficial fascia consists of a superficial fatty layer (layer of Camper) and a deeper fibrous layer (layer of Scarpa). The fibrous layer fuses with the deep fascia of the upper thigh and extends to the perineum as Colles' fascia.[4]

The medial part of the abdominal wall consists of the rectus abdominis muscle. Laterally, there are three flat muscles, from external to internal: the external oblique muscle, the internal oblique muscle and the transverse abdominal muscle.

The rectus muscle is enclosed in a sheath formed by the bilaminar aponeurosis of the three flat muscles. The sheath splits and passes anteriorly and posteriorly around the muscle, starting at the lateral border of the rectus abdominis, forming the linea alba medially, and continuing to the opposite side.

Below the arcuate line or the linea semicircularis, the transversalis fascia forms the only fascial layer posterior to the rectus abdominis muscles.

The fibers of the anterior and posterior walls of the rectus sheath come together in the anterior median line to form a complex tendinous raphe: the linea alba. Inferior to the umbilicus, the linea alba is narrow and the fibrous separation between the rectus muscles is less obvious, while superior to it, it is wider and provides a plane for midline incisions.

The abdominal wall with its muscles and aponeurosis gives protection to the intra-abdominal viscera. With inspiration, the diaphragm descends and the abdominal wall expands as its muscles relax to give space to the viscera. In contrast, when the diaphragm relaxes during expiration, the abdominal wall sinks in. When the flat abdominal muscles act together, the intra-abdominal pressure raises and force is built up as is needed for defecation, miction and parturition. The external and internal oblique muscle, when acting separately, can flex and rotate the trunk, the rectus abdominis muscles depress the ribs and stabilize the pelvis during walking. All this is achieved either by simultaneous activation of contralateral muscles or by selective innervation of functionally corresponding working pairs of muscles. The physical capacity is directly affected by the integrity of the structure of the abdominal wall.[4-7]

1.3. Primary ventral hernias

a. Classification

In 2009, a delegate committee of the European Hernia Society (EHS) proposed a practical classification for both primary and incisional hernias based on localization and size. Two midline hernias have been defined, epigastric and umbilical, and two lateral hernias, spigelian and lumbar. The size of a hernia is defined according to the diameter, resulting in three categories: small, medium and large.[8] (Table 1.2.)

EHS Primary Abdominal Wall Hernia Classification		Diameter cm	Small <2cm	Medium ≥2-4cm	Large ≥4cm
Midline	Epigastric				
	Umbilical				
Lateral	Spigelian				
	Lumbar				

Table 1.2. Classification of primary abdominal wall hernias according to the EHS.[8]

b. Clinical presentation

Umbilical hernias can present through lifetime.The umbilical orifice is a natural defect in the midline aponeurosis where the umbilical cord structures pass during fetal life. When the abdominal wall development is completed, a round opening in the abdominal wall aponeurosis remains: the umbilical ring. After birth, the umbilical ring is constricted due to contraction of the abdominal wall muscles resulting in an obliteration of the umbilical cord vessels.[9] The umbilical canal has four borders: the umbilical fascia posteriorly, the linea alba anteriorly and the medial edges of the two rectus sheaths on each side.[10]

A *congenital umbilical hernia* or omphalocele can be divided into two categories: embryonic and fetal. The embryonic omphalocele is due to failure of abdominal wall closure before week 8 in gestation and is often related to other syndromes. The fetal omphalocele develops after week 8 when

the gut returns into the abdominal cavity. In these children this development does not occur properly and a defect in the abdominal wall remains.[10]

An *infantile umbilical hernia* is a protrusion of intra-abdominal content through an incomplete closed umbilical ring. In contrast to the omphalocele, it is only a fascial defect and is always covered by skin. Premature infants are at greater risk with a high incidence in black-skinned children.[10,11]

An *adult umbilical hernia* presents as a herniation though the umbilical canal. This is due to a gradual yielding of the umbilical ring caused by increased intra-abdominal pressure, e.g. due to extreme obesity, pregnancy, ascites, or intra-abdominal malignancies.[10,11] As the neck of an umbilical hernia is narrow compared to the size of the hernia mass, strangulation is common. Therefore, these hernias should be treated promptly.[10] Only 10% of adults with an umbilical hernia exhibited these as children, in a male/female ratio of 3:1.[9]

Epigastric hernias occur at the linea alba and most commonly above the level of the umbilicus. These hernias affect more women than men, usually during their active life, from 20 to 50 years. These hernias have a high risk of strangulating as the fascial defect at the linea alba is often very tight, however, they can become large as well.[10]

Spigelian hernias are defined as a protrusion along the linea semilunaris. The inferior epigastric vessels pass across this region, making it a weak zone in the abdominal wall. Only half of the hernias are diagnosed preoperatively, most cases present as a painful, palpable mass, which leads to surgery.[12]

Lumbar hernias present as a bulge in the posterior suprailiac area. Primary lumbar hernias, mostly due to a congenital defect, typically arise in two areas of weakness: the superior (Grynfelt-Lesshaft) and inferior lumbar triangle (Petit). Acquired lumbar hernias are usually due to previous trauma or surgery, and present as a more diffuse and larger bulge.[13]

1.4 Incisional hernias

a. Definition

> "An incisional hernia is defined as any abdominal wall gap, with or without bulge, in the area of a postoperative scar perceptible or palpable by clinical examination or imaging."[14]

b. Epidemiology

Thirty years ago, a prospective 9-year follow-up study was published of 337 patients who had undergone major abdominal surgery. The reported incidence of incisional hernia was 10.9%.[15] Since then, the incidence has changed little. Incisional hernias are a common complication after laparotomy: they appear in 2-11% of all patients and are a serious cause of morbidity.[16,17]

c. Clinical presentation

Only half of the incisional hernias become apparent during the first year after surgery, whereas 75% become apparent after two years and about 90% after five years.[18,19] According to the EHS, incisional hernias are classified into medial and lateral hernias and are divided into, respectively, five (M1 – M5) and four (L1 – L4) anatomical subgroups. M1: subxyphoidal, M2: epigastric, M3: umbilical, M4: infraumbilical, M5: suprapubic. L1: subcostal, L2: flank, L3: iliac and L4: lumbar.[8] (Fig. 1.1.)

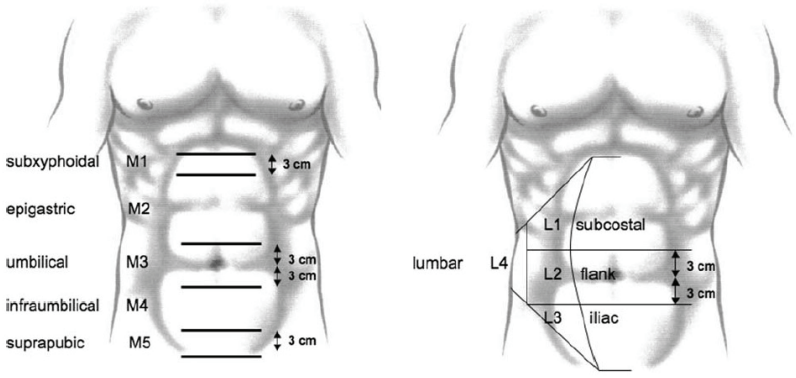


Fig. 1.1. Classification of incisional hernias according to anatomical subgroup.[8]

To describe the size of an incisional hernia, both the width and length should be used. The width of a hernia is defined as the greatest horizontal distance in cm between the lateral margins of the hernia defect. With multiple defects, the width is measured between the most laterally located margins of the most lateral defect on that side. (Fig. 1.2.) The length of the hernia defect is defined as the greatest vertical distance in cm between the most cranial and the most caudal margin of the hernia defect.

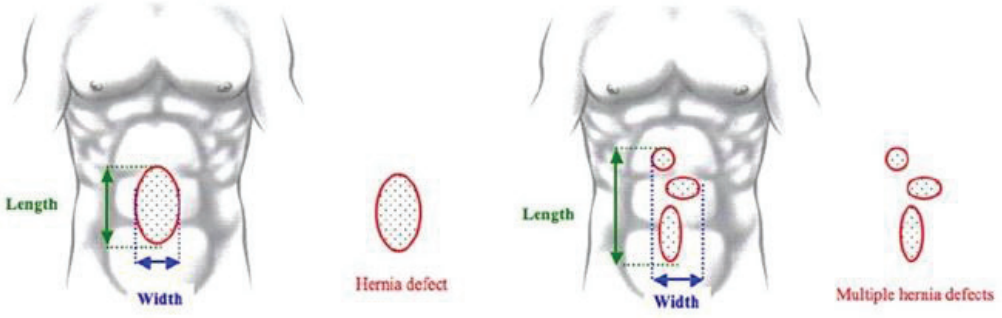


Fig. 1.2. Definition of the width and length of incisional hernias.

d. Pathophysiology

1) Development of an incisional hernia

An incisional hernia develops when normal tissue healing fails. During wound healing, a series of cellular and molecular events is activated to organise the surgical wound matrix.[20] The wound healing process can be divided in three phases. First there is an early lag period of three to four days. (Fig. 1.3.) A second phase of rapid gain of strength lasts about three weeks and is followed by a slow period of increasing strength. The early period includes hemostasis and inflammation, secondly there is a fibro-proliferation phase (scar formation) and finally the wound healing occurs, which is called the remodeling phase. A defect or delay in any of these phases can lead to the formation of a hernia.[21,22] Laparotomy wounds are dependent on the suture material until the strength of a wound is normalized. It is the time required for the recovery of its strength that determines the risk of wound failure. Hematoma formation can slow down the recovery because it can result in mechanical failure of the provisional wound matrix. A wound infection or a prolonged inflammatory reaction, as occurs when using foreign material such as mesh material, will delay the progression into the fibro-proliferation phase. A delayed inflammatory response, e.g. due to steroid intake can also inhibit the collagen synthesis. Delayed fibroblast response will impede the formation of a provisional wound matrix, prolonging the period of time the wound is dependent on suture material for strength.[20]

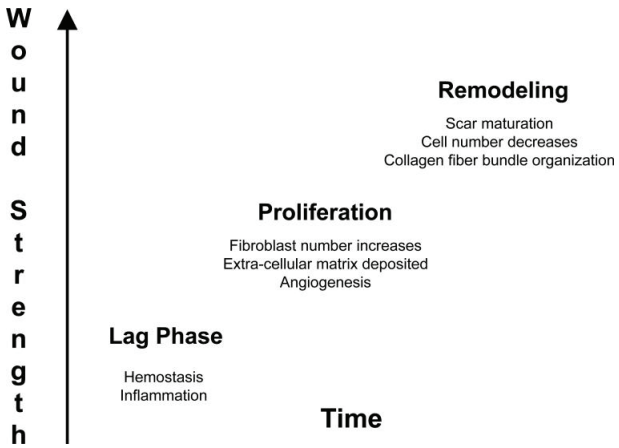


Fig. 1.3. During the initial "lag-phase" of healing, the laparotomy wound is weakest. As the patients recover, increased abdominal wall loads can cause wound failure.[20]

The first three days, plasmacells, monocytes and neutrophils, migrate to the injured tissue. Platelets are not only needed for hemostasis, but as the platelets degranulate, they release cytokines and growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β). Neutrophils and monocytes are attracted to the wound site by these cytokines as well as by other chemokines such as products of the bacterial proteins or the residues of proteolysis of fibrin and other matrix components.[23] Neutrophils arrive at first and phagocytize the wound. Within two or three days monocytes and macrophages infiltrate the tissue. Macrophages phagocytize tissue and produce growth factors. The macrophage organises tissue repair and is the only inflammatory cell really needed. During the inflammatory phase, tissue strength is low.[20]

Fibroblasts are responsible for collagen synthesis and migrate to the site of injury within two days. First, fibroblasts proliferate. Both migration to the site and proliferation are induced by the inflammatory cells. In addition, the structure of the provisional matrix, on which the fibroblasts move, is important. Receptor-mediated interactions between the wound matrix and activated repair fibroblasts are described. Fibroblasts organize the extracellular matrix (ECM) and later the collagen deposition. Wound ischemia can stop the fibroblast cell-cycle. This might occur with too much tension on the closure line or when a patient is in shock and soft-tissue perfusion is reduced.[20]

Collagen is the most important structural protein. Imbalance in repair collagen homeostasis leads to reduction in wound collagen levels, wound tensile strength and an increased risk of mechanical wound failure. Collagen diseases, such as Ehlers-Danlos, are associated with a higher incidence of hernia formation. The mechanism by which the collagen-rich early wound matrix is attached to the injured tissue at the incision is poorly understood. This mechanism is however important as acute laparotomy

wounds often fail at the interface of scar to normal tissue. Only in the first 3 to 5 days mechanical failure happens in the scar itself, at the provisional wound matrix, later, mechanical failure is more likely to occur at the interface of the scar and normal tissue.[20]

Since many years tissue engineers are investigating the process of wound healing. Besides experimental research a lot of progress has been made by theoretical work, using e.g. mathematical models. Nowadays many models are available that investigate the cellular response during the different phases of wound healing. Mathematical models predict how cell numbers will change as a result of the spatiotemporal variations in proliferation and motility. The model equations are formulated using experimental data, usually by in vitro studies on cell behaviour. The equations are then used to predict the dynamics of the cell population within a healing wound.[24] The sequence of events involved in the healing of a wound is described above. After the coagulation phase, the blood blot forms a provisional matrix along which fibroblasts and many other cells proliferate. The fibroblasts break down the clot and replace it with a collagen matrix. In the last phase, the composition of the ECM is changed over a period of months, again by the fibroblasts.[25] The interaction of the different cells with the ECM have attracted the attention of many researchers. Two main features are of interest: the details of collagen deposition and the orientation of the collagen fibers. Both differ in scar tissue and normal tissue. The balance between type 1 and type 3 collagen, the most abundant types in the dermis, is regulated by TGF-β. The proportion of type 3 collagen is higher in scar tissue than in normal tissue which results in thinner collagen fibers. Besides, in normal dermis, the collagen fibers are arranged in a random way, whereas in a scar, the fibers are aligned. The orientation of the matrix is arranged by the fibroblasts, but meanwhile the movement of the fibroblasts is directed by the orientation of the matrix, known as “contact guidance”. The composition of the ECM will also affect the speed of the fibroblasts. This interaction between fibroblasts and ECM is a key of interest for developing new mathematical models. From therapeutic point of view anti-scarring treatment is being developed, e.g. agents that work on the activity of TGF-β or the fibroblasts itself.[24-26]

Besides these mathematical models, biomechanical systems have been developed to investigate the role of physical forces on cell behavior. Mechanotransduction describes the conversion of extracellular forces into intracellular biomechanical signaling. Most cells types in the skin are mechanoresponsive and in vitro studies have shown that they react to physical stimuli such as compression, stretch and shear forces. Fibroblasts, being the main players in tissue healing, have been extensively studied in biomechanical systems. It has been described that mechanical tension can regulate the expression of matrix and inflammation involved in scar formation. Studies have shown

that fibroblasts can respond to mechanical alterations with subsequent reorientation and stimulation of the production of collagen and proteases regulating the collagen remodeling. The thicker collagen bundles in scar tissue may suggest a relationship between mechanical tension and scar formation. The research on mechanotransduction is however young and currently its therapeutic consequences are lacking.[27,28] Mathematic modelling or biomechanical investigation of healing of the fascial tissue in particular and subsequently hernia development are currently not available.

2) Predisposing factors

A number of patient-related factors correlate with the risk of developing an incisional hernia. Male gender, older age, obesity, abdominal distention and pulmonary complications have been defined as significant risk factors.[18] One recent prospective trial identified COPD (HR 2.35[1.44-3.83]) and BMI >25kg/m² (HR 1.74 [1.04-2.91]) as independent risk factors for developing an incisional hernia.[29] Another trial, investigating the incidence of incisional hernia after colorectal oncological surgery, named the amount of subcutaneous fat (HR 1.043 [1.004-1.083]) and age (HR 1.012 [1.003-1.021] as a risk factor.[30] However, the main risk factors are perioperative and occur during or just after the index operation. Laparotomy closure techniques are part of a standard surgical procedure and one of the first things scheduled in a surgical training. However, the applied materials and techniques are mainly dictated by tradition and "general house rules". The main factors concerned in the production of incisional hernia repair are extensive infection of the wound, incomplete suturing of the peritoneum and fascia, or suturing of the fascia under undue tension.[31]

Type of incision

Access to the abdomen can be obtained by a vertical or transverse/oblique incision. A midline incision is frequently used for emergency surgery and exploration of the abdomen.

Often used transverse incisions include a Mc Burney incision for an appendectomy, the Kocher incision for biliary surgery and the Pfannenstiel incision for gynecologic procedures. As mentioned above, the fascial fibers of the abdominal wall lie in a transverse orientation. When performing a midline incision, the fibers are divided and the sutures are placed between the fibers. A transverse incision goes along the fibers and closure of the incision places the sutures around the fibers. Some authors have reported a significant higher rate of incisional hernias after the use of a midline incision compared to after a transverse laparotomy. By performing a vertical midline incision, the contraction of the abdominal wall muscles is laterally on the wound's edges. Moreover, impaired wound healing is noted due to the avascular structure of the midline. These results must be nuanced by the fact that a midline incision is frequently used in cases of trauma, hemorrhage and other urgent cases.[6,7,17]

Suture technique

The fascial edges, which are approximated, must be in good condition. Recently published guidelines of EHS include following considerations. Small steps should be taken to ensure that only the aponeurotic edges are held in the suture, and not the soft tissue. It is preferred to close the wound in a single layer aponeurotic closure, rather than in different layers. The peritoneum is not needed to be included in the suture line. The distance between each suture must not exceed 1 cm and should be 1 cm beyond the margin of the wound. A continuous suture technique produces a stronger closure than an interrupted technique. The suture length to wound length ratio, with a continuous suture technique, must be at least 4/1.[32-36] The ideal suture material should maintain its strength through the healing process until the tissue has regained its original strength. Rapidly absorbable suture (e.g. Catgut, Dexon® or Vicryl®) materials lose most of their tensile strength in the first three weeks and are totally absorbed in 90 days. Slowly absorbable sutures (e.g. PDS® or Maxon®) are absorbed in 180 days. Non-absorbable sutures are nylon, polypropylene (Prolene®), polyethylene (Ethibond®) or polyamide (Ethilon®). To reduce the incidence of incisonal hernia, slowly absorbable sutures are the optimal method of fascial closure. No difference is seen with permanent sutures, but the latter need removal when infected.[37] Diener et al. reported in a meta-analysis significant lower hernia rates using a continuous, versus interrupted technique (OR 0.58, p=0.001) with slowly absorbable, versus rapid absorbable, suture material (OR 0.65, p=0.009).[38] The EHS guidelines reported a strong recommendation to use a slowly absorbable monofilament suture to decrease the incidence of incisional hernias.[36]

Wound infection

By far the most significant risk factor for developing an incisional hernia is a postoperative wound infection. In a large prospective study, following 1129 laparotomies, half of the patients who subsequently developed an incisional hernia had a postoperative wound infection (p<0.001).[39] This finding has since been confirmed.

Infection is related to contamination of the wound during the procedure. In addition, hematomas, seromas or the presence of foreign bodies promote wound infection. Therefore, actions that decrease the risk of contamination, such as drain management, changing gloves before wound closure and prophylactic antibiotics, are of great importance in preventing incisional hernia development.

2. Ventral hernia repair

2.1. Introduction

Since the Ancient Greek, many surgeons have been interested in the pathology of hernia, yet treatment options remained limited. Being a much more frequent event, the earliest reports on hernia surgery concerned mainly inguinal hernia repair. During the 16th century, with gained knowledge of the human body, operations were increasingly performed with an anatomical basis. In 1890, Eduardo Bassini (Padua, 1844-1924) was the first to publish his technique of the reconstruction of the inguinal canal into the physiological condition. Over the next decades, modifications on the so-called Bassini repair were reported on how to reinforce the posterior wall of the inguinal canal. In a Mc Vay repair, the internal oblique and transversus abdominis muscles are fastened together with the transversalis fascia to Cooper's ligament. The importance of the transversalis fascia was especially pointed out by the most influential pioneer of the primary suture repair technique; Edward Earle Shouldice (Ontario, 1890-1965). He founded a private clinic near to Toronto, Canada, where 180 000 patients were operated between 1945 and 1988. Their results were excellent but could never be reproduced outside the hospital. High recurrence rates urged surgeons to further modify their technique. Most believed failure of the repair was due to too much tension at the repair site.[40,41]

In 1878 Theodor Billroth (Bergen, 1829-1894) stated that "*If we could artificially produce tissues of the density and toughness of fascia and tendon, the secret of the radical cure of hernia would be discovered*". This opinion was published in the Beitrage zur Chirurgie (1878) and was a great support for the believers of the prosthetic repair. In 1894, Phelps (New York) modified the Bassini repair, using silver coils to induce wound fibrosis. Later the coils were transformed into silver gauzes, leading to the production of the first meshes.[42]

Although advances in inguinal hernia repair resulted in significant improvement of the surgical outcomes, the repair of a ventral hernia was more challenging. For many years, ventral hernias had been repaired with direct suture techniques. Different techniques for primary closure exists. The easiest is the approximation of the two edges of the fascial defect and closing the wound with continuous or interrupted sutures.[17,43] When the fascial edges are overlapped before suturing, this is defined as the modified Mayo technique. However, with these techniques, tension is placed on the incision line. To resolve this problem, Sitzmann and Mc Fadden proposed the use of internal retention sutures, while other surgeons used relaxing incisions to reduce tension, which was popularised as the Keel method.[17,43] For larger lower-abdomen midline defects, the Nutall procedure has been described, where the rectus abdominis and its fascia are detached from the pubis and transposed to the

opposite of the pubis.[44] The component separation technique, as promoted by Ramirez and colleagues, involves separation of the rectus muscle and its posterior sheath, followed by separation of the external oblique muscles from the underlying internal oblique muscles and reconstruction of the abdominal wall.[45]

Even with these adaptations, recurrence rates remained high for primary suture techniques. George and Ellis argued: "*Every technique applied to approximate the edges of the fascial defect will put the tissue under tension with an increased risk of ischemia and wound rupture*".[46]

With the concurrent evolution of inguinal hernia repair, the use of prosthetic material gradually gained its acceptance in ventral hernia repair. However, fear of mesh infection and fistula formation slowed wide acceptance. Along with the synthesis of plastics, the revolution of the 20th century, Usher developed in 1958 the first polypropylene mesh: Marlex®. Unlike the previous fabricated prostheses, polypropylene incorporates well with the tissue.[42,46,47]

2.2. Mesh repair

It took until the year 2000, when Luijendijk and colleagues performed a prospective randomized controlled trial to compare mesh repair and traditional suture repair.[48] Two hundred patients were enrolled in this study and were randomly assigned to undergo a suture repair or a hernia repair. The three-year cumulative rate of recurrences was 46% with suture repair and 23% with mesh repair (RR 0.4 [0.2, 0.8]) (p=0.009). A long-term follow-up study by Burger et al. confirmed these results. A 10-year cumulative rate of recurrence of 63% was reported in the suture repair group, compared to 32% in the mesh repair group.[49] Consequently, the authors stated that the suture repair should be abandoned. From then on, even in patients with small defects, mesh reinforcement became the gold standard.

Since the introduction of the polypropylene mesh, many types of prostheses have been developed, each with their specific characteristics. The main goal of a prosthesis is to retain high intrinsic tensile strength and to allow good tissue ingrowth.[50]

Mesh materials can be categorized by their characteristics: they can be either absorbable or non-absorbable, woven or knitted and have different pore sizes.[40,43,47,51]

With increased pore size, the prosthesis becomes lighter and more flexible, reducing the risk of abdominal wall stiffness. Large pores allow for macrophage and neutrophil infiltration, which provides greater resistance to infection. Pore size affects fibrovascular ingrowth and allows drainage of serum. According to the pore size, meshes are divided into four categories. Type 1 prostheses are

macroporous meshes with pore sizes larger than 75µm, e.g. polypropylene. Type 2 are uniformly microporous meshes with pore sizes less than 10µm in at least one dimension: this type includes ePTFE (expanded Polytetrafluoroethylene). Type 3 meshes are macroporous materials with multifilament or microporous components, such as Teflon® mesh, braided polyester mesh, braided polypropylene mesh or perforated ePTFE patch. Type 4 are biomaterials with a submicronic pore size.[47,51]

Meshes can be either knitted or woven. Knitted materials consists of threads with multiple loops linked to each other. They stretch in most directions, depending on the type of knit. Woven materials have threads that course over and then under consecutive perpendicular threads. These prostheses stretch diagonally between the threads.[51]

Polypropylene is the most widely used prosthesis, with Marlex® being the knitted polypropylene and Prolene® the woven polypropylene. The pore size of Marlex® is half of that of Prolene (i.e. 600 vs. 1500 µm). Polypropylene integrates well in the abdominal wall but cannot be used intra-abdominally because of the risk of bowel adhesions.[40] Polyester meshes, with Dacron® being the woven monofilament mesh and Mersilene® the woven multifilament, have been popularized by Stoppa.[42] Polyester is more prone to chronic infections and the formation of fistulas.[52] ePTFE, known as Gore-Tex®, results in less adhesion formation, due to the rapid coverage of a neoperitoneum, and is therefore mainly used in the intraperitoneal position. The absorbable meshes (Vicryl® and Dexon®) are usually used in cases with a significant risk for mesh infection. At last, composite meshes had been developed for intraperitoneal use.[40]

There are different anatomical approaches for mesh placement described. The most common are onlay, inlay or sublay mesh placement. (Fig. 2.1.) The onlay technique approximates the linea alba and, after closure of the fascia, the mesh is placed over the defect. This approach avoids contact with the bowel, but does require wide tissue undermining, which may predispose to wound-related complications. Performing an inlay repair, the hernia sac is excised and the mesh is sewn to the fascial edges to bridge the defect. This repair avoids tissue undermining dissection, however, tension is still significant at the attachment points of the fascia and the mesh. In the aforementioned study by Luijendijk et al., the sublay technique has been used, as popularized by Rives and Stoppa. The prosthesis is placed above the posterior rectus sheath and beneath the rectus muscle, while below the umbilicus, the mesh is placed in the preperitoneal space. The hernia sac is used as a buffer between the mesh and the viscera. The sublay technique can place the mesh one layer lower, in the intraperitoneal space, which involves opening the hernia sac, dissecting the bowel away from the abdominal wall, and placing a double-layer prosthesis intraperitoneally. The non-adhesive layer of the

mesh faces the abdominal viscera while the other side is placed to the peritoneal abdominal wall, which allows optimal tissue ingrowth.[43,47,48,53]

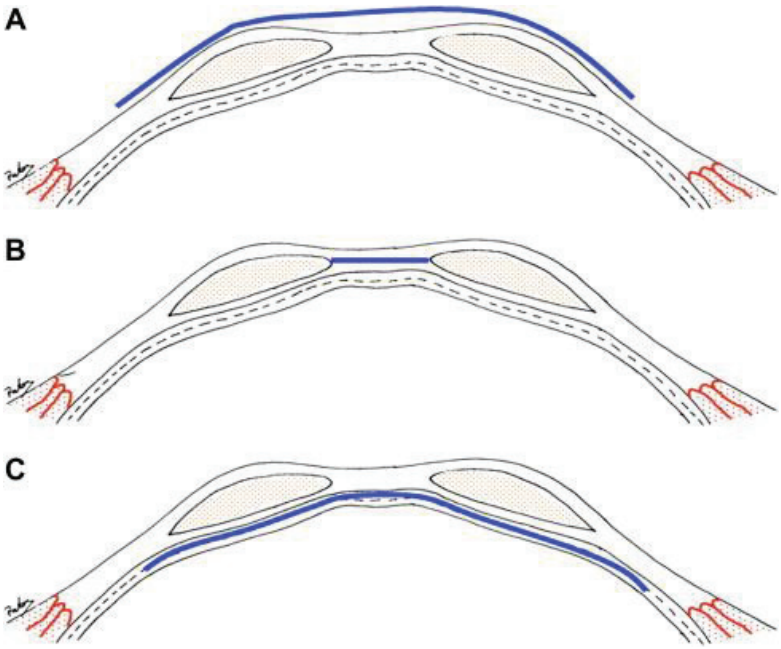


Fig. 2.1. Mesh placement techniques. A. Onlay technique. B. Inlay technique. C. Retrorectus underlay technique.[47]

In a review, Rudmik et al. compared the results of the techniques described above. Primary suture repair was associated with a failure rate of 39%. The sublay technique resulted in the lowest recurrence rate: respectively 4.5% and 8% depending on the intra- or extraperitoneal placement of the mesh. The onlay repair had a recurrence rate of 14% and, although few studies are available, the inlay procedure was reported to have a recurrence rate of 48%.[54]

The use of meshes in ventral hernia repair have significantly improved the outcomes. However, its application brings along complications. Placement of the mesh requires wide dissection of tissue which is already of poor quality, with an increased risk of postoperative complications, especially at the surgical site.

Wound infections occur more frequently in ventral hernia repair compared to other surgical interventions. A postoperative wound infection rate of about 5% is noted after ventral hernia repair, with chronic steroid use, smoking and prolonged operative time being independent predictive factors.[55, 56] On the other hand, postoperative surgical-site infection increases the risk of hernia recurrence. In the study of Luijendijk et al., both mesh repair and suture repair were associated with a

recurrence rate of 34% with a clean incision compared to an 80% recurrence rate among patients with a postoperative infection (p=0.007).[48]

Infection of the prosthetic material is the most feared complication and occurs in 5-8% of all cases. Infection of the mesh results in great morbidity, with almost always at least one reoperation for mesh removal. Thereafter, the patient is left with a recurrent and larger defect than before and less treatment options. Mesh infection is related to the type of mesh but not to the technique of mesh placement. Previous existing wound infection is a significant risk factor.[43,47,52,55,57]

Wide tissue dissection for mesh placement leaves a large dead space, which can be filled with fluid. Seroma formation is frequent after hernia repair and, although it is mostly self-limiting, seromas can be very resistant to treatment once they become infected. Rates of seroma formation of 7-45% are reported depending on the type of technique used to place the mesh.[58-60]

Overall, recurrence rates of less than 10% have been reported with mesh repair, which is a spectacular improvement compared to suture techniques.[16] Different prospective randomized controlled trials have motivated the use of a mesh in all cases. However, complications are still frequent. In an attempt to minimize these postoperative morbidities, minimal invasive techniques have been developed regarding ventral hernia repair.

3. Laparoscopic ventral hernia repair

3.1. Introduction

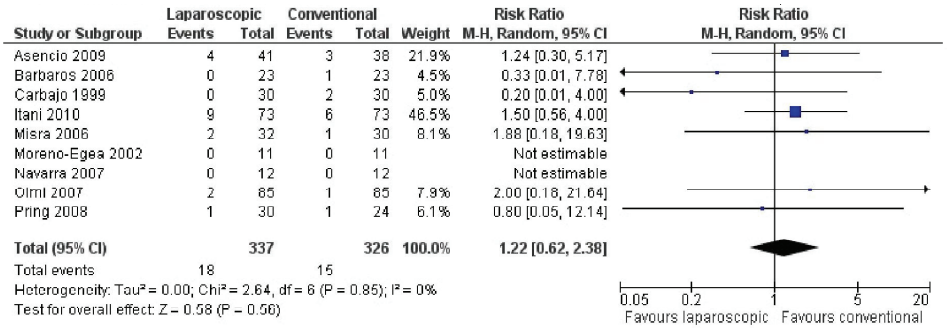
The introduction of minimally invasive procedures has been called 'the third surgical revolution'. Although this movement was merely initiated by non-surgical disciplines, with the main examples being fiber endoscopy, interventional radiology and non-invasive treatment of gallstones, nowadays almost every procedure (except organ transplantation) previously conducted by laparotomy, are now performed using laparoscopy.[61] A large retrospective analysis of six commonly performed surgical procedures (cholecystectomy, appendectomy, reflux surgery, gastric bypass surgery, colectomy and ventral hernia repair) have reported comparable surgical outcomes and a clinical benefit in favor of laparoscopic versus open surgery.[62] The progress made in other laparoscopic surgical procedures included enhanced patient recovery, shorter convalescence time and reduction of wound-related complications: which are the main issues complicating open ventral hernia repair.[61]

In 1993, LeBlanc and Booth presented the first five cases conducted using a laparoscopic technique.[63] Hernia sizes ranged from 1.5 to 6 cm^2: one was a recurrent hernia, the others were primary. First, a pneumoperitoneum was developed and three or four trocars were placed. After entering the abdomen, adhesiolysis was performed to identify the margins of the fascial defect. Before an ePTFE mesh was introduced, the mesh was placed on the exterior of the abdomen and the boundaries were marked with a cautery mark on the internal abdominal wall, making sure the mesh overlapped the defect by at least 1.5 to 2 cm on each side. The mesh was rolled and introduced into the abdomen. At one corner, the mesh was positioned to the abdominal wall with a suture. Thereafter, the edge of the mesh was stapled with 20 to 25 staples. At the end, the suture was removed.
Four years later, a series of the first 100 patients treated with this technique was published.[64] Some adaptations had been made to the technique through time, mainly regarding mesh fixation (see below). During a mean follow-up period of 51 months an overall recurrence rate of 9.3% was described, all in patients with defects larger than 25 cm^2. The major complication rate was 4.1%, including one patient (1%) with a mesh infection that required mesh removal. In 2003, the results of the first 200 patients were presented with a recurrence rate that had dropped to 4% and a total complication rate of 18%.[65] From then on, many large series have been published. The largest and most cited series was published by Heniford et al., ten years after the publication by LeBlanc and Booth.[66] The operative technique was equally performed as described by LeBlanc and Booth, and 850 patients were followed-up prospectively with a recurrence rate of 4.7% after a mean follow-up of 20 months. The

overall infection rate was 1.8%, mesh infection rate was 0.7%. A second large series was reported by Franklin et al., in which a total of 384 patients received laparoscopic surgery. There were 11 recurrences (2.9%) diagnosed during a mean follow-up time of 47.1 months.[67]

From then on, numerous studies have been published comparing the open and laparoscopic approaches to treat ventral hernias, however, only a few were prospective, randomized and well-designed studies. Carbajo et al. randomly assigned 60 patients into an open and a laparoscopic group: after 27 months, no difference in recurrence rate was shown, however, a shorter surgical time and a shorter postoperative stay were noted in the laparoscopic group.[68] The biggest randomized controlled trial was published by Olmi et al., which included 170 patients.[69] After a median follow-up of 24 months, the authors concluded that laparoscopic repair leads to shorter operative time (61.0 [54.1, 68.9] minutes vs 150.9 [132.1, 169.7]) and hospitalization (2.7 [2.2, 3.2] days vs 9.9 [5.2, 14.6]), less complications (16.4% vs 29.4%) and a faster return to work (13 [6, 15] days vs 25 [16, 55]) (p<0.05). No difference in recurrence rate could be noted. Many reviews followed and resulted in similar conclusions. Laparoscopic repair does not result in less recurrences but it is effective in reducing in-hospital stay, convalescence period and complication rate.[2,70-74] A review of the Cochrane database confirmed this statement. A recurrence rate of 18/337 for laparoscopic versus 15/327 for open mesh repair was reported (RR 1.22 [0.62, 2.38]) (p=0.56), whereas local infection was significantly more associated with the open technique (RR 0.26 [0.15, 0.46]) (p<0.001). Also, severe infections that required mesh removal, tended to occur more frequently after open repair (RR 0.32 [0.08, 1.22]) (p=0.09).[75] (Fig. 3.1.) We emphasize the small number of patient included in the studies, the large confidence intervals as well as the short follow-up terms.

One large prospective cohort study has recently been published.[76] The authors prospectively examined the surgical outcomes and, mainly, the quality of life after a ventral hernia repair. A total of 710 patients with a ventral hernia were included: 402 were treated with an open repair and 308 laparoscopically. After a mean follow-up of 17.2 months, no difference in recurrence rate was observed. The open repair (5.4 ± 4.4 days) had a longer hospital stay compared to laparoscopy (3.5 ± 2.5 days) (p<0.001), and also more hematomas (2.7% vs 0.7%) (p=0.029) and wound infections (3.0% vs 0.3%) (p=0.004). Both deep and superficial surgical-site infections were more frequent after open repair. In contrast, laparoscopic ventral hernia repair (LVHR) was associated with a reduced quality of life in the short-term follow-up. Laparoscopic repair was associated with more postoperative pain (OR 1.9 [1.2, 3.1]) and activity limitations (OR 1.6 [1.0, 2.7] in the first postoperative month. Overall quality of life in the laparoscopic group was lower at 1 month (OR 1.6 [1.0, 2.6]), but similar in all subsequent follow-up times.



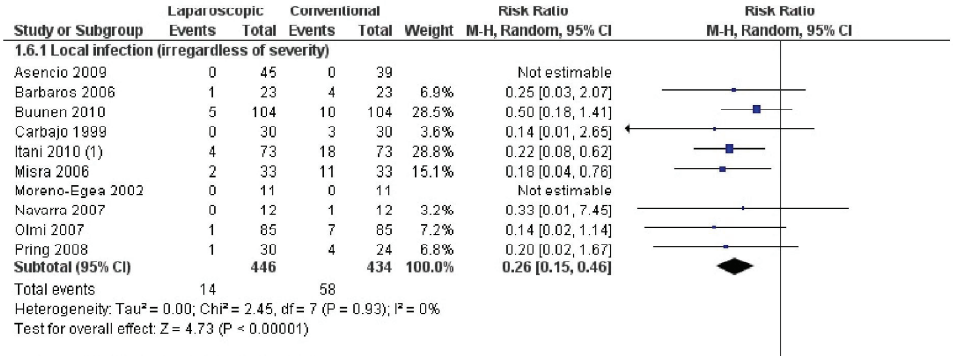


Fig. 3.1. Meta-analysis by Sauerland et al.[75] (Above) Recurrence rates are not different between laparoscopic and ventral hernia repair. (Below) Laparoscopic ventral hernia repair is associated with significantly less surgical-site infection.

3.2. Operative technique

Like every surgical intervention, numerous variations of the technique are described for laparoscopic ventral hernia repair. A few common steps are listed below.

1. Entry to the peritoneum and port placement
2. Adhesiolysis
3. Defining the defect size
4. Choice of mesh material
5. Fixation of the mesh

All patients receive general anesthesia and prophylactic antibiotics are administered intravenously. The patient is positioned in a prone position with the arms tucked close to the body.[66, 67,77-79]

1. Initial entry and port placement

The location of the hernia determines the initial port placement. The ports should be placed in a proper triangulation to allow working and an optimal visualization of the hernia defect. The operation can, in most cases, be completed with three ports. Pneumoperitoneum can be achieved by a Veress needle, by an optical trocar or by open placement. In our institute, the first trocar, a 10 mm blunt-tip port, is placed with an open technique at the crossing of the transverse umbilical line and the mid-axillairy line. This is followed by a 10 mm and 5 mm trocar placement under direct vision, respectively, at subcostal level and just cranial of the anterior superior iliac spine.[77,80,81]

2. Lysis of adhesions

Once introduced safely into the abdomen, lysis of the adhesions needs to be performed. Filamentous adhesions can be removed by blunt dissection or gentle traction using atraumatic graspers. More dense and vascularized adhesions, especially to prior incisions, may need sharp dissection. The use of any energy source should be limited as it may lead to injury to the bowel. The hernia contents are reduced without removal of the hernia sac. Once the abdominal wall is clear, careful inspection of the bowel is mandatory to ensure no injury has taken place during lysis of the adhesions.[77,80,81]

3. Defining the defect size

Once the abdominal wall is free of adhesions, the defect is inspected. A benefit of the laparoscopic approach is that it allows careful inspection of the abdominal wall and silent defects, that could be missed by an open repair, can be treated in the same procedure. Accurate measurement of the defect size is of great importance. The defect should be preferably measured internally by insertion of a

sterile ruler or a suture. External measurements are done with a lower intra-abdominal pressure, as the risk of overestimation of the defect exists with a pneumoperitoneum. In cases where there are different defects, one piece of mesh should be used to cover all defects. The diameter is calculated as the distance between the two extreme points of the different defects.

In LeBlanc's technique, the so called laparoscopic intraperitoneal onlay mesh (IPOM) repair, the hernia content is reduced and the defect is overlapped with a mesh. In such a "bridging repair", the area over the defect is formed by the mesh only and does not contribute to the restoration of the functionality of the abdominal wall. In an open repair, the fascial edges are brought together before mesh placement. Some authors suggest that, in laparoscopic repair, this defect should be sutured before mesh placement: the "augmentation repair" or IPOM plus. So far, no prospective trials are available to prove the benefit of closure of the defect. This topic will be discussed in depth in the discussion section.[63,67,79,82-84]

In the literature, a consensus exists regarding mesh overlap; it should be at least 3-5 cm in all directions, with a greater overlap preferred for larger defects and obese patients. Note that this recommended overlap is larger than in the earliest reports.[77,79,85]

4. Choice of mesh material

The ideal mesh for LVHR needs to be double-faced. The peritoneal side should allow good tissue integration into the abdominal wall while, at the other side, minimal adhesion formation to the viscera is permitted. As discussed above, three basic prosthetic materials are available: polypropylene (PP), polyester (PE) and expanded polytetrafluoroethylene (ePTFE). The pure PP and PE meshes should not be used intra-abdominally as they induce a high inflammatory reaction with the risk of adhesions and fistula formation. These meshes should be covered with an anti-adhesive barrier, the so-called "composite" meshes, which have been especially designed for intraperitoneal use. In composite meshes, the macroporous layer is placed to the parietal peritoneum and the microporous side faces the viscera. The macroporous layer allows good incorporation into the abdominal wall, mostly composed of polypropylene, as this material is superior to all other mesh products regarding strength of ingrowth. The other, microporous side, should prevent adhesion formation. For this side, many products are on the market; ePTFE can be used, with a collagen coating or an oxidized regenerated cellulose layer, but none of the present available meshes can eliminate adhesion formation completely. Table 3.1, as adapted by Eriksen et al., gives an overview of the most frequently used mesh products.[86]

The mesh is rolled up and inserted into the abdomen through a 10 mm trocar site. The mesh is unrolled and orientated to the fascial defect. Once the mesh is placed to the abdominal wall, it can be

fixed with one or more mesh fixation types. The correct placement of the mesh over the fascial defect is of great importance. A sufficient overlap must be guaranteed on all sides of the defect. Basically, four or more sutures, placed at the edges of the mesh, are brought out of the abdomen with an Endoclose® needle. Special devices are now available to position the mesh accurately over the defect. For example, the AccuMesh Positioning system® (Covidien Corp., Mansfield, MA, USA) is an expandable frame that facilitates correct positioning. In addition, the Echo PS system® (Bard, Davol Inc., Murray Hill, NJ, USA) is a balloon that is pre-attached to the mesh and unrolls the mesh once insufflated.

At the end of the procedure, the trocars are removed under direct vision. A compressive belt is placed before the patient awakes.[77,80,81]

Group	**Name of mesh**	**Material**
PTFE	Mycromesh®	ePTFE
	Dualmesh®	ePTFE
	MotifMESH®	ePTFE
Composite	Glucamesh®	Polypropylene with beta glucan coat
	Proceed®	Polypropylene with ORC layer
	Sepramesh®	Polypropylene with resorbable layer
	Parietene-Composite®	Polypropylene with collagen-coating
	Intramesh T1®	Polypropylene/ePTFE
	Dulex®	Polypropylene/ePTFE
	Composix®	Polypropylene/ePTFE
	Parietex Composite®	Polyester with collagen-coating
	Intramesh W3®	Polyester with silicone layer
	Dynamesh®	Polypropylene/polyvinyliden fluoride
	TiMesh®	Polypropylene with titanium coat
	C-QUR®	Polypropylene with omega 3 fatty acid coat

Table 3.1. The present available mesh products for LVHR.[86]

Although complications are seen less frequently with laparoscopic hernia repair compared to open surgery, they remain an important consideration. One of the most common complications is seroma formation, which occurs in 10-15% of patients. Most cases are self-limiting and resolve spontaneously, but in about 3% a residual seroma exists. However, it is recommended to treat these conservatively unless they become uncomfortable.[66,67]

A more feared complication is injury to the intestine, which can occur by introducing a trocar or by performing adhesiolysis. Enterotomy is known to occur more frequently after previous abdominal surgery and happens in 2-3% of patients.[66,87,88] If missed, an enterotomy can result in intra-abdominal sepsis and is associated with serious morbidity and even mortality. The use of any energy source should be limited, and thorough inspection of the bowel and prompt recognition of a bowel lesion is important. The largest series of LVHR procedures with their reported results are shown in Table 3.2.

Abdominal wall pain and postoperative discomfort are frequently reported after LVHR. In the immediate postoperative period, during the first month, laparoscopic repair is associated with significantly increased postoperative pain compared to the open repair.[76] Although, in the longer term, no difference in pain is reported between the procedures, a significant number of patients still suffers chronic pain after LVHR.[76,79,89].

Author	Heniford[66]	Carbajo[88]	Franklin[67]	Moreno-Egea[90]
N	850	270	384	200
Year	2003	2003	2004	2010
Operation Time (mins)	120	85	68	51
Seroma		32 (11.8%)	15-20%	6 (3%)
Enterotomy	14 (1.6%)	9 (3.3%)	12 (3.2%)	5 (2.5%)
Prolonged seroma	21 (2.6%)		12 (3.2%)	0
Recurrence	35 (4.7%)	12 (4.4%)	11 (2.9%)	11 (6.25%)
Follow-up (months)	20	44	47.1	60
Prolonged pain	13 (1.6%)	20 (7.4%)	12 (3.2%)	0
Hospital stay (days)	2.3	1.45	2.9	2.6

Table 3.2. Largest series of LVHR with their reported results.

4. Mesh fixation systems

4.1. Introduction

In the first reports of laparoscopic ventral hernia repair, the mesh was fixed with a traditional stapler.[63] After the mesh was introduced into the abdomen, one suture – previously fixed to the mesh – was picked up with an Endoclose® needle. This suture was necessary to hold the mesh in place while the edge of the mesh was stapled. High recurrence rates urged LeBlanc to adapt his technique. In the publication of the first 100 patients, a recurrence rate of 9.3% was noted.[64] According to the author, this had two main reasons. A first issue was inappropriate coverage of the fascial defect. In the later cases this was adapted to have a minimum mesh overlap of 3 cm. Secondly, the method of fixation was changed with the experience gained. In the first 75 patients, only staples or tacks were used, whereas transabdominal sutures were added later. Two ePTFE sutures were fixed to the mesh and grasped through the abdominal wall after introduction into the peritoneal cavity. These sutures are used to position the mesh over the fascial defect, then the edge of the mesh is fixed with spiral tacks, placed at 1.5 cm apart. Finally, additional ePTFE sutures are placed through the abdominal wall, each 5 cm apart.[91] All reported recurrences happened in the earlier cases where only tacks were used. With the addition of sutures, LeBlanc reported, in later publications, that the recurrence rate had dropped to 4%.[65]

Heniford et al. concurred with this finding in their large series (n=850): initially tacks alone were used to secure the mesh, but this practice was discontinued and the authors stated that suture fixation of the mesh was mandatory.[66] Franklin et al. reported 11 recurrences out of 384 patients (2.9%) operated for a LVHR, of which eight occured in patients where no transfascial sutures were used to secure the mesh. Taking only patients in consideration where transfascial fixation of the mesh was performed, the recurrence rate was further reduced below 1%.[67]

However, simultaneously, Carbajo et al. published their preliminary results on 100 patients. The authors used only helical titanium tacks to fix the mesh. They placed the tacks circumferentially at the edge of the mesh, and a second row of tacks was placed inside the first row, at the border of the fascial defect. After a mean follow-up of 30 months, they reported a recurrence rate of 2%. The use of external sutures was omitted as they believed it resulted in a higher incidence of nerve entrapment and postoperative pain.[92] This opinion was shared by Frantzides et al., who reported a recurrence rate of 3/208 (1.4%) with the use of staples as single mesh fixation.[93]

Fixation of the mesh is one of the most crucial technical issues in LVHR. Integration of the mesh in the abdominal wall tissue depends on the type of mesh, but is mostly completed in the first two weeks.[94] Until then, proper fixation is needed to hold the mesh in place.

Many studies have been performed to examine the forces working on the abdominal wall. When restoring the abdominal wall surgically, the aim of any repair must be to bring it back into its physiological condition. In a laparoscopic model, the mesh is positioned over the fascial defect and fixed to the abdominal wall. As shown in Fig. 4.1., both shear forces and muscle forces act on the mesh and its fixation. As the mesh is positioned over an open defect, the mesh is pushed inwards when the intra-abdominal pressure rises. Shear forces are developed on the mesh-tissue interface with an oblique direction towards the present defect in the abdominal wall. The force developed by the oblique muscles is perpendicular to the abdominal wall. The retention force of a fixation device must be able to withstand these forces to prevent displacement of the mesh.[95] As the intra-abdominal pressure increases, the tension on the abdominal wall is also increased. Assuming the abdomen as a cylinder and using Pascal's principle of hydrostatics, Cobb et al. calculated that the maximum tensile strength would be 11-27 N/cm.[96] The biomechanics of the abdominal wall and mesh fixation will be discussed in depth in the discussion part.

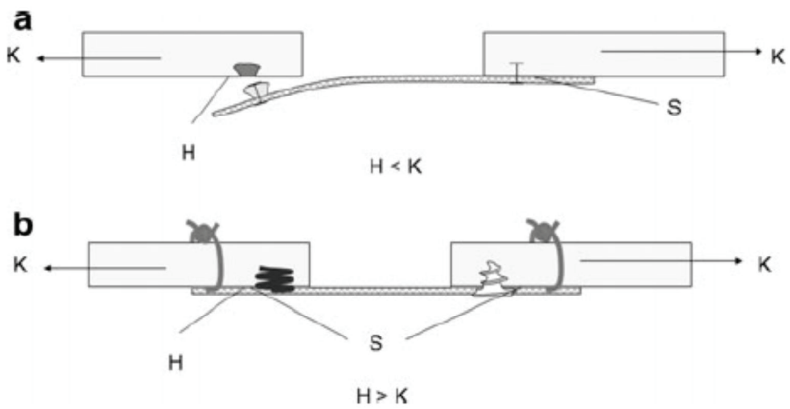


Fig. 4.1. a) Mesh rupture due to preponderance of muscle forces as opposed to retention forces. H<K . b) Rupture avoided by adequate fixation of the mesh. H<K. H: retention force, K: muscle force, S: shear surface.[95]

As mentioned above, numerous studies have compared the laparoscopic to the open technique. The rates of recurrence and complication have been defined as a surgical outcome parameter. Sufficient mesh overlap and adequate mesh fixation are primordial to prevent hernia recurrence after a LVHR. Over the last years, the results have significantly improved regards to both open and laparoscopic techniques, without a specific benefit for the latter. At the moment, quality of life is more and more important when deciding which technique to apply. Although, length of stay in the hospital and the convalescence period have significantly dropped with LVHR, an important number of patients suffers pain and abdominal wall discomfort in the postoperative period. Both in the short- and long-term follow-up periods, high pain levels have been reported. In the first month postoperatively, quality of life is significantly reduced with LVHR compared to the open technique. No doubt, this discomfort has a multifactorial etiology, however, the use of traumatic fixation devices has been suggested as an important source of this pain. As is described below, the most frequently used fixation devices are tacks, sutures or a combination of both. These devices are placed perpendicularly through the mesh in the abdominal wall. As they penetrate the tissue, they may harm nerves and vessels, which results in pain. Moreover, as the mesh is placed over an open defect, the mesh is pushed inwards it, and traction is performed on the fixation devices. This again results in pain. Most patients report pain in particular at the sites of fixation, and increased pain is reported with movement. This sensation is caused by traction on the devices when the abdominal wall extends and the mesh stays in place.[76,89,97]

The main function of a mesh fixation device is to keep the mesh in place, without causing tissue damage. This reflects the eternal balance between the strength of a mesh fixation device and its possible harm to the abdominal wall tissue, and the resulting postoperative pain.

4.2. Current available techniques

1. Transabdominal sutures

Before introducing the mesh, sutures are tied at the borders of the mesh, leaving the tails long enough to grasp through the abdominal wall once the mesh is placed. Mostly, the sutures are placed at the four corners of the mesh but more sutures can be used for larger meshes. The mesh is rolled up like a cigar with the suture ends down, and introduced into the peritoneal cavity. After being spread out, the mesh is positioned against the fascial defect. The sutures are pulled through the abdominal wall with a suture passer. The suture tail-ends come out through a small incision while making sure there is at least a 1 cm fascial bridge between each suture tail-end. After correct mesh placement is facilitated, the sutures are tied subcutaneously, performing as little traction as possible. Thus, the sutures have fixed the mesh to the entire thickness of the abdominal wall. Some authors place additional sutures at

the periphery of the mesh to provide additional strength. Afterwards, the edge of the mesh can be tacked with spiral tacks, although some authors rely on sutures only.[82,84,98-103]

The use of transabdominal sutures is the most widespread applied technique, but is adapted by each surgeon to his own experience. Most surgeons use non-absorbable, polypropylene sutures. However because it is believed that sutures are the cause of the pulling sensation at the suture site, some surgeons have started to implement absorbable sutures.[89] (Fig. 4.2.)

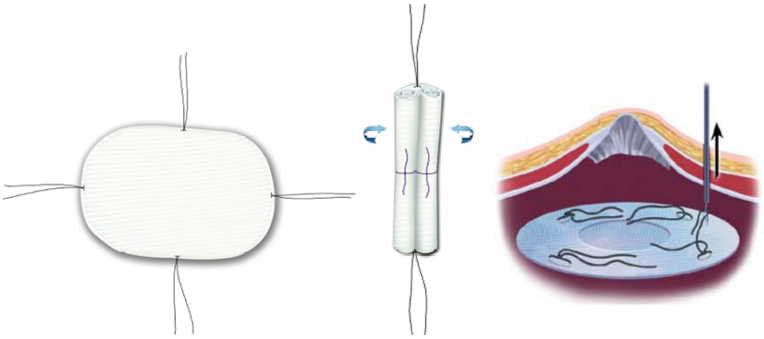


Fig. 4.2. The sutures are placed at the corners of the mesh. The mesh is rolled up and brought into the abdomen.[104] The mesh is positioned over the defect and, thereafter, the sutures are picked up with an Endoclose needle.

2. Spiral tacks

Initial reports of laparoscopic ventral hernia repair have suggested a direct relationship between hernia recurrence and the absence of transabdominal sutures: further experience could nuance these findings. In the beginning, old-style staples were used. These couldn't provide sufficient fixation, especially with the application of the thick ePTFE mesh, it was impossible for the staples to attach to the deeper layers of the abdominal wall. (Fig. 4.3.)

With the introduction of the helical tack, the traditional stapler has been abandoned by most surgeons. The old staple is clip-like, has a 7-mm longitudinal size and a penetration depth of 2 mm. It requires a 12 mm trocar to pass it into the abdomen. The helical tacks are 3 mm long and are shot into the abdomen by a fastener, which passes through a 5 mm trocar. Both staples and tacks are made of titanium; however, the tacks produce a fourfold stronger fixation compared to the staples.[105]

The method used for tack application is variable. One technique is the use of tacks in addition to sutures. When doing so, the sutures are placed at some points, while the periphery of the mesh is tacked. As introduced by Morales-Conde et al., tacks can be placed in the 'double crown' position.[106] At the margin of the mesh, a first crown of tacks is placed, with a distance of 1 cm between the tacks. Strong counter-pressure must be performed to ensure the mesh is well positioned

and captures the muscle fascia. Once the outer crown is finished, a second crown of tacks is placed at the border of the fascial defect.

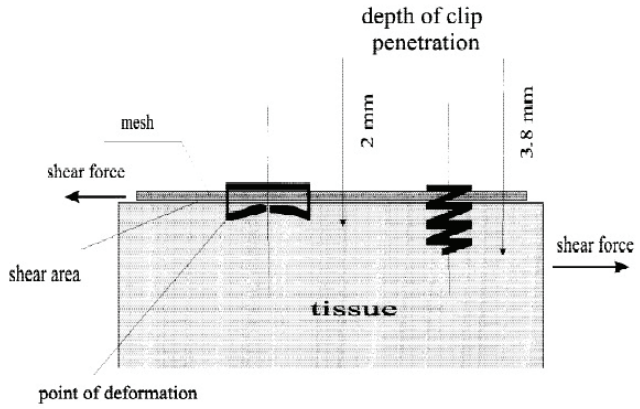


Fig. 4.3. Comparison of old staple and spiral tack fixation.[105]

3. Absorbable tacks

The presence of foreign metal bodies has given rise to significant problems in both short- and long-term evaluations, such as postoperative pain, erosion, adhesion formation and tack hernia.[97,107-109] Several absorbable tacks have been developed for temporary mesh fixation. These are intended to be resorbed in one year and should overcome the possible drawbacks.[95,110,111] (Fig. 4.4.) The current available absorbable tacks are discussed in part 3 of this work.

Fig. 4.4. Absorbable tacks. From left to right: Sorbafix®, Absorbatack®, Securestrap®.

4. Glue

Surgical adhesives can be biological (fibrin glue) or synthetic (cyanoacrylates). Although their effect on minimizing local numbness and postoperative pain have been shown in inguinal hernia repair, their application in ventral hernias is limited.

Fibrin glue, already used in different clinical applications, adheres the mesh to the peritoneal wall by creating a fibrin clot. The complete biodegradability favors the safety of biological glues. Different experimental set-ups have shown that the use of fibrin glue in mesh fixation is feasible for small ventral hernias, however, recent data do question its adhesive capacity.[112,113]

Cyanoacrylate monomers are polymerized in the presence of moisture and form a solid bond with human tissue after a few seconds. Contradictory reports have been published on its applications, questioning its possible cytotoxicity and inflammatory reaction. Although some authors report that the synthetic glue inhibits tissue integration of the mesh, secure mesh fixation has been achieved. The use of totally atraumatic mesh fixation leads to improved clinical outcomes and less postoperative pain. Whether there is evidence for routine use in ventral hernia will be discussed in part 3 & 4 of this work.[114-117] (Fig. 4.5.)

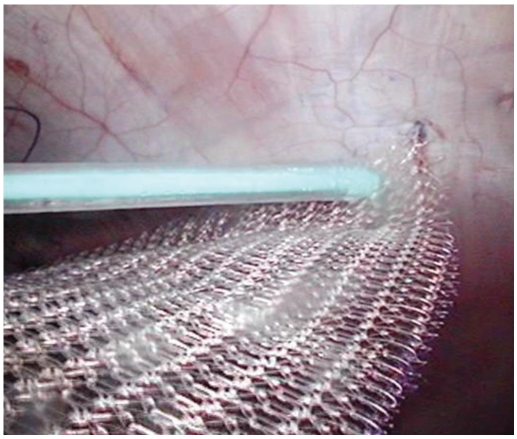


Fig. 4.5. The application of glue for mesh fixation.

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PART 2

AIM AND OUTLINE OF THIS WORK

PART 2. AIM AND OUTLINE OF THIS WORK.

Laparoscopic ventral hernia repair is a widely applied surgical procedure. However, its technical application differs between surgeons and is an ongoing matter of debate. One main point of discussion is the techniques used to fix the mesh. In LVHR, the mesh is brought into the abdomen and positioned over the fascial defect, which is mainly left open. The mesh is fixed to the abdominal wall with one of the specially designed devices. Before the mesh is incorporated into the peritoneum, particularly within the first two weeks postoperatively, good fixation is of extreme importance. If not, the mesh may move and migrate into the former defect, which results in recurrence of the hernia.

The most frequently used fixation devices are tacks and sutures. Sutures are placed through the mesh and the entire abdominal wall and then knotted outside. Tacks are shot through the mesh into the abdominal wall. Both devices provide a good mesh fixation strength. However, they are placed perpendicularly through the mesh into the abdominal wall, where they can entrap tissue. This can lead to tissue trauma and pain. Besides, because a foreign body has been introduced into the abdomen, an inflammatory reaction is provoked and adhesions can be formed with the fixation devices. Although the results of LVHR are good and low recurrence rates are reported, many patients complain of postoperative discomfort and pain at the fixation points.

In an attempt to develop mesh fixation systems that provide solid fixation while minimizing tissue trauma, new products have been launched on the market. Absorbable tacks have been introduced. Once the mesh is integrated into the abdominal wall, the need for fixation can be questioned. Keeping this in mind, absorbable constructs were developed to limit the long-term side effects of tacks. However, as these tacks are still piercing the tissue, researchers have continued to look for less traumatic fixation devices. With the use of glue, totally atraumatic fixation is achieved, which may solve the problem of fixation-related pain syndromes.

The main aim of this work was to evaluate the currently available mesh fixation devices for laparoscopic ventral hernia repair. After presenting a systematic review of the present available literature regarding intra-abdominal mesh fixation with transfascial sutures and tacks, the pros and cons of tack fixation are evaluated. In two experimental models, we evaluated the fixation strengths of these new devices, absorbable tacks and glue, as well as fixation–related inflammation and adhesion formation. Do these devices provoke an extensive foreign body reaction? Does this result in adhesion formation? We first compared the present available resorbable fixation devices with conventional non-absorbable tacks. In a second experiment the use of cyanoacrylate glue was investigated and compared with strap fixation. This leads to the following outline for this thesis:

In chapter 3.1., the most frequently used devices, tacks and sutures, are investigated. A systematic review was performed to investigate the pros and cons of both techniques. All series reporting a one defined-technique for LVHR were collected and grouped with regard to the fixation system used. The results, e.g. recurrence rates, were compared statistically. An extensive part of the discussion section has been dedicated to the fixation-related postoperative pain problem.

Chapter 3.2. discusses the presently available tacks. There are numerous devices available and all have different characteristics. They are made from different materials, are permanent or resorbable and have different lengths and shapes. The importance of their constructions and impact on the outcomes are discussed.

In chapter 3.3., an experimental study is presented that was performed to evaluate absorbable mesh fixation systems. In a porcine model, we compared three absorbable tacks with the titanium device. At both short- and long-term, fixation strengths, adhesion formation and foreign body reactions were investigated.

In the last part, chapter 3.4., a second experimental study is presented. The intraperitoneal use of cyanoacrylate glue for mesh fixation was investigated in a sheep model. The use of glue was compared to strap fixation regarding hernia recurrence, mesh fixation strength, adhesion formation and foreign body reactions. In the same experiment, we assessed whether closure of the fascial defect before mesh placement improved the strength of the repair.

In the discussion section the mesh fixation systems are discussed in depth. A literature search was performed to investigate what strength of fixation is needed and whether the presently available devices meet these criteria. An extensive part of this section has been dedicated to the pain problem and whether the investigated devices, absorbable tacks or cyanoacrylate glue can offer a solution. From this perspectives, the future of LVHR is discussed.

PART 3

RESULTS

PART 3. RESULTS

3.1. Laparoscopic ventral hernia repair: is there an optimal mesh fixation technique? A systematic review

Emmelie Reynvoet • Ellen Deschepper • Xavier Rogiers • Roberto Troisi • Frederik Berrevoet

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Purpose *The purpose of this study is to distinguish the optimal mesh fixation technique used in laparoscopic ventral hernia repair (LVHR). A particular fixation technique of the mesh to the abdominal wall is required, which should be strong enough to prevent migration of the mesh and, at the same time, keep injury to the abdominal wall minimal to prevent postoperative discomfort and pain.*

Methods *An extensive literature search was performed in the PubMed database from its onset until November 2012. All series of at least 30 patients operated by laparoscopy for a ventral hernia, with the use of a standardized surgical technique well-defined in the "Methods" section, and with a follow-up of at least 12 months were included. The series were categorized according to the technique of mesh fixation described: "tacks and sutures," "tacks only," and "sutures only." For each treatment group, the recurrence rate was adjusted to the number of patients treated and the 95% confidence interval was calculated. No overlap between two intervals was defined as a significant difference in recurrence rate.*

Results *A total of 25 series were included for statistical evaluation. Thirteen trials used both tacks and sutures, ten used only tacks, and two used only sutures. Overall recurrence rate was 2.7% (95% CI [1.9–3.4%]).*

Conclusion *None of the currently available mesh fixation techniques used for LVHR was found to be superior in preventing hernia recurrence as well as in reducing abdominal wall pain. The pain reported was remarkably high with all different fixation devices. Further research to develop solid and atraumatic fixation devices is warranted.*

Introduction

In the era of minimal invasive surgery, new techniques are developed to repair ventral hernias by laparoscopy. In applying this technique, the mesh is placed in the intra-peritoneal position and is fixed to the surrounding intact peritoneal wall. The laparoscopic approach ensures panoptical examination of the abdominal wall as well as wide overlap of the mesh over the defect. A recent meta-analysis favors the laparoscopic technique compared to open surgery, especially regarding wound morbidity; however, superiority regarding recurrence rates could not be shown.[1] An important reason for hernia recurrence is tearing off of the mesh from the tissue.[2] Therefore, adequate fixation is obligatory to stabilize the position of the mesh while tissue ingrowth occurs. Merely, proper fixation must avoid loosening of the mesh and must prevent contact of the adhesive non-protective side of the mesh with the viscera.

In 1993, LeBlanc and Booth were the first to describe the laparoscopic technique.[3] The mesh was introduced in the abdominal cavity and held in place with a suture. Thereafter, the edge of the mesh was stapled or tacked and the suture was removed at the end of the procedure. Because of high recurrence rates reported with this technique, the authors started to place, besides tacks, additional transabdominal stay sutures at the periphery of the mesh.[4–6] This opinion was shared by Franklin et al. who reported suture fixation being the best prevention for mesh migration.[7] However, gradually, the concern arose that these sutures were a causal factor for postoperative pain as they penetrate all layers of the abdominal wall with possible risk of nerve or vessel entrapment.[8–11] Tacks, which are helical coils shot into the visceral side of the peritoneum, handle a less aggressive way of penetration into the abdominal wall tissue. The risk of postoperative discomfort plays presently an important role in deciding which technique to apply.[12,13] Therefore, some authors left the use of transabdominal sutures or reduced the number of sutures and mainly relied on the use of tacks.[14]

However, as hernia surgeons are mostly strong believers of their personal technique, there is a lack of randomized control trials to investigate the optimal fixation technique. In the present systematic review, all series describing laparoscopic ventral hernia repair (LVHR) were evaluated, with special attention regarding the fixation device applied. In an attempt to correlate the fixation techniques used with the reported recurrence rates, a design for the comparison of categorical data was developed by the university's statistical department.

Search strategy

A systematic search in the PubMed database was performed by the investigators (ER, FB) to collect the publications related to LVHR with the following search terms: "laparoscopy," "ventral hernia," and "incisional hernia." Articles of interest from the reference lists of the selected articles were

incorporated as well. The language of the publications was restricted to English, French, Dutch, and Spanish. The search was completed by November 2012.

All case series describing a LVHR technique were considered for inclusion. Further criteria consisted of the following: (1) study population of at least 30 adult patients; (2) inclusion of both prospective and retrospective series when describing a patient group operated for an incisional or ventral hernia with a laparoscopic technique, using one particular mesh fixation technique well-defined in the "Methods" section; (3) recurrence rate as primary endpoint, after a follow-up of at least 12 months.

Series that described only a particular group of patients, e.g., only cirrhotic patients, were excluded as were series that only described one type of ventral hernia, e.g., small ventral hernias. If one author or a group of authors published the same series more than once, the most recent publication was included.

Methods

The present review is reported according to the MOOSE guidelines for reviewing observational studies.[15]

Data coding

A variety of fixation techniques was described in the different series; however, most of the authors used tacks or sutures or a combination of both. To compare different techniques, the method of fixation was categorized into three treatment groups: "tacks and sutures," "tacks only," and "sutures only." For further analysis, these groups were used. For each trial, the total number of procedures and the reported recurrences were noted. Only the procedures completed laparoscopically were included; if conversion to an open repair was required, these procedures were excluded from further analysis.

Quality assessment

Using strict inclusion criteria, optimal comparability between the three treatment groups was aimed for. All series included described a heterogeneous group of patients, representing an entire population, operated on using a laparoscopic technique with intra-peritoneal mesh placement. Besides clinical heterogeneity, care was taken that one technique was used for all patients to avoid interventional heterogeneity. With a minimal study population of n >30, inter-surgeon and inter-hospital variation was minimal. Sensitivity testing was performed using a subgroup analysis.[15,16]

Statistical analysis

R statistical software (version 2.12.1, The R Foundation for Statistical Computing) and the metafor package (version 1.5-0) by W. Viechtbauer were used for statistical analysis and graphical representation by means of forest plots.[17,18]

For all selected studies, the raw proportion of recurrences was estimated from the sample size and the number of recurrences. For each treatment group, the weighted proportions of recurrence were obtained from a DerSimonian–Laird random effects model.[19] Zero cell counts are problematic in obtaining summary measures; therefore, 0.5 was added to both the number of recurrences and the sample size when trials reported no recurrences.[20] Both the subgroup analysis per treatment group, an overall summary measure, and the corresponding 95% confidence interval are reported. If two 95% confidence intervals for the pooled proportion per treatment group do not overlap, a statistically significant difference is concluded.

Results

Only one database was consulted with 1,204 publications identified. (Fig. 1) All abstracts were read one by one, recruiting 77 abstracts for full text evaluation. Further study of the methods included 25 series for statistical evaluation according to the inclusion and exclusion criteria. Table 1 indicates the total number of patients per trial, the study design, the used materials for hernia repair, the number of recurrences with the recurrence rate, and the time of the follow-up period.

Figure 2 shows the forest plot with the raw proportion of recurrence rate per trial and the 95% confidence interval (CI).

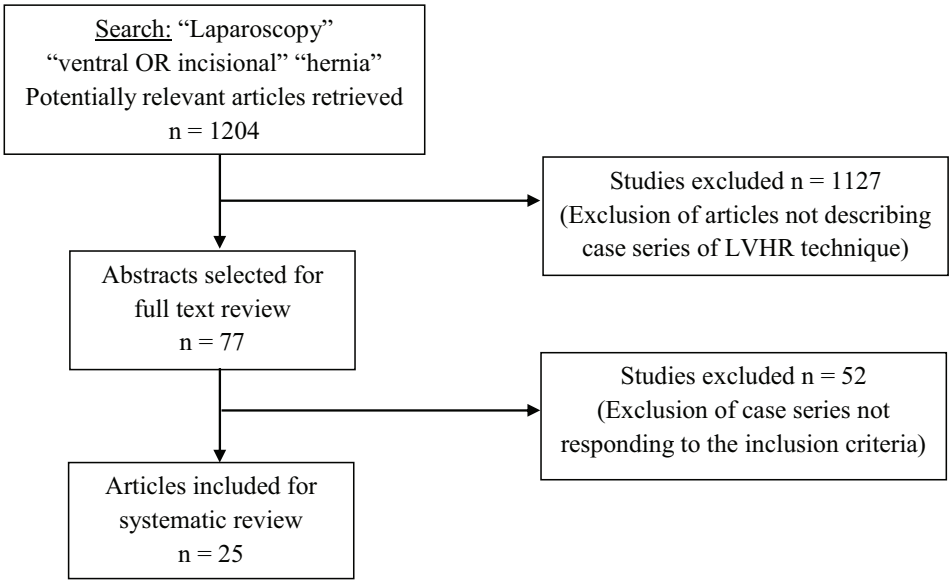

Fig. 1. Search Strategy: summary of literature search.

Author	Year	*n*	Follow – up (months)*	Study design†	Fixation category	Recurrences	Recurrence Rate (%)
Koehler[21]	1999	34	20	*R*	Tacks and sutures	3	9%
Kyzer[22]	1999	51	12*	*P*	Tacks and sutures	1	1.80%
Reitter[23]	2000	47	27	*P*	Tacks and sutures	3	7.10%
Ben-Haim[24]	2002	93	14	*P*	Tacks and sutures	2	2%
Parker[25]	2002	48	41	*R*	Tacks and sutures	0	0%
Aura[26]	2002	85	37	*P*	Tacks and sutures	6	7%
Cobb[27]	2006	270	21	*P*	Tacks and sutures	13	4.70%
Stickel[28]	2007	61	14*	*P*	Tacks and sutures	3	5.20%
Saber[29]	2008	172	28	*R*	Tacks and sutures	3	1.70%
Argawal[30]	2008	30	58	*P*	Tacks and sutures	0	0%
Gananadha[31]	2008	68	19*	*P*	Tacks and sutures	4	6%
Berger[32]	2009	297	24*	*P*	Tacks and sutures	2	0.60%
Orenstein[33]	2011	47	16	*R*	Tacks and sutures	0	0%
Carbajo[10]	2003	269	44	*P*	Only tacks	12	4.40%
Mizrahi[34]	2003	228	15	*P*	Only tacks	8	3.40%
Morales-Conde[11]	2005	137	40	*P*	Only tacks	3	2.14%
Olmi[35]	2006	178	29	*P*	Only tacks	4	2.50%
Rosenberg[36]	2008	49	17*	*P*	Only tacks	0	0%
Baccari[37]	2009	195	23	*R*	Only tacks	7	3.50%
Bencini[38]	2009	146	45	*P*	Only tacks	12	8%
Moreno-Egea[39]	2010	200	72*	*P*	Only tacks	11	6.20%
Theodoropoulou[40]	2010	40	24	*P*	Only tacks	1	2.50%
Alkhoury[41]	2011	141	40	*P*	Only tacks	6	4.2%
Chelala[42]	2007	400	28	*P*	Only sutures	6	1.50%
Palanivelu[43]	2007	714	50	*P*	Only sutures	4	0.55%

Table 1. The total number of patients per trial, the study design, the used materials for hernia repair, the number of recurrences with the recurrence rate, and the time of the follow-up period.

† *P* prospective, *R* retrospective. *All studies noted follow-up period by mean, except those by median(*)

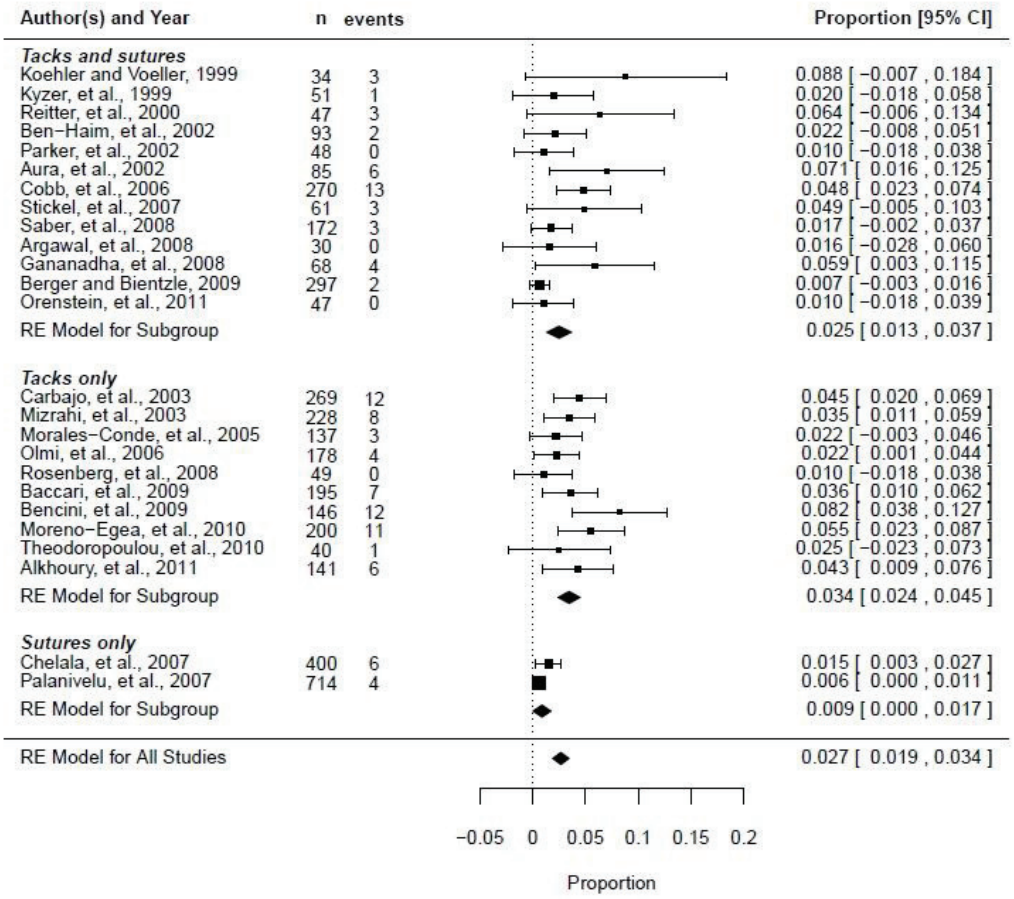

Fig. 2. Forest plot with weighted proportion of recurrence rate per treatment group as obtained by the random effects model.

Besides, the weighted proportion of recurrence rate per treatment group is reported as obtained by the random effects model. The use of tacks and sutures was described by 13 authors with a weighted proportion of 2.5% (95% CI [1.3–3.7%]). Ten series described the use of only tacks, with a weighted proportion of 3.4% (95% CI [2.4– 4.5%]). Just two series used only sutures, with a weighted proportion of 0.9% (95% CI [0–1.7%]). As the 95% confidence intervals are overlapping, no significant difference between the three fixation techniques could be defined regarding recurrence rate. Overall recurrence rate for all included studies was 2.7% (95% CI [1.9–3.4%]).

In the first category, tacks and sutures were used. Most authors use sutures at cardinal points, or some extra points for large meshes, to provide correct positioning of the mesh before tacking the edge of the mesh with one row of helical tacks.[21–23,27,29,31–33] Three authors placed sutures and even put a

double crown of tacks afterwards [25,26,28]. Argawal et al. tacked the four corners of the mesh while the edge of the mesh was fixed with sutures.[30]

The second group, tacks only, means the use of spiral titanium tacks, and most of the authors position this device in a double crown.[10,11,34–38,40,41] This technique was also categorized as tacks only when a temporary suture was used to hold the mesh in the right place but the suture was cut at the end of the procedure.

In the category sutures only, only two series were included.[42,43] These series used only non-absorbable sutures to fix the mesh, without any additional device.

Besides fixation strength, most of the above reviewed articles reported postoperative pain in their results section. Although the definition of discomfort and postoperative pain varies widely in the included series, Table 2 gives an overview of the pain described in the different studies.

Discussion

Fixation of the mesh is a crucial technical point in LVHR. Adequate fixation should permit the mesh to withstand abdominal shear forces and prevent it from migration and dislocation. In the meantime, fixation should precede to as little complications as possible. Tissue damage must be kept minimal to prevent adhesion formation and postoperative pain. Presently, the most widely used fixation techniques are transabdominal sutures and tacks.[44] Many series are published using these devices, but as there is a lack of randomized controlled trials, the discussion on what the optimal fixation should be continues. In an attempt to try to answer this question, we collected all series reported and compared their results regarding the mesh fixation technique applied.

Wassenaar et al., Greenstein et al. and Bansal et al. are the only authors who reported a case–control study and compared the impact of fixation on the outcome of the surgical technique, expressed as rate of hernia recurrence after repair.[45,46,47] After a mean follow-up of respectively 31.3, 18, and 15.3 months, none of the three authors could prove a significant difference in recurrence rate. Recently, the WoW trial could not demonstrate a difference in recurrence rate between tacks only and tacks and sutures at 24 months follow-up.[48]

Four authors previously reviewed the literature concerning mesh fixation.[49–52] Cobb et al. examined reported trials with or without the use of transabdominal sutures, Rudmik et al. grouped the series using tacks with or without sutures, and LeBlanc totaled all published trials according to their fixation method.[49,50,51] In these reviews, no consideration was done regarding inclusion criteria, size of study population, or follow-up period; results were totaled without any significance. Brill et al. examined the fixation device used in all series and comparative studies describing a LVHR technique from 1998 to 2008.[52] With caution to the statistical interpretation, the authors found that there was

no significant difference in hernia recurrence between studies using sutures and studies using tacks or staples as primary fixation device.

To group the available data and compare the outcomes according to the surgical technique applied, our statistical department developed a model for comparison based on the DerSimonian–Laird random effects model. With this model, an assignment is made of the weights that reflect the relative value of the information provided per study. An estimate of the treatment effect per fixation group is made by weighing the observed effects in relation to the sample size per study. Besides the treatment effect per fixation group, the 95% confidence interval was estimated.[19] Figure 2 shows the forest plot that implements the weighted proportion of recurrences calculated per treatment group with the 95% confidence intervals. An overall recurrence rate of 2.71% is reported (95% CI [1.9–3.4%]). The line at point 0 shows per study if the proportion is statistically different from zero. As computer software programs are used, some values in the 95% confidence are below zero; however, these numbers must be interpreted as zero.

The 95% confidence interval of the three groups overlapped; no statistical difference between the fixation techniques could be defined, although an explicit lower recurrence rate was reported for the sutures only technique.

With a systematic and structured search strategy, it was aimed to minimize possible bias. Explicit inclusion criteria were used to make sure that the series resembled a representative group of patients. The test for heterogeneity was not statistically significant ($p>0.1$ for 11 df), suggesting little variation between the different studies. To avoid clinical heterogeneity, studies that reported only on patients with risk factors, for example, obesity, were not included as well as patient groups with only one type of ventral hernia, e.g., giant hernias or suprapubic hernias. As only patient series are included, lacking a control group, selection bias is possible when authors tend to optimize their results. Moreover, bad results of personal series are not likely to be published with possible publication bias not eliminated.

Only series reporting on one well-defined surgical technique for all cases were considered. If different techniques were applied to perform mesh fixation during the mentioned study period, these studies were excluded.[6,8,9,44] This is the reason why one very large series is not included because the fixation technique was adapted through time.[44]

The series were grouped roughly in three sections: tacks only, tacks and sutures, and sutures only. A certain consistency was noticeable in the techniques used. The traditional technique is to place some sutures at strategically chosen points where after one row of tacks is added. Authors using tacks described the spiral titanium tack. When only tacks were used, they were placed in a double crown. This way, one row of tacks is placed at the outer edge of the mesh followed by a second row of tacks placed at the border of the fascial defect.

All authors described that a sufficient overlap of the mesh over the defect is mandatory. In general, when performing laparoscopic ventral hernia repair, an overlap of 3–5 cm should be achieved and all the included series mention this in their methods section.[44] For open retromuscular repair, the complete coverage of the previous fascial incision was necessary as shown by Schumpelick et al.[53] However, nowadays, more and more hernia specialists claim that the overlap should equal the width of the hernia defect repaired.

A possible drawback of this review is that no difference was made between studies describing primary or incisional hernias, and the size of the fascial defect was not taken into account. Logically, in larger defects, it is more important to have long-standing and solid fixation. In smaller defects, the existing contact of the parietal side of the mesh with the abdominal wall is larger. This allows more efficient ingrowth of the mesh. This "mesh–abdominal wall interface" can also be increased by closing the fascial defect. Four authors closed the defect before placing the mesh.[29,30,42,43]

The type of mesh used was not taken into account. There exists a difference in pattern of ingrowth of different meshes in the peritoneum.[54] Slower incorporation of the mesh in the abdominal wall needs longer fixation. Besides this, thicker and more rigid meshes are more difficult to be penetrated by the fixation device. A tack may not be sufficiently long to catch the mesh, peritoneum, and abdominal fascia. However, to the best of our knowledge, no data are available on the thickness of the peritoneum, fascia, or preperitoneal fat layer; therefore, no conclusion can be drawn regarding optimal penetration depth of a tack.

Multiple reasons for recurrences were given by the different authors, yet few were accused of insufficient fixation. Dislodgement of the tacks was described.[21,24,34] Two authors doubt whether tacks are sufficiently long to penetrate both the mesh and the fascia.[27,29] Tacks are shot in the mesh and catch only the peritoneum and the inner layers of the abdominal wall, while sutures penetrate through the complete abdominal wall plus mesh and are knotted at the outside of the body.

To investigate the strength of the different fixation devices, various experimental models have been developed.[45–47] van't Riet et al. calculated the needed force to disrupt the mesh from the tissue of a pig cadaver where it had been fixed with either sutures or tacks.[55] The tensile strength of transabdominal sutures was 2.5 times higher than the tensile strength of tacks. In a rabbit model, Joels et al. proved fixation strength being significantly higher for sutures compared to tacks immediately after surgery, but not after an 8 week nor a 16 week follow-up period.[56] Hollinsky et al. showed in a rat model after both 1 week and 2 months that fixation with transfascial sutures was significantly stronger than that with tacks, with absorbable tacks reaching equal strengths compared to permanent tacks.[2] In contrast, Winslow et al. operated pigs laparoscopically using tacks with or without additional sutures.[57] At 4 weeks, none of the implanted meshes had migrated, no signs of recurrence

could be found in both groups, and no additional fixation strength could be demonstrated by adding sutures.

Besides fixation strength, most of the articles included in this study mentioned the problem of postoperative pain. The discomfort described by patients is due to peritoneal trauma caused by the mesh fixation mechanism. Although there exists a huge variety in the way pain is reported, this article gives an overview of the pain reported. It is however impossible to draw statistically relevant conclusions regarding the pain problem. First, the definition of pain is variable and the used thresholds differ. Second, the time point in the postoperative period when the pain is evaluated is inconsistent. Table 2 gives an overview of postoperative pain described in the included series.

Author	Fixation category	In-hospital and early postoperative period	Long-term (> 4weeks)
Reitter[23]	Tacks and sutures	/	6.3% removal of suture
Parker[25]	Tacks and sutures	/	1.3% at suture site
Cobb[27]	Tacks and sutures	/	3.2% >6 months at suture site
Stickel[28]	Tacks and sutures	15% severe pain	1.6%
Saber[29]	Tacks and sutures	/	1.1%
Argawal[30]	Tacks and sutures	33% at suture site	0%
Gananadha[31]	Tacks and sutures	6% at suture site	0%
Berger[32]	Tacks and sutures	/	2.3% >3 months, one suture removed
Carbajo[10]	Only tacks	/	7.4%
Olmi[35]	Only tacks	/	1.9%
Baccari [37]	Only tacks	/	1%
Bencini [38]	Only tacks	/	3%
Moreno-Egea [39]	Only tacks	0%	/
Theodoropoulou [40]	Only tacks	/	20%
Alkhoury[41]	Only tacks	/	0.7% >2 weeks
Chelala [42]	Only sutures	2.5%	2.5%
Palanivelu [43]	Only sutures	5%	/

Table 2. An overview of postoperative pain reported in the included series.

In the early postoperative phase, distinguished as pain occurring during the in-hospital period and the following 4 weeks, 2.5–5% of patients in the suture only group suffered from pain which resolved over time.[42,43] Using tacks and sutures as fixation technique, Gananadha et al. reported that 6% of patients had pain at the suture fixation site.[31] In the group of Stickel et al. 35% of patients had moderate pain during hospital stay, while 15% had severe pain.[28]

At long term, Theodoropoulou et al., who used only tacks to fix the mesh, reported that 20% of patients had pain longer than 4 weeks.[40] In contrast, none of the patients in the series of Moreno-Egea et al. needed analgesics for longer than 1 month.[39] Bencini et al., Olmi et al., Carbajo et al., and Alkhoury et al. reported respectively that 3, 1.9, 7.4, and 0.7% had prolonged pain, and Baccari et al. said 1% had pain longer than 8 weeks.[10,35,37,38,41] In the suture only group, Chelala et al. were the only authors who reported 2.5% of patients suffering from long-term pain.[42] The authors who used tacks and sutures such as Saber et al, Stickel et al, Parker et al, and Reitter et al. reported respectively that 1.1, 1.6, 1.3, and 6.3% of their patients suffered persistent abdominal pain.[29,28,25,23] Berger et al. noted that 2.3% suffered from pain longer than 3 months, and Cobb et al. said that 3.2% had pain longer than 6 months.[32,27]

As mentioned above, it is incorrect to draw conclusions with the data described; however, it is likely that the use of transabdominal sutures contributes to the pain issue. Several authors describe pain at the suture site.[25,27,30,31] In these cases, the patient describes a pain localized at the area where the suture penetrates the abdominal wall. Two authors report that they needed to remove the sutures in order to achieve pain relief by the patient.[23,32]

Three of the four authors who closed the fascial defect before placing the mesh stated that, contrary to the expectation, this technique seems not to cause excessive pain.[30,42,43]

Only a few case–control studies are available: Bansal et al. reported higher pain scores with tacks and sutures compared to only sutures at the short term, but after long-term follow-up, no difference could be shown anymore.[47] Wassenaar et al. randomly sorted patients into three groups: absorbable sutures and tacks, non-absorbable sutures and tacks, and a double crown of tacks.[58] Pain scores were comparable between the three groups, and there was no correlation between the number of tacks and postoperative pain. Equally, Nguyen et al. reported no difference in postoperative pain between tacks and sutures and sutures only.[59] Recently, Beldi et al. randomized patients in a suture only group and a tack only group; at 6 weeks, mean pain level was not different.[60] The WoW trial is the first randomized controlled trial that investigated the pain problem at long term.[48] At 3 months, the authors stated that the use of sutures (31.4%) results in significantly more pain than the use of tacks alone (8.3%) (p=0.036). It must be remarked that even if it is reasonable that sutures cause pain, the pain levels reported are still high when the use of sutures is omitted.[12]

In an attempt to minimize pain syndromes after LVHR, new materials are presently launched in the market. Considering absorbable tacks, Duffy et al. and Reynvoet et al. showed that their use is feasible in a porcine model.[61,62] Hollinsky et al. reported equal fixation strength compared to permanent tacks.[2] Although little data on clinical effectiveness are published, their wide use in daily practice may suggest their efficacy.

Completely non-invasive mesh fixation, as with glue sealing, is gaining popularity as good results are being published for inguinal hernia repair.[63–65] Recently, Eriksen et al. and Clarke et al. independently performed a comparative study in a porcine model.[66,67] Fibrin glue was compared to other laparoscopic mesh fixation devices, with none of the meshes displaced at necropsy nor a significant difference in fixation strength or adhesion formation. Olmi et al. presented two case series of, respectively, 40 and 19 patients and proved fibrin glue sufficient as fixation device for hernias smaller than 6 cm diameter and effective in reducing postoperative pain.[68,69] Very recently, the use of fibrin glue was supported by Eriksen et al. in a small RCT.[70] These data seem promising for future research; however, with a lack of large trials and long-term follow-up, their efficacy can only be suggested.[71]

Conclusion

In this review, the current available mesh fixation methods are discussed. Roughly, the series included are divided in three groups: tacks only, tacks and sutures, and sutures only. Regarding their impact on the surgical outcome, no particular benefit for one type of mesh fixation could be demonstrated.

Adding transabdominal sutures does not improve the results of hernia repair at long term.

Fixation-associated complications, due to trauma to the abdominal wall tissue, remain an important problem. Many authors using sutures as fixation device report pain as a localized discomfort at the suture site. Authors omitting the use of sutures report lower but still high pain levels.

In the future of laparoscopic ventral hernia repair, the development of new, atraumatic mesh fixation techniques will be of major significance.

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3.2. Pros and cons of tacking in laparoscopic hernia repair

Emmelie Reynvoet • Frederik Berrevoet

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Present available fixation devices in laparoscopic hernia repair include transfascial sutures, (permanent or absorbable) tacks and fibrin or synthetic sealants, all of which have advantages and disadvantages.

Tack fixation has been applied since the introduction of laparoscopic inguinal and ventral hernia repair during the end of the 1980s and the beginning of the 1990s, respectively. However, although this type of penetrating fixation offers a reliable method to keep the mesh in place, several negative aspects have been highlighted in recent years.

Permanent metallic fixation devices such as helical titanium tacks (Protack®) provide greater fixation strength than absorbable fixation devices (AbsorbaTack®, Permasorb® or SorbaFix®), but as the titanium tacks remain in the body permanently, they have been associated with serious adverse events. Dense adhesion formation and erosion of tacks in hollow viscera have been reported as well as the formation of so-called "tack hernias".

However, the most clinically important negative aspect might be the increased acute and chronic postoperative pain. As pain and quality of life, rather than recurrence rate, gained the attention of clinicians, researchers, and patients, recent developments have been focusing on different types of absorbable materials. However, studies that investigated these issues comparing different tack materials for mesh fixation did not show any benefit from any type of fixation.

Despite the postoperative short- and long-term sequellae, tack fixation is still the most widely applied technique for laparoscopic mesh fixation.

Introduction

The first reports of laparoscopic ventral hernia repair (LVHR) date from more than 20 years ago but the technique is still evolving.[1] To perform a LVHR, a mesh, tailored for intraperitoneal use, is brought into the abdomen and positioned over the fascial defect. First, the fascial defect is measured and an appropriate mesh size is chosen with an overlap of at least 5 cm. The mesh is fixed at its outer borders to the abdominal wall with one of the fixation devices. There is ongoing debate about what the optimal mesh fixation technique should be. Solid fixation is important to prevent migration of the mesh into the former defect. As slippage of the mesh results in hernia recurrence, this should be overcome.

Conventional ways of fixation include the use of transabdominal sutures, tacks, or a combination of both. Transabdominal sutures are fixed at the mesh before its introduction and grasped out the abdomen with a grasping needle. Thereafter sutures are tied outside the abdomen and the knots are buried subcutaneously.

Tacks are shot perpendicularly to the abdominal wall and penetrate 3.8–6.7 mm. They can be either helical or alternatively shaped and are permanent or absorbable. Tacks are easy to place and significantly reduce operation time.[2] Compared with sutures, which pierce all abdominal wall layers, there is less risk for nerve or vessel entrapment with the use of tacks.

Some authors use sutures at four or, especially with larger defects, more cardinal points. Thereafter the edge of the mesh is tacked.[3] Many others only rely on tacks and place them in the so-called “double crown” position.[4] This way, one row of tacks is placed at the outer circle of the mesh and a second row at the border of the fascial defect. Although initial experimental research reported a significantly higher fixation strength for transabdominal sutures compared with tacks, their benefit on long-term repair could never be proven.[5] Nowadays, sufficient data exists to agree that the use of sutures results in significant pain in the postoperative period without adding strength to the repair, and therefore their use can be omitted.[6–8]

With the single use of tacks still very high pain levels are reported, and tack-associated complications have been published. In an attempt to reduce this morbidity, absorbable tacks were introduced. In this article an overview is given of the present available tack devices, their impact on the strength of repair, and the reported tack-related morbidity.

Overview of available tack materials

In the first reports of LVHR, titanium composed staples were used as mesh fixation.[1] Titanium, named after its namesakes in Greek mythology, is a widely used material because of its practical properties. It is very strong, light, and resistant to humidity and extreme temperatures. Moreover, it is chemically inert and often used in prosthetic materials.

The EMS stapler provides titanium clip-shaped staples. The staples are longitudinal and 7 mm in size, their depth of penetration in the tissue is 2 mm.[9]

Many years later, tacks were developed. Tacks have different shapes and subsequently different mechanisms of penetration into the tissue. (Fig. 1.)

Fig. 1. The present available tacks described in the text. From left to right: Protack®, Salute Q-ring®, Sorbafix®, Absorbatack®, Permasorb®. Securestrap®.

The first produced and by far the most widespread used tack is Protack® (Covidien Corp, Mansfield, MA). This is a permanent titanium device with a helical shape, a sharp pin, and a length of 3.8 mm.[10] The Salute® fixation system (Bard Davol, Maryhill, NY) with Q-ring-shaped fasteners was designed with a blunt tip but is no longer available and was replaced by PermaFix® (Bard Davol, Maryhill, NY). The latter is made of a molded, polymer-based material. It is a permanent hollow tack with an atraumatic tip. The length of the fastener is 6 mm, the head is another 0.7 mm (total 6.7 mm). SorbaFix® (Bard Davol, Maryhill, NY) is the resorbable copy of PermaFix® and has exactly the same shape. It is made of poly(D,L)-lactide and should be absorbed 12 months post-implantation. AbsorbaTack® (Covidien Corp, Mansfield, MA) is a copolymer, poly (glycolide-co-L-lactide), of 4.1-mm penetration length, plus a head of 1 mm. According to its manufacturers, significant absorption rate is seen between 3 to 5 months and absorption of the tacks should be complete by 12 months. Another absorbable fixation device is Permasorb® (Bard Davol, Maryhill, NY), formerly known as EasyTac®. It is made of poly(D,L)-lactide and has a pushpin form with two little hooks and a total length of 6.4 mm. Its absorption time takes 16 months. Equally, the I-Clip® (Covidien Corp, Mansfield, MA) is composed of poly(D,L)-lactide and has an I-shaped construct. The tacks have a height of 7.5 mm and are designed to completely resorb within 12 months.[11,12] Most recently Securestrap® (Johnson & Johnson Medical Limited, Livingston, UK) has been launched. Securestraps

are hook-shaped absorbable straps, composed of a blend of polydiaxonone and L(-)-lactide/glycolide copolymer dyed with violet. They use two points of fixation, penetrate 6.7 mm in the abdominal wall tissue, and should be resorbed after a period of 12 to 18 months.

Fixation strength

The available fixation devices have been thoroughly investigated in different experimental models.

The fixation strength of staples has been compared to titanium tacks by Hollinsky et al. in a human cadaver model. The shear force resistance of mesh fixed by a tack is up to four times that of a mesh fixed by a stapler. The author stated that in terms of statics, the adhesive force of screw fixation is superior to that of clip fixation.[9] Besides, the depth of penetration of a tack is twofold higher compared with a staple.

We previously published an experiment performed in a pig model where the titanium tack was compared with three different absorbable tacks.[10] At two weeks, Protack (32 N/cm² ± 12) was associated with a significant higher tensile strength than SorbaFix (26 N/cm² ± 11) (p=0.036), AbsorbaTack (17 N/cm² ± 14) (0.001) and Permasorb (11 N/cm² ± 7) (p=0.0001). At six months, Permasorb (9 N/cm² ± 4) (p=0.001) had still the lowest tensile strength while SorbaFix (29 N/cm² ± 13) reached equal strength as Protack (28 N/cm² ± 11) (p=0.56). AbsorbaTack was the only absorbable tack that had completely disappeared by six months.

Hollinsky et al. investigated Protack, AbsorbaTack, and the I-Clip in a rat model. After both one week and two months equal shear strength was reached with Protack (5.6 N/cm² - 9.7 N/cm²) compared to AbsorbaTack (5.7 N/cm² - 8.7 N/cm²), both significantly higher than the I-Clip (3.3 N/cm² - 4.5 N/cm²).

Deeken et al. were the first to investigate Securestrap and compared it to SorbaFix in pigs with a 14 day survival. SorbaFix was fixed in a Ventralight® (Bard Davol, Maryhill, NY, USA) mesh and exhibited a significantly greater tensile strength of tissue ingrowth compared to Securestrap, placed in a Physiomesh® (Johnson & Johnson Medical Limited, Livingston, UK).[13]

One may question what is expected from a fixation device? What is the minimal fixation strength needed? The primary function of a fixation device is to keep the mesh in place until tissue ingrowth has occurred. Integration of the mesh in the tissue depends on the type of mesh but is usually achieved very rapidly from implantation until 2 weeks postoperative. Overall, shear strength is reached for 74% during the first two weeks; until then proper fixation is needed.[14]

In a laparoscopic model, the mesh is positioned over the fascial defect and fixed at its borders to the abdominal wall. As the intra-abdominal pressure rises the mesh is pushed into the former defect. Shear forces are developed at this mesh/abdominal wall interface. Mesh fixation systems must be able to withstand these forces to prevent displacement of the mesh.[12]

The physiological intra-abdominal pressure has been thoroughly examined.[15] Assuming the abdomen as a cylinder and using Pascal's principle of hydrostatics, Cobb et al. calculated that the maximum tensile strength at the abdominal wall would be 11-27 N/cm.

The force acting on a single fixation device increases linearly with increased hernia size.[16,17] Increasing the number of fixation points reduces the maximum force per single tack, but experimental research concluded that the addition of more than three fixation points per 7 cm of length does not add to fixation strength. The optimal distance between tacks is determined at 1.8 cm.[5]

An important difference in length of tack exists. Although, Protack is the shortest, it showed the highest fixation strength in all experiments.[10,12] The needed length is variable. From interiorly to exteriorly the thickness of the mesh can differ, the peritoneum, the extraperitoneal fat layer and the muscular tissue are variable. It is clear that tacks do not always reach the muscle layer. Moreover, the contact between the tacks and the muscle layer can be hindered by adhesions, by the round ligament of the liver, or by preperitoneal fat. Therefore, Muysoms et al. earlier stressed the importance of what they call "preparing the landing zone."[18] Before the mesh is placed, the ventral wall should be clear of all fatty tissue. This way the tack is shot through the mesh immediately in the fascia without preperitoneal fat in between it. One experiment evaluated the influence of depth of fixation. In a physiological model they mimicked the abdominal wall with a synthetic muscular and peritoneal layer The authors compared the pull-out force of tacks when those were fixed in the muscular layer and the peritoneal layer. No statistical difference could be proven.[19] This concerns, however, a physiological model, and a skeptical view is needed. These are the only data available on what the optimal tack length should be. We can assume that tacks behave better when they are fixed properly in the muscular layer.

The length of the tack is important, but even more important is its shape and its mechanism of fixation. It is known that the screwing shape is superior to the former clip fixation.[9] In our experiment as in the study by Hollinsky et al., the screw design was superior to the pushpin form.[10,12] Although Protack is not as long as the other devices, its structural design is better at capturing tissue. With the sharp point, Protack penetrates the tissue without difficulty. The screw fasteners with hollow tip are, however, less traumatic and do provide excellent fixation strength as well. The two available devices that have a non-screwing design are not as effective. Both Permasorb and Securestrap were independently included in one of our experiments, and twice the same observation was made. The two little hooks at the tip of the tack are not strong enough to capture the tissue. The tacks are shot deep in the tissue but then fall down and only capture the peritoneum.[10,13] To facilitate their performance, tacks should be fired perpendicularly to the tissue. This way they take optimal advantage of their length. However, at the outer borders of the mesh this may be challenging.

One study investigated the influence of the firing angle on the fixation strength in a pig cadaver model.[20] A shear test was performed with five different tacks shot at a perpendicular angle (90°) or an acute angle (30°). Protack performed best, but a significant reduction was measured at 30°(p=0.01). Protack fired at an acute angle had a fixation strength equal to or greater than all other tacks fired at a perpendicular angle. When the same construct was compared at different angles, all devices decreased in their performance when fired at 30°. However, this difference was not statistically different for SorbaFix (p=0.2) and Securestrap (p=0.07), in contrast to AbsorbaTack (p=0.004) and PermaFix (p=0.003).

Tack-related complications

Although tacks do provide an excellent fixation strength and are easy to place, their use is associated with significant morbidity. Both the permanent and resorbable devices do penetrate the abdominal wall, which may cause nerve and vessel entrapment. As a result, a significant number of patients suffer pain in the postoperative period. Moreover, as in LVHR the mesh is placed over an open defect, traction is performed on the fixation devices when the mesh is pushed into the former hernia, which again results in pain. Eriksen et al. performed a prospective study to characterize postoperative pain, period of recovery, and quality of life after LVHR in detail.[21] The authors systematically used a double crown of Protack as fixation device. At days14, 30, and after 6 months, respectively, 13%, 3%, and 7% of patients had a VAS score ≥5.0. Different authors investigated the benefit of using tacks compared with sutures regarding postoperative pain.[6,7] Although it can be concluded that tacks do induce less pain syndromes than transabdominal sutures, very high pain levels are still reported.[3]

As a foreign body is introduced in the abdomen an inflammatory reaction is provoked and adhesions can be formed at the devices. Compared with the resorbable tacks, the titanium tacks induce a significantly higher inflammation and foreign body reaction and are associated with higher adhesion formation (Fig. 2).[10,12]

During our experiment, we found that in 4 out of 6 animals some Protacks had migrated out of the mesh and were found back in the omentum.[10] This was not observed with the use of resorbable tacks. Migration of tacks has been previously described, causing possible harm to the intra-abdominal content. One case report described the presence of two spiral tacks integrated in the seromucosal layer of the small bowel encountered during a laparotomy three years post-LVHR.[22] Another report has been published about a dislodged tack that caused a liver hemorrhage. The tack was still in the mesh but not fixed to the abdominal wall, allowing the sharp edge of the tack to be free, which caused a laceration in the liver.[23] The development of hemopericardium has been described due to a migrated tack after a hiatal hernia repair.[24] Erosion of tacks in the bladder has as well been noted.[25] As

these tacks are designed with a sharp tip, an explicit danger arises when the tack dislodges and the tip becomes adjacent to the intra-abdominal content.

In addition, migration of tacks farther in the abdominal wall has been described. Dislodgment of a tack, followed by fascial disruption, can push the tack deeper in the wall. This way a new fascial defect is created, which can result in what is called a "tack hernia."[26] It is clear that this hernia can cause symptoms such as bulging or incarceration and can easily be overlooked. A second report described migration of a tack anteriorly to the abdominal wall.[27] A patient presented with two sinuses at the anterior abdominal wall formed by spiral tacks that had moved from the fascia up to the skin.

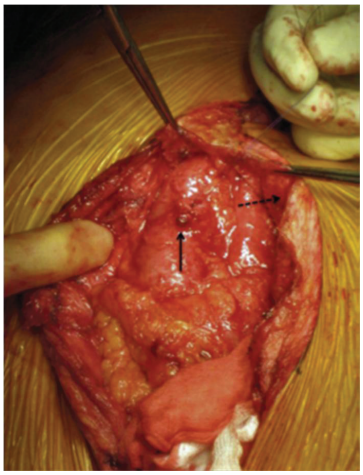

Fig. 2. Eroded tack in small bowel tissue.

In contrast to the absorbable tacks, the titanium spiral tack is associated with significant morbidity. Considering the low inflammation, less adhesion formation, and the good long-term tensile strength, SorbaFix and AbsorbaTack are currently the devices of choice. However, the reason these tacks were developed was to reduce postoperative pain. So far, this potential benefit could not be shown. The resorbable tacks found their entrance earlier in inguinal hernia repair, but in this setting an improvement in postoperative pain could not be observed and very little data is presently available.[28]

The future

All the presently available devices pierce the tissue and may cause harm to nerves and vessels. Consequently, a significant number of patients still suffer abdominal wall pain post-LVHR. In an attempt to solve these pain syndromes, some authors started to use glue. Two groups of sealants can

be distinguished: biological products, such as fibrin glue, and synthetic sealants, cyanoacrylate-based polymers.[29] Although early experience with fibrin glue was promising, the long-term results are disappointing. One recent trial reported a one-year follow-up of 40 patients treated with laparoscopic ventral hernia repair, previously randomized to fibrin sealant and titanium tack fixation.[30] Five patients (26%) developed a hernia recurrence in the fibrin group and one in the tack group (6%) (p=0.182). Later, animal experiments revealed incomplete incorporation of the mesh when fixed with fibrin glue.[31,32] The use of cyanoacrylate glue as mesh fixation is less frequently reported. Initial reports described good integration in the abdominal wall and low inflammation.[33-35] However, further research is needed before widespread application in the intraperitoneal position is possible.

Conclusion

The introduction of absorbable tacks resulted in a lot of progress in laparoscopic ventral hernia repair, and these tacks are currently the fixation device of choice. Compared with the spiral titanium tack, significantly less inflammation and adhesion formation are seen. Several reports have been published concerning migration of the titanium tack and the subsequent morbidity; therefore, its use should be abandoned. However, the absorbable tacks are also damaging the abdominal wall tissue, and up until now no benefit could be seen regarding postoperative pain. In the future, the use of cyanoacrylate glue may decrease or eliminate the need for traumatic fixation, but further experiments are wanted.

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3.3. Tensile strength testing for resorbable mesh fixation systems in laparoscopic ventral hernia repair.

Emmelie Reynvoet • Frederik Berrevoet • Filip De Somer • Griet Vercauteren • Ingrid Vanoverbeke • Koen Chiers • Roberto Troisi

Surg Endosc (2012) 26:2513–2520

Background *In an attempt to improve patient outcome and quality of life after laparoscopic ventral hernia repair, resorbable fixation devices have been developed to allow adequate mesh fixation while minimizing accompanying side-effects as tack erosion and adhesion formation.*

Materials and methods *In experimental set-up, 24 pigs were treated by laparoscopic mesh placement. Two different meshes (PP/ORC and PP/ePTFE) and four fixation devices were evaluated: a 6.4 mm poly(D,L)-lactide pushpin (tack I), a 6.8 mm poly(D,L)-lactide with blunt tip (tack II), a 4.1 mm poly(glycolide-co-L-lactide) (tack III) and one titanium tack (control tack). A first group of animals (n=12) was euthanized after 2 weeks survival and a second group (n=12) after 6 months. At euthanasia, a relaparoscopy was performed to assess adhesion formation followed by laparotomy with excision of the entire abdominal wall. Tensile strength of the individual fixation systems was tested with the use of a tensiometer by measuring the force to pull the tack out of the mesh. Additionally, the foreign body reaction to the fixation systems was evaluated histologically as was their potential degradation.*

Results *At 2 weeks the tensile strength was significantly higher for the control tack (31.98 N/cm^2) compared to the resorbable devices. Except for tack II, the tensile strength was higher when the devices were fixed in a PP/ePTFE mesh compared to the PP/ORC mesh. After 6 months only tack III was completely resorbed, while tack I (9.292 N/cm^2) had the lowest tensile strength. At this timepoint similar tensile strength was observed for both tack II (29.56 N/cm^2) and the control tack (27.77 N/cm^2). Adhesions seem to be more depending on the type of mesh, in favor of PP/ePTFE.*

Conclusion *At long term, the 4.1 mm poly(glycolide-co-L-lactide) tack was the only tack completely resorbed while the 6.8 mm poly(D,L)-lactide tack with blunt tip reached equal strengths to the permanent tack.*

Introduction

Laparoscopic ventral hernia repair (LVHR) using an intra-abdominal mesh is a widely accepted treatment option. Many studies promoted LVHR pointing at a shorter operative time, lower wound morbidity and a shorter hospital stay compared to open repair.[1,2] A recent meta-analysis favors the laparoscopic approach, especially regarding wound morbidity, however, superiority regarding recurrence rates could not be shown.[3–5] The main reason for hernia recurrence after LVHR seems to be rupture of the mesh from the tissue, or migration and protrusion of the mesh into the former defect, together with mesh contraction due to an extensive inflammatory reaction.[6] Therefore adequate fixation is of extreme importance in preventing hernia recurrence.

Several mesh fixation techniques are presently available, with the use of spiral tacks and transabdominal sutures being the two most popular. In different experimental models, transabdominal sutures have shown to give significant stronger fixation compared to both permanent and resorbable tacks.[6,7] Besides fixation strength, fixation related morbidity and long-term quality of life are nowadays important issues.[8] Once introduced in the peritoneal cavity, the fixation devices initiate an inflammatory and foreign body reaction, potentially leading to adhesion formation.[9–11] Patients treated with LVHR report a considerable pain up to 30 days postoperative, and 2–7% is suffering from prolonged pain.[12,13,14]

To improve long-term quality of life resorbable tacks were developed, although there are little data on both their effectiveness and their clinical outcome.[6,15]

The present study was designed to evaluate tensile strength, adhesion formation and inflammatory reaction of these new resorbable devices compared to the traditional helical tack, when implanted in two different composite meshes with a follow-up up to 6 months.

Materials and methods

Twenty-four female Yorkshire pigs, between 60 and 80 kg body weight, (Rattlerlow Seghers N. V., Lokeren, Belgium) were treated by laparoscopic synthetic mesh placement. Three resorbable devices were investigated and compared to the current gold standard, a permanent titanium tack (control tack) (Covidien Corp., Mansfield, MA, USA). It is a helical device with a length of 3.8 mm.(Fig. 1) The first absorbable tack (tack I) (C. R. Bard, Davol Inc., Murray Hill, NJ, USA), made of Poly(D,L)lactide, has a pushpin form with two little hooks and is 6.4 mm in length. Tack II (C. R. Bard, Davol Inc., Murray Hill, NJ, USA), made of Poly(D,L)-lactide, is a 6.8 mm long helical device with an atraumatic blunt tip. Tack III (Covidien Corp., Mansfield, MA, USA) is a copolymer; poly(glycolide-co-L-lactide), of 4.1 mm length. According to its manufacturers, resorption of the resorbable tacks should be completed by 12–16 months.

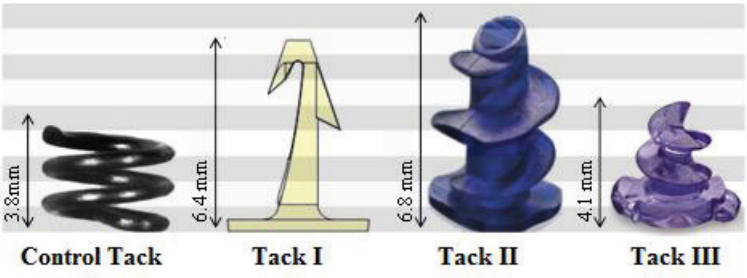

Fig. 1. The different fixation devices used.

To evaluate the efficacy of fixation in various types of meshes, two different composite polypropylene meshes were used in this study. PP/ORC (Ethicon Corp, a Johnson and Johnson company, Somerville, NJ, USA), a large pore polypropylene mesh, is encapsulated in a polydioxanone polymer film (PDS) and covered by a layer of resorbable oxidized regenerated cellulose (ORC) as anti-adhesive barrier. PP/ePTFE (C.R. Bard, Davol Inc., Murray Hill, NJ, USA) uses a polypropylene component and an ePTFE layer as tissue separating component. PP/ORC is thin and easy to penetrate by a fixation device, in contrast with PP/ePTFE, which is thicker, more rigid, less flexible and more difficult to penetrate by the tack.

The study protocol was approved by the institutional ethical committee for animal studies of the Ghent University.

Operative procedure

Before and after surgery, the animals were housed in the faculty of Veterinary medicine and had free access to food and water. Anesthesia and intra-operative management was performed by a qualified veterinary doctor (I.V.). All animals were anaesthetized with a 0.22 ml/kg intramuscular injection of a solution of Tiletamine 250 mg and Zolazepam 250 mg (Zoletil) in 25 ml Xylazine 2%. After intubation, vascular access was obtained and one bolus of 4 mg/kg Propofol was given intravenously. Intraoperatively, Propofol 20 mg/ml, Fentanyl 10 ml and Esmeron 50 mg IV were administered. Monitoring was performed via ECG and capnography. At the end of the procedure all animals received prophylactic antibiotics, Ceftiofur 1 g IM, which was continued for 3 days. Analgesics were administered at the end of the procedure using 1 ml intramuscular injection of Methadone 10 mg/ml.

The abdomen was shaved and disinfected and a pneumoperitoneum of 12 mmHg was established using a Veress needle at the umbilical level. At both flanks, one 10 mm and two 5 mm trocars were inserted. The abdominal cavity was inspected for adhesions and specific abnormalities. Both meshes were introduced in the abdominal cavity and positioned against the opposite wall. The mesh was fixed

cranially and caudally with two different tacks, alternating the choice of mesh and type of tacks in each animal. This way, each tack was evaluated in six different animals at two different time points, i.e. 2 weeks and 6 months. To prevent any bias in fixation technique, all meshes were fixed with the same number of tacks.(Fig. 2) At completion of the procedure, mesh placement and fixation were checked and all trocar entry points were closed in double layer fashion using resorbable sutures.

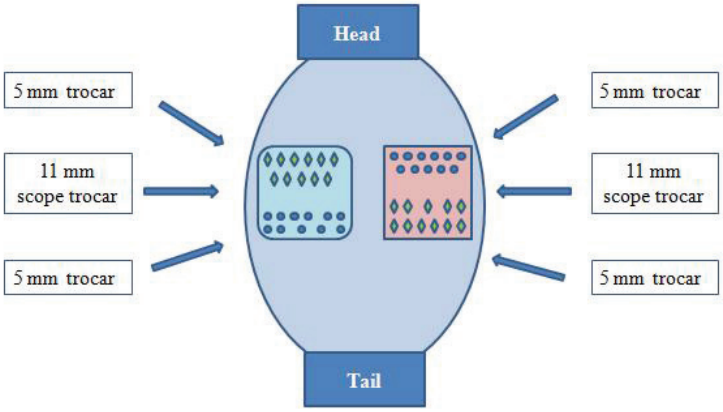

Fig. 2. Standardized operative procedure.

Follow-up

One group of animals (n=12) was euthanized after 2 weeks and a second group of animals (n=12) was euthanized after 6 months. At both time points, fixation strength, inflammatory reaction and possible adhesion formation were evaluated. At long-term evaluation extra attention was given to potential degradation or resorption of the resorbable tacks. At time of euthanasia, a relaparoscopy was first performed to assess adhesion formation, followed by a laparotomy with excision of both meshes and the entire abdominal wall.

Outcome parameters

Adhesions

Adhesions were assessed for extensiveness and severity according to a validated scoring system as introduced by Martin–Cartes et al.[11] Both the extension of the adhesions, i.e. the percentage of the mesh covered, and the severity were evaluated. (Table 1)

Criteria	Score	Observation
Extension	0	No adhesions
	1	0–25%
	2	25–50%
	3	50–75%
	4	75–100%
Severity	0	No adhesions
	1	Filmy adhesions
	2	Omental adhesions
	3	Bowel adhesions which can be disrupted by gentle manual distraction
	4	Bowel adhesions which require sharp dissection for lysis

Table 1. Adhesion Scoring System adapted by Martin– Cartes.[11]

Tensile strength

A Lloyd LF Plus^{TM} (Lloyd Instruments Ltd., Ametek, Inc., UK) universal material tester, equipped with a 1,000 N load cell, was used to measure the force necessary to pull the tack out of the mesh. The build in ‘‘pull to break’’ program (Lloyd Instruments Nexygen Software^{TM}, Lloyd Instruments Ltd., Ametek, Inc., UK) was used for analysis of the measured data. To measure the tensile strength at the tack itself, a suture was fixed to the tack. The samples (mesh and tack) were positioned under a metal plate with a hole in it at the position of the tack. The tensile strength tester applied force to the suture in a vertical upward direction.(Fig. 3) The test was terminated when the load suddenly decreased with more than 50%. The force measured at this point was taken as maximum tensile strength of the tack.

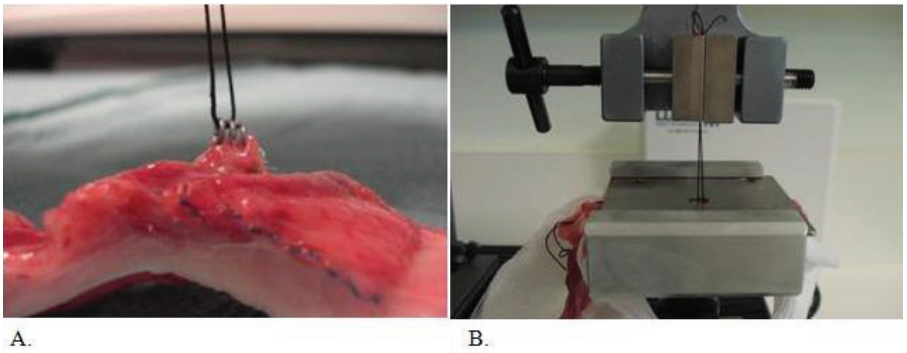

Fig. 3. Setup for tensile strength testing. A/ A suture was fixed to the tack. B/ Illustration of the Lloyd LF plus™ testing machine pulling at the suture in upward direction.

Histology

Histological evaluation was independently performed by two researchers (E.R., G.V.). Inflammation and foreign body reaction was scored by evaluating infiltration of lymphocytes, plasma cells, macrophages and giant cells. 1 x 1 cm ‘‘mesh-tack-abdominal wall’’ samples were cut and placed in 10% formalin for 1 week. Thereafter, slices were cut longitudinally next to the tack through the mesh and abdominal wall and put in paraffin. This way the longitudinal surface next to the tack was investigated. After cutting 5 mm slices, these samples were stained with Haematoxylin and Eosin (H&E) according to standard techniques for light microscopic examination. Using a 10x objective the sample was scanned. If an area of high cellularity was spotted, this was investigated closer by using a 40x or, if necessary, a 100x objective.

To each sample a score was given for lymphocytes, plasma cells, macrophages and giant cells according to their presence. ‘‘Low’’ indicated that the particular cell was absent or present in very limited numbers, ‘‘High’’ indicated a significant presence of the particular cell type and ‘‘Medium’’ was a level of presence in between. If there was too much difference for a given sample a third researcher was counseled (C.K.).

Statistical analysis

Statistical analysis was done with SPSS Windows for 17.0. For continuous variables a student t-test was used, for categorical data a Chi Square test was performed. The level of significance for all data was set at a $p<0.05$.

Results

All animals survived the procedure and follow-up period. Intra-operatively, one animal suffered an iatrogenic injury to the spleen after Veress needle placement, which resulted in a minor bleeding that stopped spontaneously. The placement of the meshes was adequate and fixation to the tissue seemed satisfying with all four tacks.

At re-laparoscopy both meshes could be visualized easily, while localizing the fixation points was more difficult due to adhesion coverage and neoperitoneal formation. After 6 months, tack III was the only device that was not identifiable as such, while at the other tacks no obvious signs of degradation could be observed. In four out of the six animals, some permanent tack were migrated out of the meshes into the omentum, not related to omental adhesion formation. Migration of resorbable devices was not noticed.

Adhesion formation

At 2 weeks, adhesion formation was much more extensive than at 6 months, when most adhesions had disappeared. After short follow-up, the parts of the meshes that were fixed with the control tack and tack I had a higher adhesion score. The control tack had a significant higher adhesion score than both tack II (p=0.024) and tack III (p=0.006), while tack I had a significant higher score than tack III (p=0.046), but not than tack II (p=0.13). All PP/ORC samples had a significant higher adhesion formation than PP/ePTFE (p=0.001), but the statistical significant difference between the tacks persisted when fixed in a different mesh. (Fig. 4)

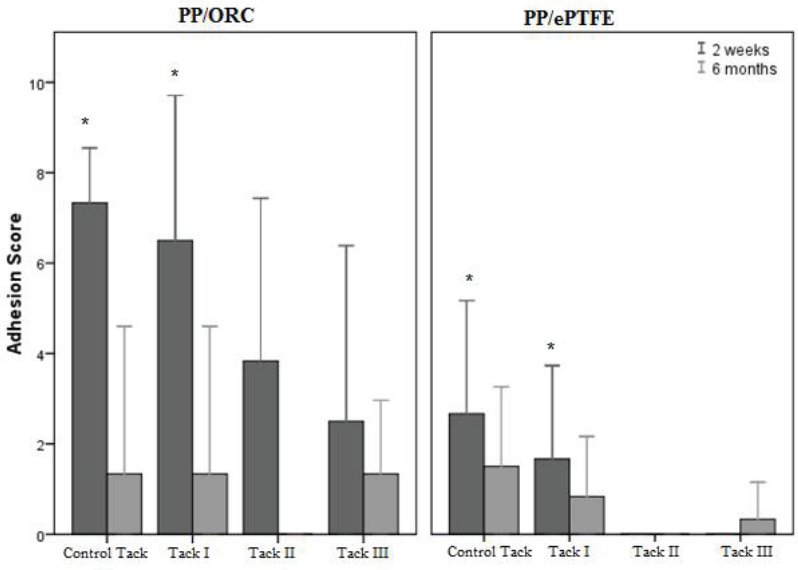

Fig. 4. Adhesion scores for both composite meshes after 2 weeks and 6 months.* p< 0.05

Tensile strength

At 2 weeks, except tack II, all tacks had a higher tensile strength using a PP/ePTFE mesh than when placed in a PP/ ORC mesh, while at 6 months no difference between the two meshes was measured.

At 2 weeks, the control tack (32 N/cm^2 ± 12) was associated with a significant higher tensile strength than tack II (26 N/cm^2 ± 11) (p=0.036), tack III (17 N/cm^2 ± 14) (p=0.001) and tack I (11 N/cm^2 ± 7) (p=0.0001). (Fig. 5) At 6 months, tack I (9 N/cm^2 ± 4) (p=0.001) had still the lowest tensile strength while tack II (29 N/cm^2 ± 13) reached equal strength as the permanent fixation (28 N/cm^2 ± 11) (p=0.56). (Fig. 6)

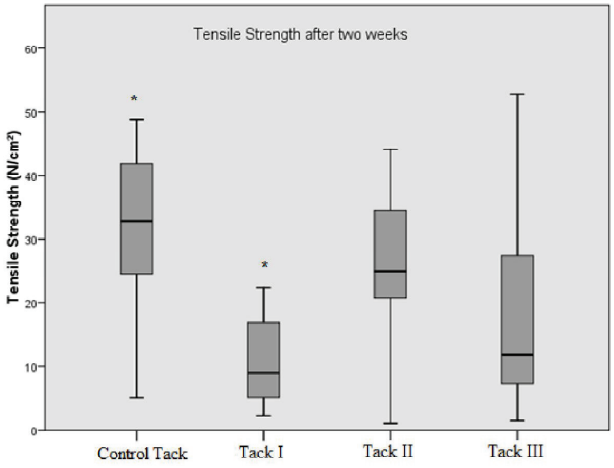

Fig. 5. Fixation strength of the different fixation types at 2 weeks follow-up. *p<0.05

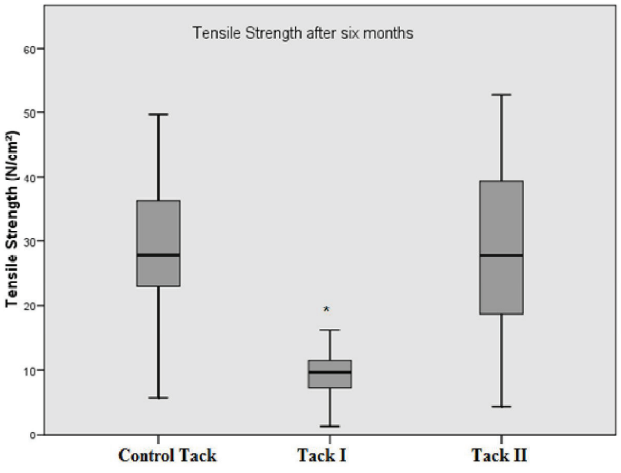

Fig. 6. Fixation strength of the different fixation types at 6 months follow-up. *p< 0.05

Histology

Inflammatory cells and foreign body reaction were omnipresent at the H and E samples at 2 weeks, while at 6 months overall cellularity was much lower. At that time, a neoperitoneum had formed over 74.5% of the PP/ORC meshes and 44% of the PP/ePTFE meshes ($p<0.05$). In the acute phase, the control tack had the highest inflammation and foreign body reaction; both were significantly higher compared to tack III and tack II, but were equal to the scores of tack I. At long-term evaluation, inflammation was comparable for all fixation devices, but tack III had a more intense foreign body reaction than the control tack ($p<0.05$). At both short and long-term follow-up, foreign body reaction was significantly more pronounced for PP/ORC compared to PP/ePTFE ($p<0.05$).

Discussion

When performing a LVHR with the use of a composite prosthetic mesh, adequate mesh fixation is one of the most critical technical points.[16,17] Fixation should be strong enough to withstand abdominal forces and friction till the mesh has integrated in the abdominal wall.[6] For many years, the permanent titanium tack was the only available option for tack fixation and therefore the gold standard. However, at both short and long-term evaluation significant problems have been reported, as postoperative pain, erosion, adhesion formation and even tack hernias.[12,18–20] As postoperative pain has been blamed to the traumatic penetration of the abdominal wall by the fixation devices, resorbable fixation was developed in an attempt to minimize these pain syndromes.[8,21] One prospective double blind study could not show a difference in short-term postoperative pain between Absorbatack® and Protack® used in laparoscopic inguinal hernia repair.[22] We are not aware of any published comparative clinical data concerning this issue in ventral hernia repair.

Although a pig model is evidently not suitable to evaluate postoperative pain, yet it is a valid set-up to investigate possible adhesion formation and strength of fixation of newly developed fixation systems. Previously, Duffy et al. and Hollinsky et al. both demonstrated comparable tensile strength for permanent versus resorbable fixation at respectively one and 2 months follow-up. [6,15] In our model we observed a higher tensile strength for permanent fixation after 2 weeks follow-up. As both the fixation mechanism and the shape of the tack are different for some of the tested resorbable fixation devices compared to the helical titanium tack this could be one of the possible explanations for the increased strength. The depth of the penetration into the abdominal wall tissue, related to the length of the fixation device, can also play a role regarding this issue. Considering the resorbable fixation systems, this penetration depth of tack II, besides its different method of fixation, is highest of all devices tested (6.7 vs 6.4 and 4.1 mm for tack I and tack III, respectively). However, the clinical importance of these different lengths has still to be determined. Regarding the expectations for mesh

fixation related to the abdominal wall forces, Cobb et al. studied the intra-abdominal pressure measuring urinary bladder pressure; maximum tensile strengths ranged from 11 to 27 N/cm.[23] Estimations using Pascal's hydrostatic principle indicated that a maximum tensile strength of 16 N/cm is working on abdominal cadaver walls.[24] In our study, only tack I did not fulfill this expectation, however no real mesh migration was observed, not even after 6 months.

To measure the force at the tack itself, a specific experimental design was constructed. The mesh was placed under an inox platform, pulling the tack out of the mesh through a hole in the platform. The use of a tensiometer to perform tensile strength testing is a well-documented and validated method.[6,9,25] On the other hand, it may be a matter of debate whether these experimental designs do actually reflect the reality of the elasticity of the abdominal wall and the shear forces exerted on the mesh. Hollinsky et al. reported that shear forces acting on the mesh are opposite to the retention forces of the tissue-mesh connection.[6,26] The active forces working within the abdominal wall are mainly axial and lateral pressing forces, rather than pulling forces as studied in this experimental set-up. Although Schug-Pass et al. and Schwab et al. do meet the reality of the abdominal wall forces closer, the advantage of our design is that the strength of the fixation device itself is measured without interference of tissue adherence due to mesh ingrowth.[27,28]

At long-term evaluation, we found an important amount of the permanent tacks had migrated into the abdominal cavity. This has been described before and was then dedicated to too close placement of the separate tacks.[18,29] In the present set-up tacks were placed 1.5 cm from each other, it was remarkable that the observation of migrated tacks could only be identified with the control tack while placement of the tacks was standardized.

When a foreign body is entered in the abdominal cavity an inflammatory reaction is induced and adhesions may develop. Adhesions to mesh materials is widely discussed, but to which extent fixation is contributing to adhesion formation is little investigated, yet frequently suggested. [10,11,30] Recently, the group of Karahasanoglu et al. described a significantly higher adhesion formation to tacks compared to sutures.[31,32] Regarding the use of resorbable tacks, Duffy et al. couldn't confirm a difference in adhesion formation between a titanium and another resorbable tack (Pariefix®; Sofradim Corporation, Trévoux, France), while Hollinksy et al. showed significantly higher adhesion scores with titanium tacks compared to two resorbable devices (Absorbatack® and I-clip®; Covidien Corp., Mansfield, MA, USA).[6,15] The latter data correspond with the present series; the permanent tack resulted in significant higher adhesion formation compared to the resorbable devices tack II and tack III. The difference in adhesion formation between the control tack and the other devices is, on itself, not difficult to explain. First, the sharp point is more harmful to the peritoneum with local ischemia and local tissue injury resulting in more intense adhesion formation.[17] Secondly, the tip of

the permanent helical tack does often not completely penetrate the abdominal wall and small parts remain uncovered by peritoneum; small foreign materials in direct contact with viscera result in adhesions to both omentum and small bowel. The assumed advantages of resorbable fixation, namely less dense adhesions, could not be confirmed in this series.

Our histological data at 2 weeks showed a significantly higher inflammation and foreign body reaction with the control tack than with tack II and tack III, while overall cellularity was much lower at long-term evaluation. Hollinsky et al. showed similar findings as these, after seven days and 2 months follow-up.[6] After 6 months dense adhesions were hardly observed, nor with the permanent nor with the resorbable fixation devices. Tack III was fully resorbed at 6 months and at that time point had a more pronounced foreign body reaction than the control tack, while inflammation was comparable.

Regarding the resorption capacities of the different devices, little clinical data are available and the follow-up period of the experimental reports is rather short.[6,15] So far, mainly company driven data have been reported regarding the time needed for resorption and degradation of the tacks. Zinther et al. described, equally to our observation, the explicit resorption of Absorbatack®[29]. Tack III was the only fully resorbed device after 6 months, while the other two resorbable devices didn't show any signs of degradation at the 6 months' time point.

Tissue incorporation and adhesive strength of mesh filaments occurs in the first 2 weeks postoperatively. Until then, adequate fixation is important to allow proper tissue ingrowth. As the ingrowth into the abdominal wall differs from mesh to mesh, it is of interest to evaluate the tensile strength of the devices in various types of meshes. Here we evaluated two types of prostheses, both containing polypropylene. PP/ORC incorporates reduced weight polypropylene, while PP/ePTFE includes a layer of standard heavyweight polypropylene with an assembled layer of ePTFE, resulting in a much more rigid mesh structure, more difficult to penetrate for fixation devices. The lightweight mesh is more compliant and seems easy to penetrate.[33] At 2 weeks, the fixation for all four devices was stronger in PP/ePTFE, but after 6 months no difference was observed. Therefore no conclusion can be drawn regarding the optimal mesh for resorbable tack fixation.

Conclusion

Permanent fixation still shows highest tensile strength, but adhesion formation is significantly higher compared to resorbable devices. However, at this point, as mesh ingrowth was not studied here, and the optimal point in time for absorbable fixation to be resorbed is not elucidated, it could only been shown that the 4.1 mm poly(glycolide-co-L-lactide) tack was the only studied device that resorbed fully after 6 months, and that concerning length of penetration, long term tensile strength and an acceptable inflammatory response, the 6.8 mm poly(D,L)-lactide tack with blunt tip performed best in this experimental study. Whether these aspects also contribute to postoperative pain after LVHR has to been determined in prospective clinical trials.

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3.4. The use of cyanoacrylate sealant as simple mesh fixation in laparoscopic ventral hernia repair: a large animal evaluation.

Emmelie Reynvoet • Stijn Van Cleven • Ingrid Van Overbeke • Koen Chiers • Patrick De Baets • Roberto Troisi • Frederik Berrevoet

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Purpose *The use of glue as mesh fixation in laparoscopic ventral hernia repair (LVHR) significantly reduces fixation associated morbidity. This experiment evaluates the intraperitoneal use of synthetic glue as single mesh fixation.*

Methods *A total of 21 sheep were operated using a hernia model with two fascial defects of 2 cm² at the linea alba. One week later two polypropylene meshes (Dynamesh®) were implanted laparoscopically, using cyanoacrylate glue (Ifabond®) or conventional fixation (Securestrap®). In half of the animals the fascial defect was closed before mesh placement. After 1 day (n=6), 2 weeks (n=8) and 6 months (n=6), a second laparoscopy was performed at which hernia recurrence, mesh integration and adhesion formation were evaluated. After euthanasia, burst strength testing and histopathology were evaluated.*

Results *One animal died due to intestinal incarceration. In 20 surviving animals, no hernias were diagnosed and mesh placement was satisfying. Adhesions could hardly be observed after one day but were omnipresent in both groups at two weeks and six months. Burst strength testing exceeded 100N in all samples, independent of the fixation device used. Not after 1 day, but after 2 weeks the inflammatory cell response was significantly higher in the glue group. At six months minor inflammation was seen, as was foreign body reaction (FBR).*

Conclusion *Using a standardized biomechanical testing system, synthetic glue can be considered an effective fixation tool in LVHR. The possible tissue toxicity of cyanoacrylates does not lead to an increased FBR. No difference in burst strength was observed for closing or not closing the defect.*

Introduction

Nowadays, laparoscopic ventral hernia repair with mesh reinforcement is common practice. However, no consensus can be found regarding the optimal fixation technique of the mesh to the abdominal wall. For many surgeons, the strong fixation of the traditional devices, tacks and sutures, compensates for their high morbidity and postoperative pain. Others believe that we must continue to look for less traumatic fixation to improve patients' comfort.

Tissue sealants have already been introduced in hernia surgery long time ago and are widely used in inguinal hernia repair to fix the mesh.[1] Roughly, two groups of sealants exists : biological products, such as fibrin glue, and synthetic sealants, cyanoacrylate based polymers.[2] Today, there is evidence that the use of glue can reduce postoperative pain and fixation associated morbidity.[3,4] However, other reports raise doubts about the strength of fibrin sealant as mesh fixation.[4-6] Higher recurrence rates, more mesh migration and insufficient mesh incorporation have been reported. Application of fibrin glue to the peritoneum does not provide sufficiently strong fixation.[6]

Cyanoacrylates (CA) are synthetic glues with a high adhesion strength.[2] They are very cheap compared to their biological equivalent.[7] The present application ranges from surgical wound closure to endoscopy, ophthalmology, otology and interventional radiology.[8] CA's already found a way in inguinal hernia repair with good results.[7,9,10] Little data are available about the use of CA in ventral hernia repair. Except one experiment, recent data demonstrated that CA glue allows good tissue integration of the mesh in the abdominal wall without extensive inflammatory reaction.[11,12,13]

The hypothesis of the present experiment is whether glue fixation is feasible and as effective in terms of burst strength as conventional fixation. The use of CA glue as single mesh fixation in LVHR is compared to the use of straps on both short- and long-term (one day, two weeks and six months) in a large animal model. The primary outcome parameter to be evaluated is burst strength. Secondly, adhesion formation and inflammatory reaction are evaluated, as is technical applicability of the fixation device.

Methods

The study protocol was approved by the institutional ethical committee. Three groups of six Suffolk sheep (35-50kg) were included for this experiment, two animals were added to test the biomechanical testing device. Twenty animals were included to evaluate mesh placement, adhesion formation and histological examination. The two animals in the two weeks survival group used for testing were not included for burst strength evaluation. The care and housing of the animals was supervised by the faculty of Veterinary Medicine of our university. The animals were kept sober 24 hours before surgery but were at unlimited access of food and water during the survival period. Twenty animals were included to evaluate mesh placement, adhesion formation and histological examination. Two animals, in the two weeks survival group, were used to test the biomechanical testing device and were therefore not included for this part of the experiment.

Two mesh fixation devices were compared in this experiment. Securestrap® (Johnson & Johnson Medical Limited, Livingston, UK) are hook-shaped absorbable straps, composed of a blend of polydiaxonone and L(-)-lactide/glycolide copolymer dyed with violet. They use two points of fixation and penetrate 6.7 mm in the abdominal wall tissue. The polymer should be resorbed after a period of 12-18 months. The second mesh fixation is a synthetic glue, Ifabond™ (IFA Medical, Quincie en Beaujolais, France), composed of n-hexyl-cyanoacrylate. The product polymerizes when in contact with a moist environment and forms within 60 seconds after application a flexible adhesive film. According to its manufacturer the glue is resorbable over a period of six months. In this experiment, Dynamesh IPOM® (FEG Textiltechnik, Aachen, Germany) was used. This is a large-pore monofilamentous mesh composed of a synthetic two-component textile structure with polypropylene and polyvinyldenefluoride (PVDF).

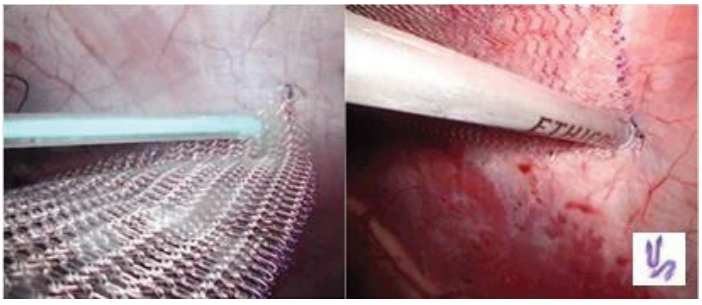

Fig. 1. The glue (left) was applied by a disposable device that provides drops of glue. Three positional sutures place the mesh over the fascial defect. Straps (right) are placed in a standardized way, one row at the border of the mesh and an inner crown around the fascial defect.

Each animal was operated three times. First, two hernia defects were created at the midline. After one week a laparoscopy was performed with the placement of two meshes. In half of the animals the fascial defects were closed before mesh placement. In each animal, both meshes were alternating fixed with one of both fixation devices. After a survival period of one day, two weeks or six months a second laparoscopy was performed to evaluate adhesion formation, mesh placement and mesh migration. Thereafter, the animals were euthanized with excision of the abdominal wall to facilitate burst strength testing and histopathological evaluation.

Operative procedure

Anesthesia and intra-operative management were performed by a qualified veterinary doctor (I.V.). As premedication, Ketamine 12 ml (50 mg/ml), Midazolam 6ml (15mg/ml) and Morphine 0.6 ml (10 mg/ml) were administered by intramuscular injection. Before intubation, vascular access was obtained and a bolus of Propofol 5 ml (10 mg/ml) and Fentanyl 10 ml (0.05 mg/ml) was given intravenously. A gastric tube was placed to facilitate gastric empting. Intraoperatively, Sevoflurane gas (20 ml/hour) was administered. Monitoring was performed via ECG and capnography. At the end of the procedure, all animals received prophylactic antibiotics, Cefenil 20 ml (50 mg/ml) intramuscularly, as well as the following three days. Analgesics were administered at the end of the procedure using an intramuscular injection of Buprenorphine 2 ml (0.3 ml/mg) and Carprophene 1.5 ml (50 mg/ml).

In a first operation, two fascial defects were created. The animals were positioned backside, shaved and disinfected. Two longitudinal incisions were made at the linea alba, one above and one under the umbilicus. Once in the abdomen two cm^2 of peritoneum and posterior fascia was excised. The skin was closed over the defect.

One week later, a first laparoscopy was performed. (Fig. 1) A pneumoperitoneum of 12 mmHg was developed after Verress needle introduction in the right hypochondrium. Two 11 mm and one 5 mm trocars were placed in the right flank. After introduction of the laparoscope, the fascial defects were inspected. In half of the animals these defects were closed using two resorbable sutures (Vicryl 2/0), placed using an Endoclose® needle. The 10x10 cm PVDF-mesh was introduced in the abdomen after it was marked with three sutures (two at the distant corners of the mesh and one in the center). Using these sutures the mesh was positioned over the defect. In each animal one mesh was fixed with straps and one with glue. Twenty straps were placed in a standardized way, placing one row at the border and an inner circle around the defect. Before applying the glue, a sterile gauze was introduced in the abdomen to protect the intestines. The glue was applied by a disposable device that provided drops of glue. After a first layer of glue drops placed at the most distant part of the mesh, the two distant sutures were tightened. Manual pressure was put on the mesh with a clamp. Thereafter a second layer

of drops was placed in the middle and at the end the nearest side was glued. After the glue was dropped, the mesh is pushed against the abdominal wall. Due to the contact with the tissue, the glue polymerizes. This process takes 30 to 60 seconds. The positional sutures were cut and removed at the end of the procedure. At the end of the procedure, the distance between both meshes was measured, as was the distance to xyphoid and pubis. The skin was closed with non-resorbable sutures.

After one day (n=6), two weeks (n=8) and six months (n=6) a second laparoscopy was performed. Adhesion formation was assessed and adhesiolysis was performed. Mesh placement, mesh migration and buckling were evaluated. After euthanasia the entire abdominal wall with both meshes was excised. Immediately after this procedure, burst strength testing was performed. Thereafter the samples were cut and fixed in formaldehyde 5%.

Outcome parameters

Seroma formation

The formation of a seroma was evaluated clinically as a palpable mass over the fascial defect.

Adhesions

Adhesion formation was scored according to a validated score as was described by Martin-Cartes.[14] Both extension, the percentage of the mesh covered with adhesions, and severity were evaluated. (See Table 1, part 3.3)

Mesh placement

At the end of the procedure, the distance between both meshes was measured, as was the distance to xyphoid and pubis to have clear landmarks. During the second laparoscopy, after adhesiolysis, a laparoscopic ruler was brought into the abdomen and the distances from these landmarks were measured again. Possible mesh migration was detected that way.

Mesh shrinkage was measured both laparoscopically and after mesh excision. Shrinkage of the mesh was calculated as percentage of the original surface (10x10 cm).

Biomechanical Evaluation

The strength of mesh fixation was evaluated by burst strength testing. A testing machine was developed as was described by Schug-Pass.[15] The sample, abdominal wall plus mesh, was excised after euthanasia. The abdominal wall was clamped between an aluminum frame with the fascial defect positioned in the middle, the mesh was not retained by the frame. A round-shaped stumper moved with a constant speed of 313 mm/min towards the middle of the frame. The pressure needed for this movement was measured digitally. Tearing of the tissue or mesh, or rupture of the mesh results in a sudden decrease of pressure. The maximum pressure that could be developed was registered with a maximum of 100 N. This movement was repeated twice per sample. (Fig. 2)

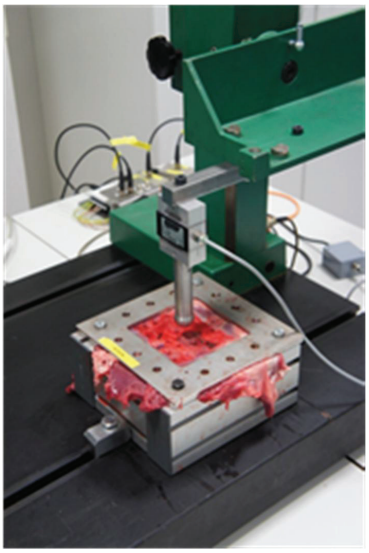

Fig. 2. The sample was clamped between an aluminum frame. A round-shape stumper moved with a constant speed towards the middle of the frame. The pressure developed (max 100 N) was measured digitally.

Histology

Inflammation and foreign body reaction was scored by evaluating infiltration of lymphocytes, plasma cells, macrophages, giant cells and neutrophils.

The mesh plus abdominal wall was excised and placed in formaldehyde 5% for maximum 36 hours. Thereafter, four longitudinal slices were cut for histological evaluation. A Haematoxylin and Eosin (H&E) staining was performed and samples were examined by light microscopy. At a 10x objective the sample was scanned. If an area of high cellularity was spotted, this was investigated closer with a 40x and if necessary, a 100x objective. An overall score was given to the sample for lymphocytes, plasma cells, macrophages, giant cells and neutrophils according to their presence. For each sample a score was given for lymphocytes, plasma cells, macrophages and giant cells according to their presence. “Low” indicated that the particular cell was absent or present in very limited numbers, “High” indicated a significant presence of the particular cell type and “Medium” was a level of presence in between.[16]

Statistical analysis

Because no representative data are available in literature, no power calculation could be performed. Data were analyzed with SPSS version 17.0 for Windows. Chi Square test of independence was used for categorical variables as was the student t-test for continuous variables. Significance was defined with a p-value ≤ 0.05.

Results

A total of 21 animals was operated, one animal died because of intestinal incarceration after creation of the hernia defect and was replaced. All other animals survived the survival period. No hernia recurrences could be observed after mesh placement. No wound or mesh infections were seen. After one day, three seromas were observed in three animals. In two animals the seroma developed at the side where glue was used, in one animal it considered the strap side. At two weeks a seroma was seen in four animals. In two cases the seroma was formed at the side were straps were used, in two cases at the glue side. At six months, no seromas were observed. In the animals where the fascial defect was closed before mesh placement significantly less seromas (1/9) developed compared to the animals were the defect was not closed (6/11) (p=0.001).

In one animal of the group of 1 day survival one mesh had detached and laid down on the viscera, for this sample glue was used as fixation. All other meshes showed good incorporation and mesh migration was minimal (<0.5 cm in all samples). Mean mesh shrinkage was 13.86% +/- 9.1 (mean +/- S.D.). In the strap group mesh shrinkage was significantly higher (17.43% +/- 8.5) than in the glue group (10.10% +/-8.3) (p=0.01). Mesh shrinkage was comparable at all time-points in the survival period.

Adhesions were not frequently observed in the one day survival group. In one animal there were extensive but filmy adhesions (grade 1) over both meshes and in one animal omental adhesions (grade 2) were seen at the glue side. At two weeks, adhesions were seen in all animals. It considered extensive and dense adhesions at both meshes (grade 2-4). No difference was seen between the fixation groups. At six months adhesion formation was still extensive in both fixation groups. In the glue group it considered more dense adhesions compared to the strap group, although this difference was not statistically different (p=0.10). (Table 2)

Burst strength testing was performed immediately after euthanasia. (Fig. 3) In the group of two weeks and six months all the samples could stand the maximum force of 100 N without detachment of the mesh or fall of pressure. In the group of one day survival, the meshes fixed with glue could all stand the maximum force, except one mesh that had dropped onto the viscera. In the strap group, one mesh became detached during the testing procedure. This detachment was associated with a sudden decline in pressure. The maximum pressure before tearing off was 86.08 N. All other meshes could stand the maximum force (100 N). Regarding closure versus non-closure of the defect, no difference was seen in burst strength testing.

Histopathological evaluation showed numerous lymphocytes, plasmacells and neutrophils in the one day survival group. (Fig. 4A) Little giant cells and macrophages could be seen. No difference in cell count was observed between the fixation groups (p=1.0).

At two weeks, lymphocytes and plasmacells were significantly more seen in the glue group (p=0.01) while these inflammatory cells were not predominant in the strap group. (Fig. 4B) Macrophages and giant cells were abundantly present in both fixation groups, as were neutrophils.

At six months, minor inflammatory cells were seen, as were the foreign body cells. No neutrophils could be detected. (Table 2)

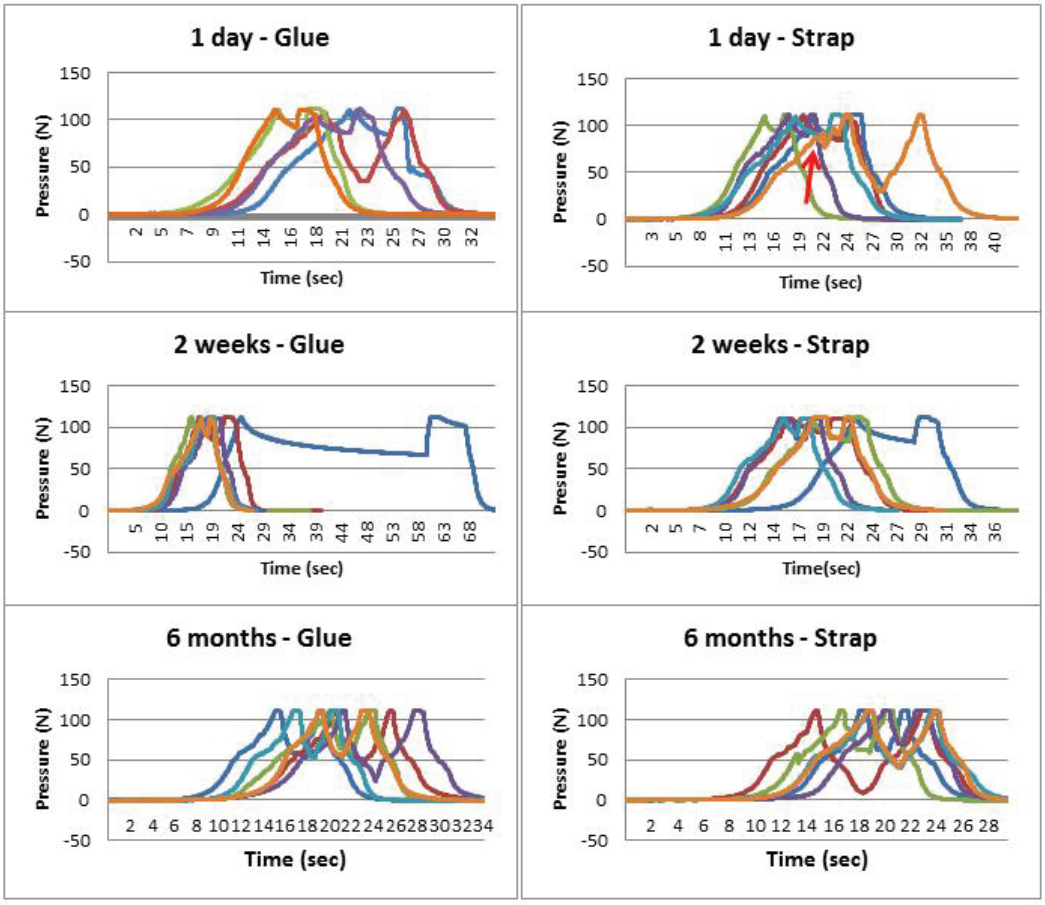

Fig. 3. Burst strength testing was performed immediately postoperative. All samples except one reached 100 N. One sample in the strap group at one day (red arrow) reached 86.08 N.

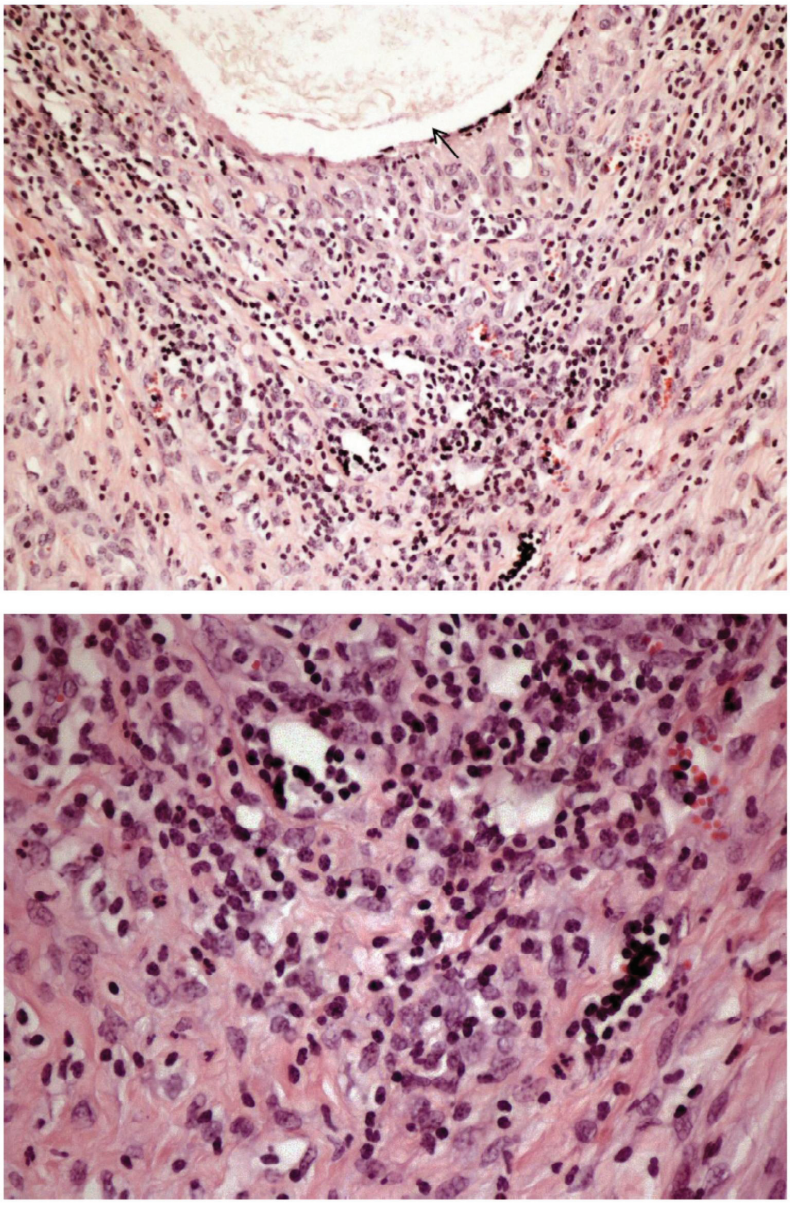

Fig. 4A. *One day survival*. Above : (20x objective) A piece of mesh (arrow) with surrounding presence of plasmacells. Down : (40x objective) Presence of plasmacells (grade “high”)

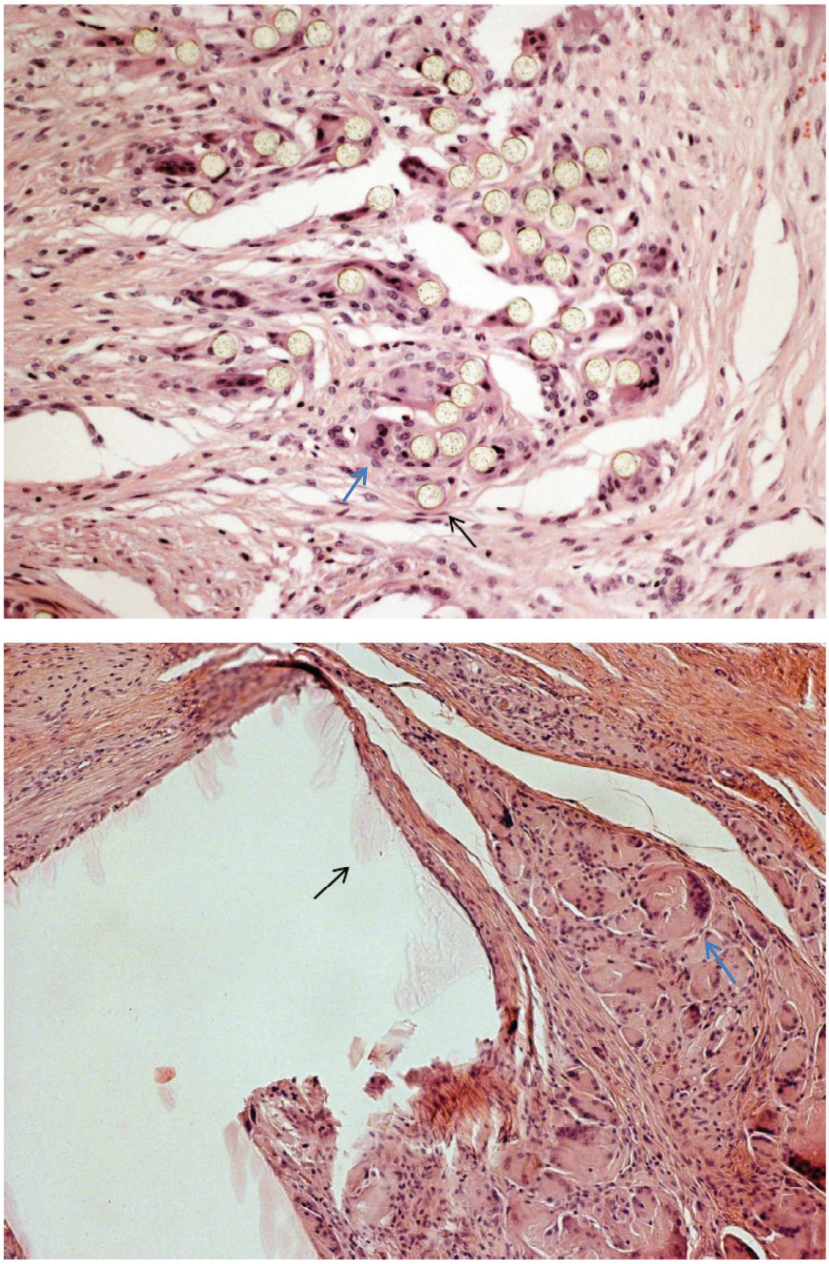

Fig. 4B. Two weeks survival. Above : Particles of glue (black arrow) with surrounding multinucleated giant cells (blue arrow) (grade “high”). Down : Rests of glue (arrow) with giant cell reaction (blue arrow) (grade “high”)

Animal	Fixation	Inflammation	FBR	Adh. Extension	Adh. Severity
		(0-3)	(0-3)	(0-4)	(0-4)
1.1	Strap	1	0	1	1
	Glue	1	0	2	1
1.2	Strap	1	0	1	1
	Glue	1	0	0	0
1.3	Strap	2	1	0	0
	Glue	2	1	1	1
1.4	Strap	2	1	4	1
	Glue	2	1	4	1
1.5	Strap	3	0	1	1
	Glue	3	1	1	1
1.6	Strap	3	1	1	3
	Glue	3	1	4	2
2.1	Strap	2	3	4	2
	Glue	1	3	4	4
2.2	Strap	3	2	2	4
	Glue	3	2	1	2
2.3	Strap	2	3	0	0
	Glue	3	2	2	2
2.4	Strap	1	2	2	4
	Glue	3	2	3	2
2.5	Strap	1	2	2	4
	Glue	2	2	3	4
2.6	Strap	2	3	2	2
	Glue	3	2	3	2
2.7	Strap	1	3	3	2
	Glue	2	3	4	4
2.8	Strap	1	2	4	4
	Glue	2	3	4	2
6.1	Strap	2	2	2	1
	Glue	1	2	0	0
6.2	Strap	1	2	2	1
	Glue	1	1	2	4
6.3	Strap	1	1	4	2
	Glue	1	1	4	4
6.4	Strap	0	1	4	1
	Glue	1	1	2	4
6.5	Strap	1	1	4	4
	Glue	1	2	4	2
6.6	Strap	0	1	4	2
	Glue	1	1	4	4

Table 2. Results of histological examination per sample. For each animal four samples were taken per fixation device, this number gives the mean value. “0” means no presence, “1” means low, “2” medium and “3” high presence of lymphocytes and plasmacells (inflammation) and macrophages and giant cells (foreign body reaction, FBR). Right the adhesion formation is shown according to extension and severity of the adhesions (values as explained in Table 1).

Discussion

From the moment the first report of laparoscopic ventral hernia repair was published in the early nineties, the debate started on what the ideal technique should be.[17] Likewise, mesh fixation had since been a matter of debate. So far, none of the currently used fixation techniques could prove a difference in postoperative pain, neither if the number of tacks and sutures was reduced.[18-20]

As the traditional fixation devices do not succeed in resolving these pain syndromes the interest for atraumatic fixation is gaining. A recent systematic review supports the use of fibrin sealant as an option for mesh fixation in hernia repair.[1] Today there is clinical evidence to agree that the use of fibrin glue for mesh fixation is effective in reducing postoperative pain and convalescence period.[3,21]. However, doubts are rising about the long-term quality of hernia repair and possible hernia recurrence. One recent trial reported a one-year follow-up of 40 patients treated with laparoscopic ventral hernia repair, previously randomized to fibrin sealant or titanium tack fixation.[4] Five patients (26%) developed a hernia recurrence in the fibrin group and one in the tack group (6%) (p=0.182). In animal experiments controversial data were published regarding the use of fibrin glue as mesh fixation and incorporation of the mesh in the abdominal.[3,5,6,22,23] Two authors reported incomplete integration of the mesh when fixed with fibrin glue and a significant increase in mesh migration.[5,6] To continue the path of totally atraumatic fixation there is a need for a safe and potent sealant.

CA’s are monomers containing esters of cyanoacrylic acid. They polymerize rapidly, in 5-30 s, when in contact with hydroxyl groups and have a powerful adhesive strength. CA retains its adhesive qualities even in the presence of moisture and also has bacteriostatic and hemostatic actions. CA’s include methyl-2-cyanoacrylate and ethyl-2-cyanoacrylate, commercially sold as “Super Glue” and widely used in industry as well as in domestic atmosphere. N-butyl-cyanoacrylate (e.g. Histoacryl® or Liquiband, 2-octyl-cyanoacrylate (e.g. Dermabond®) and n-hexyl-cyanoacrylate (e.g. Ifabond®) are used in medical, veterinary and first aid applications. Nowadays their application varies from surgical wound closure and cosmetics to hemostasis of bleeding gastric varices, interventional radiology and ophthalmology.[2,8] The biggest concern remains toxicity due to occupational exposure, contact dermatitis and conjunctivitis has been described after exposure of CA

products.[2,8,24] Toxicity and chemical properties depends on the length of the alkyl chain. Short-chain CA's are stronger but show a rapid degradation and induce necrosis and severe inflammation, while longer-chain CA's are weaker but have a slower degradation and evoke only mild, transient inflammation.[7,12,25] Recently, a large, long-term biocompatibility study has been published. In an experimental model, tests were performed for cytotoxicity, sensitization, irritation, systemic toxicity, genotoxicity and implantation. The (n-butyl-) CA extracts were non-mutagenic, non-irritating and no evidence of systemic toxicity could be shown. Thereafter, a total of 1336 inguinofemoral hernias was treated with a TAPP technique and CA as single fixation. No adverse reaction, directly or indirectly related to its use was observed.[26] The use of CA has already found its entrance in laparoscopic inguinal hernia repair with good primary results, however, less data exists regarding its intraperitoneal use.[9, 10] One experimental study is available where the mesh has been placed in an IPOM position in a rabbit model. After twelve weeks a more pronounced inflammation was noted in the CA group compared to the use of tacks.[12, 13] In the present study a more intense inflammation was seen at two weeks, but this had disappeared after six months. Fortelny et al. described impaired tissue integration of an onlay placed mesh at the sites of the glue drops in a rat model.[11] These findings are in contrast to our observations as well as to the findings of Kukleta et al.[26]

Considering the experimental setup, this is the first study that investigates the use of CA glue as single mesh fixation device in laparoscopic ventral hernia repair in larger animals. In this experiment, sheep were used to permit a long-term survival of at least six months. As the weight gain of these animals is limited to a maximum of 80 kg, they allow a more practical management and handling than pigs. During the experiment we experienced that sheep have a thin abdominal wall with little preperitoneal fat. It is true that, as they are quadruped, the mesh is pushed against the abdominal wall which is in contrast to the upward position of the human. However, the sheep model is very useful in experimental surgery as the mesh has to withstand a substantial friction during moving and the ingrowth of the mesh to the peritoneum is equal as in humans.[27]

The biomechanical testing device was developed analogous to the test plunger as described by Schug-Pass.[15] It is generally accepted that intra-abdominal pressure does not exceed 32 N.[28,29] A mesh fixed to the abdominal wall should at least withstand this pressure. Previous experiments with an equal testing device reached maximum values of 97.3 N with a mean value of 61.86 N.[15] According to this data the maximum of our testing device was scaled at 100 N.

The survival periods were chosen according to our points of interest. A one day survival was included to evaluate the strength of mesh fixation before integration of the mesh in the abdominal wall tissue. In this period the position of the mesh totally relies on mesh fixation. Although we ask the patients to wear an abdominal belt, high intra-abdominal pressures are reached in the postoperative period, e.g.

by coughing during arousal. A two weeks evaluation is of interest to estimate the acute inflammatory reaction and adhesion formation. By that time the mesh should be integrated in the abdominal wall. A long-term assessment is especially of interest to evaluate mesh migration and new hernia formation. At the same time, the biodegradability of the fixation devices can be evaluated.

Concerning the outcome of the present study, all the samples, except two, reached the maximum value of 100 N. Both the straps and the CA glue provide a strong fixation in the immediate postoperative period as well as on the long-term.

As expected at day 1, an inflammatory reaction was induced but no adhesions could be seen yet. At two weeks an explicit foreign body reaction was seen in both fixation groups, while a significantly higher acute inflammatory reaction was seen with glue. At six months, adhesions were still extensively present. Adhesions were predominantly formed to the entire surface of the mesh rather than to the site of fixation. After removing the adhesions a thick neoperitoneal layer had formed above the visceral layer of the meshes. These findings motivate the fact that adhesion formation was mainly due to the type of mesh used.[30]
Tissue integration was good with both devices, and, in contrast to a previous report, certainly not impaired when using glue.[11] Two experimental studies that investigated the inflammatory reaction of CA glue confirm our findings.[12,13]
Despite the more pronounced inflammatory reaction with glue, mesh shrinkage was significantly higher when straps were used compared to glue. This fact was confirmed at the three different time points. Looking at these data, mesh contraction cannot be assigned to an inflammatory response only. When using straps as fixation, little folds are made in the mesh during placement. When the glue is applied, the mesh is more spread out and flattened to the abdominal wall. Mesh shrinkage was calculated as percentage of the original mesh surface before its placement. Moreover, as the difference in mesh shrinkage already existed after one day this cannot be due to inflammation. The difference in shrinkage between straps and glue is of little clinical significance.

More dense adhesions were formed to the meshes fixed with glue compared to straps, although this difference was not statistically different. This may be due to spillage of glue to the intestines. In this experiment a gauze was placed over the intestines to protect them from glue drops falling of the mesh. It is, however, with the present devices impossible not to have spillage of glue. The laparoscopic introducer is a special designed catheter to make the glue only polymerize when in contact with tissue. With a syringe at the other side of the catheter drops of glue are placed on the mesh. The catheter is very bendable which makes it difficult to place drops at a certain position. However, we could not observe drops falling between the pores of the mesh. The viscosity of the glue allows good spreading

of the glue. The bigger problem was drops rolling off the mesh. Ideally, a device should be developed to hold the mesh in place and curl its borders up to prevent leakage of glue. A spraying device could be useful if the particles are big enough not to fall between the pores. A self-adhering mesh could be nice if introduction of the mesh in the abdomen and correct placement to the wall can be guaranteed before gluing.

In the two weeks survival group, half of the animals developed a seroma. By six months, no seromas could be observed. Formation of a seroma was independent to the type of fixation. Almost all seromas were formed in animals in which the fascial defect was not closed. In this experiment, this is the only benefit that was seen for the closure group. No difference in burst strength testing could be observed whether the fascial defect was closed or not.

Mathematically, the force acting on one fixation device can be described in relation to the radius of the hernia orifice and the pressure acting inside the abdominal cavity.[31] In LVHR the mesh is placed over the fascial defect, leaving an 'open space' where the mesh is not in contact with the abdominal wall and an overlap zone where the mesh is fixed to the peritoneum. Normal forces acting on the mesh, the effective intra-abdominal forces, create shear forces in the overlap zone of the mesh around the orifice. Hence, the mesh is "pushed" into the former defect. The larger is the orifice, the greater are the shear forces acting on the fixation devices. By closing the fascial defect, a reduction of the shear forces is expected, needing for less fixation. With closure of the defect, the effective contact of the mesh with the abdominal wall is enlarged, which promotes mesh incorporation. With the use of glue as mesh fixation the contact of the mesh with the tissue is further augmented. Moreover, the shear forces working on the mesh fixation complex are more homogeneously distributed and the dead space is minimalized.[20,32] This may result in a stronger repair on the long-term and a decrease in tension on the fixation points resulting in less postoperative pain. The possible benefits of closure of the fascial defect has however not been reported yet. A single trial has been published, with a mean follow-up of 797.2 days.[33] A recurrence rate of 6.25% in the defect closure group was reported compared to 19.18% in the non-closure group, this difference was however not statistically significant.

This study is the first to investigate the intraperitoneal use of CA glue and to compare it with conventional fixation in a large animal model. The most important limitation of this study is a small fascial defect. As mentioned above, the radius of the defect is in direct relation to the force working on a fixation device. In this experiment, a small defect (2 cm^2) was created at the linea alba. We can conclude that CA provides a solid fixation for repair of small hernia, whether the device can be used

in larger defects has to be proven yet. Moreover, this concerns an experimental study and therefore comparison to the human situation should be done carefully.

Conclusion

The use of sealant as mesh fixation significantly reduces fixation related morbidity in laparoscopic ventral hernia repair. CA glue is a cheap alternative and provides a strong mesh fixation with burst strength equal to straps. In this experiment, no long-term disadvantages of its intraperitoneal use could be identified. To allow widespread use, technical adaptations are needed to allow a more easy application of the glue to the mesh and to the abdominal wall.

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PART 4

DISCUSSION

PART 4. DISCUSSION

1. *Introduction*

Many years ago, primary suture repair was the standard technique for repairing ventral hernias. However, this type of repair placed tension on the edges of the defect leading to hernia recurrence. With the introduction of the polypropylene mesh, this tension could be reduced and a randomized controlled trial has shown that the use of a mesh significantly reduces recurrence rates compared to suture repair.[1,2] In the early 1990s, laparoscopic techniques were introduced, resulting in a shorter hospital stay, rapid recovery and fewer wound complications compared to the open technique.[3] LeBlanc et al. were the first to describe this technique for the laparoscopic treatment of ventral hernia.[4] Since then, the development of numerous types of mesh materials, designed for intraperitoneal use, as well as fixation devices to attach these meshes to the abdominal wall, have further improved the procedure of laparoscopic ventral hernia repair.

When performing a laparoscopic ventral hernia repair (LVHR), the mesh is brought into the abdomen by one of the trocars and placed over the open fascial defect. Thereafter, the mesh is fixed to the abdominal wall by one of the available fixation devices. These devices must be able to keep the mesh in place until the mesh has been incorporated into the abdominal wall. Tissue integration of the mesh depends on its composition, but has usually been completed within two weeks.[5]

One recent very large prospective trial reported shorter hospital stay and less wound morbidity as the main advantages of the laparoscopic technique compared to open repair. Moreover, occult hernias can be detected and treated optimally. However, laparoscopic repair was associated with significantly more postoperative pain and activity limitations in the first postoperative month compared to the open technique.[6]

One possible explanation for the postoperative discomfort associated with LVHR is the use of tissue penetrating fixation devices. Currently, the most frequently used devices are transabdominal sutures or tacks, or a combination of both. As these devices pierce the abdominal wall, they may cause tissue injury or nerve entrapment, which may result in pain. This has motivated researchers to develop other, less traumatic, fixation devices.

2. *Postoperative pain*

Pain is a subjective sensation and its measurement and analysis are difficult. Pain is a multifactorial problem and is both affected by sensory stimuli as well as by cultural and social factors. Most trials that evaluate postoperative pain use the Visual Analogue Scale (VAS 0-10). This is an easy method of assessment but comparisons between trials are difficult. The results can be affected by administering analgesics and the time point within the postoperative period.

The reduction of postoperative pain is desirable for multiple reasons. Better pain control would magnify the other advantages of laparoscopy such as earlier discharge from the hospital and a rapid recovery time. Moreover, with less pain, the patient is more mobile resulting in less complications, such as pneumonia or embolism.

Pain after LVHR remains a problem and is greater in the first postoperative month compared to open hernia repair.[6] Eriksen et al. performed a prospective detailed study to characterize postoperative pain, the period of recovery, and quality of life after LVHR.[7] The highest median VAS score was observed the first postoperative days. During rest, VAS scores returned to the preoperative level by day 14, during activity this was only at day 30. The scores dropped to below the baseline values after six months. At days 14, 30, and after 6 months, respectively, 13%, 3% and 7% of patients had a VAS score ≥5.0. The authors reported that pain had a significant negative influence on the rate of recovery. Compared to other laparoscopic procedures, such as cholecystectomy and inguinal hernia repair, LVHR is very painful.

There are several mechanisms responsible for the pain after LVHR: for example, trauma to the abdominal wall tissue. Mass peritoneal injury can cause local 'peritonitis'. There is evidence to suggest that the dominant source of pain after laparoscopy, in general, is from the peritoneum rather than the skin or the abdominal wall.[8] The parietal peritoneum is innervated by numerous somatic nerve fibers. In LVHR, the peritoneum is injured by the trocars, but also by the penetrating mesh fixation devices. Infiltration of the peritoneum and suture sites with local anesthesia is effective in reducing postoperative pain.[9,10]

A second factor that causes pain, is traction on the fixation devices. In LVHR, the mesh is placed over the defect and fixed at the outer circle. The intra-abdominal forces push the mesh into the former defect. Traction is performed on the fixation devices which results in more pain. The larger the fascial defect, the more traction is performed, the more risk for pain at the fixation sites.[10] Eriksen et al. reported a significant difference in pain intensity during rest and activity, with greater pain levels during activity.[7] This supports the evidence that a mechanical factor plays a role in the pain problem. During activity, the intra-abdominal pressure rises and the abdominal wall is stretched. Traction is performed on the tacks because the wall is expanding while the tacks stay in place.

3. *Tacks or sutures?*

Several experimental models have shown a significant higher tensile strength for transabdominal sutures compared to tacks.[11-13] However, regarding their impact on surgical outcomes, no benefits for one type of mesh fixation has been demonstrated yet.[14-16]

The WoW trial (with or without sutures) was a prospective randomized trial that compared two groups of mesh fixation: "tacks only, double crown" (n=33) and "sutures & tacks" (n=43). There were no differences in recurrence rate after a follow-up of two years. The primary endpoint of the study was abdominal wall pain, defined as a VAS score ≥1.0. At three months after the operation, 31.4% of patients in the sutures & tacks group were suffering pain compared to 8.3% in the double crown group (p=0.036).[17]

Another, smaller, randomized controlled trial that included 32 patients, reported a VAS score of ≥ 2.0 after 6 weeks in 28% of patients where tacks were used and in 61% in the suture group (p=0.02). After six months, still 38% of patients in the tack group were still suffering pain, compared to 50% in the suture group (p=0.31).[18]

In the systematic review performed for this thesis, we noticed that many authors that had used sutures reported pain as a localized discomfort at the suture site. However, even after the use of transabdominal sutures had been omitted, very high pain scores were reported. Looking at only the tack groups of the two above mentioned RCT's, pain levels are still very high: the WoW trial reported 8.3% (VAS ≥1.0) and Beldi et al. 38% (VAS ≥2.0) of patients suffered significant pain.[17,18] Some authors have stated that the use of tacks and transabdominal sutures are equally associated with postoperative pain.[19,20] Eriksen et al., who used only tacks as mesh fixation device, reported that 7% of patients had a VAS of ≥ 5.0 after six months.[7] Although they couldn't demonstrate a correlation between the number of tacks and postoperative pain, they still thought tacks were a causal factor for the postoperative pain in LVHR.

The etiology of pain after LVHR is multifactorial, with trauma to the peritoneum and traction on the fixation devices being the main causative factors. Nowadays, not only the strength of fixation but also the risk of abdominal wall pain, play a role in deciding which technique to apply. Stronger fixation does not mean better fixation if it comes at cost of pain. This motivates us to continue searching for less traumatic fixation devices.

4. *Absorbable tacks*

In an attempt to solve this problem absorbable tacks were introduced. Regarding fixation strength, absorbable screwing devices (Sorbafix® and Absorbatack®) do meet these expectations, whereas the pushpin formed devices (e.g. I-clip®, Permasorb®) show more disappointing results.[13,21]

Although the absorbable screwing tacks provide good fixation strength, the reason why they were developed was to reduce postoperative pain. However, so far, this potential benefit has not been proven. There are no data available regarding the effect of absorbable tacks on postoperative pain.

Regarding fixation-related morbidity, absorbable tacks are superior to the titanium tack. Compared to absorbable tacks, titanium tacks induce significantly more severe inflammation and foreign body reaction, and they are associated with more adhesion formation.[13,21] Moreover, in our experiment, we noticed that an important amount of tacks had migrated out of the mesh and were found back widespread within the abdomen. This does not occur with absorbable devices. Tack migration can cause serious morbidity. As tacks have a sharp point, they can cause severe harm when they are dislodged and the sharp end is free to the intra-abdominal content.

Absorbable tacks (Sorbafix and Absorbatack) are associated with high tensile strength and low fixation-related complications and, therefore, they are currently the fixation devices of choice. However, up till now, no benefit has been proven regarding their impact on postoperative pain.

5. *Fixation strength*

Different forces work on the mesh–abdominal wall interface. In a laparoscopic model, the mesh is positioned over the fascial defect and fixed to the abdominal wall. Both shear forces and muscle forces act on the mesh and its fixation. As the mesh is positioned over an open defect, the mesh is pushed inwards when the intra-abdominal pressure rises. Shear forces are developed on the mesh-tissue interface with an oblique direction towards the present defect in the abdominal wall. The force developed by the oblique muscles is perpendicular to the abdominal wall. The retention force of a fixation device must be able to withstand these forces to prevent displacement of the mesh.[13]

The physiological intra-abdominal pressure has been thoroughly examined by Cobb et al., and is low in the supine position, but increases with each maneuver.[22] There is no difference between genders, but there is a linear relationship between BMI and increased intra-abdominal pressure. Maximum pressure is generated during jumping (mean 171 mmHg, max 252 mmHg) and coughing (mean 81.4 mmHg, max 127 mmHg). As the intra-abdominal pressure increases, the tension on the abdominal wall is also increased. Assuming the abdomen as a cylinder and using Pascal's principle of hydrostatics, Cobb et al. calculated that the maximum tensile strength would be 11-27 N/cm. Earlier, Junge et al. studied the elasticity and tensile strength of the abdominal wall. Their calculations

predicted a maximum tensile strength to the abdominal wall of 16 N/cm.[23] (Fig. 1.) The force working on one fixation device may however not be equalized to the tensile strength of the abdominal wall or the intra-abdominal pressure. The forces working on one tack were investigated by Smietanski et al. [5, 24] (Fig. 2.) The authors developed a mathematical model to calculate the force working on a single fixation device. The force acting on the surface of the hernia orifice is the product of the radius of the hernia orifice (*r*) and the pressure acting inside the abdomen (*Fp*). This is divided by the theoretical number of tacks in place (*n*) to calculate the force acting on a single tack (*Fn=Fp/n*). The force acting on a single tack increases linearly with increased hernia size.

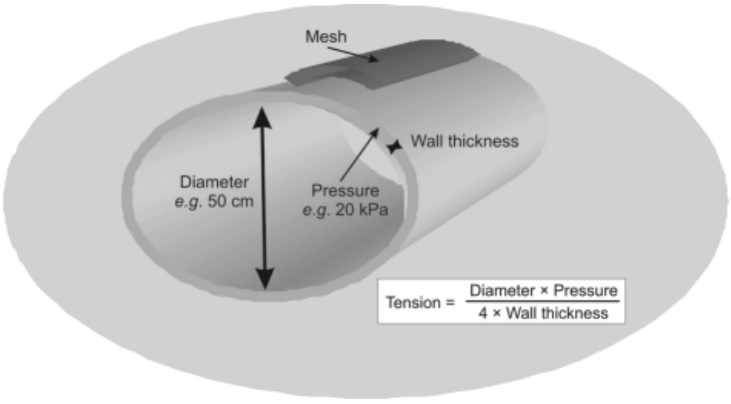

Fig. 1. The tension placed on the abdominal wall calculated by the law of La Place. Theoretically the maximum tensile strength is 16 N/cm.[25]

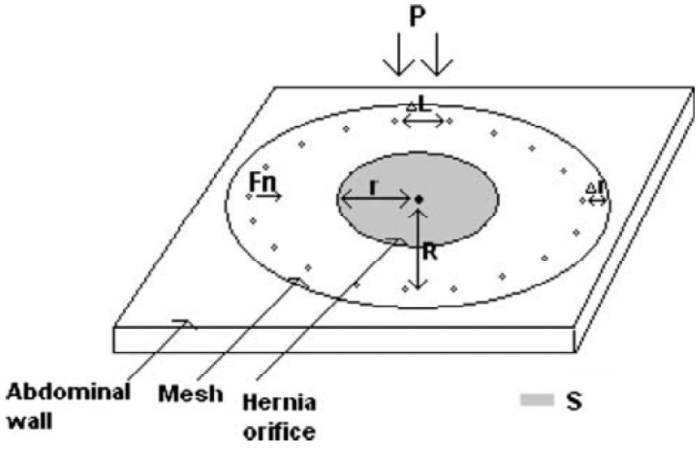

Fig. 2. Mathematical model described by Smietanski et al. View from inside the abdominal cavity of a ventral hernia covered with a mesh.[5]

The time just after the operation is crucial for the strength of the hernia repair. After two weeks, the mesh should have been incorporated into the abdominal wall and the mesh-tissue system becomes less vulnerable. Postoperative coughing is the first, and simultaneously the most extreme force, that a fixation device needs to withstand, set at a maximum of 270 mmHg. Assuming a hernia defect of 5 cm diameter, and tacks placed at 1.5 cm distance Smietanski et al. calculated a force of 8 N is developed on one tack during a cough. However, this force rises with increased hernia size: with a defect of 10 cm a force of 18 N is calculated, and with a defect of 15 cm the force on one tack rises up to 32 N.[5]

Besides these mathematical models, numerous experimental setups have been developed to examine the fixation strength of a device. The most frequently used models investigate the tensile strength or the burst strength. Tensile strength can be defined as the maximum stress that a material can withstand while being stretched or pulled before breaking and is mainly noted as force per unit area (N/cm or N/cm^2). By testing tensile strength, the shear forces working on the mesh-tissue interface have been examined in an uni-axial model. Using this model, the force at one device can be measured accurately, and this allows comparison between two or more devices. However, the tensile strength model does not account the stretching and the dynamics of the abdominal wall, nor does it takes into account the influence of the hernia size.

Burst strength is the ability of a material to withstand pressure without rupture; it is the hydraulic pressure required to burst a material. Burst strength testing takes the whole mesh–abdominal wall into consideration in a three-dimensional model, with its elasticity and strength, and not only the surface between the mesh and the tissue. However, with this model, it is difficult to filter out the influence of mesh type and the elasticity of the abdominal wall and to measure the strength of one single fixation device.

In this thesis two different animal models were used. In the first experiment a pig model was used. After a survival period of six months, the pigs had grown a lot. Their weight has rosen to more than 120 kilogram. This made the practical handling very difficult. Therefore we decided to use sheep in the second experiment as they have a maximum weight of 80 kilogram.

Van ‘t Riet et al. performed their experiment on pig cadaver tissue. A mesh was fixed to the specimen with either tacks or sutures. The cranial side of the abdominal wall specimen was clamped. The caudal margin of the mesh was grasped by clamps and connected to a dynamometer. The mesh was pulled in the direction of the caudal margin. The force needed to disrupt the fixation of the mesh was measured. The tensile strength of a single transabdominal Prolene 0 suture (67 N) was 2.5 times higher than the tensile strength of a single tack (28 N).[11]

Hollinsky et al. used a similar model. Two pieces of mesh (2x3 cm) were fixed to the peritoneum of rats with transfascial sutures, titanium tacks and two kinds of absorbable tacks. After the survival

period the mesh and abdominal wall were excised and cut into pieces (1x1.5 cm). The mesh was fixed to one side and the abdominal wall was fixed to the other side of a testing machine. Traction was performed until the mesh became detached from the abdominal wall. After one week and after two months (values given), tensile strength was significantly higher for sutures (13.2 N/cm²) versus titanium tacks (Protack® 9.7 N/cm²) or absorbable tacks (Absorbatack 8.7 N/cm² and I-clip® 4.5 N/cm²).[13]

The first experiment included in this thesis used an similar setup. The force needed to tear the tack out of the tissue was measured. To make sure the tensile strength was measured at only one device, the mesh plus abdominal wall was placed under a platform. In this way, we were more convinced that we were measuring the tensile strength of the tack itself without the influence of the elasticity/strength of the abdominal wall or mesh. This allowed a more accurate comparison of the different tacks. At two weeks, Protack (32 N/cm²±12) was associated with significantly higher tensile strength than Sorbafix (26 N/cm²±11) (p=0.036), Absorbatack (17 N/cm²±14) (p=0.001) and Permasorb (11 N/cm²±7) (p=0.0001). At six months, Permasorb (9 N/cm²±4) (p=0.001) still had the lowest tensile strength whereas Sorbafix (29 N/cm²±13) had reached equal strength as Protack (28 N/cm²±11) (p=0.56).
The conclusion of these experiments was that transabdominal sutures provide the highest tensile strength. According to van ‘t Riet et al. and Hollinksy et al. their use remains mandatory.[11,13] Smietanski et al. recommend their use for large hernia that have a diameter of more than 10 cm.[5] However, in both the study of van ‘t Riet and in our experiment Protack reached a tensile strength of 28 N. This is higher than the values needed as reported by Cobb et al. (27 N/cm) and Junge et al. (16 N/cm).[22,23] Hollinksky et al. reported lower values, probably because their experiment was performed in a small animal model.[13]

The primordial function of a fixation device is to keep the mesh in place while tissue ingrowth occurs. If a mesh moves or migrates into the former defect, a hernia recurrence may occur. A good fixation device is defined by its capacity to prevent hernia recurrence. In our first experiment, mesh placement was scored at the time of re-laparoscopy. Mesh movement was evaluated rather arbitrarily regarding its position to the abdominal wall. In the second experiment, a fascial defect was created. During placement, the position of the mesh was noted accurately. The distance of the borders of the mesh to some cardinal points (xyphoid and pubis) was measured. Those distances were again measured after the survival period. Mesh migration was less than 0.5 cm in all cases. This means that the fixation devices met their goal in terms of preventing mesh movement.

Regarding prevention of hernia recurrence, no benefit has been proven for the addition of transabdominal sutures. Although, a large randomized controlled trial is still lacking, there is no

evidence that a difference exists in hernia recurrence rates between the use of sutures or tacks as a primary fixation device. The literature on this topic have been extensively discussed in part 3.1. The conclusion of this systematic review is that, regarding surgical outcome, no particular benefit can be demonstrated for one type of fixation.
Although the tensile strength of transabdominal sutures is significantly greater than tacks, adding them does not improve the results of LVHR in the longer term.

Nowadays, numerous tack materials are available. In part 3.2, an overview is given of the presently available tack materials. Tacks do differ in length and shape and subsequently the mechanism of tissue penetration. Although Protack is the shortest, it has shown the highest fixation strength in animal experiments.[13,21] There are limited data available on what the optimal tack length should be, but we can assume that tacks fix stronger when they capture the fascial layer. As Protack is the shortest but is also the strongest, the shape, and thus the mechanism of fixation and the firing mechanism may be even more important than tack length. The screwing design is superior to the clip or pushpin form. The tacks are shot forcefully into the tissue and, with its sharp tip, Protack is very effective in capturing tissue.
In our experiment, the screwing absorbable device, Sorbafix, reached equal strengths to Protack. Absorbatack was the only tack that had effectively resorbed after six months. Mesh migration was not observed in any of the animals. Although, Protack is stronger in the short-term, regarding fixation strength, Sorbafix and Absorbatack do meet expectations. At both the short- and long-term evaluations, no mesh migration was observed and tensile strength was higher than 16 N/cm.[23]

In our second experiment, the single use of cyanoacrylate glue (CA) was evaluated as fixation device. In our opinion, a burst strength testing model was more convenient for this purpose. Schug-Pass et al. developed a biomechanical model that suited as an example for our model.[26] For this test, 18x23cm pieces of muscle tissue with a hole in the middle were clamped in a frame. A mesh was placed over the defect and fixed with fibrin glue. Three minutes after application of the glue, a plunger was moved towards the defect and the force needed to disrupt the mesh was recorded digitally. In this model, the muscular tissue was clamped and the mesh was placed behind, to mimic a TAPP repair. In our model, the plunger was moved towards the fascial defect, but the mesh-abdominal wall sample was positioned with the mesh upwards. The mesh was pushed through the defect as occurs in real-life LVHR. For this experiment, the described setup was preferred to enable evaluation of entire mesh-abdominal wall defect (closed or not), rather than one particular fixation point. The maximum force that this system could develop was set on 100 N; all samples, except one, resisted this force and no mesh migration was observed.

In contrast to fibrin glue, cyanoacrylate provides a solid fixation of the mesh to the abdominal wall.[26] As noted above, mesh migration was measured very carefully and was negligible in all samples. Considering the limitations of the study, naming the animal model and the limited defect created (2 cm^2), we conclude that the single use of CA offers a good mesh fixation in small fascial defects.

6. Closure of the defect

The size of the fascial defect is a contributing factor to the repair of a hernia. A larger hernia requires a different approach. Larger mesh material is needed to allow sufficient overlap. This makes it more difficult to handle; to bring the mesh into the abdomen and to position it over the defect. Nowadays different tools are available to facilitate this position. Larger meshes also need more fixation points. Moreover, with a larger defect, more tension is put on the different fixation devices. Therefore, some surgeons have begun closing the fascial defect before mesh placement.

In the literature, different techniques have been described to approximate the fascial edges. The defect can be closed percutaneous with separate stiches brought into the abdomen through small skin incisions and then taken out again, using an Endoclose needle. The sutures are knotted outside and buried subcutaneously. This technique has been described by Chelala et al., Franklin et al. and Orenstein et al.[27-29] Palanivelu et al. close the defect with intracorporeal running sutures and knot them externally.[30] Intracorporeal defect closure can be performed with a standard needle driver or with an Endo Stich device.[31] The authors, above mentioned, have reported large series with long-term follow-up periods and good results. They have practiced closure on almost all defect sizes and experienced no increase in pain due to their procedure. The results are presented in Table 1. However, there is still no randomized controlled trial that can prove the benefit of closure of the defect without increased abdominal wall pain. Especially with larger defects, sometimes considerable tension is needed to approximate the fascial edges.

Several benefits can be proposed for the so named “augmenting repair”. First, the effective contact of the mesh with the peritoneum is enlarged. Performing a “classic” LVHR, the mesh is positioned over the fascial defect and is fixed at its borders, usually called a “bridging repair”. This means that only this part of the mesh is in contact with the peritoneum and that tissue integration is only achieved at this outer circle. By closing the defect, the mesh–peritoneum contact is augmented and integration of the mesh is increased, which reduces the need for fixation. Secondly, as mentioned above, the forces working on the surface of the hernia orifice depend on the radius of the defect. A decreased radius means less forces, which reduces the need for more fixation. Thirdly, with closure of the defect, the mesh will not be pushed into the defect and less traction is placed on the devices, resulting in less

pain. Fourth, by approximating the fascial edges, improved physiological restoration of the abdominal wall is achieved. The "bulging phenomenon", as is seen without closure, does not occur, resulting in a better cosmetic result. Finally, in our experiment, although only small defects of 2 cm² were created, we saw a significant decrease of seroma formation with fascial closure.

Zeichen et al. retrospectively compared closure versus non-closure of the defect using recurrence rate as the primary endpoint.[31] After a mean follow-up of 797.2 days they found a recurrence rate of 6.25% in the closure group compared to 19.18% in the non-closure group. Although this difference was not statistically different a trend was shown. In our experiment no difference was seen regarding the strength of repair, but a significant reduction in seroma formation was seen with closure of the defect.

Author	*n*	Mean FU (M)	Closure achieved	Mean defect size	Recurrence rate	Chronic pain
Chelala 2007 [27]	400	28	95.5%	2-14 cm	6 (1.5%)	10 (2.5%)
Franklin 2004 [28]	384	47.1	100%	Not given	11 (2.9%)	12 (3.1%)
Palanivelu 2007 [30]	736	4.2 years	721 (97.9%)	96 cm² (11-128)	4 (0.55%)	36 (5%)

Table 1. This table summarizes the results of authors that systematically close the facial defect before mesh placement.

7. Cyanoacrylate glue

As none of the available fixation devices succeed in resolving postoperative pain syndrome, the interest in atraumatic fixation is growing. A few trials suggest that the use of glue is effective in reducing fixation-associated postoperative discomfort.[32,33] Cyanoacrylates (CA) are a group of fast-acting adhesives. In general, CAs consist of monomers of cyanoacrylate molecules. They rapidly polymerize in the presence of water and have extremely strong binding capacities. CAs do have a large application field. In industry or domestic situations, they are known as Superglue or Crazy glue, and in medical practice for skin closure and hemostasis.

Although Woodward et al. had already reported in 1965 on CAs limited toxicity in medical use, many surgeons are still skeptical.[34] Superglue is 100% ethyl-cyanoacrylate whereas the adhesives used in clinical practice are n-butyl cyanoacrylate, hexyl-cyanoacrylate or n-octyl-cyanoacrylate.

Another benefit of the use of cyanoacrylate glue is its low price. The production of commercial cyanoacrylate is very cheap. The products used in medical setting are more expensive but still cheaper

compared to other devices. Moreno-Egea et.al performed a cost analysis of the use of n-hexyl-α-cyanoacrylate in inguinal hernia repair.[35] The price of cyanoacrylate is only one third of the price of straps. Besides, there is an additional cost saving through reduced operation time and hospital stay. In Belgium it is however difficult to make a correct price comparison. The factory price is not published. The price of the fixation products differs in each hospital depending on the negotiated contracts. The price of a tack varies between 250 euros and 350 euros, with Protack being the cheapest and the resorbable devices being more expensive. The price of one equivalent dose of cyanoacrylate glue is around 200 euro.

The length of the alkyl chain determines their adhesive strength, but also the toxicity. Whereas methyl-2-CA is nectrotizing and pyogenic, hexyl- and 2-decyl-CA provoke only a mild and transient inflammatory reaction. These findings were very recently confirmed through a large biocompatibility test performed by Kukleta et al.[36] The cyanoacrylate extracts were non-mutagenic, non-irritating and no evidence could be found for systemic toxicity. CA was also injected in the peritoneal cavity without adverse effects.

In our experiment, no adverse effect could be observed. Although the use of CA was associated with a pronounced inflammatory reaction in the acute phase, this was not seen in the longer term, and it did not induce mesh shrinkage. CA allows good tissue integration and does not cause chronic inflammation.

Previously, Larduner et al. examined the use of CA in the intraperitoneal position. In a first experiment in a rabbit model, they performed a tensile strength test at twelve weeks after implantation. No mesh migration was noticed. The tensile strength of the ePTFE meshes fixed with tacks was equal to the PP meshes fixed with CA (6.6±2.7 N) while poor results were reported for ePTFE meshes fixed with glue. Later, the authors performed a similar experiment with a PP mesh only. Although a higher tensile strength for glue was reported (9.64±0.78 N) in the second experiment, this was significantly less than the suture and tack group (14.15±0.97 N and 14.84±0.74 N respectively). The authors concluded that the use of glue would not yet replace tacks, but could reduce the number used.[37,38]

Fortelny et al. performed an similar experiment in a rat model. Biomechanical testing was performed after 12 weeks. Although, no mesh migration was seen and burst strength testing was successful for all samples, the authors did not recommend the use of CA. They reported an impaired tissue integration at the points of glue disposition.[39] This observation is in contrast to previous findings. In our experiment, the different meshes were all well incorporated into the abdominal wall after six months. So far, the group of Fortelny et al. are the only authors who have described tissue impairment. It may

be difficult in a small animal model, where small mesh pieces are used, which makes it more difficult to applicate the glue drop wise.

With the application of glue the mesh is placed flat onto the abdominal wall. The striking maneuver promotes a flat position and ensures the entire surface of the mesh is in contact with the peritoneum. Tissue ingrowth is then enhanced over the whole mesh surface. With the use of tacks, the mesh is only in contact with the wall at the points of fixation. In between, the mesh “cupps” or “tents”, and tissue integration is impaired at these points.

With the use of glue, the more extreme points of the mesh can be fixed as well. For example, the xyphoid or pubis may be challenging locations to place a tack, but these points can be easily reached with the glue applicator. However, the application of glue is still challenging. From an ergonomic point of view, tacks are very easy to handle whereas application of glue is still more difficult. In our experiment, we had some difficulty to apply the glue properly to the mesh. Positional sutures were used to hold the mesh in place while the glue was applied. The glue was placed in three rows starting from the back. However, this was a difficult maneuver as the available applicator was very bendable, which made it hard to reach the most distant points. The glue itself is liquid and drops of glue rolled off the mesh, as the borders were hanging down during placement. Although we placed a gauze to protect the intestines, contact with glue could not be prevented. Recently developed devices that provides glue drops may overcome this problem. There are also more practical tools available to facilitate mesh positioning. The AccuMesh Positioning system® (Covidien Corp., Mansfield, MA, USA) is an expandable frame that allows positioning of the mesh over the defect while the mesh is tacked. The Echo PS system® (Bard, Davol Inc., Murray Hill, NJ, USA) is a balloon that is pre-attached to the mesh and facilitates unrolling of the mesh to the abdominal wall when insufflated. With this devices it may be more practical to hold the mesh while the glue is applied. However, it remains difficult to prevent the glue drops from rolling off the mesh, as the borders of the mesh are not curled upwards. Self-gluing meshes are available for inguinal hernia repair but, to the best of my knowledge, so far, their use is not suitable for ventral hernias.

There are no data yet on which type of mesh should be used with CA glue. In my experience, the positioning of the glue is one decisive factor. If the glue is placed on the mesh first and then pulled against the wall, a coated mesh can be used. If the mesh is positioned first and the glue must diffuse through the pores afterwards, a non-coated, permeable, mesh need to be used. However, with this approach the only option for laparoscopic hernia repair is then an ePTFE mesh.

So far everyone agrees glue can be effective in reducing pain syndromes, but no data are available. With the use of glue, the side effects of tissue penetrating devices can be overcome. However, if the mesh is positioned over an open defect, the mesh can be pushed into the defect and a pulling sensation

may still be present. This discomfort will be distributed over the entire mesh rather than at one fixation point as occurs with tacks and sutures.

8. Future perspectives

The search for atraumatic fixation continues. For both the absorbable tacks as for cyanoacrylate glue sufficient experimental data exists regarding fixation strength. Concerning their role as fixation device we can assume they achieve their goals. Whether these devices will result in less pain syndromes is an unsolved question yet. Future research should focus on large, prospective randomized controlled trials to prove the effectiveness in reducing tissue trauma of the studied devices. The absorbable tacks are already widely spread in daily surgical practice as their fixation mechanism is similar to that of the well-known permanent tacks. The use of glue however is a totally new concept and not many surgeons are familiar with this technique. More user-friendly devices should be developed. First, the application of the glue must be facilitated. The applicator needs to allow positioning of the glue at the entire surface of the mesh without spillage. Secondly, a thorough investigation is needed on what the optimal mesh – glue combination should be. Which intraperitoneal mesh is the most appropriate when glue is used as mesh fixation? Third, the positioning of the mesh over the defect before glue deposition must be simplified. There are tools available (cfr. supra) but none of them are developed with the aim to use glue as fixation. A cupped mesh, with curled up borders might be useful to prevent leakage of glue. With the use of sutures on different positions the glue can be disposed but easier devices could be developed. Eventually, the use of self-gluing meshes might give an answer to this question. Basically, the long-term result of a LVHR will depend on the ingrowth of the mesh in the peritoneal tissue. Further research should focus on mesh reinforcement and which role CA will play in enhancing mesh incorporation.

9. *Conclusion*

The primordial function of a mesh fixation device is to keep the mesh in place until tissue ingrowth has occurred. Failure in this early phase results in mesh migration, buckling and mesh contraction, and weakens the repair. Integration of the mesh into the abdominal wall can be augmented by enlarging the effective surface of the mesh in contact with the tissue. If tissue integration is enhanced, the need for fixation can be reduced. One way to achieve an augmented repair is to close the fascial defect before mesh placement. A second way is to use a glue for mesh fixation. With glue, the mesh is spread to the abdominal wall and the entire surface is then in contact with the peritoneum. The traditional fixation devices, tacks and sutures, provide strong mesh fixation. Although the use of transabdominal sutures is associated with significantly greater tensile strength in experimental settings, their use does not improve the long-term results compared to the single use of tacks. There is no significant difference in hernia recurrence rates with the use of transabdominal sutures compared to tacks. As they penetrate the entire abdominal wall, it is suggested that the use of transabdominal sutures is associated with greater postoperative pain rates. However, those that omit them and only rely on tacks still report high pain levels. The introduction of resorbable tacks diminished tack-associated complications, such as inflammation, adhesion formation and tack migration. Their benefit regarding postoperative pain is, however, still questioned. The use of cyanoacrylate glue could be a valid alternative: it is likely that the use of glue will diminish postoperative pain syndromes as it is not traumatic to the tissue, although no data are yet available. Before the widespread use of glue, guidelines are needed for correct application and, until now, there is no evidence for its use as single fixation method for large defects. With systematic closure of the fascial defect and the use of cyanoacrylate glue, the mesh-abdominal wall contact is intensively augmented. This concept can reduce or even eliminate the need for tissue-penetrating mesh fixation, which may further enhance the future of laparoscopic ventral hernia repair.

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PART 5

SUMMARY

PART 5. SUMMARY

The introduction of mesh materials significantly improved the treatment of ventral hernia. The use of minimal invasive techniques further enhanced the results because laparoscopy made it possible to avoid the extensive tissue dissection needed to place the mesh in an open repair. This resulted in less wound morbidity. Compared to the open technique, both wound and mesh infections are significantly less frequent with laparoscopic ventral hernia repair (LVHR).
However, looking at the surgical outcomes of LVHR, recurrence rates are not better compared to open repair. Moreover, nowadays it is known that LVHR is associated with more pain and a lower quality of life, especially in the first postoperative month.

The technique of LVHR involves the introduction of a mesh, suitable for intraperitoneal placement, into the abdomen through one of the trocars. Subsequently, the mesh is positioned over the fascial defect and fixed to the abdominal wall with one of the available fixation devices. A fixation device must be able to hold the mesh in place until the mesh has been incorporated in the abdominal wall tissue, which usually has occurred after two weeks.

The traditionally used fixation devices, tacks and sutures, provide excellent fixation strength. Tacks are shot through the mesh into the abdominal wall. Sutures are placed through the entire abdominal wall plus the mesh and are knot outside the abdomen. However, because these devices penetrate the abdominal wall, they are traumatic to the tissue and may cause nerve or vessel entrapment. This results in postoperative discomfort. Moreover, as the fascial defect is left open in LVHR, the mesh is pushed into the defect. This way traction is performed on the fixation devices which causes a pulling sensation at the fixation points. After LVHR, up to 30% of patients suffer pain in the first postoperative month and 3-7% suffer chronic pain.

In an attempt to reduce fixation-related morbidity, without compromising mesh fixation strength, new systems were introduced. The aim of this thesis was to evaluate the available mesh fixation devices regarding fixation strength and fixation related morbidity.

In a review the most widely used fixation devices, tacks and sutures were compared. According to the inclusion criteria, 25 series were included. All series reported a recurrence rate in a patient group of at least 30 patients, who were operated for a ventral hernia, using a well-defined mesh fixation technique. The series were grouped in three fixation categories: “tacks and sutures”, “tacks only”, and “sutures only”. Overall recurrence rate was 2.7%, without a significant difference between the three fixation groups. Regarding prevention of hernia recurrence, no benefit could be proven for the

addition of transabdominal sutures. Although, a large randomized controlled trial is still lacking, there is no evidence that recurrence rates differ between the use of sutures or tacks as primary fixation device. Although the tensile strength of transabdominal sutures is significantly higher than tacks in many experimental models, adding them does not improve the results of LVHR on the long-term.
As they penetrate the entire abdominal wall, it is likely that the use of transabdominal sutures contributes to postoperative pain. Several authors described pain as a discomfort localized at the suture site. However, even after the use of transabdominal sutures was omitted, high pain scores were reported. Independent of fixation type used, the reported pain levels are remarkably high after LVHR.

Nowadays, numerous tack materials are available. Tacks differ in length and shape, and subsequently in mechanism of tissue penetration. Although the titanium tack, Protack®, is the shortest, it showed the highest fixation strength in animal experiments. There are limited data available on what the optimal tack length should be, but we can assume that tacks fixate stronger when they capture the fascial layer. As Protack is the shortest but meanwhile the strongest, the shape, e.g. the mechanism of fixation and the firing mechanism may be even more important than the tack length. Regarding fixation strength, the screwing design is superior to the clip or pushpin form.

In the first experiment three resorbable tacks (Permasorb®, Sorbafix® and Absorbatack®) were compared to the titanium tack (Protack). In a pig model two different composite polypropylene meshes were implanted to the abdominal wall by laparoscopy, each fixed with two of the four different tacks. After two weeks and six months the following observations could be done:

- Migration of the spiral titanium tacks was observed in 4/6 animals. The tacks had migrated out the mesh into the omentum, however, without causing visible complications. This observation could not be done with the resorbable devices.
- Absorbatack was the only tack that could not be identified anymore at six months.
- At two weeks, the titanium tack (32 N/cm²) had a significant higher tensile strength than Sorbafix (26 N/cm²)(p=0.036), Absorbatack (17 N/cm²)(p=0.001) and Permasorb (11 N/cm²)(p=0.0001). At six months, Permasorb (9 N/cm²) (p=0.001) was still the weakest, while Sorbafix (29 N/cm²) reached equal strength to the titanium tack (28 N/cm²)(p=0.56).
- Both adhesion formation and inflammatory reaction were significantly higher with the titanium tack compared to the resorbable tacks at short-term, but at long-term these were comparable.

The use of absorbable screwing devices (Sorbafix and Absorbatack) is associated with high tensile strength and low fixation-associated complications and are therefore currently the fixation devices of choice. However, regarding its impact on postoperative pain, no benefit could be proven yet.

A second experiment was performed to evaluate the intraperitoneal use of cyanoacrylate glue as mesh fixation in LVHR. In a sheep model two meshes were implanted laparoscopically, either fixed with straps or with cyanoacrylate glue. After one day, two weeks and six months, mesh placement was satisfying: we observed good incorporation in the abdominal wall and mesh migration was less than 0.5 cm for all samples, except one mesh in the one day group that had detached. Cyanoacrylate glue provides a strong fixation. During the burst strength testing procedure, all samples could withstand the maximum pressure of 100 N. Although the use of cyanoacrylate glue was associated with a pronounced inflammatory reaction in the acute phase, this was not seen at long-term, nor did it induce mesh shrinkage. Adhesion formation was similar in the glue group compared to the strap group and adhesions predominantly formed to the entire surface of the mesh rather than to the site of fixation.
In one half of the animals the fascial defect was closed before mesh placement. Significantly less seroma formation was seen with fascial closure, while no benefit could be demonstrated regarding strength of repair.

The use of cyanoacrylate glue as single fixation can be recommended in small ventral defects. Because of high fixation strength and acceptable inflammatory reaction it can be used to reduce the use of tissue penetrating fixation devices in larger defects. Its use can diminish postoperative pain syndromes but no data are yet available. Moreover, its technical application needs to be further improved. The present available applicator is not capable to position the glue at the right place. New mesh positioning tools and other devices are currently investigated which could make the use of glue more practical.

The integration of the mesh in the peritoneal tissue determines the long-term durability of hernia repair. By enlarging the effective mesh–abdominal wall contact, tissue integration is promoted. With the application of glue, the effective contact is augmented because the mesh is spread out to the abdominal wall while with tacks, the mesh is only in contact at the particular fixation points. A secondary way to increase the mesh-abdominal wall surface is by closing the fascial defect before mesh placement. Moreover, with closure of the defect, the mesh cannot be pushed into the remaining orifice and traction on the fixation devices is reduced. With systematic closure of the defect and the use of cyanoacrylate glue the need for tissue-penetrating devices can be diminished or even eliminated which can further enhance the technique of laparoscopic ventral hernia repair.

SAMENVATTING

Het gebruik van een mesh bij de behandeling van een ventrale hernia heeft de uitkomst van het heelkundig herstel significant verbeterd. De introductie van minimaal invasieve technieken droeg verder bij in de vooruitgang van de behandeling van ventrale hernia. Bij een laparoscopisch buikwandherstel kan de weefsel dissectie, die noodzakelijk is om de mesh te plaatsen bij een open herstel, vermeden worden. Ten gevolge hiervan noteert men een significante daling van de morbiditeit ter hoogte van de wondnaad. In vergelijking met een open herstel, treden er bij laparoscopie minder frequent wond- en mesh-infecties op. Wanneer de resultaten van laparoscopisch buikwandherstel op lange termijn beschreven worden, kan men geen verschil aantonen wat betreft het optreden van een recidief hernia in vergelijking met een open hernia herstel. Men vermeldt in de eerste postoperatieve maand zelfs een hogere pijnratio, en een lagere kwaliteit van leven na een laparoscopisch buikwandherstel in vergelijking met een open benadering.

De techniek van een laparoscopisch buikwandherstel bestaat er allereerst in de mesh, speciaal ontworpen voor de intraperitoneale positie, door een van de trocars in het abdomen te brengen. Hierna wordt de mesh gepositioneerd over het fasciadefect en bevestigd tegen de buikwand met een van de beschikbare fixatiematerialen. De gebruikte fixatie moet voldoende stevig zijn om de mesh ter plaatse te houden tot deze in de buikwand is ingegroeid. Ingroei van de mesh in de buikwand is voltooid na twee weken.

Het is aangetoond dat de traditionele fixatietechnieken, tacks en transabdominale suturen, voldoende fixatiesterkte bieden. De tacks worden door de mesh in de buikwand geschoten. De suturen worden door de volledige buikwand en de mesh geplaatst en dan langs de buitenzijde van het abdomen geknoopt. Omdat deze materialen de buikwand doorboren, zijn zij traumatisch voor het weefsel en kunnen zij zenuwen of bloedvaten raken. Hierdoor klagen veel patiënten van pijn aan de buikwand na een laparoscopisch herstel. Bovendien wordt bij een laparoscopisch herstel het fascia defect opengelaten waardoor de mesh in de bestaande holte wordt geduwd. Hierdoor wordt tractie uitgeoefend op de fixatiematerialen wat opnieuw aanleiding tot pijn kan geven. Na een laparoscopisch buikwandherstel klaagt tot 30% van de patiënten van abdominale wandpijn in de eerste postoperatieve maand; 3-7% van de patiënten klaagt van meer langdurige pijn.

Om deze morbiditeit te verminderen, weliswaar zonder toegift wat betreft de sterkte van fixatie, werden nieuwe fixatiematerialen gelanceerd. Het doel van dit werk is om de fixatietechnieken te evalueren, meer bepaald betreffende fixatie sterkte en fixatie-gerelateerde morbiditeit.

Ten eerste werd in een review de meest gebruikte materialen, tacks en transabdominale suturen, vergeleken. Er werden 25 studies opgenomen die voldeden aan de inclusie criteria. Alle series vermelden een recidief ratio bij een groep van tenminste 30 geopereerde patiënten. Hierbij gebruikt de auteur een goed beschreven techniek. De studies werden vervolgens gegroepeerd in drie fixatie categorieën: “tacks en transabdominale suturen”, “tacks alleen”, en “transabdominale suturen alleen”. De gemiddelde recidief ratio over alle studies heen was 2.7%. Er kon geen verschil aangetoond worden tussen de drie fixatie categorieën. Er is bijgevolg geen voordeel voor het gebruik van transabdominale suturen wat betreft de preventie van een recidief hernia. Alhoewel er nog geen grote gerandomiseerde studie beschikbaar is, kan men aannemen dat er geen verschil is wat betreft het optreden van een recidief bij het gebruik van tacks of transabdominale suturen als primaire fixatietechniek. In dierexperimenteel onderzoek werd aangetoond dat de trekkracht van suturen significant hoger is dan die van tacks. Echter, op lange termijn kan geen voordeel aangetoond worden voor het gebruik van suturen.

Omdat zij de volledige buikwand doorboren, kan men ervan uitgaan dat het gebruik van suturen aanleiding geeft tot abdominale wandpijn. Verschillende auteurs beschreven postoperatieve pijn als een oncomfortabel gevoel ter hoogte van de plaats van de suturen. Echter, wanneer het gebruik van suturen achterwege werd gelaten, werden nog steeds hoge pijnscores gerapporteerd. Patiënten klagen van significante pijn na een laparoscopisch buikwandherstel, onafhankelijk van het type fixatie dat gebruikt wordt.

In een tweede review worden verschillende tacks beschreven. Tacks zijn verschillend in lengte en vorm en dus in mechanisme van fixatie. Hoewel Protack®, de titanium tack, de kortste is, toonde deze tack de hoogste fixatie sterkte in dierexperimenteel onderzoek. Er is weinig geweten over de optimale lengte van een tack. We kunnen echter veronderstellen dat een tack beter de mesh fixeert wanneer deze ook de fascia mee fixeert. Gezien de kortste tack, Protack, ook de sterkste is, is tevens de vorm van de tack en het afvuurmechanisme van belang. Wat de vorm betreft, opteert men beter voor een schroefvorm dan wel voor de vorm met twee haakjes.

In een eerste experimenteel onderzoek wordt de titanium tack vergeleken met drie resorbeerbare tacks (Permasorb®, Sorbafix® en Absorbatack®). In een varkensmodel worden twee verschillende meshes geïmplanteerd in de buikwand, telkens gefixeerd met twee van de vier verschillende tacks. Na een overlevingsperiode van twee weken en zes maanden konden de volgende vaststellingen worden gedaan :

- In vier van de zes dieren zagen we een migratie van de tacks uit de mesh in het omentum. Er werden weliswaar geen complicaties vastgesteld ten gevolge van de tack migratie. Deze migratie kon niet worden vastgesteld bij de resorbeerbare tacks.
- Absorbatack was de enige resorbeerbare tack die niet meer kon teruggevonden worden na zes maand.
- Na twee weken had Protack (32N/cm²) een significant hogere trekkracht dan Sorbafix (26N/cm²)(p=0.036), Absorbatack (17 N/cm²)(p=0.001) en Permasorb (11 N/cm²)(p=0.0001). Na zes maand was Permasorb (9 N/cm²) (p=0.001) nog steeds de zwakste tack. Sorbafix (29 N/cm²) bereikte toen een gelijkaardige trekkracht als Protack (28 N/cm²)(p=0.56).
- Op korte termijn waren zowel adhesie vorming als inflammatoire reactie significant hoger met de titanium tack in vergelijking met de resorbeerbare tacks. Op langere termijn was adhesievorming en inflammatie echter vergelijkbaar.

Het gebruik van resorbeerbare tacks (Sorbafix en Absorbatack) biedt voldoende mesh fixatie sterkte en geeft aanleiding tot minder fixatie-gerelateerde complicaties. Daarom is het gebruik van deze materialen heden de gouden standaard. Of zij echter effectief minder aanleiding geven tot pijn is nog niet bewezen.

Een tweede experiment werd uitgevoerd om het gebruik van cyanoacrylaat lijm als fixatietechniek te onderzoeken. In een schapenmodel werden twee meshes geïmplanteerd, de ene gefixeerd met lijm, de andere met straps. Na een dag, twee weken en zes maand was de mesh plaatsing steeds correct. We zagen een goede incorporatie van de mesh in de buikwand en migratie van de mesh bedroeg minder dan 0.5cm bij alle dieren, behalve één mesh die volledig was losgekomen en op de darmen lag.
Cyanoacrylaatlijm voorziet voldoende stevige fixatie. Tijdens de burst test bleven alle stalen geïmmobiliseerd bij een druk van 100N. Op korte termijn gaf het gebruik van lijm aanleiding tot een belangrijke inflammatoire reactie, dit kon niet weerhouden worden op lange termijn. Er was evenmin een krimping van de mesh meetbaar. Adhesies werden gevormd bij beide fixatiematerialen en dit eerder aan de volledige oppervlakte van de mesh dan enkel aan de plaats van fixatie.
Bij de helft van de dieren werd het fascia defect gesloten voor het plaatsen van de mesh. Er werd significant minder seroma vorming gezien bij de dieren waar het defect gesloten was. Wat betreft sterkte van herstel, de burst test, kon echter geen voordeel bewezen worden voor al dan niet sluiten van het defect.

Het gebruik van cyanoacrylaatlijm als enig fixatiemiddel kan aanbevolen worden bij kleine fasciadefecten. Een goede fixatiesterkte en aannemelijke inflammatoire reactie maakt hun toepassing

eveneens bruikbaar bij grotere defecten, dan wel om het gebruik van de traditionele materialen te verminderen. Het gebruik van lijm zou pijnsyndromen kunnen verminderen, maar er is nog geen data voorhanden. Bovendien dient de toepassing nog geoptimaliseerd te worden. De huidige pipet om de lijm te positioneren kan de lijm niet nauwkeurig genoeg ter plaatse brengen. Heden worden materialen getest om de mesh ter plaatse te houden en nadien te lijmen, alsook andere lijmpipetten. Dit zou het gebruik van lijm als fixatie meer praktisch kunnen benaderen.

Het resultaat van een buikwandherstel op lange termijn wordt bepaald door de ingroei van de mesh in het peritoneum. Door het contactoppervlak van de mesh met het peritoneum te vergroten kan deze ingroei geoptimaliseerd worden. Wanneer lijm wordt gebruikt, wordt de mesh tegen de buikwand gestreken, terwijl bij tacks de mesh enkel in contact is met de buikwand op de plaats van de fixatiepunten. Een tweede manier om het contactoppervlak te verhogen is door het sluiten van het fascia defect voor de mesh geplaatst wordt. Wanneer dit defect gesloten is kan ook minder tractie uitgeoefend worden op de fixatie punten. Met sluiten van de fascia en het gebruik van cyanoacrylaatlijm kan het gebruik van traumatisch fixatie verminderd worden of zelfs geëlimineerd. Dit zal de toekomst van laparoscopisch ventraal buikwandherstel verder bepalen.

RÉSUMÉ

L'utilisation d'une prothèse pour le traitement d'une hernie abdominale a amélioré le résultat de la reconstruction chirurgicale de manière significative. L'introduction de techniques minimales invasives a contribué au progrès fait au niveau du traitement d'une hernie abdominale. Dans le cas d'une reconstruction de la paroi abdominale, la dissection du tissu, nécessaire au positionnement de la prothèse dans le cas d'une reconstruction ouverte, peut être évitée. La conséquence est une diminution significative de la morbidité à la hauteur de la suture. En comparaison avec une reconstruction ouverte, les infections de la suture et de la prothèse sont moins fréquentes dans le cas d'une laparoscopie. L'étude des résultats à long terme d'une cure de hernie abdominale laparoscopique ne montre aucune différence quant à la hernie récidivante en comparaison avec une reconstruction ouverte de hernie. Dans le premier mois postopératoire, l'on constate même un degré de douleur plus élevé et une qualité de vie moindre après la cure de hernie abdominale laparoscopique par rapport à une reconstruction ouverte.

La technique d'une cure de hernie abdominale laparoscopique consiste en premier lieu en l'application de la prothèse, créée spécialement pour la position intrapéritonéale, par le biais d'un des trocarts dans l'abdomen. Par après, la prothèse est positionnée par-dessus du déficit aponévrotique et fixée contre la paroi abdominale avec les matériaux de fixation disponibles. La fixation utilisée doit être assez solide afin de garder la prothèse en place jusqu'à ce qu'elle s'insère définitivement dans la paroi abdominale. L'insertion de la prothèse dans la paroi abdominale est complète après deux semaines.

Il a été démontré que les techniques de fixation traditionnelles, agrafes et sutures transabdominales offrent une force de la fixation suffisante. Les agrafes sont posées à travers de la prothèse sur la paroi abdominale. Les sutures sont posées sur la paroi abdominale complète et sur la prothèse, pour ensuite être nouées à l'extérieur de l'abdomen. Vu que ces matériaux percent la paroi abdominale, ils sont traumatiques pour le tissu et peuvent toucher des nerfs ou des vaisseaux sanguins. Il s'en suit que bien des patients se plaignent d'avoir mal à la paroi abdominale après une reconstruction laparoscopique. De plus, le déficit aponévrotique reste ouvert lors d'une reconstruction laparoscopique, poussant la prothèse dans la cavité existante. Ainsi, une traction est exercée sur les matériaux de fixation, ce qui peut de nouveau provoquer une sensation de douleur. Après une cure de hernie abdominale laparoscopique, presque 30% des patients se plaignent de douleurs à la hauteur de la paroi abdominale pendant le premier mois postopératoire; 3-7% des patients se plaignent d'une douleur de plus longue durée.

Afin de diminuer cette morbidité, sans diminuer la force de la fixation, de nouveaux matériaux de fixation ont été lancés. L'objectif de cette étude est l'évaluation des techniques de fixation, plus concrètement la force de la fixation et la morbidité liée à la fixation.

Dans un premier temps, les matériaux les plus utilisés, agrafes et sutures transabdominales, ont été comparés. Vingt-cinq études répondant aux critères d'inclusion ont été prises en considération. Toutes les séries mentionnent un taux récidivant pour un groupe d'au moins 30 patients opérés. À cette fin, l'auteur a utilisé une technique bien décrite. Par la suite, les études ont été réparties selon trois catégories de fixation : « agrafes et sutures transabdominales », « agrafes » et « sutures transabdominales ». Le taux récidivant moyen dans toutes les études était de 2,7%. Une différence entre les trois catégories de fixation n'a pas pu être démontrée. L'utilisation de sutures transabdominales n'offre donc pas d'avantages quant à la prévention d'une hernie récidivante. Même si une grande étude randomisée n'est pas encore disponible, nous pouvons croire qu'il n'y a pas de différences quant à la récidive dans le cas d'utilisation d'agrafes ou de sutures transabdominales comme technique de fixation primaire. Grâce à une expérimentation animale, il a été démontré que la force tractrice des sutures est significativement plus élevée que celle des agrafes. Néanmoins, à long terme, l'on ne peut pas démontrer l'avantage de l'utilisation de sutures.

Vu que les sutures percent entièrement la paroi abdominale, l'on peut supposer que l'utilisation de telles sutures provoque une douleur de la paroi abdominale. Différents auteurs ont décrit la douleur postopératoire comme une sensation inconfortable à la hauteur des sutures. Néanmoins, lorsque les sutures n'étaient pas utilisées, l'on rapportait encore des degrés élevés de douleur. Les patients se plaignent d'une douleur significative après une cure d'hernie abdominale laparoscopique, quel que soit type de fixation utilisé.

Dans un deuxième temps, les différentes sortes d'agrafes sont décrites. Les agrafes diffèrent de longueur et de forme et donc également de mécanisme de fixation. Protack®, l'agrafe en titane, est l'agrafe la plus courte. Toutefois, cette agrafe montre la force de la fixation la plus élevée lors des études expérimentales animales. Les connaissances concernant la longueur optimale d'une agrafe sont limitées à l'heure actuelle. Pourtant, nous pouvons supposer qu'une agrafe est capable de mieux fixer la prothèse lorsqu'elle assure également une fixation au niveau aponévrotique. Vu que l'agrafe la plus courte, Protack, est également l'agrafe la plus solide, la forme de l'agrafe et la manière de poser l'agrafe sont aussi de grande importance. Quant à la forme, il vaut mieux opter pour une forme hélicoïdale (en spirale) que pour une forme avec deux crochets.

Dans une première étude expérimentale, l'agrafe en titane est comparée à trois autres types d'agrafes résorbables (Permasorb®, Sorbafix® et Absorbatack®). Dans l'expérimentation avec des cochons, deux prothèses différentes ont été implantées dans la paroi abdominale, à chaque fois fixées avec deux des quatre agrafes différentes. Après une période de survivance de deux semaines et six mois, les constations suivantes ont été faites:

- Dans quatre des six animaux, nous avons pu observer une migration des agrafes de la prothèse dans l'omentum. Néanmoins, la migration des agrafes n'a pas causé de complications. Cette migration n'a pas été constatée dans le cas des agrafes résorbables.
- Absorbatack était la seule sorte d'agrafe résorbable qui n'a pas pu être retrouvé après une période de six mois.
- Après deux semaines, Protack (32N/cm²) avait une force tractrice significativement plus élevée en comparaison avec Sorbafix (26N/cm²)(p=0.036), Absorbatack (17 N/cm²)(p=0.001) et Permasorb (11 N/cm²)(p=0.0001). Après six mois, Permasorb (9 N/cm²)(p=0.001) était toujours l'agrafe la plus faible. Sorbafix (29 N/cm²) représentait alors la même force tractrice que Protack (28 N/cm²)(p=0.56).
- À court terme, tant la formation d'adhésion que la réaction inflammatoire étaient significativement plus élevées dans le cas de l'agrafe en titane qu' avec les agrafes résorbables. Par contre, à long terme, la formation d'adhésion et la réaction inflammatoire étaient comparables.

L'utilisation d'agrafes résorbables (Sorbafix et Absorbatack) offre assez de force de fixation pour la prothèse et mène à moins de complications liées à une moindre fixation. Par conséquent, l'utilisation de ces matériaux est dès maintenant l'utilisation standard. Toutefois, l'on n'a pas encore pu prouver si cette sorte d'agrafe mène à une sensation de douleur moins élevée.

Une deuxième étude expérimentale a été menée afin d'examiner l'utilisation d'une colle cyanoacrylate comme technique de fixation. Dans l'expérimentation avec des moutons, deux prothèses ont été implantées, l'une fixée à l'aide de la colle, l'autre fixée à l'aide de 'straps'. Après un jour, deux semaines et dix mois, le placement de la prothèse était- toujours correct. Nous avons pu observer une bonne incorporation de la prothèse dans la paroi abdominale et la migration de la prothèse était limitée à moins de 0,5 cm chez tous les animaux. Il n'y avait qu'un cas unique dans lequel la prothèse s'était détachée complètement et se trouvait à hauteur des intestins.

La colle cyanoacrylate offre suffisamment de fixation. Lors du « burst test », tous les échantillons restaient immobilisés sous une pression de 100N. À court terme, l'utilisation de la colle a mené à une réaction inflammatoire importante qui n'a pas été retenue à long terme. Un rétrécissement de la

prothèse n'était pas mesurable. Des adhésions ont été formées au niveau des deux matériaux de fixation, et ce plutôt sur la superficie entière de la prothèse qu'uniquement à l'endroit de la fixation.
Chez la moitié des animaux, le déficit aponévrotique a été fermé avant le placement de l'agrafe. La formation de sérome était significativement moins élevée chez les animaux avec un déficit aponévrotique fermé. Par contre, en ce qui concerne la force de récupération (le «burst test»), l'on n'a pas pu démontrer un avantage pour l'exclusion ou non du déficit.

L'utilisation de la colle cyanoacrylate peut être recommandée comme seul moyen de fixation dans le cas de petits déficits aponévrotiques. Une bonne force de fixation et une réaction inflammatoire acceptable fait de sorte que la colle cyanoacrylate peut également être utilisée dans le cas de plus grands déficits aponévrotiques, surtout pour limiter l'utilisation de matériaux traditionnels. L'utilisation de la colle pourrait atténuer les sensations de douleur, mais nous ne disposons pas encore de données suffisantes. De plus, l'application doit encore être optimisée. La pipette utilisée à l'heure actuelle ne permet pas de positionner la colle de manière assez précise. L'on est en train de tester des matériaux qui permettent de garder la prothèse en place pour ensuite appliquer la colle, ainsi que de nouvelles pipettes de colle. Ainsi, l'utilisation de la colle comme matériel de fixation pourrait être vue de manière plus pratique.

Le résultat d'une cure de hernie abdominale à long terme est déterminé par l'insertion de la prothèse dans le péritoine. En agrandissant la superficie de contact de la prothèse avec le péritoine, cette insertion peut être optimisée. En utilisant la colle, la prothèse est posée sur la paroi abdominale, tandis qu'en utilisant les agrafes, la prothèse est uniquement en contact avec la paroi abdominale à l'endroit des points de fixation. Une deuxième possibilité d'agrandir la superficie de contact est de fermer le déficit aponévrotique avant que la prothèse ne soit placée. Lorsque le déficit est fermé, une moindre traction sera exercée sur les points de fixation. En fermant le déficit aponévrotique et en utilisant la colle cyanoacrylate, l'utilisation de la fixation traumatique peut être diminuée, voire même éliminée. Ces constats détermineront l'avenir de la cure de hernie abdominale laparoscopique.

PART 6

ADDENDUM

PART 6.
ADDENDUM 1 - Intraperitoneal mesh devices for small midline hernias. Mesh behavior in a porcine model.

Emmelie Reynvoet • Koen Chiers • Ingrid Van Overbeke • Roberto Troisi • Frederik Berrevoet - Hernia (2015) *Epub ahead of print*

Purpose *Although clinical data on long-term efficacy are lacking, the use of self-expanding devices for intraperitoneal placement in the management of small midline hernias has been popularized. In the present experimental study two different devices were investigated regarding tissue ingrowth, adhesion formation and solid mesh placement.*

Methods *Two devices of 4.3 cm diameter, one ePTFE-containing small pore polypropylene mesh (PP/ePTFE) and a multi-layered large pore polypropylene patch with an oxidized cellulose anti-adhesive barrier (PP/ORC), both containing a self-deployment system, were placed intraperitoneally at the linea alba of 24 female pigs. A first laparoscopy was performed to evaluate mesh positioning against the abdominal wall. One (n=6), two (n=6), four (n=6) and twelve weeks (n=6) later, mesh appearance was inspected and adhesion formation was assessed. All meshes were excised for histological evaluation.*

Results *Folding of the patch was more frequently observed at PP/ePTFE, yet no excessive cupping was noticed. Adhesions predominantly presented at short-term evaluation. Overall adhesion formation at all samples was significantly more extensive for PP/ORC ($p=0.048$). Massive shrinkage was observed for PP/ORC: after a 12-week period 22% residual surface was preserved, compared to 83% for PP/ePTFE ($p<0.001$). While at short-term inflammatory reaction was comparable, at long-term PP/ORC induced a significant more pronounced inflammatory and foreign body reaction.*

Conclusions *Although a strong deployment system provides adequate initial placement, shrinkage and excessive adhesion formation are much more prominent in the large pore multi-layered resorbable devices compared to the ePTFE patch. This might influence long-term clinical outcome and caution seems warranted.*

Introduction

Umbilical and para-umbilical hernias are frequent types of primary hernia in adults. For the treatment of this type of hernias, the recurrence rates after pure tissue repair have been reported up to 15%.[1] Therefore, during recent years, even for small midline hernias of 1-3 cm the need for mesh reinforcement has been shown.[2-4] To avoid extensive dissection for these “in-between-sized” hernias, self-expanding mesh devices for intraperitoneal placement were developed.

The first device available combined polypropylene with ePTFE as an anti-adhesive barrier, and was created as a circular patch with two straps. The mesh can be introduced in the peritoneal cavity through a small incision at the level of the hernia. After self-deployment of the patch, traction on the straps should obtain appropriate and flat placement to the abdominal wall. These devices have been embraced by many surgeons as a quick and elegant technique with initial experience reporting promising results [5-8]. However, later studies revealed inadequate deployment, serious complications and higher recurrence rates of this device compared to the traditional retromuscular mesh placement.[9-13]

In an attempt to solve the problem of inadequate deployment a new device was introduced which contains 9 layers of different fabrics, including a three-ring memory system. With this design adequate ingrowth of the mesh might be questioned as extensive inflammatory and foreign body reaction may be expected.

In the present experimental study, two different devices for intra-abdominal use were compared, in particular focusing on adequate and safe deployment, inflammatory and foreign body reaction, adhesion formation and mesh shrinkage.

Methods

The institutional Ethical Committee of the University of Ghent approved the study protocol.

For the experimental setup, each of 24 female pigs (weight 60-80 kg) had two meshes implanted at the midline of the abdominal wall. The animals were housed in the Faculty of Veterinary Medicine, Ghent University and had free access to food and water.

Operative procedure

Anesthesia and intra-operative management was performed by a qualified veterinary doctor (I.V.). All animals were anaesthetized with a 0.22 ml/kg intramuscular injection of a solution of Tiletamine 250 mg and Zolazepam 250 mg (Zoletil) in 25 ml Xylazine 2%. After intubation, vascular access was obtained and one bolus of 4mg/kg Propofol was given intravenously. Intraoperatively, Propofol 20 mg/ml, Fentanyl 10 ml and Esmeron 50mg IV were administered. Monitoring was performed via ECG and capnography. At the end of the procedure all animals received prophylactic antibiotics, Ceftiofur 1g IM, as well as the following three days. Analgesics were administered at the end of the procedure using a 1ml intramuscular injection of Methadone 10mg/ml.

Two composite mesh devices were compared in this analysis. The first is a polypropylene mesh with an ePTFE layer as tissue-separating component and incorporates a polyethylene terephthalate (PET) polymer ring as memory system [PP/ePTFE] (Ventralex®, Davol Inc., C.R. Bard, Inc., RI, USA). The second is a multi-layered device, consisting of an absorbable oxidized regenerated cellulose layer as anti-adhesive barrier and a polypropylene layer as parietal side. In between absorbable polydioxanone rings are constructed as deployment system [PP/ORC] (Proceed Ventral Patch® (Ethicon Inc., J&J Co, NJ, USA). Both are depicted in Fig. 1.

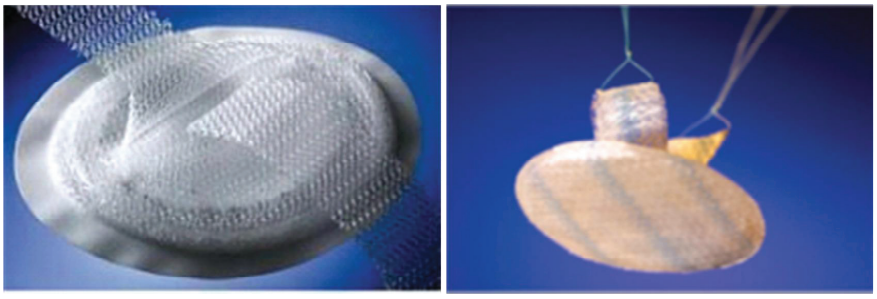

Fig. 1. Left: [PP/ePTFE]: polypropylene + ePTFE layer and a PET polymer ring as memory system. Right: [PP/ORC]: Polypropylene + ORC layer and absorbable polydioxanone rings as deployment system.

For both devices, the small size, i.e. a 4.3 cm diameter – circular shape patch, was compared in this study. Surgically, the patches were inserted at the linea alba, alternating at supra- or infra-umbilical level in a randomized pattern. After reaching the fascial layers, a 1 cm^2 sample was cut out at the level of the anterior fascia to create a weak spot at the level of mesh introduction. The peritoneum was then incised and using finger sweeps possible adherent tissue was removed from the peritoneal surface. The mesh was then inserted in the peritoneal cavity and by traction on the straps the mesh was positioned against the abdominal wall as described by Martin et al. [7]. The straps were fixed using one absorbable suture at each strap and then cut at the level of the overlying fascia. Thereafter, a 5 mm trocar was positioned in the flank of the animal and a pneumoperitoneum was developed up to 12mmHg. A laparoscope was introduced and mesh placement was evaluated. Finally, the anterior fascia was closed over the device using absorbable sutures. The skin was closed subcutaneously with absorbable monofilament sutures.

Follow-up

Four groups of each six animals were euthanized after one, two, four or twelve weeks respectively. Before euthanasia a laparoscopy was performed to evaluate mesh placement, possible adhesion formation, acquired hernia recurrence, or mesh shrinkage. After euthanasia, administering T61 intravenously, the abdominal wall plus both meshes were excised. The samples were cut and placed in formaldehyde 5%.

Adhesions

Adhesions were scored according to a validated score as described by Martin-Cartes [14]. Both extension, i.e. percentage of the mesh covered with adhesions, and severity were evaluated. (See Table 1, part 3.3)

Mesh placement

To adequately evaluate cupping of the device, all meshes were assessed for flat positioning against the peritoneal surface, in contact with the peritoneum at all places, especially at its borders. If the mesh was not in contact with the abdominal wall at all its circumference, this was expressed as cupping. A score was given according to the amount of the mesh border cupped. (Table 2) The appearance of possible folds or buckles in the mesh was evaluated according to the score as adapted by Clarke et al. [15] (Table 3) Hernia recurrence was evaluated and noted as ‘yes’ or ‘no’.

Score	Observation
0	Flat position of the mesh to the abdominal wall entire circumference
1	< ¼ of the mesh borders does not attach to the abdominal wall
2	< ½ of the mesh borders does not attach to the abdominal wall
3	Excessive cupping, whole surface involved

Table 2. Cupping Score.

Score	Definition
None-trace	≤1 buckle
Mild-Moderate	>1 buckle; <75% of the mesh surface involved
Significant	Any fold, buckling of ≥75% of the mesh surface involved

Table 3**.** Buckling Score adapted by Clarke et al.[15]

Mesh shrinkage

After excision of the sample, the size of the mesh was measured at two perpendicular diagonals. The surface was calculated as for an ellipse ($r_1 * r_2 * \pi$) and expressed as percentage of the original surface ($14.52 cm^2$).

Histology

Histological evaluation was done by a qualified veterinary pathologist (C.K.). Inflammation and foreign body reaction (FBR) was scored by evaluating infiltration of lymphocytes, plasma cells, macrophages and giant cells.

After euthanasia, the mesh plus abdominal wall was excised. Thereafter the sample was cut longitudinally in four parts and placed in the paraffin box with the longitudinal side facing down. After staining, slices were cut and placed on the cover glass for microscopic evaluation. The microscopic includes a piece of the parietal side of the mesh, preperitoneal fat, the peritoneum and the muscle layer. A Haematoxylin and Eosin (H&E) staining was performed and samples were examined by light microscopy. At a 10x objective the sample was scanned. If an area of high cellularity was spotted, this was investigated closer with a 40x objective and if necessary, a 100 x objective. An overall score was given to the sample according to the overall presence of lymphocytes, plasma cells, macrophages and giant cells and additionally each sample was scored for lymphocytes, plasma cells, macrophages and giant cells separately according to their presence. “Low” indicated that the particular cell was absent or present in very limited numbers, “High” indicated a significant presence of the particular cell type and “Medium” was a level of presence in between.

Statistical analysis

Data were analyzed with SPSS version 17.0 (SPSS for Windows, Chicago: SPSS Inc.). Chi Square test of independence was used for categorical variables as was the student t-test for continuous variables. Significance was defined with a p-value ≤ 0.05.

Results

Initial deployment of the 4.3 cm patches was excellent for all PP/ORC devices (n=24), as no signs of folding or cupping could be distinguished at laparoscopy. Eighteen out of 24 PP/ePTFE patches showed a satisfying initial position (75%), four (17%) exhibited grade 1 cupping and two (8%) meshes showed significant cupping (grade 2).

All animals survived the procedure and the complete follow-period of 1, 2, 4 and 12 weeks. One animal (group 4 weeks survival) presented with a severe pityriasis rosea skin infection, which also affected the deeper layers of the abdominal wall. No mesh infection could however be documented in this case. Two animals (8%) in the PP/ORC group presented new hernia formation at the level of previous device. One animal showed evidence of a PP/ORC mesh infection (4%), diagnosed at necropsy, without apparent clinical symptoms.

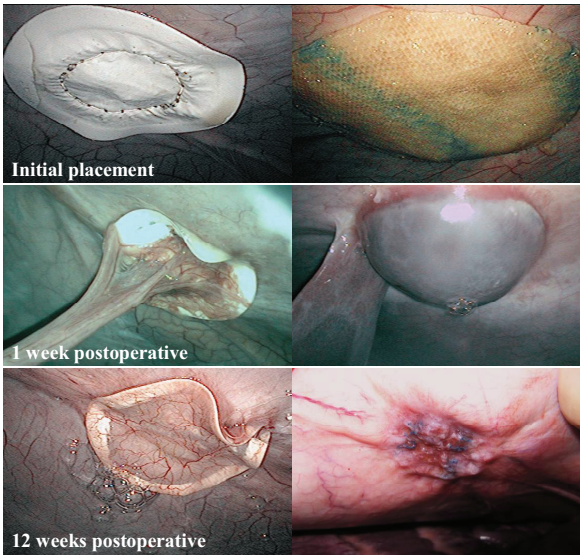

Fig. 2. Laparoscopic view of mesh placement. Left column PP/ePTFE – Right column PP/ORC

The results considering adhesion formation are depicted in table 4. At one week, only two animals in the PP/ORC group (8%) showed severe and extensive adhesion formation. (Fig. 2) At two weeks, adhesion formation was most pronounced, with 5/6 animals presenting impressive adhesions at PP/ORC meshes. At the PP/PTFE mesh one animal showed severe adhesions of small bowel and two animals had extensive omental adhesion formation. At four weeks PP/ORC was covered with extensive, but no dense adhesions while PP/ePTFE meshes showed minimal adhesion formation. After twelve weeks almost all adhesions had disappeared, except for one animal that showed complete mesh covering adhesion formation after PP/ORC placement.

Based on the scoring system used PP/ePTFE meshes (score=1.33) had a non-significant but lower adhesion score than PP/ORC meshes (score=3.15) (p=0.31) at one week.

For both meshes the highest adhesion scores were noted at 2 weeks post-surgery, but no significant difference could be measured between the meshes PP/ePTFE (score=3.5) and PP/ORC (score=6.5) (p=0.13). Regarding all the devices that have been implanted in this study PP/ORC induced a significant higher adhesion formation compared to PP/ePTFE (score=3.5 versus score=1.7, p=0.048).

Table 4. Adhesion formation		PP/ePTFE	PP/ORC	
1 week survival	*Adhesion score*	*1.33*	*3.15*	*p=0.31*
	Samples with grade 4 severity	0/6	2/6	
	Samples with grade 4 extension	0/6	2/6	
2 weeks survival	*Adhesion score*	*3.5*	*6.5*	*p=0.13*
	Samples with grade 4 severity	1/6*	5/6*	
	Samples with grade 4 extension	1/6	4/6	
4 weeks survival	*Adhesion score*	*1.00*	*3.33*	*p=0.19*
	Samples with grade 4 severity	0/6	1/6	
	Samples with grade 4 extension	0/6	3/6	
12 weeks survival	*Adhesion score*	*1.00*	*1.00*	*p=1.00*
	Samples with grade 4 severity	0/6	0/6	
	Samples with grade 4 extension	0/6	1/6	
Overall	*Adhesion score*	*1.71**	*3.5**	*p=0.048*
	Samples with grade 4 severity	1/24*	8/24*	
	Samples with grade 4 extension	1/24*	10/24*	

*$p < 0.05$

Evaluation of cupping and buckling was complicated for 21/24 PP/ORC meshes placed (87.5%) due to excessive adhesion coverage. It was not possible to distinguish the mesh surface by laparoscopy in these cases. The remaining 3 patches (12.5%) showed no cupping or buckling. Evaluation of flat placement of PP/ePTFE patches was not possible to evaluate in 7 animals (29.1%) due to overgrowth of a thick neoperitoneal layer. At 10 patches (41.7%) no cupping was present, 5 (20.8%) presented with grade I cupping, one (4.2%) with grade II, one (4.2%) with excessive cupping (grade 3). However, no association between cupping and adhesion formation could be confirmed. Two PP/ePTFE patches had moderate buckling and one patch showed significant buckling.

At necropsy massive shrinkage was recognized for the PP/ORC mesh, extending with survival time, while PP/ePTFE devices maintained almost their original surface. (Fig. 2) After one week mean mesh surface was respectively 14.18 cm² (SD±0.51) and 14.51 cm² (SD±0.00) for PP/ePTFE and PP/ORC ($p=0.143$). At two weeks post-surgery mean mesh surface was 13.96 cm² (SD±0.65) and 13.46 cm² (SD±0.74) for PP/ePTFE and PP/ORC respectivly ($p=0.264$), while at 4 weeks 14.46 cm² (SD±0.14) for the PP/PTFE and 7.47 cm² (SD±1.13) for the PP/ORC meshes was observed ($p<0.0001$). After 12 weeks survival, PP/ePTFE preserved 83% of its original surface (12.07cm² (SD±2.7), while for PP/ORC devices only 3.19cm² (SD±0.71) remained ($p<0.0001$), which is only 22% of the original surface. (Fig. 3)

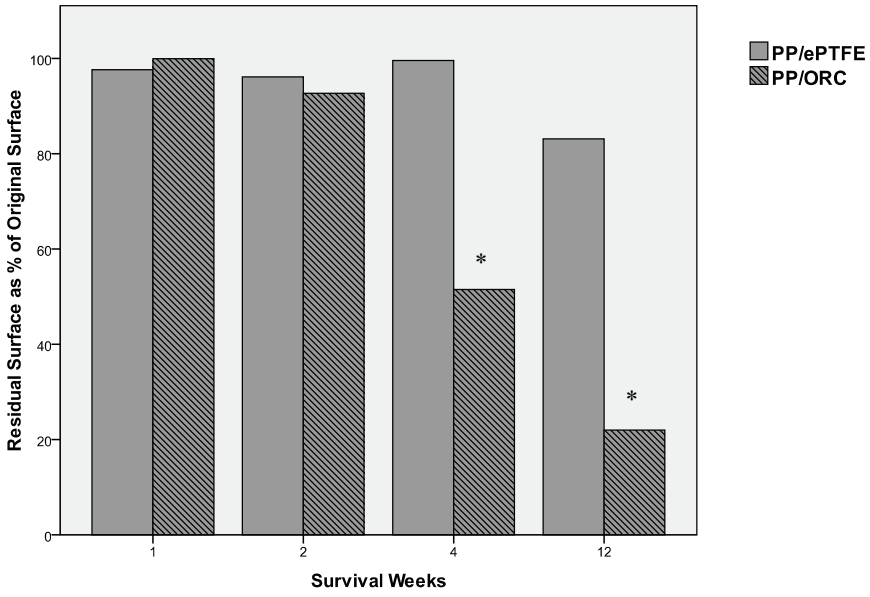

Fig. 3. Shrinkage of composite meshes. *$p<0.05$

Histological examination was performed at all times after necropsy. Considering inflammatory reaction, measured by the presence of lymphocytes & plasma cells, the strongest inflammatory reaction was observed after one and 2 weeks for both devices, while by 12 weeks the number of plasma cells and lymphocytes significantly diminished ($p=0.006$, $p=0.0001$ and $p=0.001$ for 1, 2 and 4 weeks respectively). (Fig. 4) Although comparable after 1 and 2 weeks ($p=0.1$ and $p= 0.61$), long-term evaluation revealed a significantly stronger inflammatory response at the PP/ORC patches ($p=0.018$ after 4 weeks, $p=0.035$ after 12 weeks).

In contrast to the inflammatory reaction, macrophages and giant cells, representing the FBR, were most prominently present after 1 week for the PP/ePTFE patch and after 2 and 4 weeks for the PP/ORC device, in both cases diminishing after that time period ($p<0.0001$). Comparing the two devices, the FBR was more pronounced at 1 week for PP/ePTFE ($p=0.019$) compared to PP/ORC, while at 2, 4 and 12 weeks PP/ORC was associated with a significantly more intense FBR than PP/ePTFE devices ($p=0.003$, $p<0.001$, $p<0.001$ respectively).

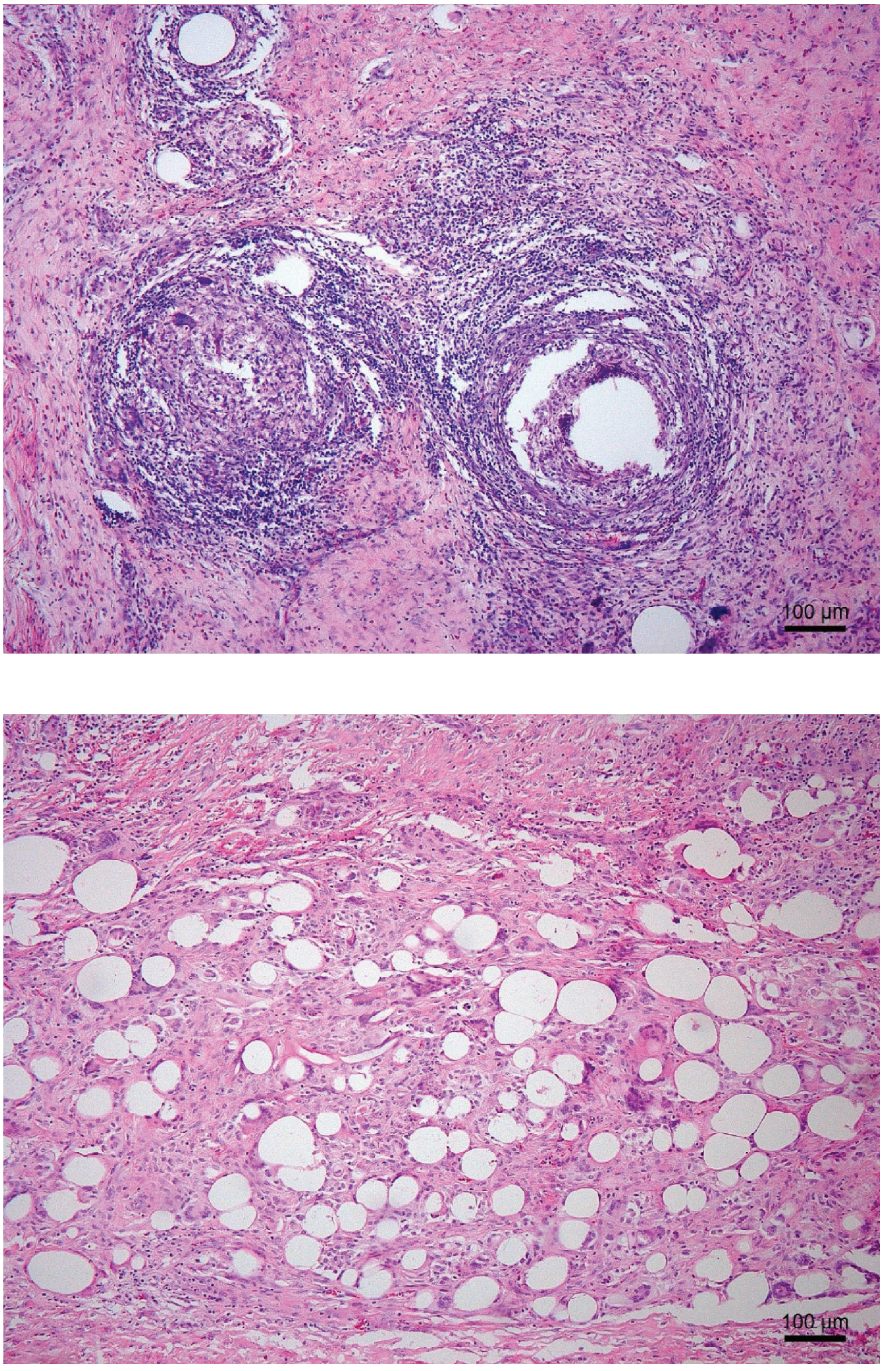

Fig. 4. Two samples of PP/ORC after two weeks. Notice high presence of lymfocytes and plasmacells (above), intensive foreign body reaction (under) with many giant cells and macrophages.

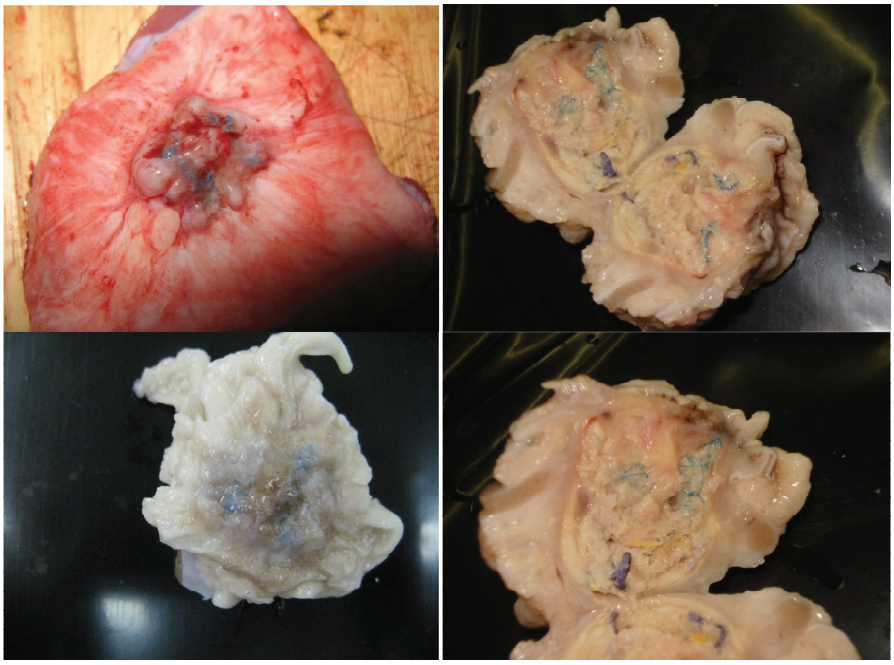

Fig. 5. A mesh-abdominal wall sample of PP/ORC excised after 12 weeks survival. When cutting the sample lengthwise complete loose of integral structure of the mesh was noticed.

Discussion

For both primary ventral as for small incisional hernias the traditional methods using fascial approximation or vest-over pants techniques by primary suturing has been replaced by tension free mesh repair, achieving a significant decrease in recurrence rate. Using an onlay or retromuscular mesh technique, wide tissue dissection is required, which might contribute to a higher wound morbidity and infection rate. With the use of new self-expanding mesh devices, which are introduced into the peritoneal cavity, this issue might be avoided.

After initial enthusiasm, with further popularization of the self-expanding PP/ePTFE device, a prospective cohort study, comparing intraperitoneal versus retromuscular mesh placement, demonstrated high recurrence rates up to 15%, despite significant benefit regarding pain and postoperative wound morbidity in the early postoperative period for the intraperitoneal mesh repair group.[10]

Furthermore, severe deployment insufficiencies were demonstrated using laparoscopic evaluation with severe cupping of the mesh surface, probably because of lack of memory in the deployment ring.[11] In the latter, one case of small bowel obstruction was reported due to contact of the bowel with the polypropylene side of the device, later confirmed in another case report.[12] Several surgeons therefore started to position this device preperitoneally to avoid intraperitoneal problems, but no postoperative data were published so far.

More recently, a second device consisting of polypropylene with an ORC anti-adhesive barrier was introduced, offering a different design of the memory ring that might be beneficial to the above mentioned issues. It is a polydioxanone (PDS) ring composed of three circular rings with connecting spokes and a central load ring on top. It is designed so that the outer ring is raised higher than the inner ring to enable the device to cup against the peritoneum completely. On the other hand, to assemble the different essential components of the device, i.e. the large pore prolene mesh, the PDS memory load ring and the ORC barrier layer, several ‘extra’ layers had to be added including 0.2mm PDS, a piece of vicryl mesh and 2 other PDS layers of 0.2 and 0.8mm respectively, resulting in a 9 component device of which 8 should absorb within 180-200 days as suggested by the manufacturer. Surgeons therefore wondered whether these absorbable components would not increase the inflammatory response instead of reducing it, possibly leading to increased scar tissue formation and mesh contraction.

According to the results in this experimental series, the deployment of the PP/ORC device seems very reliable concerning its flat positioning and its conformity with the abdominal wall physiology in 100% of the cases. However, it has to be pointed out that pigs do not have a prominent umbilical ligament and as this ligament is the most frequent reason for cupping or potatoe chip deformities our results

probably cannot be completely extrapolated to the human situation.[11] For the same reason, also the PP/ePTFE device performed rather well in this setting (75% adequate positioning). It has also to be mentioned that the use of small diameter devices of only 4.3cm in this study might relate to the adequate positioning in most of the animals. In clinical setting the hypothesis that the larger patches might be more vulnerable for malpositioning than smaller ones was already hypothesized by Iversen et al.[6] As the large diameter of 8cm is not available for the PP/ORC device this cannot be checked for.

During follow-up cupping and buckling of the PP/ePTFE patches were minimal or even absent in more than 50% of the cases, while encapsulation was observed in 29% of these patches, due to known encapsulation of the ePTFE component. Despite the finding of severe buckling and cupping in more than 13% of the devices, no association between cupping and adhesion formation could be confirmed in the PP/ePTFE group. In contrast, adhesions in the PP/ORC group were the main reason (87.5%) not to be able to evaluate cupping and buckling. The anti-adhesive ORC barrier has been criticized previously as being insufficient for prevention of adhesions in laparoscopic ventral hernia repair.[16,17] On the other hand, a recent systematic review and meta-analysis on adhesives in general and abdominal surgery showed reduction of small bowel adhesions for oxidized regenerated cellulose.[18] As in our series overall adhesion formation was significantly higher in the PP/ORC group versus the PP/ePTFE group, it can be questioned whether the anti-adhesive substance itself is responsible for the anti-adhesive properties, or that interaction between different materials change the clinical effect to a greater extent than might be expected. Even more important for clinical outcome is the correlation between the observed adhesion formation and our histological findings. As for any mesh material, both meshes induced an inflammatory and foreign body reaction, which was most pronounced at short term, i.e. after 2 and 4 weeks, but diminished at 12 weeks period, as also reported by Schreinemacher et al.[19] The PP/ORC patches however revealed a significantly stronger inflammatory response than the PP/ePTFE patches, leading to a more extensive foreign body reaction and, 12 weeks post-surgery, a mesh contraction value of 78% versus only 17% in the PP/ePTFE group was observed. Schoenmaeckers et al. as well as Carter and colleagues reported limited shrinkage for ePTFE meshes in clinical practice, but no data are available for the ORC meshes used in laparoscopic ventral hernia repair.[20,21]

In our opinion there are several factors contributing to the extensive FBR and shrinkage/mesh contraction of the PP/ORC device. First, the composition of the PP/ORC device out of 9 different layers will lead to a more extensive FBR. Secondly, absorption of 8 of these 9 layers will create a severe inflammatory reaction as e.g. shown with vicryl mesh absorption, also being one of the components of the PP/ORC device.[22]

A third possible explanation is delamination of the device. Despite excellent initial alignment to the abdominal wall, it could macroscopically be observed that the different layers of the PP/ORC mesh had delaminated in several animals; when the mesh-abdominal wall samples were cut lengthwise for histopathological investigation, the integral structure of the device was lost and the mesh was fumbled to a plug. (Fig. 5) It is clear that this disintegration of the different components allows the various textiles to be in contact with the surrounding tissues and induces a considerable inflammation leading to adhesion formation, activation of macrophages and giant cells and mesh shrinkage or so-called mesh-contraction.

Whether these findings are also responsible for the 8% recurrence rate in the PP/ORC group is plausible, but can't be proven in this setting, in which of course also technical factors play a role. It is however a fact that there was no recurrence observed in the PP/ePTFE group. Regarding the clinical consequences of these findings, the reports on the PP/ORC device as well as on the PP/ePTFE device are growing, but with variable success. The first report on the PP/ORC device was by Tollens et al. who reported a safe introduction, but a follow-up of 32 patients of only 80 days does not give any information on mesh behavior and recurrence rates.[23] Shortly thereafter, Muysoms et al. reported 3 complications with both PP/ePTFE (n=2, both 8cm diameter patches; small bowel perforations due to cupping) and PP/ORC devices (n=1, 6.4cm diameter; recurrence because of extensive shrinkage of 77.9%).[12] This latter is very much in line with our findings of an overall percentage of mesh shrinkage in the PP/ORC group of 78%. Ambe et al. reported a series of 57 patients in which only 1 recurrence occurred after an incisional hernia repair after ileostomy closure during a 5-19 months follow-up.[24] This can however not being considered the ideal indication for a mesh device repair with a suggested mesh overlap of at least 5cm for incisional hernias. The reason for failure was not mentioned in this series. The main complication reported was wound infection and fistula in 4/57 patients (5.4%). In our experimental setting only 1 skin infection and 1 mesh infection was observed, both in the PP/ORC group. The largest series so far considering the PP/ORC device is reported by Bontinck et al. including 101 patients with different types of primary ventral and incisional hernias.[25] The recurrence rate was 5.1% after a mean follow-up of 16 months and both type of hernia as well as the size of the hernia orifice were determining factors for recurrence. Although this authors placed the mesh in the preperitoneal plane, during ultrasound follow-up (n=74) the mesh was visualized in 63.5% of the cases and mesh contraction was noticed in 10 out of these 47 patients.

Recently other similar newer devices have been launched on the market. Cabs'air Composite® (Cousin biotech, France) is a round polypropylene mesh with an ePTFE layer. It is delivered with two or four fixation sutures and a balloon to deploy the mesh once introduced intraperitoneally. One study of Bensaadi et al. reported its placement and outcome after a 42 months' follow-up.[26] They claim

the Cabs' air facilitates superior deployment of the prosthesis and showed less recurrences compared to the Ventralex patch. Parietex Composite Ventral Patch® (Covidien Sofradim, Trévoux, France) is a polyester mesh, diameter 4.6, 6.6 or 8.6cm coated with a resorbable hydrophilic collagen film and contains an absorbable poly (glycolide-co-L-lactide) expandable ring. The patch has four polyester flaps and two removable handles as fixation system. Its intraperitoneal behavior was examined in a rabbit model.[27] The initial placement showed to be consistently flat to the abdominal wall and subsequent evaluations were encouraging as well, with little adhesion formation and good incorporation into the abdominal wall. However no clinical series have been reported yet. C-Qur V-Patch® (Atrium Medical Corporation, New Hampshire, USA) is a polypropylene mesh composed of two layers sewn together around an omega 3 fatty acid coated ring and two straps for positioning. No results on its use are available yet.

In conclusion, this experimental pig study shows the limitations of both intraperitoneal mesh devices studied. Although a strong deployment system provides adequate and improved initial placement of the PP/ORC patch, shrinkage and excessive adhesion formation are much more prominent in this large pore multi-layered resorbable device compared to the ePTFE patch. This might influence both short- and long-term clinical outcome as shown in recent clinical case series. Whether these devices behave differently when placed in the preperitoneal space remains to be investigated.

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ADDENDUM 2 - CURRICULUM VITAE

1. PERSONAL INFORMATION

Name	Emmelie Reynvoet
Address	Langestraat 47A/201 8000 Brugge
Phone number	+32 486 37 13 66
E-mail	emmelie.reynvoet@ugent.be
Date of Birth	22 June 1984
Place of Birth	Rotherham (UK)
Nationality	Belgian
Marital status	Married with Bernard Dubois (°03/06/1984), 1 daughter Rosalie (°30/01/2013)

2. EDUCATION

Secondary school
1996-2002
Science – Mathematics (8hrs)
Pleinschool, Kortrijk

University
2002-2009
Master of Medicine
Faculty of Medicine and Health Sciences
Ghent University, Ghent

Postgraduate
2009-2010
Master International Health and Tropical Medicine
Institute of Tropical Medicine, Antwerp

Additional education
Conservatorium voor Piano
Conservatorium Kortrijk, Kortrijk

Certificate of Laboratory animal science
Faculty of Veterinary Medicine
Ghent University, Ghent

Spanish course
University Language Centre
Ghent University, Ghent

Beginselen van de elektrocardiografie
Department of Cardiology, Faculty of Medicine and Health Sciences
Ghent University, Ghent

3. PROFESSIONAL EXPERIENCE

2010 – 2011 : Doctorandus Department of General and Hepatobilairy Surgery and Liver Transplantation Service, Prof. Dr. F. Berrevoet

2011 – Present : Surgical Trainee - Prof. Dr. P. Pattyn
2011-2012 : University Hospital Ghent, Prof. Dr. P. Pattyn
2012-2013 : University Hospital Brussels, Prof. Dr. G. Delvaux
2013-present : Sint-Jan Hospital Bruges, Dr. B. Dillemans

4. PUBLICATIONS

International publications:

Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S, Buyle FM, Vanholder RC, Hoste EA (2009) Epidemiology of infection in critically ill patients with acute renal failure. ***Critical Care Medicine*** 37(7) : 2203-9

Reynvoet E, Berrevoet F, De Somer F, Vercauteren G, Vanoverbeke I, Chiers K, Troisi R (2012) Tensile strength testing for resorbable mesh fixation systems in laparoscopic ventral hernia repair. ***Surg Endosc*** 26(9) : 2513-20

Reynvoet E, Deschepper E, Rogiers X, Troisi R, Berrevoet F (2014)
Laparoscopic ventral hernia repair: is there an optimal mesh fixation technique? A systematic review. ***Langenbecks Arch Surg*** 399:55-63

Reynvoet E, Berrevoet F (2014) Pros and cons of tacking in laparoscopic hernia repair. ***Surg Techn Int*** 25:136-140

Reynvoet E, Van Cleven S, Van Overbeke I, Chiers K, De Baets P, Troisi R, Berrevoet F (2015) The use of cyanoacrylate glue as single mesh fixation in laparoscopic ventral hernia repair : a large animal evaluation. ***Hernia*** *(Epub ahead of print)*

Reynvoet E, Chiers K, Van Overbeke I, Troisi R, Berrevoet F (2015) Intraperitoneal mesh devices for small midline hernias. Mesh behavior in a porcine model. ***Hernia*** *(Epub ahead of print)*

National publications:

Vandijck DM, Reynvoet E, Blot SI, Vandecasteele E, Hoste EA (2007) Severe Infection, Sepsis and Acute Kidney Injury. ***Acta Clin Belg*** 62: 332-336.

5. PRESENTATIONS

Presentations on international congresses:

Tensile strength testing for resorbable mesh fixation systems in laparoscopic ventral hernia repair.

- International Congress of the European Hernia Society 2010, European Hernia Society, Istanbul, Turkey.

Intraperitoneal mesh reinforcement in the surgical management of small midline hernias. A comparative study of two composite meshes in a porcine model.

- American Hernia Congress 2012, American Hernia Society, New York, USA.
- Congress of the European Society Surgical Research 2012, European Society Surgical Research, Lille, France.

The use of cyanoacrylate glue as mesh fixation device in laparoscopic ventral hernia repair.

- International Congress of the European Hernia Society 2013, European Hernia Society, Gdansk, Poland.
- Science Day Faculty of Medicine 2013, Ghent University, Ghent, Belgium.
- International Congress of the European Hernia Society 2014, European Hernia Society, Edinburgh, United Kingdom.
- World congress of Endoscopic Surgery 2014, European Association for Endoscopic Surgery, Paris, France.

Laparoscopic ventral hernia repair with the use of a new mesh positioning system.

- International Congress of the European Hernia Society 2014, European Hernia Society, Edinburgh, United Kingdom.
- World congress of Endoscopic Surgery 2014, European Association for Endoscopic Surgery, Paris, France.

Presentation on national congresses:

Tensile strength testing for resorbable mesh fixation systems in laparoscopic ventral hernia repair.

- Belgian Surgical Week 2010, Royal Belgian Society for Surgery, Ostend, Belgium.

Intraperitoneal mesh reinforcement in the surgical management of small midline hernias. A comparative study of tow composite meshes in a porcine model.

- Belgian Surgical Week 2012, Royal Belgian Society for Surgery, Spa, Belgium.

Video-assisted thoracoscopic surgery for a bronchial carcinoid tumor. Trainer versus trainee. BAST session.

- Belgian Surgical Week 2012, Royal Belgian Society for Surgery, Spa, Belgium.
  Award for best presentation.

Regional presentation:

Baby breaks my heart. Postpartum dissection of a coronary artery.

- Postgraduaat Heelkunde Casuïstiek 2011, Ghent University, Ghent, Belgium.
  Award for best presentation.

Presentation as second author:

The use of cyanoacrylate glue as mesh fixation device in laparoscopic ventral hernia repair.

- Belgian Surgical Week 2014, Royal Belgian Society for Surgery, Spa, Belgium.

Systematic review on fixation in laparoscopic ventral hernia repair.

- International Congress of the European Hernia Society 2011, European Hernia Society, Ghent, Belgium.
- European congress of Endoscopic Surgery 2012, European Association for Endoscopic Surgery, Brussels, Belgium.

Poster presentations:

Epidemiology of infection in critically ill patients with acute renal failure.

- International Symposium on Intensive Care and Emergency Medicine (ISICEM) 2007, Belgian Society of Intensive Care and Emergency Medicine, Brussels, Belgium.

Tensile strength testing for resorbable mesh fixation systems in laparoscopic ventral hernia repair.

- Annual Clinical Congress 2010, American College of Surgeons, Washington D.C., USA.
- Science Day Faculty of Medicine 2011, Ghent University, Ghent, Belgium.
- International Congress of the European Association for Endoscopic Surgery 2010, European Association of Endoscopic Surgery, Geneva, Switzerland.

A tailored approach for recurrent incisional hernia repair seems effective after midterm follow-up.

- International Congress of the European Hernia Society 2011, European Hernia Society, Ghent, Belgium.

Intraperitoneal mesh reinforcement in the surgical management of small midline hernias. A comparative study of tow composite meshes in a porcine model.

- Annual Clinical Congress 2011, American College of Surgeons, San Francisco, USA.

The use of cyanoacrylate glue as mesh fixation device in laparoscopic ventral hernia repair.

- American Hernia Congress 2014, American Hernia Society, Las Vegas, USA.

Recycling the selfexpandable mesh in the laparoscopic repair of small ventral hernias: a series of 33 consecutive patients.

- American Hernia Congress 2014, American Hernia Society, Las Vegas, USA.
- International Congress of the European Hernia Society 2014, European Hernia Society, Edinburgh, United Kingdom.
- World congress of Endoscopic Surgery 2014, European Association for Endoscopic Surgery, Paris, France.

Posters presentation as second author :

Tissue ingrowth and adhesion formation differ significantly comparing two different self-expanding composite meshes for small ventral hernias.
Berrevoet F, Reynvoet E, Vercauteren G, Van Overbeke I, Chiers K, Troisi R,
Annual Clinical Congress 2011, American College of Surgeons, San Francisco, USA.

Complete vs. Partial Midline reinforcement in Incisional Hernia Repair: a randomized controlled trial (NCT 00498810).
Berrevoet F, Reynvoet E, Vanlander A, Rogiers X, Troisi R,
Annual Clinical Congress 2011, American College of Surgeons, San Francisco, USA

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Emmelie Reynvoet

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