PREPARE AND REPAIR

MANAGEMENT OF INCISIONAL HERNIAS

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1 General introduction

This chapter will first introduce hernias by describing their anatomical origin, will then illustrate why hernias are problematic, and will subsequently go into detail about hernia risk factors, treatment, and prevention.

Anatomy and function

The anterolateral abdominal wall covers and protects the abdominal organs, thereby ensuring these to maintain their anatomical position, and assists critical bodily functions like expiration and coughing [1]. In addition, the abdominal wall stabilizes the trunk, allowing us humans to walk upright [2,3]. The muscles responsible for these functions are the transverse abdominis, the internal oblique, the external oblique, and the rectus abdominis. These muscles also compress the abdominal viscera, thereby preventing herniation. An abdominal wall hernia is generally defined as a defect in the connective tissue of the abdominal wall, through which preperitoneal fat or abdominal contents protrude. These hernias occur at weakened spots of the abdominal wall, either already present from birth, such as hiatal, umbilical, or inguinal hernias, or created due to abdominal surgery. When a hernia occurs in a scar from previous surgery, it is called an incisional hernia.

The problem of hernias

Incisional hernia is not uncommon, with reported incidences of approximately 10% to 20% [4-6]. Incisional hernias can cause discomfort or pain, limitation of daily activities, cosmetic complaints, and a reduced body image, therefore contributing significantly to a reduction in quality of life [7]. In addition to this burden for the patient, risks exist in the form of a fold of bowel that can become strangulated in the hernia, requiring emergency surgery [8].

Hernias do not only impose a considerable burden upon patients suffering from it, also nationally, hernias have a large economic impact. The average costs of surgical hernia repair are $7,750 [9], and the amount of incisional hernia repair surgeries in the Netherlands is estimated at 8,500 on a yearly basis [10]. This results in nearly 66 million dollars spent on hernia repair surgery per year.

Summarized, hernias form an underestimated social problem. On an individual level, they reduce quality of life [7], and on a societal level are associated with high health care costs [11].

Risk factors

As illustrated above, the problem that incisional hernias pose is large, partly due to their incidence. Despite that "all men are created equal" (American Declaration of Indepen-

dence), not all abdominal walls are created equal. An increased incidence is found in so called "high-risk groups". These high-risk groups possess risk factors that are associated with an increased risk of incisional hernia development. Obesity, high age, infection, smoking, and treatment with chemotherapy are some of the most researched risk factors [6,12-16]. Based on these commonly acknowledged risk factors, surgeons have tried to define what would be a "complex hernia", yet this definition is complex in itself, comprising four categories of variables, which can only be comprehensively depicted in a table [17]. The categories are size and location of the hernia, the contamination and soft tissue condition of the surgical site, the patient history and risk factors, and the clinical setting.

This suggests that not only the reduction of patient risk factors should take place, but that possibly other treatments or preoperative strategies might be needed to achieve incisional hernia repair, depending on the patient and the hernia; *id est*, the requirement of a more "tailored approach".

Treatment

For hernias that cause complaints, repair is usually indicated. Most surgeons believe that anatomical fascial closure should be achieved during (median) hernia repair, in which the defect edges of the fibrous connective tissue surrounding the rectus abdominis muscle – called the rectus fascia or rectus sheath – are reapproximated. This forms a contrast to bridging repair, where reapposition of the fascial edges cannot be achieved and the defect is covered with a patch. Fascia closure is suggested to result in less hernia recurrences compared to bridged repair [18,19], and is therefore often pursued. Techniques to facilitate fascial closure often consist of component separation, in which collagen or muscle layers are separated from each other to obtain extra length towards the midline [20]. Several component separation techniques have been described, such as the anterior component separation technique (known as "Ramirez" technique) [21] and the transverse abdominis release (known as "TAR") [22], both resulting in satisfactory outcomes [23].

Not only inventive surgical methods have been developed for the treatment of incisional hernias, also new surgical materials have appeared on the market. Ever since the first use of polypropylene mesh in the 1950s for hernia repair [24], the use of prosthetics has become common practice. It has been proven that mesh repair reduces recurrence rates compared to simple suture closure [25-27]. However, many different types of meshes are currently available on the market. After regular synthetic meshes, biological meshes became available, which were hypothesized to be infection-resistant, and therefore useful in contaminated settings [28]. Also meshes of slowly resorbable materials have been developed, which are thought to cause abdominal wall remodelling [29,30]. This remodelling would be a result of gradual mesh resorption, in which the muscles and aponeuroses of

the abdominal wall are restored and reshaped due to the impact of natural forces. This is hypothesized to be similar to the "use it or lose it" concept known in bone remodelling [31]. However, the vast amount of meshes available on the market illustrates the inconclusive evidence of superiority of one mesh over another.

Aside from the surgical aspects in reducing hernia recurrence rates, patients can also be prepared preoperatively to achieve maximal surgical results. This has been studied in many oncological studies, in which the concept of "better going in is better going out" or "prehabilitation" in tumour resection surgery was researched [32-35]. Examples of general patient preparation before surgery are losing weight, cessation of smoking, and commencing physical activity to build muscle [36]. Other methods to prepare patients in hernia surgery are a preoperative pneumoperitoneum which is inflated progressively, preoperative Botulinum Toxin A injections in the three abdominal wall muscle layers, or the use of tissue expanders [37-39]; all with the goal to achieve fascial closure during surgery. Unfortunately, these methods are not commonly known by surgeons, as these hardly pass by in the surgical curriculum.

As both preoperative and surgical methods require expertise and are costly, the surgeon has to consider which methods would be required to achieve hernia repair, and which would be suitable for each individual patient, again showing the need for individual customization in treatment strategies.

Prevention

In medicine, preventing is usually better than treating or healing. This also goes for hernias, due to their associated burden and costs. Mesh augmentation can prevent hernia recurrence [25-27] and even hernia occurrence in patients with obesity or an abdominal aneurysm of the aorta [40]. However, the use of mesh is also associated with complications such as infections, chronic pain and fistula formation [27,41,42], which could cause harm in patients with a low risk of recurrence. Therefore, mesh use should preferable be deployed in high-risk patients only, as these would benefit most from preventive measures. This asks for surgeons and researchers to consider and study targeted prevention further in order to optimally select patients.

OUTLINE OF THIS THESIS

Central themes in this thesis are the preparation and treatment of incisional hernias in different high-risk patient groups, which are often outside the window of "standard practice". This might offer further insight in the modularization of hernia management.

In ***PART I,*** risk factors for incisional hernia will be addressed.

In **Chapter 2**, the progressive loss of muscle mass – also known as sarcopenia – will be studied for its predictive value in the development of incisional hernia. As sarcopenia has been shown to be a risk factor for morbidity and mortality in oncological surgery, it was hypothesized to be associated with incisional hernia too.

PART II highlights studies that involve preoperative preparation and the choice for treatment in high-risk hernia patients.

In **Chapter 3**, a group of patients with large and complex incisional hernias, that underwent a preoperative trajectory with progressive pneumoperitoneum (PP), Botulinum Toxin A (BT) injections, or a combination of both, will be described.

Chapter 4 is a systematic review of the literature, exploring the perioperative value of preoperative PP and BT. In addition, indications and complications for these preoperative techniques are researched, as well as the postoperative recurrence and infection rate.

In **Chapter 5** a conservative approach will be compared to elective umbilical hernia repair in patients with liver cirrhosis and ascites with regard to 2-year morbidity.

In ***PART III*** of this thesis, the use of a new type of mesh in incisional hernia treatment will be evaluated, in particular with regard to preventing hernia recurrences.

In **Chapter 6**, the set-up for a prospective study that focuses on the use of a slowly resorbable biosynthetic mesh in Ventral Hernia Working Group grade 3 patients will be outlined. This group is at risk for postoperative complications; the use of a biosynthetic mesh is hypothesized to be beneficial due to its mechanical strength directly after implantation and its remodelling properties after degradation.

In **Chapter 7**, the short-term results after the use of the biosynthetic mesh will be presented, mainly focusing on surgical site occurrences such as infection, haematoma, seroma, and wound dehiscence.

In **Chapter 8**, the subsequent long-term results after the use of the biosynthetic mesh from **Chapter 6** and **7** will be presented. As the mesh is resorbed after 12 to 18 months, the focus will be placed on hernia recurrences and quality of life outcomes.

In ***PART IV*** future perspectives on treatment, prevention and research will be considered.

In **Chapter 9**, a short comment is made on a previously published systematic review about midline closure techniques and materials, naming some additional factors that should be taken into account during midline closure and the future of abdominal wall research.

The results from all chapters will be summarized and discussed in **Chapter 10**, with further perspectives for future research.

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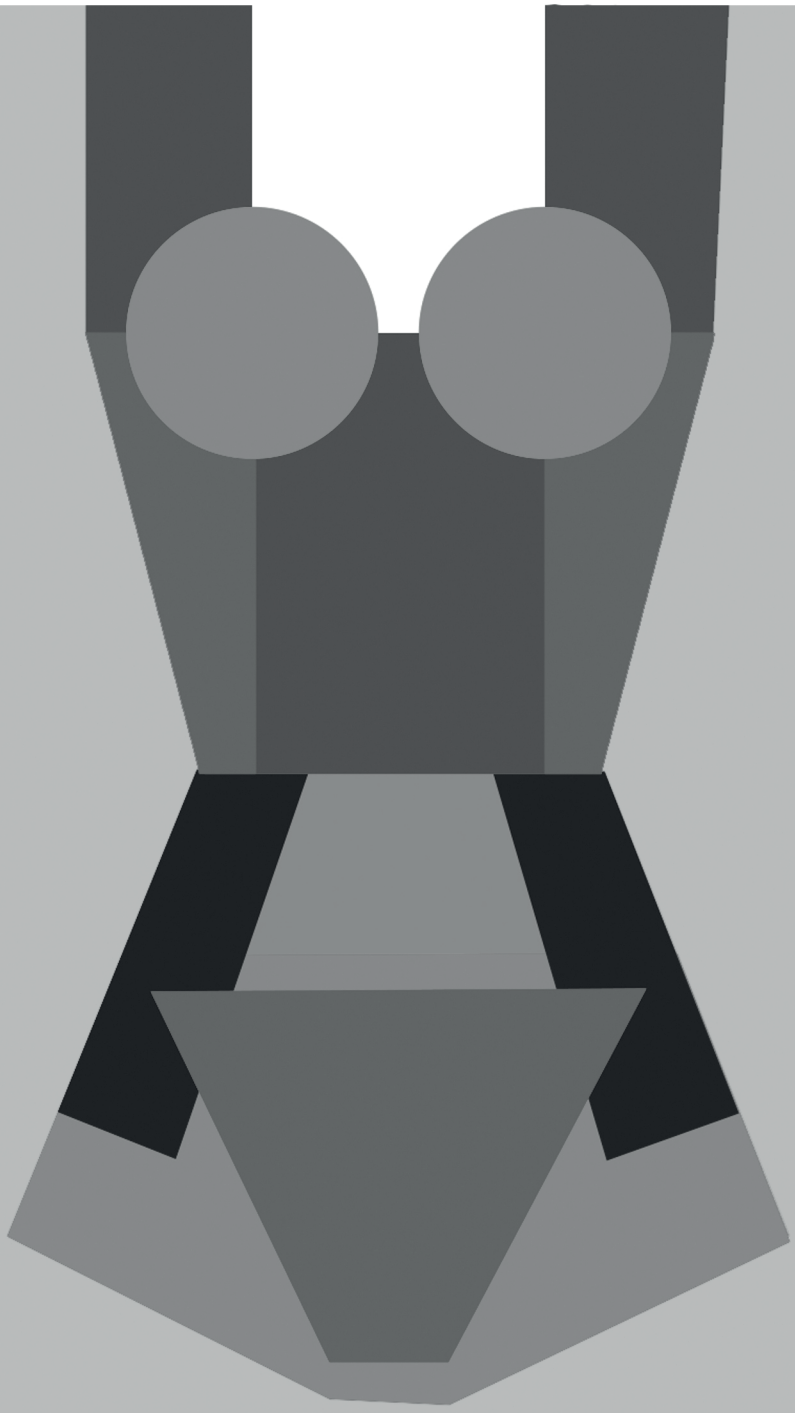
PART I: Incisional hernia risk factors



2 Sarcomania? The inapplicability of sarcopenia in predicting incisional hernia development

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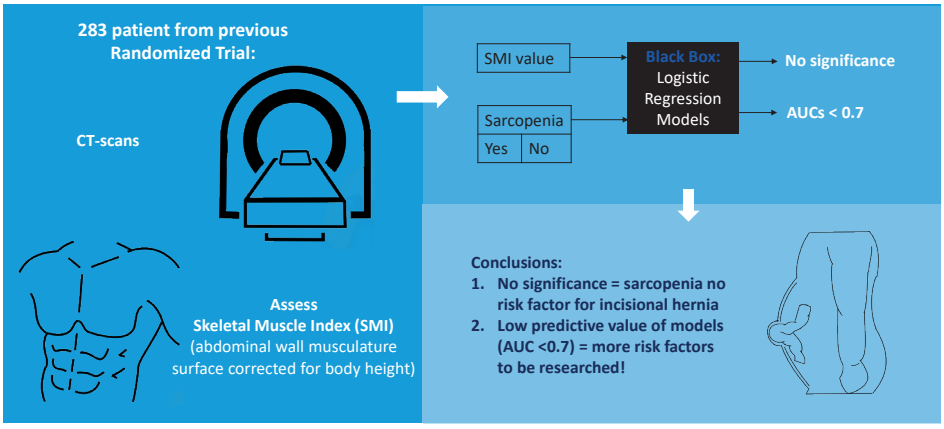

ABSTRACT

Background: Incisional hernia is a frequent complication after abdominal surgery. A risk factor for incisional hernia, related to body composition, is obesity. Poor skeletal muscle mass might also be a risk factor, as it may result in weakness of the abdominal wall. However, it remains unknown if sarcopenia (i.e. low skeletal muscle mass) is a risk factor for incisional hernia. Therefore, this study aims to investigate whether a relation between sarcopenia and incisional hernia exists.

Methods: Patients from the STITCH trial, who underwent elective midline laparotomy, were included. Computed Tomography (CT) examinations performed within 3 months preoperatively were used to measure the skeletal muscle index (SMI; cm^2/m^2). Primarily, SMI measured continuously, sarcopenia based on previously described cut-off values for the SMI, and sarcopenia as the lowest gender-specific SMI quartile, were assessed as measures to predict incisional hernia occurrence. Secondary, the association between these three measures and postoperative complications was investigated.

Results: In total, 283 patients (45.2% male; mean age 63.7 years; mean BMI 25.36 kg/m^2) were included, of whom 52 (18%) developed an incisional hernia. Mean SMI was 44.23 cm^2/m^2 (SD 7.77). The Nagelkerke value for the three measures of sarcopenia was about 0.020 (2.0%) for incisional hernia development. Logistic regressions with the three measures of sarcopenia did not show any predictive value of the model (area under the curve (AUC) of 0.67 for incisional hernia; 0.69 for post-operative complications).

Discussion: In this study, sarcopenia does not seem to be a risk factor for the development of an incisional hernia.

INTRODUCTION

An incisional hernia is a protrusion of abdominal fat tissue, the greater omentum or the intestines through the abdominal wall, at the site of a surgical incision [1]. Incisional hernias may cause discomfort, pain, and reduction of quality of life [2]. In the United States alone, nearly 350,000 hernia repairs are performed annually, costing approximately $3 billion dollars [3].

A great number of studies have been conducted to assess the optimal closing technique for midline incision laparotomies, but the risk for incisional hernia remains about 5-20% [4-6].

Major risk factors for incisional hernia, such as obesity, high age, infection, chemotherapy and smoking, are well known [6-12]. Sarcopenia is the progressive decline of muscle mass, which results in decreased functional capacity of the muscles [13]. It could be a potential risk factor for incisional hernia, as it may result in weakness of the abdominal wall. However, no studies up to now have been done to assess this potential predictor.

In oncological surgery, however, sarcopenia is a relatively newly discovered risk factor. It can be measured at the level of the third (L3) or fourth lumbar vertebra (L4). When sarcopenia is measured as total skeletal muscle cross-sectional area (CSA) at the level of the third lumbar vertebra (L3), it is associated with a lower long-term survival in patients undergoing colorectal cancer resection [14,15], in patients with colorectal liver metastasis [16], and in patients undergoing hepatectomy for hepatocellular carcinoma [17,18]. Additionally, sarcopenia measured as CSA on L3 can predict postoperative complications [18-20] and is associated with a longer length of stay after surgery [19].

When sarcopenia is measured at the level of the fourth lumbar vertebra (L4), through psoas muscle measurement, it approximates lean core muscle mass. This psoas muscle measurement is associated with mortality in patients undergoing liver transplantation [21], abdominal aortic aneurysm repair [22], emergency abdominal surgery [23] and in patients after the resection of a pancreatic adenocarcinoma [24]. Moreover, sarcopenia through psoas muscle measurement is associated with morbidity and can predict postoperative complications in several patient groups [25-27].

A systematic review endorsed the abovementioned findings; sarcopenia is associated with an increased number of postoperative complications and an increased long-term mortality (>1 year) after abdominal surgery [28].

There is only limited knowledge on the relation between sarcopenia and post-operative outcomes after ventral hernia repair [29,30]. The presence or absence of an association of sarcopenia with the occurrence of incisional hernia after elective midline laparotomy has not been described. Therefore, we assessed the predictive value of sarcopenia for the occurrence of incisional hernia. We hypothesized that patients with sarcopenia will have a higher incidence of incisional hernia after surgery.

MATERIALS AND METHODS

Study design and data acquisition

Patients who underwent elective midline laparotomy in 4 of the participating hospitals of the STITCH trial were included [31]. The STITCH trial is a multicentre, randomized controlled trial, performed from October 2009 to March 2012, in 545 patients 18 years or older undergoing elective midline laparotomy. The trial compared small bites with big bites for abdominal closure, with incisional hernia as the primary outcome measure. Excluded from participation were patients with a history of incisional hernia or fascia dehiscence after a midline laparotomy, patients who had undergone abdominal surgery through a midline incision within the past 3 months, patients who were pregnant, or patients participating in another intervention trial [31]. Included patients had at least one follow-up visit up to 15 months after surgery. Incisional hernia was diagnosed by physical examination, ultrasound imaging, or both.

Preoperative CT examinations (within 3 months before surgery) of the STITCH trial patients were collected and anonymized before assessment. Data regarding predictive parameters for incisional hernia (i.e. the closure method used in the STITCH trial, age, smoking status, diabetes mellitus, body mass index (BMI), and gender) were extracted from the trial database.

Sarcopenia assessment

The presence of sarcopenia was assessed with the method previously described by Vledder et al. [16]. Skeletal muscle mass was measured at the level of the third lumbar vertebra (L3), on which both the transverse processi were visible. By manual outlining of the skeletal muscle, the cross-sectional area (CSA) in cm^2 was automatically calculated based on a Houndsfield Unit (HU) threshold for muscle (-30 HU to +150 HU). The obtained CSA was then adjusted for patients' height squared (m^2), resulting in the skeletal muscle index (SMI; cm^2/m^2).

Additional to the continuous measure SMI, two other measures for muscle mass were used to explore the effect of low skeletal muscle mass compared to high skeletal muscle mass in patients. The first measure was established using the cut-off values described by Martin et al. [32] (<41 cm^2/m^2 for females, <43 cm^2/m^2 for males with a BMI <25, and <53 cm^2/m^2 for males with a BMI >25); patients were divided in a sarcopenia and non-sarcopenia group. The second measure was the creation of gender-specific quartiles; patients in the lowest gender-specific quartile were considered to have sarcopenia.

Outcome measures

The primary outcome measure for the study was the development of an incisional hernia. In order to assess whether sarcopenia is a risk factor for incisional hernia development, patients with a follow-up of less than 6 months were excluded from the analysis; it is unlikely that this time frame is sufficiently long to observe incisional hernia development. The secondary outcome measure was the occurrence of postoperative complications.

Statistical analysis

Categorical data are reported as counts and percentages; continuous data are either reported as means with standard deviation (SD) or median with interquartile range (IQR). Means were compared with a chi-square test, medians with a Mann-Whitney U test. A logistic regression model for the primary outcome was created to assess the predictive value of the three muscle mass measurements (continuous SMI, gender-specific quartiles, and cut-offs based on Martin et al.[32]). We controlled for known risk factors for incisional hernia: age, gender, BMI, smoking status, diabetes, and the closure method during the surgery, since small bites showed a significantly better result in the STITCH trial. The 95% confidence intervals of the AUCs were calculated by bootstrapping.

To predict the occurrence of postoperative complications, another logistic regression model was created, controlling again for age, gender, BMI, smoking status, diabetes, and the closure method, and additionally for ASA (American Society of Anesthesiologists)-classification, blood loss during surgery, wound length, and the presence of cardiovascular comorbidities.

Statistical analyses were performed using R Studio version 1.0.136 (RStudio, Inc.) and SPSS 24.0.0.0 (IBM Corporation).

RESULTS

Patient characteristics

A total of 502 of the STITCH patients was treated in the 4 hospitals participating in our study (Figure 1). Of these patients, 286 (57%) had a preoperative CT examination available within 3 months before surgery. On three CTs the CSA was not measurable due to the low quality of the images or the incomplete visibility of the muscles of interest; these patients were excluded from the analysis.

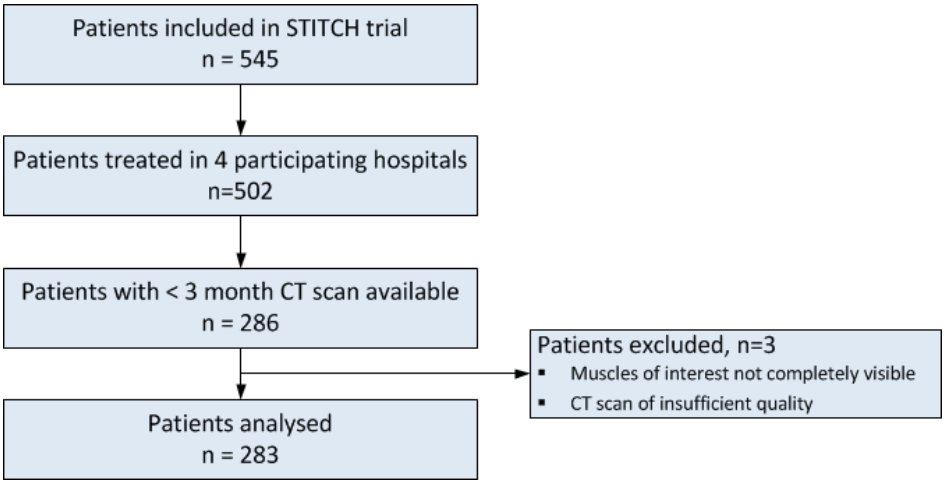

Figure 1. Flowchart of included patients

The remaining 283 patients form the study cohort, of which 52 patients (18%) developed an incisional hernia. The number of patients undergoing surgery for a malignant disease were comparable between and within both groups. Baseline characteristics of these patients are shown in Table 1.

Prevalence of sarcopenia

Sarcopenia determined through the lowest gender specific quartile resulted, by definition, in 25.0% of males and 25.2% of females having sarcopenia. The cut-off values of SMI were determined on 43.3 cm^2/m^2 for males, and 36.5 cm^2/m^2 for females. When sarcopenia was determined through the cut-off values of Martin et al. [32], 43.8% of males and 59.4% of females were considered sarcopenic.

The average SMI for males was 49.0 cm^2/m^2 and for females 40.3 cm^2/m^2 (Table 2).

Table 1. Baseline characteristics per sarcopenia-group, expressed in mean (SD) or n (%).
[a] median (IQR)

Characteristics	Lowest Gender Specific Quartile			According to Martin et al. (32)		
	No sarcopenia n = 212	Sarcopenia n = 71	p-value	No sarcopenia n = 135	Sarcopenia n = 148	p-value
Gender			0.975			0.009
Male	96 (45.3%)	32 (45.1%)		72 (53.3%)	56 (37.8%)	
Female	116 (54.7%)	39 (54.9%)		63 (46.7%)	92 (62.2%)	
Age (years)	63.1 (12.8)	65.5 (13.0)	0.174	62.0 (12.9)	65.3 (12.7)	0.030
BMI (kg/m^2)	26.2 (4.5)	22.9 (3.7)	< 0.001	26.4 (4.8)	24.4 (4.1)	<0.001
Smoking	46 (21.7%)	10 (14.1%)	0.319	34 (25.2%)	22 (14.9%)	0.051
Diabetes	32 (15.1%)	11 (15.5%)	0.935	24 (17.8%)	19 (12.8%)	0.248
Cardiovascular disease	87 (41.0%)	28 (39.4%)	0.812	52 (38.5%)	63 (42.6%)	0.489
ASA			0.036			0.593
1	53 (25.0%)	8 (11.3%)		31 (23.0%)	30 (20.3%)	
2	122 (57.5%)	45(63.4%)		81 (60.0%)	86 (58.1%)	
3	37 (17.5%)	18 (25.4%)		23 (17.0%)	32 (21.6%)	
Closure method			0.919			0.069
Large bites	109 (51.4%)	37 (52.1%)		62 (45.9%)	84 (56.8%)	
Small bites	103 (48.6%)	34 (47.9%)		73 (54.1%)	64 (43.2%)	
Blood loss (L)[a]	0.6 (1.00)	0.4 (0.85)	0.087	0.6 (1.14)	0.5 (0.88)	0.225
Wound length (cm)	22.2 (4.7)	22.0 (5.2)	0.814	22.5 (4.6)	21.9 (5.0)	0.346
SMI (cm^2/m^2)	46.9 (6.8)	36.2 (4.0)	<0.001	39.4 (5.5)	49.5 (6.4)	<0.001
Follow-up time (months)[a]	12 (11-14)	13 (12-15)		12 (11.5-13)	12 (12-15)	

Table 2. Average continuous SMI measures in cm^2/m^2 (mean, standard deviation)

	Males N =128	Females N =155
SMI (mean, SD)	49.0 (7.3)	40.3 (5.7)
Lowest Gender Specific quartile (SMI)		
No sarcopenia	52.1 (5.4)	42.6 (4.5)
Sarcopenia	39.6 (3.0)	33.5 (2.2)
According to Martin et al. (SMI)		
No sarcopenia	52.9 (6.0)	45.6 (4.1)
Sarcopenia	43.9 (5.6)	36.7 (3.3)

Hernia development

When sarcopenia was measured through the lowest gender-specific quartile, 18.8% of people with sarcopenia developed a hernia, compared to 18.6% of people without sarcopenia.

When sarcopenia was measured through cut-off values from literature, 19.9% of people with sarcopenia developed a hernia, compared to 17.3% of people without sarcopenia.

Three different logistic regression models were developed with hernia as dependent outcome variable, and with continuous SMI (model 1); sarcopenia based on literature cut-offs (model 2); and sarcopenia as lowest gender-specific quartile (model 3) as independent variables (Table 3).

Table 3. Obtained Odds Ratios (OR) and their respective 95% Confidence Intervals (CI) from the three models. Model 1 with continuous SMI, Model 2 with sarcopenia based on literature cut-offs, Model 3 with sarcopenia as lowest gender-specific quartile.

Variable	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Closure method	0.50	0.25 – 0.98	0.51	0.26 – 1.00	0.48	0.24 – 0.94
Age	1.02	0.99 – 1.05	1.02	0.99 – 1.05	1.02	0.99 – 1.05
Smoking	1.94	0.81 – 4.55	1.82	0.76 – 4.22	1.78	0.75 – 4.11
Diabetes mellitus	1.52	0.53 – 4.09	1.57	0.55 – 4.21	1.42	0.50 – 3.77
BMI	1.09	1.00 – 1.20	1.05	0.97 – 1.14	1.07	0.98 – 1.16
Gender	0.48	0.20 – 1.16	0.78	0.39 – 1.55	0.85	0.43 – 1.68
SMI	0.94	0.88 – 1.00				
Sarcopenia			1.52	0.76 – 3.12	2.08	0.89 – 4.79

The models rendered a Nagelkerke value of approximately 0.135; this means that 13.5% of the variation in the occurrence of incisional hernias is explained by the covariates. The Nagelkerke value for the specific sarcopenia measures was approximately 0.020, meaning that sarcopenia accounted for approximately 2.0% of the variation in occurrence of incisional hernias (Table 4).

Table 4. The Nagelkerke values and AUC values of the created ROC curves for incisional hernia prediction

	Nagelkerke total	Nagelkerke sarcopenia-factor	AUC (95% CI)
Model 1	0.1396	0.027	0.6690 (0.5814 – 0.7510)
Model 2	0.1250	0.010	0.6538 (0.5703 – 0.7330)
Model 3	0.1346	0.021	0.6670 (0.5787 – 0.7521)

In Figure 2, the created logistic regression models are depicted in a Receiver Operating Characteristic (ROC) curve. The black curve is a model without any sarcopenia measure.

The corresponding AUC values with 95% confidence intervals (CI) are in Table 4.

Post-operative complications

Logistic regression models were also created with post-operative complications as dependent outcome variable. In total, 124 (43.8%) patients developed a post-operative

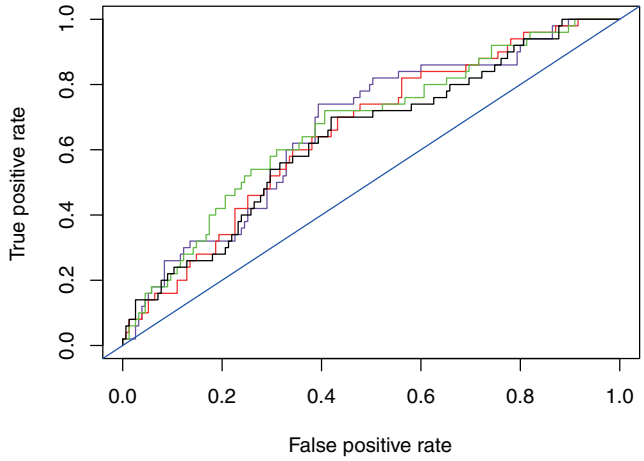

Figure 2. ROC curves of model 1 (continuous SMI, green); model 2 (sarcopenia literature cut-offs, red); and model 3 (sarcopenia gender-specific quartile, purple) for the prediction of incisional hernia. The black line corresponds to a logistic regression model without any sarcopenia measure.

complication. These included postoperative ileus, pneumonia, cardiac complications, urinary tract infection, hematoma, Surgical Site Infection (SSI; superficial, deep, or organ), seroma, and burst abdomen. Again, three models were created, in the same way as for the hernia occurrence, only controlling for more independent variables.

Model 1 again shows the continuous SMI (green), model 2 sarcopenia based on literature cut-offs (red), model 3 sarcopenia based on gender-specific quartiles (purple), and the black line shows a model without any of the sarcopenia measures (Figure 3).

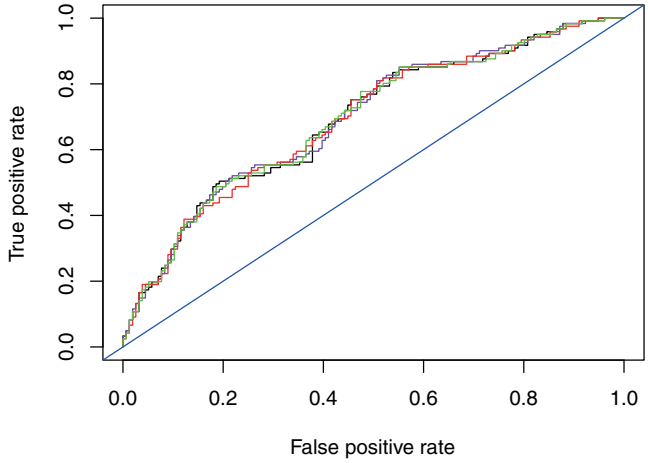

Figure 3. ROC curves of model 1 (green); model 2 (red); and model 3 (purple) for the prediction of post-operative outcomes. The black line corresponds to a logistic regression model without any sarcopenia measure.

The corresponding Nagelkerke, AUC, and OR values can be found in Table 5.

Table 5. The Nagelkerke values, AUC values, and OR values of the created models and ROC curves for post-operative complication prediction.

postoperative outcomes	**Nagelkerke total**	**Nagelkerke sarcopenia-factor**	**AUC (95% CI)**	**OR (95% CI) of sarcopenia measure**
Model 1	0.1832	0.000	0.6927 (0.6310 – 0.7563)	0.99 (0.94 – 1.04)
Model 2	0.1845	0.002	0.6912 (0.6335 – 0.7485)	1.18 (0.69 – 2.06)
Model 3	0.1855	0.003	0.6941 (0.6300 – 0.7580)	1.28 (0.68 – 2.42)

DISCUSSION

Our results point towards a lack of an association between sarcopenia and incisional hernia.

According to Nagelkerke's R^2, sarcopenia has a 1.0% to 2.7% share in the variation in occurrence of incisional hernia. This seems rather a lot when the total model seems to explain at maximum 14% in the variation of incisional hernia occurrence. However, none of the produced models rendered an AUC value of over 0.70, which is considered the cut-off value for acceptable discrimination.

Despite the low AUCs, the Nagelkerke's R^2 of 0.14 is interesting. Many authors have identified the same risk factors for incisional hernia, such as obesity (high BMI) and smoking [6,8-11]. Having included the largest, most commonly identified risk factors in our models, we would have expected a much higher proportion of variation in incisional hernia occurrence to be explained by the variables in the model.

Concerning the secondary outcomes, our results point toward the absence of predictive value of sarcopenia for the development of post-operative complications. A recent publication endorses our finding, not showing a relation between postoperative outcomes and sarcopenia in patients undergoing ventral hernia repair [29]. It states that most muscle index cut-offs were validated in patients with cancer [14,32] and might therefore not be applicable to non-malignant patients. Patients with malignancy and liver disease could have differences in metabolic state, hormonal, pharmacological, and endocrine factors, resulting in a difference in post-operative outcomes compared to non-malignant patients.

However, in the population-pool for our study, most patients had malignant disease. Then, the absence of predictive value of sarcopenia is contradictory to previous findings; multiple studies describe the importance of sarcopenia for the development of post-operative complications in oncological surgery [18,19,25,27]. However, most of these studies included a number of consecutive patients, whereas we used patients that were randomized for a trial on surgical techniques. In randomized controlled trials (RCT), patients are selected differently: if patients are too frail, they might not be invited, or might not want to participate. So, whereas previous research in malignant patients stresses the importance of sarcopenia as a predictor for post-surgical outcomes, we have found little to no predictive value of sarcopenia.

Limitations

A limitation of sarcopenia studies in general, is the limited comparability between studies due to the methods used for measuring or defining sarcopenia. Sarcopenia is often defined and measured differently, for example low muscle strength measured as low handgrip strength or abnormal body composition measured with bioimpedance [13]. Our study, in which sarcopenia is based on the SMI, is not comparable to studies using other definitions or measurements.

In our study, a limitation might be that we have used logistic regression instead of Cox regression. Cox regression is meant for outcome development over time, while logistic regression focuses on outcomes on one point in time. However, our data come from the STITCH trial, in which hernia occurrence was measured 12 months after surgery. Some people could have developed the hernia at an earlier point in time, but hernias were only registered when patients actively came to the doctor with a developed hernia, or when a hernia was diagnosed during a follow-up visit of the study. Therefore, we decided it would be better to not look at the time-to-event with Cox regression, but to use logistic regression.

Another limitation might be that we looked at CT scans up to 3 months before surgery. Within 3 months, muscle quantity can increase or decrease significantly. Patients not having sarcopenia 3 months before surgery could possibly be sarcopenic at the time of surgery. They would have been included in the wrong group in our study. Three months, however, is not an uncommon timeframe [18,21,22] and can increase comparability with other literature.

With regard to post-operative examinations, hernias were diagnosed through physical examination, ultrasound, or both. No postoperative CT examinations were done for

hernia assessment in the STITCH trial. According to a recent review, it remains unclear whether CT examinations have an additional benefit to ultrasound examinations [33]

Moreover, it can be argued that more risk factors should have been added to the model for incisional hernia. However, the relatively limited number of patients hindered investigating more predictors such as chronic obstructive pulmonary disease (COPD) or aneurysms of the abdominal aorta (AAA); in our current models this would have led to overfitting. Also no adjustment took place for other operative risk factors, such as spillage.

In our database, sarcopenia and BMI were highly correlated (Spearman's rank correlation of 0.48). This is visible in the significant difference in baseline BMI between sarcopenia groups in Table 1, and also found by other authors [29]. We adjusted for BMI in our models, to show the additional value of sarcopenia. This positive correlation is interesting; while a high BMI is related to worse postoperative outcomes, the effect estimate of SMI shows a protective effect for developing an incisional hernia. When patients with a BMI between 25 and 30 gain weight, usually they gain both muscle and either visceral or subcutaneous fat. The real danger is for patients with sarcopenic obesity, having a high BMI but a low SMI. Multiple studies show this as well [14,25,34].

Implications

Measurement of CT scans for SMI is very labour-intensive, but it does not seem to have significant predictive value. Since it is highly correlated with BMI, we would suggest using BMI, because it is easier to determine and to use in practice.

The low AUCs make our models questionable in predicting hernia development and post-operative complication development. However, we included the largest, most commonly acknowledged risk factors. This could suggest that there are other, large and unknown risk factors for the development of incisional hernia, that have yet to be discovered.

Conclusion

Despite the current interest in sarcopenia, which is shown to be useful in oncological surgery research, sarcopenia might not have much predictive value in the development of incisional hernia. Our models with low AUC values indicate that further research should be conducted to other potential risk factors. Measurement of sarcopenia through CT scans seems, for now, too labour-intensive for its respective returns, and clinicians could better use currently known risk factors.

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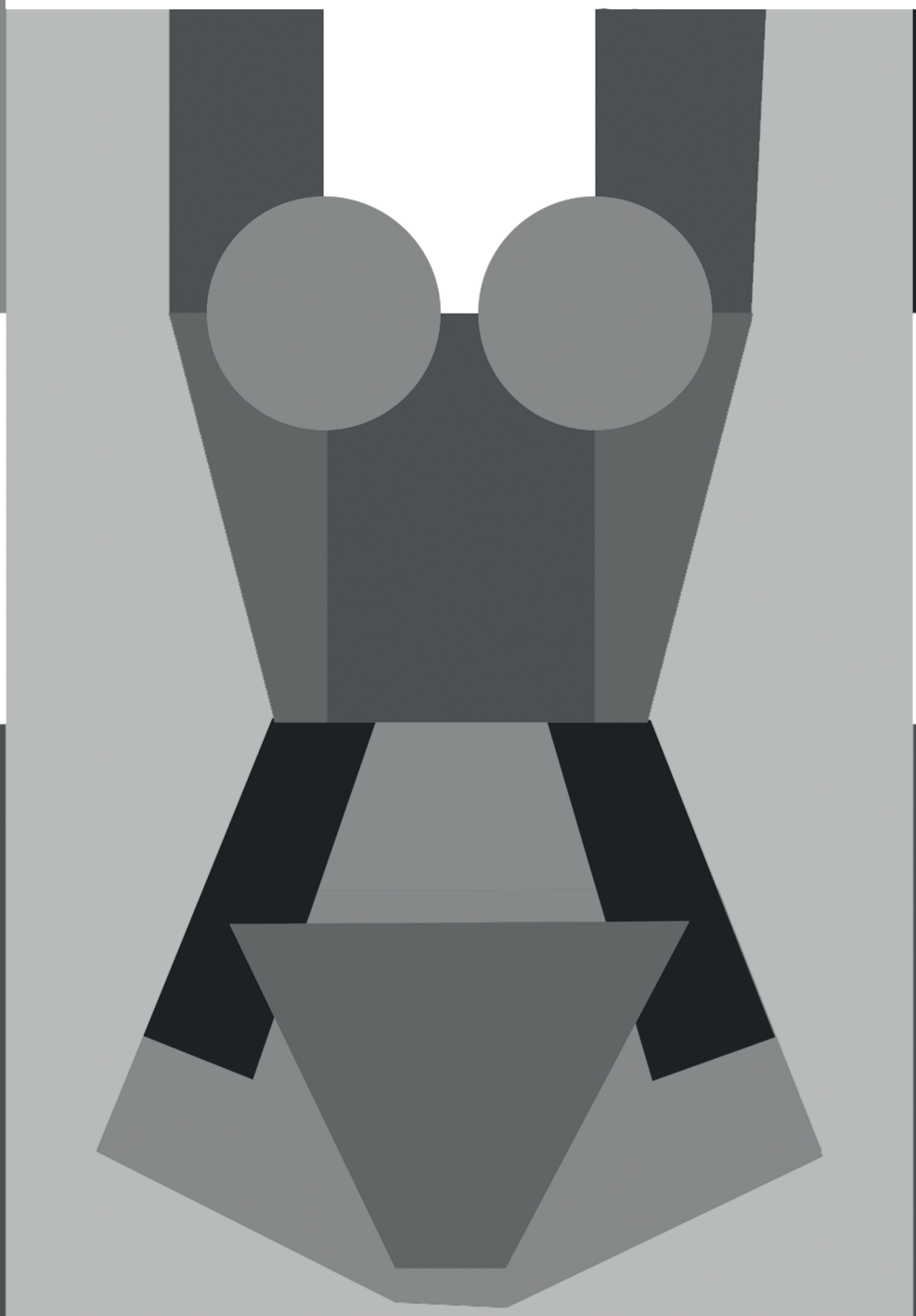
PART II: Preoperative patient preparation and treatment decisions



3 Implementing preoperative botulinum toxin A and progressive pneumoperitoneum through the use of an algorithm in giant ventral hernia repair

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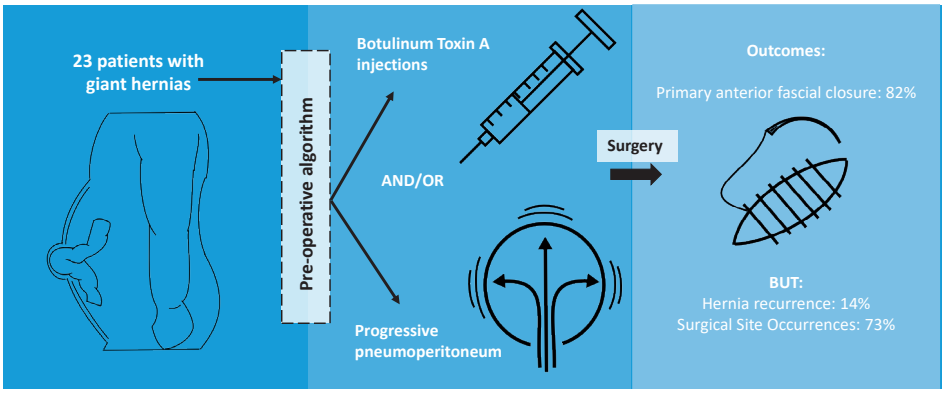

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ABSTRACT

Background: Repair of large ventral hernias with loss of domain can be facilitated by preoperative Botulinum toxin A (BTA) injections and preoperative progressive pneumoperitoneum (PPP). The aim of this study is to evaluate the outcomes of ventral hernioplasty by using a standardized algorithm, including component separation techniques, preoperative BTA and PPP.

Methods: All patients between June 2014 and August 2018 with giant hernias (either primary or incisional) of more than 12 centimetres width were treated according to a previously developed standardized algorithm. Retrospective data analysis from a prospectively collected dataset was performed. The primary outcome was closure of the anterior fascia. Secondary outcomes included complications related to the preoperative treatment, postoperative complications, and recurrences.

Results: Twenty-three patients were included. Median age was 65 years (range 28-77) and median BMI was 31.4 (range 22.7-38.0 kg/m^2). The median loss of domain was 29% (range 12-226%). For the primary and secondary endpoints, 22 patients were analyzed. Primary closure of the anterior fascia was possible in 82% of all patients. After a median follow-up of 19.5 months (range: 10-60 months), 3 patients (14%) developed a hernia recurrence and 16 patients (73%) developed 23 surgical site occurrences, most of which were surgical site infections (54.5%).

Conclusion: Our algorithm using both anterior or posterior component separation, preoperative BTA injections and PPP, achieved an acceptable fascial closure rate. Further studies are needed to explore the individual potential of BTA injections and PPP, and to research whether these methods can prevent the need for component separation, as postoperative wound morbidity remains high in our study.

INTRODUCTION

One of the most prevalent complications after midline laparotomy is an incisional hernia [1]. Incisional hernias often require surgical repair as they may cause discomfort and pain [2]. Giant hernias, which are more than 10 centimeters (cm) in width, or hernias with loss of domain (LOD) of more than 20%, in which the abdominal cavity is unable to fully accommodate the abdominal contents within its fascial boundaries, pose additional difficulties [3,4]. In these hernias, closure of the fascia is impossible or will cause high pressure with a substantial risk of complications, such as an abdominal compartment syndrome and pulmonary dysfunction [4]. Despite the risk of complications, surgical closure of a hernia with LOD might be indicated when quality of life is low. LOD can cause long term disability, loss of core muscles, back pain, paradoxical respiratory motion, mesenteric edema, poor bowel function, skin necrosis, enterocutaneous fistula, and cosmetic issues [4]. For the repair of a giant hernia (with or without loss of domain), additional medialization of the rectus abdominis muscles might be required to achieve tension free closure. Anterior or posterior component separation techniques (*i.e.* (modified) Ramirez [5] or transverse abdominis release (TAR)) can be used in order to obtain additional medialization of the rectus abdominis muscles [6]. In addition to component separation techniques, a progressive preoperative pneumoperitoneum (PPP) has shown to be a safe way to facilitate closure in hernias with LOD [7-10]. The use of PPP was first described by Goñi Moreno in 1947 [11]. PPP causes gradual expansion of the abdominal muscles and pneumatic lysis of adhesions in the abdominal cavity or hernia sac.

A more recent finding is that Botulinum toxin A (BTA) can be used to facilitate closure too, as it lowers the tension on the lateral abdominal muscles [12-14]. The combination of BTA and PPP, however, has been little described; the few studies that have been done suggest positive results [15]. This combination, however, is not always necessary for adequate repair. Additionally, PPP is rather expensive because it might require preoperative hospital stay [16].

A standardized preoperative strategy is required for patients with a giant hernia, as preoperative BTA and/or PPP can aid fascial closure, but their effects cannot be adjusted intra-operatively.

This preoperative strategy would ideally distinguish between patients with a giant hernia that [1] could be treated without preoperative aids, [2] patients in whom BTA alone would suffice, and [3] patients that would need the combination of BTA and PPP. As current literature is void of recommendations for use of these preoperative aides, an empirical algorithm was developed based on clinical experience. This retrospective analysis aimed to

determine the closure rate of the anterior fascia aided by Botulinum toxin A and/or preoperative progressive pneumoperitoneum by the use of the algorithm, and could also serve as an evaluation of whether the algorithm is valuable in determining the need for these preoperative tools in specific patient groups. Secondary outcomes included complications related to the preoperative treatment, postoperative complications, and recurrences.

METHODS

First, a preoperative strategy or algorithm for the treatment of complicated giant ventral hernias was developed in a large tertiary care university hospital in Ghent, Belgium. The algorithm was based on both hernia width and the presence or absence of loss of domain (Figure 1). The rationale behind the algorithm was based on the primary goal of achieving anterior fascial closure after hernia repair. With this in mind, the interventions used in sequential fashion were: (1) the gold standard retromuscular repair (Rives-Stoppa [17,18]); (2) anterior component separation technique; (3) BTA injections; and (4) PPP. In hernias with a width of up to 10 centimeters, retromuscular repair was performed. The size of the defect at which the additional tool of anterior CST was added, was set on 14 centimeters. BTA can be considered when the surgeon believes anterior fascia closure might still not be achievable despite the use of anterior CST, and from 18 centimeters hernia width, PPP can be considered to implement some "reserve" to prevent the surgeon from being unable to close the fascia intraoperatively. In large hernias over 22 centimeters of width, volume reduction and maximal medial advancement of the rectus muscles is desired; all tools are hypothesized to be needed in this specific complicated subset of patients.

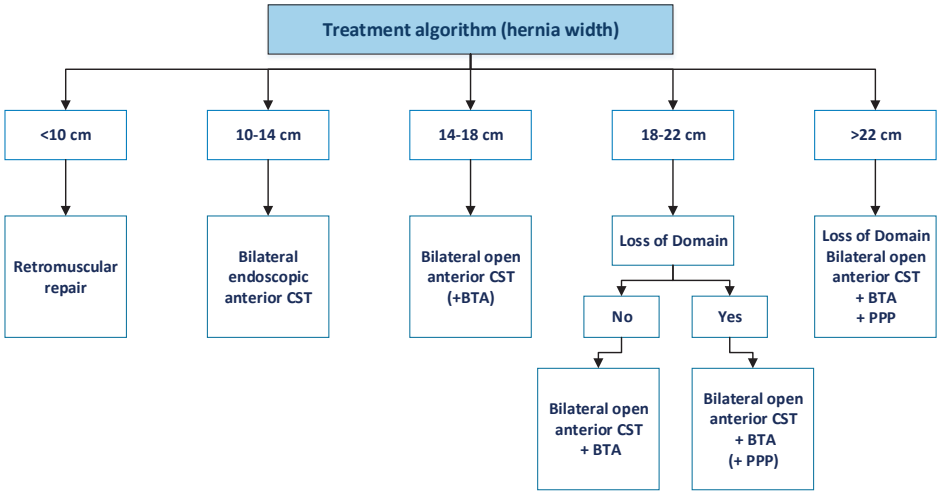

Figure 1. Treatment algorithm

Approval of the Medical Ethics Committee was obtained prior to this study. Adult patients with an elective repair of a giant hernia, either primary or incisional, who presented between June 2014 and August 2018 were treated accordingly.

As illustrated in Figure 1, BTA injections (Botulinum Toxin A, Allergan, Inc., Irvine, California) and PPP were administered to patients with a clinically estimated hernia width of more than 18 centimeters, thickened oblique muscles based on Computed Tomography (CT) examinations and/or a LOD ≥ 20% based on volumetric measures on CT [19]. BTA injections were administered according to the protocol written by Zielinksi *et al.* [20]: 300 units dissolved in 150 cc 0.9% sodium chloride solution were given at three levels bilaterally. The injections were performed under ultrasound guidance by an experienced radiologist, using a Philips iU22 device equipped with a 3-9MHz linear transducer and a biopsy guide. The injections were given into the transverse abdominal muscle, internal oblique, and external oblique muscle.

For PPP, after cardiopulmonary evaluation, a catheter (Medionics' Swan Neck Coil 2 cuff peritoneal dialysis, inner diameter of 2.6 mm and outer diameter of 5 mm) was placed through open surgery, under general anesthesia, subcostally in the right or left hypochondriac region at the day of admission. Up to 2 liters of ambient air was insufflated into the abdominal cavity at day zero. On daily basis and until hernia repair, a variable amount of ambient air was insufflated into the abdominal cavity through a microporous filter, up until the point where the patient was no longer comfortable. All patients were hospitalized during insufflation. Thromboprophylaxis (low molecular weight heparin) at therapeutic dose was administered daily.

Mesh was used for all hernia repairs, which was fixated with continuous suture of prolene 2-0.

Anterior fascial closure after hernia repair surgery took place with a running long-term absorbable polydioxanone suture 0, in a small step fashion with a small bite configuration. Suture length to wound length ratio was not measured.

Data collection

Retrospective data extraction from this prospectively collected data was performed. The following data were extracted from medical records: achievement of primary anterior fascial closure, baseline characteristics (age, gender, body mass index (BMI), smoking, medical history, and previous hernia surgery), hernia characteristics based on the EHS classification [21], data on the surgical procedure (ASA classification, surgery duration, type of repair, antibiotic prophylaxis, type and location of mesh), and follow-up time. Postop-

erative data in the form of postoperative complications, the surgical site occurrences (SSO), hernia recurrences, and reoperations were collected. A surgical site occurrence was defined as a surgical site infection (superficial, deep, mesh infection), seroma, hematoma, wound and fascia dehiscence, or enterocutaneus fistula formation. Information about BTA and PPP (side of the catheter (right or left), number of days for insufflation, amount of insufflated air) were collected. Additionally, the size of the hernia defect and volume of the hernia sac were measured from CT examinations before and after BTA and/or PPP, when available. The pre- and post-BTA abdominal muscle length was measured at the level of the mid third lumbar vertebra and the inside of the abdominal wall. Measurements started at the paravertebral muscles and ended in the midline (or hernia) using post-processing analyses with SyngoVia Version VB20A (Siemens). All data were analyzed using SPSS ® Statistics for Windows, version 24.0.0.1, IBM corp. Armonk, NY.

RESULTS

A total of 23 patients (12 males and 11 females), with a median age of 65 years (range: 28 - 77 years) were treated between June 2014 and August 2018. Median BMI was 31.4 kg/m^2 (range: 22.7 - 43.3 kg/m^2). Three patients (13%) were current smokers, 10 (43.5%) were ex-smokers, and 10 (43.5%) were non-smokers. Seven patients (30.4%) had diabetes mellitus. All patient characteristics are listed in Table 1.

Hernia characteristics

Fourteen patients (60.9%) had a recurrent hernia and 9 patients (39.1%) had a primary hernia. CT-scans to evaluate preoperative loss of domain were available for 17 patients (73.9%). The median LOD was 29% (range 12%-226%), based on hernia sac volume to abdominal cavity volume ratio.

BTA and PPP

Twenty patients (87%) received BTA injections with a median of 45 days before surgery (range 28 - 119 days). The median difference in muscle length on the right side pre- and post-BTA injections was 3.6 centimeters (cm) (range: 0.4-7.6 cm) and on the left side 2.7 centimeters (0.7-7.9 cm).

Seventeen patients (73.9%) underwent PPP. A median of 10.2 liters of air, with a range of 6.4 to 19.1 liters, was insufflated over a median period of 12 days (range: 7 - 21 days). The insufflation of the abdominal cavity was initiated 14 days before surgery (median, range: 5-43).

Table 1. Patient characteristics

Patient characteristics	Overall **N = 23**
Age, years, median (range)	65 (28-77)
Male (%)	12 (52.2)
BMI, kg/m^2 (range)	31.4 (22.7-43.3)
Smoking (%)	3 (13.0)
ASA Classification (%)	
II	14 (60.9)
III	9 (39.1)
Diabetes Mellitus (%)	7 (30.4)
Hypertension (%)	16 (69.6)
Cardiac disease (%)	9 (39.1)
Pulmonary disease (%)	8 (34.8)
Hepatic disease (%)	3 (13.0)
Renal disease (%)	0 (0)
History of malignant disease (%)	8 (34.8)
Corticosteroids use (%)	1 (4.3)
Primary hernia (%)	9 (39.1)
Recurrent hernia (%)	14 (60.9)
Number of previous herniotomies	
1	9 (39.1)
2	3 (13.0)
4	2 (8.7)

BMI: body mass index, ASA: American Society of Anaesthesiologists.

The hernia sac volume (HSV) to abdominal cavity volume (ACV) ratio was 0.29 before BTA and/or PPP (median, range 0.12 - 2.26, 6 CT scans missing) and 0.33 after BTA and/or PPP (range 0.09 – 2.00, 6 CT scans missing). Fourteen patients (60.9%) received the combination of BTA injections and PPP. Data regarding patients having both BTA and PPP are summarized in Table 2. Several patients did not require both BTA and PPP based on their clinical presentation and our algorithm. For example, in case LOD was present without thickened lateral abdominal wall musculature, only PPP was administered preoperatively. When we evaluate the practical usefulness of our algorithm, in the hernia group with widths between 14 and 18 centimeters, the actually performed pre- and intra-operative treatment differed in seven out of nine patients (77.8%) from what was suggested according to the algorithm. In contrast, in all patients from both groups with hernias over 18 centimeters, the proposed surgical technique from the algorithm was used. Only three out of 14 patients in those two groups (21.4%) received different preoperative management than suggested by the algorithm. Details on the pre- and intraoperative operative treatment per treatment group from the algorithm are summarized in Table 3. Additionally, the hernia characteristics using the EHS classification are presented in Table 3 [21].

Table 2. BTA and preoperative progressive pneumoperitoneum

Treatment	Overall (N = 23)
BTA, number (%)	20 (87.0)
Days before surgery	45 (8-120)
Δ muscle length pre- and post-BTA, right (cm)	3.6 (0.4-7.6)
Δ muscle length pre- and post-BTA, left (cm)	2.7 (0.7-7.9)
PPP, number (%)	17 (73.9)
Side drain, right (%)	16 (94.1)
Total air (liters)	10.2 (6.4-19.1)
Total days of air insufflation	12 (7-21)
Days before surgery	14 (5-43)
HSV/ACV ratio before BTA and/or PPP	0.31 (0.12-2.26)
HSV/ACV ratio after BTA and/or PPP	0.33 (0.08-2.00)
BTA + PPP combination, number (%)	14 (60.7%)
Days before surgery, BTA	43 (8-120)
Δ muscle length pre- and post-BTA, right (cm)	4.3 (0.4-7.6)
Δ muscle length pre- and post-BTA, left (cm)	4.2 (1.3-7.9)
Days before surgery, PPP	14 (5-37)
Side drain, right (%)	13 (92.9)
Total air (L)	10.4 (6.4-19.1)
Total days of air insufflation	11 (7-21)

All values are median (range) or n (%). PPP: preoperative progressive pneumoperitoneum, HSV: hernia sac volume, ACV: abdominal cavity volume, Δ: difference in muscle length.
** Only 1 measurement available*

Complications of PPP and BTA

The administration of BTA injections did not result in complications. The use of PPP, however, resulted in complications in 5 patients. One patient had a cardiac arrest at day 5 of PPP and cardiopulmonary resuscitation was performed successfully. Post hoc evaluation showed an AV block grade II, with no signs of pulmonary or air embolisms. A PPP catheter was replaced approximately two weeks after the cardiac arrest. Consequently, the patient developed a liver hematoma, which was drained surgically. Another patient had a hematoma retro rectus at the site of the catheter during PPP, confirmed with a CT-scan, which was drained during hernia repair. One patient was admitted to the intensive care unit due to hemorrhagic shock based on an extensive hematoma after placement of the PPP catheter at day 5. This hematoma was drained surgically. One patient developed an enterocutaneous fistula during PPP. The fifth patient died preoperatively due to hemorrhage at the site of the bursa omentalis and multi-organ failure after five days of PPP, and was therefore not evaluated in further analyses (Figure 2).

Table 3. Surgical characteristics per subgroup from the algorithm

Hernia width	**Width 14-18 cm N = 9**	**Width 18-22 cm N = 6**	**Width >22 cm N = 8**
Treatment algorithm	Bilateral anterior CS (+BTA)	Bilateral anterior CS + BTA (+ PPP)	Bilateral anterior CS + BTA + PPP
Age, years, median (range)	67 (46-74)	68 (63-77)	63 (28-69)
BMI, kg/m^2 (range)	31.4 (24.7-43.0)	29.8 (22.7-36.8)	36.3 (25.5-43.3)
Recurrent hernia (%)	5 (55.6)	3 (50.0)	6 (75.0)
EHS classification			
M1-M4W3	1 (11.1)	2 (33.3)	2 (25.0)
M1-M5W3	0 (0)	2 (33.3)	1 (12.5)
M2-M4L2W3	1 (11.1)	0 (0)	0 (0)
M2-M5W3	0 (0)	1 (16.7)	4 (50.0)
M2-M5W2	1 (11.1)	0 (0)	0 (0)
M2-M5L2W3	0 (0)	0 (0)	1 (12.5)
M3-M4W3	1 (11.1)	0 (0)	0 (0)
M3-M5W3	4 (44.4)	0 (0)	0 (0)
L2-W3	1 (11.1)	0 (0)	0 (0)
Missing	0 (0)	1 (16.7)	0 (0)
BTA only (%)	3 (33.3)	2 (33.3)	1 (12.5)
PPP only (%)	1 (11.1)	0 (0)	2 (25.0)
PPP + BTA (%)	5 (55.6)	4 (66.7)	5 (62.5)
Surgery (%)	9 (100.0)	5 (83.3)	8 (100.0)
Surgery time, minutes (range)	265 (150-399)	260 (220-370)	323 (215-396)
Type of surgery			
Anterior CS, bilateral (%)	2 (22.2)	5 (83.3)	8 (100.0)
TAR, bilateral (%)	1 (11.1)	0 (0)	0 (0)
Anterior CS, unilateral (%)	1 (11.1)	0 (0)	0 (0)
TAR, unilateral (%)	1 (11.1)	0 (0)	0 (0)
Comb. anterior CS and TAR (contralateral sides) (%)	3 (33.3)	0 (0)	0 (0)
No CS (%)	1 (11.1)	0 (0)	0 (0)
No repair (%)	0 (0)	1 (16.7)	0 (0)
Mesh location			
Intraperitoneal	4 (44.4)	5 (83.3)	8 (100.0)
Retromuscular	5 (55.6)	0 (0)	0 (0)
Mesh type			
Synthetic	9 (100)	5 (83.3)	7 (87.5)
Biologic	0 (0)	0 (0)	1 (12.5)

BMI: Body Mass Index, EHS: European Hernia Society, BTA: botulinum Toxin A, PPP: progressive preoperative pneumoperitoneum, CS: component separation, TAR: transverse abdominal release, Comb.: combination

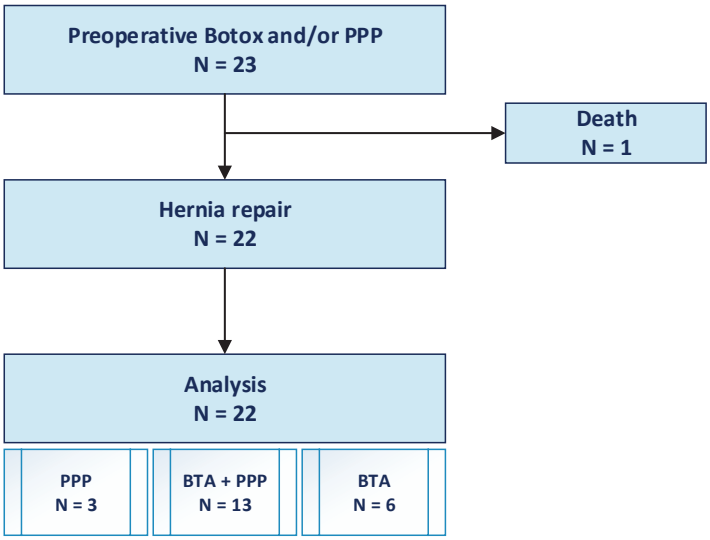

Figure 2. Flowchart of treatment and analysis

Surgical characteristics

All abdominal hernia repairs (N = 22) were elective laparotomies. Hernia repair was performed by either anterior component separation or transversus abdominis release, except in one patient. This patient did not need component separation and could be repaired without this technique. Intra-operatively, the median length of the hernia was 20 cm (range: 8 – 30 cm) and the median width was 21 cm (range: 12 – 30 cm). Mesh localization was either intraperitoneal (N = 17, 77.3%) or retromuscular (N = 5, 22.7%). Median length of the meshes used was 42 centimeters (range: 28-50 cm) and median width was 32 cm (range 26-38 cm). Median mesh surface (length x width) was 1344 cm^2 (range 572-1850 cm^2). All patients were clinically re-evaluated in July 2019. The follow-up period therefore ranged from 10 to 60 months, with a median follow-up of 19.5 months. All surgical characteristics can be found in Table 3.

Intra- and postoperative complications

With regard to the primary outcome, in four patients (18.1%), the anterior fascia could not be closed during the initial operation. One patient had a small bowel perforation during adhesiolysis, which was repaired immediately during the first operation, but a second stage repair a few days later was required. In three other patients (13.6%) the anterior layer could only be closed using a small part of the hernia sac to cover the intraperitoneal mesh. With regard to the secondary endpoints, 16 patients (72.7%) developed 23 surgical site occurrences (SSOs) postoperatively (summarized in Table 4).

Table 4. Recurrences and Surgical Site Occurrences (SSOs) per subgroup from the algorithm.

Hernia width	**Width 14-18 cm N = 9**	**Width 18-22 cm N = 5***	**Width >22 cm N = 8**
Treatment algorithm	Bilateral anterior CS (+BTA)	Bilateral anterior CS + BTA (+ PPP)	Bilateral anterior CS + BTA + PPP
Direct fascial closure achieved (%)	9 (100)	4 (80.0)	5 (62.5)
Recurrence (%)	0 (0)	1 (20.0)	2 (25.0)
Reoperation for either recurrence or complication (%)	0 (0)	2 (40.0)	3 (37.5)
Patients with ≥ 1 SSO	5 (55.5)	3 (60.0)	8 (100.0)
Total SSO	7	4	13
Surgical site infection (%)	4 (44.4)	3 (60.0)	6 (75.0)
Superficial or wound dehiscence	4 (44.4)	1 (20.0)	2 (25.0)
Deep	0 (0)	2 (40.0)	4 (50.0)
Seroma (%)	1 (11.1)	0 (0)	3 (37.5)
Hematoma (%)	2 (22.2)	0 (0)	2 (25.0)
Fascia dehiscence (%)	0 (0)	1 (20.0)	2 (25.0)
Enterocutaneous fistula formation (%)	0 (0)	0 (0)	0 (0)
Follow-up, months (median, range)	17 (10-40)	13 (12-31)	32.5 (19-60)

** 5 as one patient did not receive repair.*

Twelve patients (54.5%) had a surgical site infection (SSI), of which six patients (26.1%) had a deep infection. One deep infection was managed by antibiotic treatment alone, two deep infections required (partial) surgical mesh removal, and the remaining three were treated with negative pressure therapy. No other SSO required additional therapy, except for one seroma, which was drained by ultrasound guidance and subsequently drained during surgery.

Other complications included pneumonias in three patients, of whom two needed admission to the intensive care unit. A total of three patients (13.6%) experienced a hernia recurrence, of which one received surgical repair with an intraperitoneal synthetic mesh. Cumulatively, five surgical interventions took place; one for hernia recurrence and a deep SSI (4.5%) and four (18.2%) for other postoperative complications.

DISCUSSION

Preoperative preparation of patients with giant ventral and incisional hernias is essential to obtain the best possible outcomes in terms of fascial closure rate. However, the effects of preoperative aides cannot be further enhanced intraoperatively; the needed effect size has to be determined beforehand. Therefore, a standardized preoperative

strategy based on clinical and radiological parameters would be useful to estimate the needed effect size, informing on whether there is need for the use of BTA, PPP, or both. This cohort of 23 patients, treated according to a standardized algorithm for a giant ventral hernia with or without LOD, shows that BTA and PPP facilitate closure in ventral hernia repair. The primary fascial closure rate is 82%.

Component separation technique

Component separation techniques were used as the first tool in our algorithm to facilitate medialization of the rectus muscles and closure of the anterior fascia. Surgeons that refrain from using component separation techniques might not achieve anterior fascial closure in all patients, as illustrated by Renard et al. (primary closure in 42 out of 45 patients, 94%) [7]. In our study, anterior CST and TAR were applied in all but one patient; anterior CST was planned in addition to BTA for this patient, but BTA alone made anterior fascial closure possible. Despite being associated with more wound complications than TAR [22], anterior CST renders nearly 6 centimetres of medialization of the rectus sheath (in post mortem human specimens), which can contribute to tension-free fascial closure [6]. In three patients in our study, to avoid intraperitoneal mesh placement and obtain anterior fascia closure, a unilateral TAR was done on one side to facilitate the closure of the posterior layer, and a unilateral anterior CST was done on the other side to ensure anterior fascial closure. In none of the patients both anterior CST and TAR were performed at the same side. Another component separation method could be represented by the endoscopic external oblique release as described by Rosen et al. [23], but as the achieved fascial advancement is limited to approximately 80% of what can be achieved by an open technique, the latter was used in our study.

BTA

If anterior CST was estimated not to be enough for achieving anterior closure of the fascia, BTA was applied four to six weeks preoperatively. Only two protocols for BTA injections have so far been described; a 3-point and 5-point technique, respectively [20,24]. Either one of these does not seem preferable over the other. BTA alone has been reported to give a 0.5 to 1.5 centimetres extra muscle length on each side of the abdominal wall on average. Other authors, however, found 1 to 5 centimetres of myofascial advancement with the use of BTA [12,13,25-27]. In this study, the addition of BTA injections resulted in an extra increase in length of 2.0 to 3.0 centimetres of the lateral abdominal wall muscles, without causing additional complications. This finding is in line with current literature; no complications of BTA use as a preoperative aid have been recorded, only minor inconveniences such as bruising after injection or a sensation of bloating [12]. One study even found an additional analgesic effect postoperatively of BTA [28].

PPP

In case a significant loss of domain of more than 20% was calculated preoperatively, the use of PPP was indicated, as shown in our algorithm (Figure 1). PPP insufflations were performed daily with ambient air, until the patient experienced scapular pain, abdominal pain, or dyspnoea. The use of ambient air has been advocated, because nitrous oxide, carbon dioxide and oxygen are absorbed 4 times faster in the peritoneal space than ambient air [10,29]. This causes the necessity to top up the volume often and with large quantities, while the use of ambient air results in easier maintenance of the pneumoperitoneum. No current consensus has been reached with regard to the amount of air to be injected, the frequency of the insufflations, and the length of the period the pneumoperitoneum should be maintained. Therefore, we used 2 liters at the time of catheter placement intra-operatively and 1 liter daily. It is suggested that PPP does not cause further benefit after 6 to 10 days [29]. However, CT-scans at 7 days after starting PPP showed only partial reduction of the hernia content in most of our patients, with limited air accumulation in the abdominal cavity itself. Therefore, we continued PPP for a maximum of 21 days. The average LOD was 53% before admission (median 29%). PPP caused a mean increase in HSV/ACV-ratio of 4%. This increase is understandable from the law of Laplace, and was also found by Sabbagh et al. [8], who reported a 1%-increase in the ratio incisional hernia volume to total peritoneal content. Other authors, however, report a significant decrease in this ratio, from 5% to 22% [7,15,30]. Their findings could justify the use of an abdominal binder between PPP sessions, to restrict air going to the hernia sac. However, air inside the hernia can cause lysis of possible adhesions and facilitate fascial closure [31]. Complications related to PPP in our study are predominantly hematomas, and one patient died because of an extensive bleeding and hemodynamic shock (however probably also related to his frail preoperative state). We treated all our patients with a therapeutic dosage of low molecular weight heparin from the start of PPP to prevent pulmonary embolisms. This serious complication has been described using laparoscopy [32] and is probably caused by increasing pressure at the level of the caval vein. However, in the light of our current findings – showing a high incidence of hematomas and bleeding complications – it might be better to use prophylactic dosage LMWH during PPP. Other authors describe complications such as subcutaneous emphysema, shoulder pain, abdominal pain, nausea, anxiety, intestinal perforation, and even mortality [7,10,15,29,31,33]. Therefore, PPP asks for deliberate use in specific patient groups only. An evidence-based cut-off for LOD should be established in order to help surgeons decide on when to use PPP as a preoperative aid for hernia repair. As the primary goal is to close the anterior fascia, lenient cut-offs for LOD should be utilized.

Complications

Surgical repair of these giant hernia defects was accompanied by several complications. Twelve patients (54.5%) experienced a surgical site infection (superficial or deep) and 3 patients (13.6%) had a recurrence. Five patients (22.7%) had to have a reoperation for either a recurrence or postoperative complication. These complications could not have entirely been avoided, as this is a very complex patient group. More than 90% of the patients were overweight (BMI > 25 kg/m2) and many had comorbidities (as shown in Table 1). Yet when compared to the literature on ventral hernias with LOD, our SSI rate of 54.5% seems high. This might be partially be explained by the fact that we included wound dehiscence without proof of positive cultures in the superficial SSI rate. Other authors describe infection rates between 5% and 26% [7,19,34-38]. Also, the number of patients receiving a reoperation seems relatively high with 22.7%, compared to a 10% to 15% re-operation rate [35,38]. A possible explanation might be that we considered negative pressure wound therapy, as initiated with wound debridement in the OR, as a reoperation. Only one other study – more in line with our data - finds that one-third of the patients had to be reoperated [36]. These relatively high numbers could be due to the rather extreme width of the hernias researched in this study. Patient selection may have differed from abovementioned studies. Additionally, the large number of comorbidities present in the researched group hinders the direct comparison of outcomes with findings from other authors. The number of patients having a recurrence (13.6%) is within line of expectations for these complicated hernias. Other authors report 4% to 16% recurrences [7,19,34-38].

Limitations

This is a retrospective cohort study, which is sensitive to bias. Also, only 23 patients were analyzed. The results must therefore be interpreted with caution, as these numbers are insufficient to provide sound statistical comparisons. Additionally, some patients had a relatively short follow-up period, and CT scans were not always available to confirm that an indication for PPP (as through our algorithm) was indeed present; these are both drawbacks of presented study. However, LOD is most of the time obvious at clinical examination, so bias on this point would be relatively low. Despite these limitations, the data of these patients add to the current body of knowledge about the combined use of BTA and PPP; what it can offer in hernia defect closure and the potential risks.

Implications

The combination of anterior CST and BTA seems safe and effective, leading to an anterior fascial closure rate of 82% in our study. PPP use might require more critical deliberation whether it is worth the risk as it resulted in a high complication rate of 29%. The standardized treatment algorithm prevented the surgeon from facing unforeseen intraoperative difficulties in closing the anterior fascia. However, the issue we came across during the

usage of proposed algorithm in clinical practice, is that it cannot always be successfully applied, as it is not a validated instrument. LOD was only measured when the estimated hernia width was >18 centimeters, but had implications for the preoperative treatment, while LOD can also be present in hernias of less than 18 centimeters width. Meaning, undertreatment might have taken place: patients with LOD, but with an estimated effect width of <18 centimeters, could possibly also have benefited from the additional PPP treatment. On the other hand, overtreatment might also have been present, as the exact benefits and limitations of BTA treatment remain unclear; in some patients, fascial closure might have been achieved without the use of BTA or PPP. Using BTA is expensive and, as BTA is not reimbursed by the insurance companies in Belgium, it poses an additional cost of approximately 500-600 euros for the patient.

PPP is described to cause a decrease in the LOD of the hernia, facilitating tension-free closure of the fascia during repair. An additional advantage of PPP is the lysis of adhesions caused by the insufflated air [31]. A drawback of PPP is that it is even more expensive than BTA, as it required preoperative hospital stay in our study. As reported by Renard et al. [7], admission is not mandatory, but safety was considered of utmost importance in our study (as was observed with the patient suffering an AV-block during insufflation). Moreover, PPP showed a high complication rate of 29% which included severe complications, PPP can cause pain, and PPP is generally experienced as unpleasant by patients; all possibly resulting in a lower quality of life. An evidence-based protocol might be of help with indications for its use, and with regard to the amount of air to be insufflated and the number of days the pneumoperitoneum should be maintained. However, as it involves a very heterogeneous and relatively small group of patients with many variables influencing the final outcome, this might be elusive. The individual value of BTA, PPP, and CST cannot be determined based on the results from this study, nor has their value been elucidated in other studies, which only suggest optimistic results of the combined use of these methods [35]. The value of a specific preoperative aid is difficult to determine as the number of patients treated in the current study is too small and overtreatment might have taken place to be certain to achieve fascial closure. Because BTA is associated with less complications, it would be useful to distinguish between patients with a hernia with LOD that could be treated with BTA alone, CST alone, and patients that would need the combination of BTA and PPP, and possibly additional CST. This analysis clearly demonstrates, however, that a standardized algorithm may be considered as a guidance during the pre- and intra-operative surgical decision making, but both preoperative CT assessment and clinical examination remain mandatory to determine the best approach for each individual patient. Larger studies and pooling of data would be required to give recommendations with regard to optimal selection of preoperative preparation methods.

Conclusions

This study is a description of 23 patients with complex ventral hernia repair facilitated by Botulinum toxin A and preoperative progressive pneumoperitoneum. BTA seems safe to aid closure, whereas PPP requires critical consideration before its use. Further research should be conducted to determine both indications and outcome parameters for each of these preoperative tools in abdominal wall reconstruction.

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4

Fascial closure in giant ventral hernias after preoperative botulinum toxin A and progressive pneumoperitoneum: a systematic review and meta-analysis

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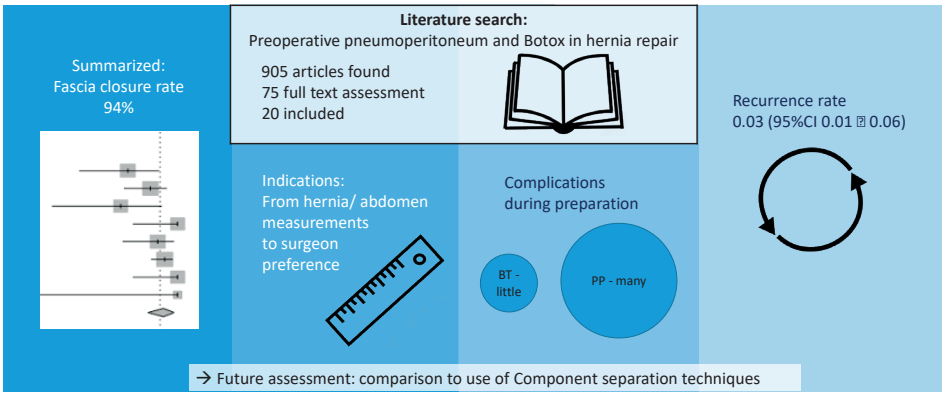

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ABSTRACT

Background: The primary objective was to assess the perioperative efficacy of the preoperative use of progressive pneumoperitoneum (PP) or Botulinum Toxin A (BT) injections in ventral hernia repair.

Methods: Embase, Medline Ovid, Web of Science, Cochrane Central, and Google Scholar were systematically searched. Studies in English reporting on fascial closure, indications, complications or postoperative outcomes in adult patients that had undergone PP, BT, or both prior to ventral hernia repair were included. Study quality was assessed with the Oxford Levels of Evidence guidelines and the Methodological Index for Non-Randomized Studies criteria. A pooled fascial closure rate and recurrence rate were calculated with random effects models.

Results: Twenty studies were included from the 905 identified, comprising the use of PP (n=11), BT (n=6), and both techniques (n=3). The overall fascial closure rate was 0.94 (95% confidence interval 0.89 – 0.98). Indications for the use of PP or BT were based on objective (e.g. CT measurements) or subjective measures (e.g. foreseen surgical problems). In contrast to the use of BT, reported complications with the use of PP were ample and sometimes severe. The cumulative reported recurrence rate was 0.03 (95% confidence interval 0.01 – 0.06).

Discussion: Preoperative PP and BT can facilitate fascial closure without causing significant numbers of adverse events. BT qualifies for low-threshold use, yet PP should be used cautiously due to a larger number of complications. Definitive recommendations cannot be made as the quality of included studies is low, bias is present, and comparative information is scarce.

Registration number PROSPERO, CRD42020181679.

INTRODUCTION

Large abdominal hernias with fascial defect diameters over 10 centimeters pose a problem in surgery, especially in the presence of loss of domain, where the hernia content cannot be fully reduced into the abdominal cavity [1]. For the patient, this loss of domain can influence quality of life through back pain, respiratory problems, and cosmetic complaints [1]. For the surgeon, these hernias with loss of domain complicate fascial closure and increase the risk of high postoperative abdominal pressure, which may lead to loss of pulmonary capacity [2] and abdominal compartment syndrome [3].

Fascial closure is desirable in hernia surgery, as it reduces the hernia recurrence rate [4-6]. To achieve repair of giant hernias, Goni Moreño described – in 1947 – the preoperative progressive pneumoperitoneum (PP) for the stretching of the abdominal wall musculature [7]. However, this technique did not come without complications [8-10], and – when performed on an inpatient basis – additional costs of care.

More recently, the use of preoperative Botulinum Toxin A (BT) infiltrations in the abdominal wall has been described [11, 12]. BT infiltrations result in lowered tension and elongation of the abdominal muscles, therefore facilitating hernia repair [13, 14]. However, the use of BT also has a looming price tag, as insurance companies do not always cover for the costs of BT when used for the preoperative preparation of giant hernia repair.

Despite the increasing number of reports on PP, BT, or a combination, it remains unclear how much can be gained preoperatively with these techniques, and whether this preoperative gain outweighs the complications that can occur by using these techniques. Therefore, no consensus on standardized indications exists for the use of PP and BT, and surgeons often use these preoperative aides based on their own clinical experience.

Therefore, the objective of this study was to give a comprehensive overview of the published articles on the use of PP and/or BT (excluding case reports or case series), aiming at assessing the efficacy of these aides intraoperatively through the fascial closure rate. Additionally, the described indications for PP and BT, the complications that occurred due to their use, and postoperative complications and recurrences that arose in the patient groups that have been prepared with these techniques were reviewed.

METHODS

In this study, information on fascial closure during ventral hernia repair, after preoperative preparation with PP, BT, or a combination of both, was collected. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42020181679). For the reporting of the study, the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16] were followed.

Search

A systematic computerized literature search was performed on the 28th of July 2020, in the online databases Embase, Medline Ovid, Web of Science, Cochrane Central, and Google Scholar. A medical librarian specialized in conducting systematic reviews prepared the search strategy and database search. The syntax with the search strategy per database can be found in Appendix 1.

Outcomes

The primary outcome was the fascial closure rate. Secondary outcomes included the indications for PP, BT, or their combination; the complications after the use of these preoperative aides; and postoperative complications in the form of SSO – including SSI – and recurrences.

Study selection and data extraction

Studies reporting on the use of PP or BT (or their combination) in preparation of ventral hernia repair were included. There was no limit on publication date. Two reviewers (MMJvR and YY) independently screened all records by title and abstract for eligibility, using a standardized method [17]. Subsequently, the full texts of the eligible articles were independently assessed. Discrepancies in article selection were discussed between both reviewers, and included or excluded after reaching consensus.

Randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies in English were included. Case reports, case series reporting on less than 10 patients, letters, reviews, and comments were excluded. The following criteria were applied for inclusion: 1) patients aged 18 years or older; 2) patients had undergone PP or BT prior to abdominal ventral hernia repair; 3) reported outcomes included either fascial closure, complications with the use of PP or BT, post-operative surgical site occurrences (SSO), or hernia recurrences. All types of surgical techniques were allowed. Studies reporting on inguinal, scrotal, hiatal, or port-site hernias were excluded, along with studies not reporting outcomes split up for the (sub)group that received PP or BT.

Data extraction was performed using a standard form covering study characteristics (study type, year, evidence, number of patients), patient characteristics (age, BMI, smoking, COPD, hypertension, diabetes, cardiorespiratory disease, malignant disease, hernia type), type and protocol of preoperative treatment (indications for PP and/or BT; for PP: type of insufflation gas, catheter location, number of days, insufflated volume; for BT: units, infiltration location), complications of preoperative treatment, surgical characteristics (hernia width, hernia length, loss of domain, type of repair, mesh use, component separation technique (CST) use, operation time, fascial closure), post-operative outcomes (SSO, SSI, recurrence, mortality, reoperation, length of hospital stay), and follow-up.

In case of uncertainty around duplicate data, the authors of these studies were contacted and asked for confirmation or further elaboration. Upon confirmation of the contacted author, the article with the most patients treated was selected, and the remaining articles were excluded. Additionally, authors reporting the use of both techniques (PP and BT) in separate patients, without presenting data per subgroup, were contacted for information on the outcomes of the separate subgroups.

Quality assessment

Each article was assessed by two independent reviewers (MMJvR and MA) for its level of evidence according to the Oxford Centre for Evidence-Based Medicine levels of evidence [18]. Methodological quality of included nonrandomized studies was assessed using the Newcastle-Ottawa Scale criteria [19] and the Methodological Index for Non-Randomized Studies (MINORS) criteria [20].

Data synthesis

An inverse variance random-effects model was used to calculate a pooled proportion for fascial closure and recurrence, using the Freeman-Tukey double arcsine transformation. Between-study variance was calculated through tau-squared with the DerSimonian-Laird estimator. All analyses were performed with R Statistical software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Indications and complications described with the use of PP or BT are presented descriptively.

RESULTS

Search and study characteristics

The selection of articles is depicted in a PRISMA flow diagram in Figure 1. Of the 905 articles identified (after removing duplicates), 75 remained for full-text assessment after title and abstract screening. Of these 75, 20 articles were selected for inclusion [10-12, 14, 21-36].

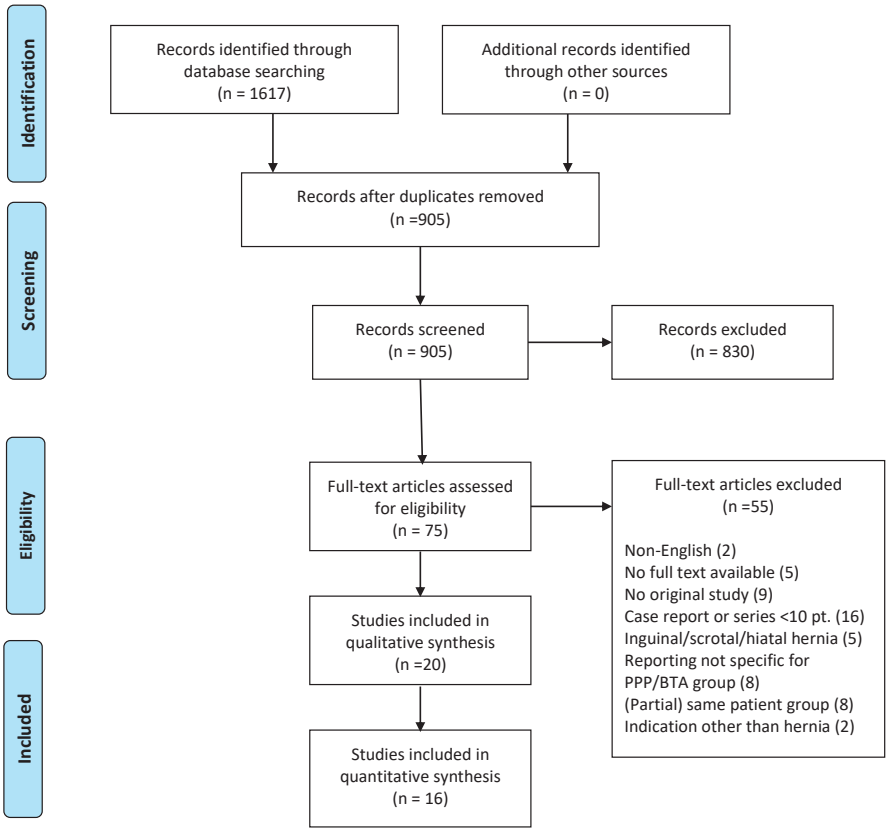

Figure 1. PRISMA flow diagram of article selection

One article was a case-control study [11], two articles were non-randomized trials [34, 36], one was a case series with selected controls [29], and all other articles were single-arm prospective or retrospective studies [10, 12, 14, 21-28, 30-33, 35]. Due to the large number of single-arm studies, a minor deviation from the originally registered protocol [37] took place in the form of the additional use of the MINORS checklist for quality assessment, as this checklist is both applicable for comparative and non-comparative studies [20]. All articles scored between 25% and 75% of the maximum MINORS score, yet nonetheless, all were included for analysis. None of the studies had a blind evaluation of the endpoint or a prospective calculation of the study size.

Eleven studies reported on the sole use of PP in 466 patients, 6 studies reported on preoperative BT infiltrations only in 164 patients, and 3 studies reported on the use of both techniques in 179 patients. These techniques were reported to have been used for incisional, midline, lateral, transverse, or parastomal hernias. Complete study details, including the Level of Evidence and MINORS score, are shown in Table 1.

Table 1. Article characteristics from included articles. Mean values reported (age in years, BMI in kg/m^2, hernia width in centimeters, follow-up in months). * median instead of mean

Name	Study type	LoE	MINORS	n	Age	BMI	Interven-tion	Hernia width	Open/ Lap. (n)	Mesh use	CST	Follow-up	FU range	Outcomes
Hamer 1972 [29]	Case series with selected controls	4	4/24	10	53.3	NR	PP	10.8	Open	20.0%	NR	NR	12 to 72	I C PC R
Astudillo 1986 [36]	Prospective non-randomized trial	3	9/24	12	NR	NR	PP	NR	Open	0%	0%	24	NR	I PC R
Caldironi 1990 [33]	Retrospective	3	4/16	41	58.5	NR	PP	5 to 15	NR	39.0%	0%	25.3	6 to 108	I C PC R
Coelho 1993 [31]	Retrospective	3	4/16	36	52	NR	PP	NR	Open	16.7%	NR	10	1 to 48	F I C PC R
Tonatio 2002 [23]	Retrospective	3	7/16	77	56.6	NR	PP	15.8	Open	100%	0%	38.8	24 to 60	F I C PC R
Dumont 2009 [30]	Prospective	3	10/16	21	NR	38	PP	10.1	NR	61.9%	14.3%	NR	NR	F I C
Ibarra-Hurtado 2009 [12]	Prospective	4	7/16	12	36.3	NR	BT	13.9	Open	0%	50.0%	9	4 to 18	F I PC R
Tanaka 2010 [25]	Prospective	3	4/16	23	55.6	38.5	PP	NR	Open	100%	4.3%	NR	0 to 24	F I PC R
Zendejas 2013 [11]	Case-control	4	15/24	22	61.8	30.9	BT	NR	Open 10 Lap. 12	100%	18.2%	15.6	NR	F I C PC R
Ibarra-Hurtado 2014 [28]	Prospective	3	12/16	17	34.9	NR	BT	14.7	Open	23.5%	52.9%	49	37 to 61	F I C PC R
Renard 2016 [26]	Prospective	3	9/16	45	60.5	NR	PP	14.7	Open	82.2%	0%	18.6	3 to 68	F I C PC R
Rodriguez-Aceveco 2018 [14]	Prospective	3	6/16	56	59.7	30.9	PP + BT	11.6	Lap. 41 LOL 15	100%	14.3%	NR	NR	F I C PC R
Valezi 2018 [22]	Prospective	3	8/16	16	44	33	PP	NR	Open	100%	0%	2 days	NR	I C
Bueno-Lledo 2020 (Front Surg) [35]	Retrospective	3	9/16	100	59.4	NR	PP + BT	16.1	Open	100%	89.0%	34.5	11 to 62	F I C PC R
Mancini 2020 [10]	Retrospective	3	6/16	162	57.8	33.2	PP	16.2	Open	87.3%	NR	NR	NR	F I C PC
Nielsen 2020 [27]	Retrospective	3	7/16	37	59.5	31.1	BT	12.1	Open	100%	40.5%	1	NR	F I C PC
Tang 2020 [24]	Retrospective	3	7/16	23	63.4	NR	PP	NR	Lap. 20 LOL 3	100%	NR	24	13 to 40	F I C PC R
Bueno-Lledo 2020 (Surg) [34]	Prospective non-randomized trial	3	13/24	40	51.5	NR	BT	15.5	Open	100%	0%	19.6*	11 to 35	F I C PC R
Catalan-Garza 2020 [32]	Retrospective	4	7/16	36	60.9	20.7	BT	13.9	Open	NR	58.3%	NR	Up to 24	F I C PC R
Yurtkap 2020 [21]	Retrospective	3	12/16	23	61.9	32.6	PP + BT	20.2	Open	100%	95.5%	25.1	10 to 60	F I C PC R

LoE: Level of Evidence[18], BMI: Body Mass Index, Lap.: laparoscopic, CST: Component separation technique, FU: follow-up, NR: not reported, PP: progressive pneumoperitoneum, BT: botulinum toxin A, LOL: laparoscopic-open-laparoscopic, F: Fascial closure, I: indications, C: complications, PC: postoperative complications including surgical site occurrences and/or surgical site infections, R: recurrences

Fascial closure

The primary outcome of interest was the fascial closure rate. Sixteen studies reported the fascial closure rate after the use of PP or BT. A 94% cumulative fascial closure rate was found under a random effects model (95% CI 0.89 - 0.98). In addition to this overall fascial closure rate, the cumulative rate per intervention is plotted in Figure 2.

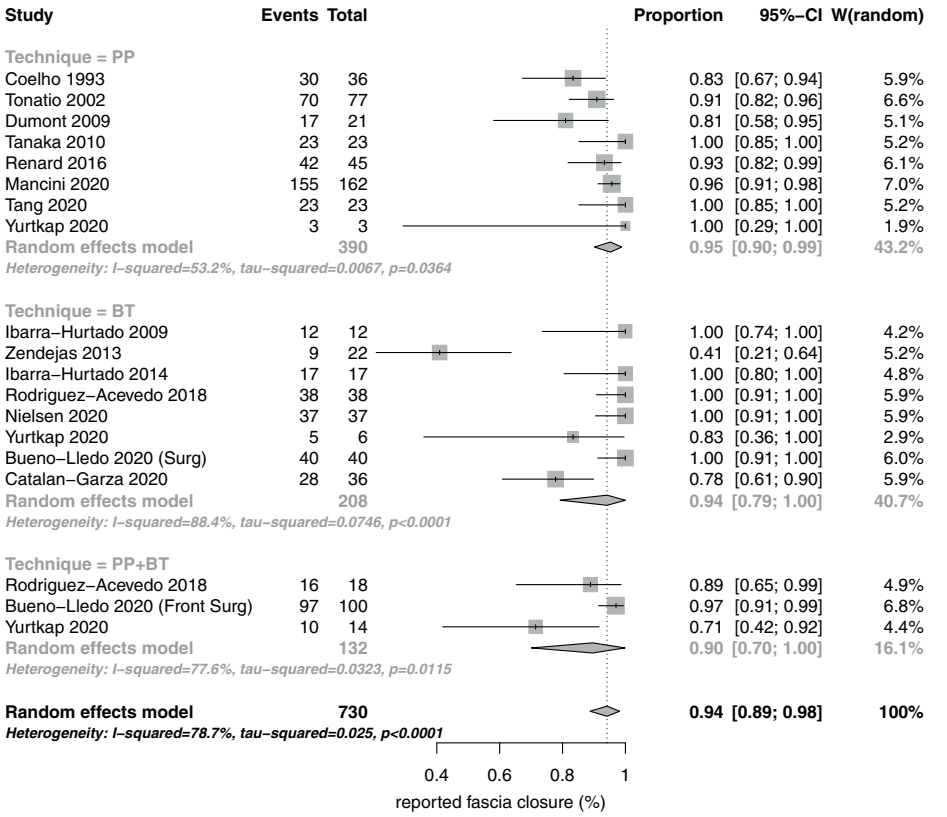

Figure 2. Forest plot for fascial closure rate

Indications for PP and BT

All articles were assessed for the described indication for PP and BT use. The authors identified 6 main themes for the use of PP, and 3 main criteria for the use of BT infiltrations; both can be viewed in Table 2.

Table 2. Identified indications for the use of preoperative PP and BT

PP indications	BT indications
Loss of domain ratio > 20% or > 25% [22, 24, 25, 35]	Measurements (hernia width or loss of domain ratio) [14, 21, 32, 34, 35]
Hernia width > 10 cm [23, 30]	
Hernia width cut-off + loss of domain ratio > 20% [14, 21]	Surgeon preference or expected difficulty closing midline [11, 27]
Hernia contents cannot be reduced back to abdominal cavity [26]	
Foreseen problems during surgery [29]	Open abdomen [12, 28]
Undefined/ surgeon's decision [10, 31, 33, 36]	

PP: progressive pneumoperitoneum, BT: Botulinum Toxin A, cm: centimeter

Complications during PP and BT

Along with the indications, the reported complications with the use of both techniques were reviewed. A total of 124 complications were mentioned in the 14 articles reporting on (combined) PP use. Complications reported more than once can be viewed in Figure 3. Death has been reported 3 times: once in a patient with a history of severe respiratory failure, and one time PP caused acute respiratory failure due to abdominal

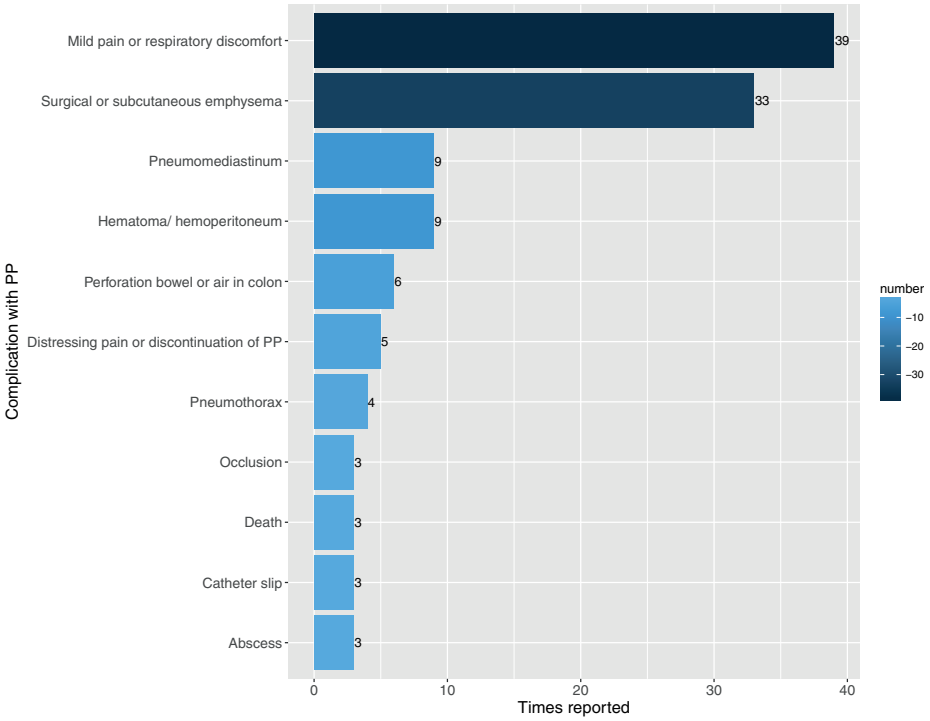

Figure 3. Complications after the use of PP, reported more than once.

compartment syndrome, which subsequently led to multi-organ failure and death. The third patient died due to a hemorrhage after catheter insertion for insufflation, which caused multi-organ failure. The one-off reported complications included, among others, the need for emergency surgery, respiratory distress, pneumocardium, metabolic acidosis, enterocutaneous fistula, and cardiac arrest. However, many more complications might have occurred, as reporting bias most certainly has taken place. The complications mentioned with the use of BT were a sense of bloating, a weak cough, back pain or pain in general, and superficial bruising at the site of the injections [14, 27].

Post-operative complications

Secondary outcomes of interest were SSOs, SSIs and recurrences. Eighteen articles reported on postoperative complications, of which 2 on SSOs only, 5 on SSIs only, and 11 on both SSOs and SSIs. In the 13 articles that mentioned SSO rates, 582 patients experienced 178 SSOs (30.6%), of which some patients experienced multiple SSOs. With regard to infections, a cumulative SSI rate of 10% (95% CI 0.04 – 0.18) was found after the use of PP, 7% after the use of BT (95% CI 0.01 – 0.18) and 19% after the use of PP and BT combined (95% CI 0.0 – 0.52).

With regard to recurrences, 16 authors reported a recurrence rate after the use of PP or BT. A random effects model renders a pooled proportion of 0.03 (95%CI 0.01 – 0.06). The recurrence rate per study, along with the mean follow-up is depicted in Figure 4. Three studies have not been included in this figure as they did not report a mean follow-up time. Diagnosis of recurrence was solely clinical in 2 studies (12.5%), clinically detected and confirmed by CT in 3 studies (18.8%), and the method of detection was not reported in 11 studies (68.8%).

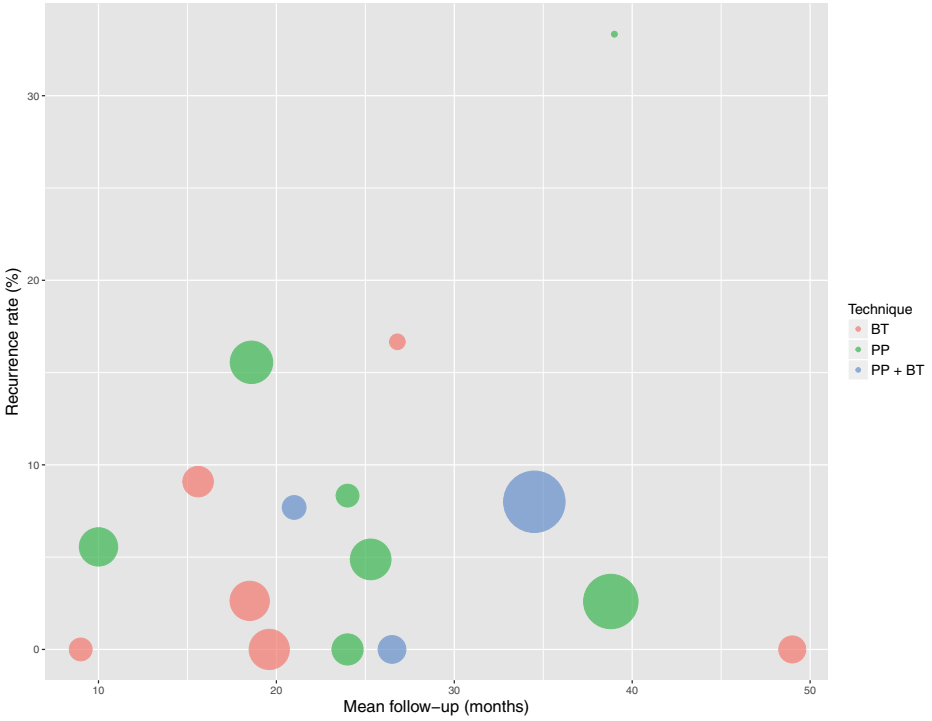

Figure 4. Bubble plot depicting the recurrence rate and mean follow-up per study. Bubble size represents the number of patients included per study, bubble color represents the used preoperative technique.

DISCUSSION

The primary goal of this study was to assess the efficacy of PP and BT intraoperatively through the fascial closure rate. From the synthesis of 16 articles, a fascial closure rate of 94% was observed after the use of PP, BT, or a combination of these preoperative aides. This is an acceptable rate, suggesting that the use of PP or BT is of additional value in preparation for complex hernia repair, as fascial closure probably will reduce hernia recurrence rates when compared to bridged repair[4, 5]. This decent fascial closure rate might be explained by the gain in muscle length in the axial plane after the use of BT [28, 38]. PP has been reported to decrease the hernia-to-abdominal-cavity volume ratio [8, 22, 26], and to lead to lysis of adhesions in the hernia sac [39], also facilitating hernia repair.

The recurrences and postoperative complications when PP or BT is used preoperatively, are low compared to "regular" open hernia surgery without the use of these preoperative techniques, with 3% recurrences and 31% SSO. This number of recurrences may be distorted as many studies had no standardized follow-up protocol, lacked imaging, and

had varying follow-up times. The number of postoperative SSI is rather high, especially in the group that was prepared with both PP and BT. However, this might not directly be related to the preoperative technique used, but to the "difficulty" of the patient population and specifically their hernia characteristics; *id est* the combination of PP and BT is likely to have been used in more extensive, complex hernias, that also resulted in more postoperative complications (confounding by indication). Nonetheless, the decision to use of PP or BT preoperatively does not seem to significantly influence the postoperative course.

However, *when* these preoperative techniques should be deployed, remains a matter of debate. Indications for the use of PP and BT varied from CT measurements with strict cut-off values to surgeon preference, or even remained undefined. We suggest that BT can be used when fibrosed or thickened muscles are observed and without clear loss of domain. For defects with more pronounced loss of domain, PP could be used, and the possible additional effect of BT is thought to be small.

Not only did the included studies describe different indications, also different application methods of both techniques are presented. PP can be performed on an inpatient or outpatient basis, created with the use of air, nitrous oxide, or carbon dioxide, with varying lengths before surgery, and with volumes varying from less than 5 to over 25 liters. With regard to BT injections, the use of 200 to 500 units has been described, divided over 6 to 10 injection sites, in two or all 3 lateral abdominal muscle layers, and timeframes ranging from 45 to 6 days before surgery [11, 12, 14, 21, 27, 28, 35]. One study even described the use of BT injections on the day of surgery itself, barely allowing the BT to enter into force and therefore, the observed effects could be obelized as the result of a placebo effect [11].

The reported complications after the use of BT seemed minor; complications during or after the use of PP, however, were frequent and sometimes severe. In addition, both techniques are costly. The costs of BT vary per country and depend on the amount of units used [40]. Costs are rarely reported, but are estimated to be between 400 and 600 euros when BT is injected into the abdominal wall musculature [21, 34]. These numbers seem considerable, but become less so when reoperations due to recurrences and severe postoperative complications – consequences of invasive techniques to obtain fascial closure – can be prevented. PP is a costly procedure, in particular when performed on an inpatient basis. Therefore, the use of these techniques should be in agreement with the patient and after careful consideration.

Limitations

Unfortunately, this study cannot provide comparative results, as nearly all articles lacked a comparison group. Only four studies reported outcomes for a comparison group. Additionally, the quality of included studies is very low; the maximum reached MINORS score was 75% of the maximum score. Most studies are exploratory in nature, aiming to present the limited experience with the use of PP or BT. Small numbers of patients are included and often no prospective protocol for data collection is described. This results however, in non-comparative studies with selective reporting. Due to this reporting bias, the presented summary values for fascial closure rate and recurrences probably do not reflect the true general values of these outcomes and have wider confidence intervals.

In addition to reporting bias, selection bias might have taken place in the studies included in the analysis. The indications for the use of the preoperative aides were not always clearly reported, therefore it is possible that PP and BT were only applied in a selected group of patients (sampling bias), and that the combination of both techniques was only used in patients with very complex hernias. In addition, the inclusion of consecutive patients has not been described in all studies, which might indicate that some form of confirmation bias – "good results from a new and promising technique" – could have taken place. Further, the data used in this review might have been affected by unmeasured confounders, such as surgeon effort or differences in ethnicity, therefore possibly biasing the found summary measures. Not only unmeasured confounders, but also different types of hernias (incisional, primary ventral, or parastomal) and repairs (open, laparoscopic, use of CST) contribute to the found heterogeneity and prevent comparison.

A further limitation is that many included studies in this review had no standardized follow-up protocol for the assessment of hernia recurrence, which might cause the pooled recurrence rate to be unreliably low. Another factor that might have led to underdetection of hernia recurrences is that the method for detection is often not described, implicating that recurrence assessment was performed by physical examination only. Small hernia recurrences can be easily missed without the use of radiological imaging[41].

Implications

Due to the possible presence of above forms of bias and the lack of comparative data, it remains hard to say how preoperative PP and BT compare to other surgical tools and techniques. The relative effect size of these preoperative aides, compared to tissue expanders, different component separation techniques, or other surgical ingenuities, remains unexplored. The lack of randomized clinical trials can be explained by the rarity of indications and the heterogeneity of groups. Nonetheless, the use of both preop-

erative techniques should be more widely explored, as lack of comparison hinders the possibility to judge the utility of both aides. Ideally, a randomized controlled trial would be performed to compare BT to CST, first in smaller hernias (for example with 10-15% loss of domain), to confirm the hypothesized non-inferior intraoperative effect, and to observe whether similar or less postoperative complications occur. Subsequently, the use of BT in larger hernias can be researched. Comparative research ideally takes place in a multicenter design, as CST can be subject to considerable inter-surgeon variability. The use of mesh should be standardized in these studies. Additionally, a meeting between specialized abdominal wall surgeons should take place to discuss the development of guidelines, including a proposal for standardized guidelines concerning the use of PP and BT. If such guidelines were to be created, intra- and postoperative results would be more comparable, and the true value of these aides in fascial closure could be better evaluated.

Conclusion

In conclusion, the results from this review suggest that PP and BT can facilitate fascial closure, and do not seem to have radical adverse effects on postoperative outcomes. Therefore, BT seems to qualify for low-threshold use. However, surgeons should have some reservations on the use of PP, as complications are frequent and sometimes severe. Since no standardized indications for the use of both techniques exist, guidelines should be composed to make future effect assessment easier, and to stimulate comparative research with other surgical techniques.

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APPENDIX 1 – SEARCH STRATEGY PER DATABASE

embase.com

('abdominal wall hernia'/de OR 'incisional hernia'/de OR 'abdominal wall closure'/de OR ((hernioplasty/de OR herniorrhaphy/de) NOT ('inguinal hernia'/de)) OR (((abdom* OR incision* OR midline* OR massive OR ventral OR giant OR large OR complex OR loss-of-domain*) NEAR/6 (hernia* OR eventrat*)) OR ((abdom* OR midline* OR ventral OR herni*) NEAR/6 (reconstruct* OR repair OR closure*)) OR ((pneumoperiton* OR pneumo-periton*) NEAR/3 (progress* OR artificial* OR preoperat* OR presurg* OR pre-operat* OR pre-surg*)) OR megahernia* OR ((hernioplast* OR herniorrhaph*) NOT inguinal*)):ab,ti) AND ('pneumoperitoneum'/de OR 'artificial pneumoperitoneum'/de OR 'botulinum toxin A'/de OR 'botulinum toxin'/de OR ('tissue expansion'/de AND ('air'/de OR 'carbon dioxide'/de OR 'nitrous oxide'/de)) OR (pneumoperito* OR pneumo-perito* OR botox OR 'botulinum toxin' OR ppp OR pppp OR bt-a OR bta OR (chemical* NEAR/3 relax*) OR ((intraabdom* OR intra-abdom* OR insufflat* OR insuffat*) NEAR/3 ('carbon dioxide' OR co2 OR co-2 OR oxygen OR o2 OR 'nitric oxide' OR 'nitrogen oxide' OR 'nitrous oxide' OR gas OR air))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ('case report'/de OR 'case report':ti) NOT ([Conference Abstract]/lim)

Medline Ovid

(Hernia, Ventral/ OR Incisional Hernia/ OR ((Herniorrhaphy/) NOT (Hernia, Inguinal/)) OR (((abdom* OR incision* OR midline* OR massive OR ventral OR giant OR large OR complex OR loss-of-domain*) ADJ6 (hernia* OR eventrat*)) OR ((abdom* OR midline* OR ventral OR herni*) ADJ6 (reconstruct* OR repair OR closure*)) OR ((pneumoperiton* OR pneumo-periton*) ADJ3 (progress* OR artificial* OR preoperat* OR presurg* OR pre-operat* OR pre-surg*)) OR megahernia* OR ((hernioplast* OR herniorrhaph*) NOT inguinal*)).ab,ti.) AND (Pneumoperitoneum/ OR Pneumoperitoneum, Artificial/ OR exp Botulinum Toxins/ OR (Tissue Expansion/ AND (air/ OR Carbon Dioxide/ OR exp Nitrogen Oxides/)) OR (pneumoperito* OR pneumo-perito* OR botox OR botulinum toxin OR ppp OR pppp OR bt-a OR bta OR (chemical* ADJ3 relax*) OR ((intraabdom* OR intra-abdom* OR insufflat* OR insuffat*) ADJ3 (carbon dioxide OR co2 OR co-2 OR oxygen OR o2 OR nitric oxide OR nitrogen oxide OR nitrous oxide OR gas OR air))).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la. NOT (case reports/ OR case report.ti.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.

Cochrane CENTRAL

((((abdom* OR incision* OR midline* OR massive OR ventral OR giant OR large OR complex OR loss NEXT of NEXT domain*) NEAR/6 (hernia* OR eventrat*)) OR ((abdom* OR midline* OR ventral OR herni*) NEAR/6 (reconstruct* OR repair OR closure*)) OR

((pneumoperiton* OR pneumo NEXT periton*) NEAR/3 (progress* OR artificial* OR preoperat* OR presurg* OR pre NEXT operat* OR pre NEXT surg*)) OR megahernia* OR ((hernioplast* OR herniorrhaph*) NOT inguinal*)):ab,ti) AND ((pneumoperito* OR pneumo NEXT perito* OR botox OR 'botulinum toxin' OR ppp OR pppp OR bt NEXT a OR bta OR (chemical* NEAR/3 relax*) OR ((intraabdom* OR intra NEXT abdom* OR insufflat* OR insuffat*) NEAR/3 ('carbon dioxide' OR co2 OR co NEXT 2 OR oxygen OR o2 OR 'nitric oxide' OR 'nitrogen oxide' OR 'nitrous oxide' OR gas OR air))):ab,ti)

Web of science

TS=(((((abdom* OR incision* OR midline* OR massive OR ventral OR giant OR large OR complex OR loss-of-domain*) NEAR/5 (hernia* OR eventrat*)) OR ((abdom* OR midline* OR ventral OR herni*) NEAR/5 (reconstruct* OR repair OR closure*)) OR ((pneumoperiton* OR pneumo-periton*) NEAR/2 (progress* OR artificial* OR preoperat* OR presurg* OR pre-operat* OR pre-surg*)) OR megahernia* OR ((hernioplast* OR herniorrhaph*) NOT inguinal*))) AND ((pneumoperito* OR pneumo-perito* OR botox OR "botulinum toxin" OR ppp OR pppp OR bt-a OR bta OR (chemical* NEAR/2 relax*) OR ((intraabdom* OR intra-abdom* OR insufflat* OR insuffat*) NEAR/2 ("carbon dioxide" OR co2 OR co-2 OR oxygen OR o2 OR "nitric oxide" OR "nitrogen oxide" OR "nitrous oxide" OR gas OR air))))) AND DT=(Article OR Review) AND LA=(english)

Google scholar

"abdominal|incisional|midline|massive|ventral|giant|large|complex hernia|eventration" pneumoperitoneum|"pneumo-peritoneum"|botox|"botulinum toxin"

5 Conservative treatment versus elective repair of umbilical hernia in patients with liver cirrhosis and ascites: results of a randomized controlled trial (CRUCIAL-trial)

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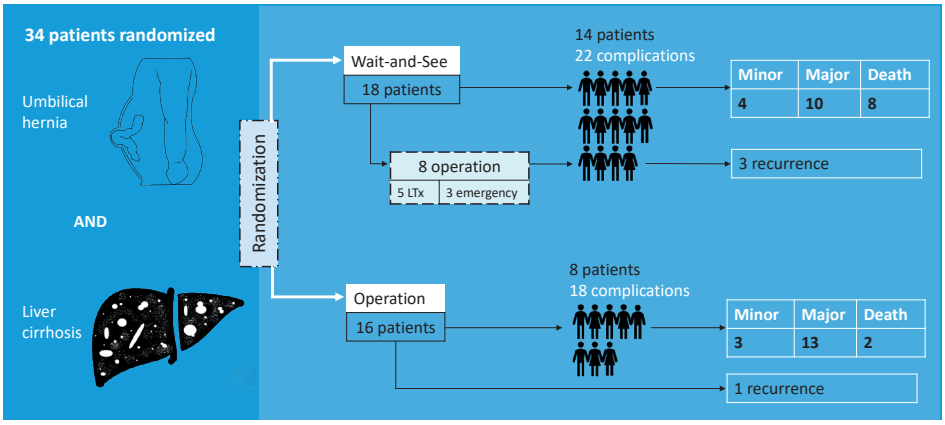
406(1); pages 219-225.



**Shared first authorship*

ABSTRACT

Purpose*:* To establish optimal management of patients with an umbilical hernia complicated by liver cirrhosis and ascites.

Methods*:* Patients with an umbilical hernia and liver cirrhosis and ascites were randomly assigned to receive either elective repair or conservative treatment. Primary endpoint was overall morbidity related to the umbilical hernia or its treatment after 24 months of follow-up. Secondary endpoints included the severity of these hernia-related complications, quality of life, and cumulative hernia recurrence rate.

Results: Thirty-four patients were included in the study. Sixteen patients were randomly assigned to elective repair and 18 to conservative treatment. After 24 months, 8 patients (50%) assigned to elective repair compared to 14 patients (77.8%) assigned to conservative treatment had a complication related to the umbilical hernia or its repair. A recurrent hernia was reported in 16.7% of patients who underwent repair. For the secondary endpoint, quality of life through the physical (PCS) and mental component score (MCS) showed no significant differences between groups at 12 months of follow-up (mean difference PCS 11.95, 95%CI -0.87 to 24.77; MCS 10.04, 95%CI -2.78 to 22.86).

Conclusion: This trial could not show a relevant difference in overall morbidity after 24 months of follow-up in favour of elective umbilical hernia repair, because of the limited number of patients included. However, elective repair of umbilical hernia in patients with liver cirrhosis and ascites appears feasible, nudging its implementation into daily practice further, particularly for patients experiencing complaints.

Registration: Clinicaltrials.gov, NCT01421550, on 23 August 2011.

INTRODUCTION

Umbilical hernias are common in patients with liver cirrhosis and ascites, with an incidence of up to 20% [1,2]. The presence of ascites increases the risk of developing an umbilical hernia, due to increased abdominal pressure. Weakening of the abdominal wall, muscle wasting when nutritional status is poor, and dilatation of the umbilical vein – enlarging the pre-existent fascial opening – in patients with portal hypertension, are additional contributing factors. [3,4]

Currently, there are no guidelines for the management of an umbilical hernia and its timing of surgical repair in patients with liver cirrhosis and ascites. Traditional surgical dogma dictates not to perform umbilical hernia repair under these circumstances, because of the presumed high surgical risks and high recurrence rates after surgery [5,6]. Additionally, portal hypertension is common in cirrhotic patients with ascites, and this requires special caution because a patent umbilical vein is often present. A reopened umbilical vein can be an important outflow for the portal circulation in patients with severe portal hypertension. In these patients, elective repair without liver transplantation has been reported to result in acute portal vein thrombosis due to ligation of the umbilical vein during hernia repair, which in turn causes subsequent liver failure, necessitating emergency liver transplantation [7].

However, refraining from umbilical hernia repair under these circumstances can also result in serious complications: incarceration or evisceration of the bowel could occur, followed by necrosis of the overlying skin, necessitating emergency surgery [4,7,8]. Even after liver transplantation, incarceration and strangulation can still occur in untreated umbilical hernias [8]. Moreover, several studies have shown that emergency surgery is generally associated with even higher risks of morbidity and mortality compared to elective surgery, particularly in patients with liver cirrhosis [6,8-12]. This underlines that emergency surgery in this group of frail patients should be avoided and that elective umbilical hernia repair might be the most optimal management [13,14]. Concordingly, several retrospective and prospective series have shown good results with elective umbilical hernia repair for patients with liver cirrhosis [8,12,14]. However, no randomized controlled trial on this matter has been performed. The aim of this study was to compare conservative treatment with elective repair of umbilical hernia in patients with liver cirrhosis and ascites. We hypothesized that elective repair of the umbilical hernia would result in a significant reduction of the overall complication rate and a better quality of life compared to conservative treatment.

METHODS

Study design

The CRUCIAL-trial is a randomized controlled trial conducted in two centers. Patients with liver cirrhosis and ascites older than 18 years and a primary umbilical hernia were included in the study. Presence of ascites had to be proven on imaging or had to have been drained previously. Patients were randomized into one of two groups: patients in group 1 would undergo elective surgical repair, those in group 2 would receive conservative treatment. Irrespective of randomization group, in the case of liver transplantation, patients would receive umbilical hernia repair simultaneously if repair had not yet been performed. Excluded from participation were patients with a recurrent umbilical hernia following a midline laparotomy in the medical history, patients who presented with American Society of Anesthesiology (ASA) score IV or above, patients presenting with incarcerated hernia requiring emergency repair at the moment of inclusion, patients with a patent umbilical vein of more than 5 millimeters in diameter, and patients with an expected time to liver transplantation of less than 3 months.

The study protocol was approved by the institutional medical ethical review board of the Erasmus University Medical Center, Rotterdam, before the start of inclusion. All patients gave written informed consent. An independent data and safety monitoring board was constituted before the start of the trial, consisting of two independent surgeons and one biomedical statistician. All serious adverse events were reported to the institutional review board of the Erasmus University Medical Center. The progress of the trial and adverse events were reported to the safety monitoring board.

Randomization and masking

Patients were randomly allocated to either conservative treatment or elective repair by means of sealed, numbered envelopes that were opened in sequence. The randomization procedure was stratified for participating center and for Model of End-stage Liver Disease (MELD) score ≤15 and >15, and took place after collection of baseline information. Blinding for allocation did not take place for the participants, evaluators and surgeons.

Procedures

All repairs (elective or during liver transplantation) took place using a (separate) infra-umbilical incision, dissection (avoiding resection) of the hernia sac, and restoration of the sac and its contents into the abdominal cavity. Intra-operative resection of the sac had to be recorded on the patient's operation report. As mesh repair has been proven to reduce recurrence rates [15], non-absorbable monofilament sutures were combined with a flat

circular polypropylene mesh placed in the onlay position or in the pre-peritoneal plane. The overlap of the mesh had to be at least three centimetres in each direction. Closure of the subcutaneous tissue and skin were performed at the discretion of the surgeon.

The preferred method of anaesthesia was general anaesthesia, allowing for local or spinal anaesthesia in the case of contra-indications for general anaesthesia. Antibiotic prophylaxis was administered 10 to 30 minutes preoperatively.

Patients were followed-up at the outpatient clinic at two to three weeks, three months, 12 months, and 24 months after surgery. During these visits, patients underwent physical examination, and at the 12-month visit they underwent abdominal ultrasonography to diagnose hernia recurrence. Quality of life measurements took place at baseline, three, six, 12 and 24 months through the Short Form-36 (SF-36) and the EuroQoL-5D (EQ-5D) questionnaire. Pain was evaluated through the visual analogue scale (VAS), anchored by "no pain" (score of 0) and "worst imaginable pain" (score of 100) on a 100 millimetre scale. To avoid clustering of scores around a preferred numeric value, numbers of verbal descriptors at intermediate points were not provided.

Outcomes

Primary outcome consisted of the hernia (and when applicable, its surgery)-related complications during two years of follow-up. Superficial or deep surgical site infection (SSI) [16], seroma, pneumonia, hematoma, urinary tract infection, and non-closure or delayed closure of the surgical wound at 4 weeks were considered minor complications. Major complications were mortality, evisceration, incarceration, necrosis of the overlying skin of the umbilical hernia, postoperative (>2 weeks) leakage of ascites, liver failure, bacterial peritonitis, decompensated ascites, organ space SSI, or unexpected intensive care unit (ICU) admission related to the hernia or its repair.

These hernia-related complications were assessed for severity through the National Surgical Complication Registry ("Landelijke Heelkundige Complicatie Registratie" (LHCR)) grading tool (Table 1), scoring the maximal observed grade of hernia-related complications in each patient. Secondary endpoints were the cumulative hernia recurrence rate, pain, and quality of life.

Statistical analysis

The sample size was determined at 100 patients. This calculation was based on χ^2-tests with $\alpha = 0.05$, power of 90% and an expected decrease in overall complication rate at 2 years from 50% to 15% due to elective repair of the umbilical hernia [8]. This requires 42 patients per treatment arm; 50 when accounting for a 20% loss to follow-up.

Table 1. The National Surgical Complication Registry ("Landelijke Heelkundige Complicatie Registratie" (LHCR)) score.

Grade	Description of complication
0	No health disadvantage, no real complication
1	Temporary health disadvantage, recovery without reoperation
2	Recovery after (re)operation
3	(Likely) permanent damage or invalidity
4	Death

All patients were analyzed in the group randomized to (intention-to-treat). For the primary outcome – cumulative complication rate of the umbilical hernia in the two study arms – Kaplan-Meier curves were constructed and compared with the Logrank-test. The maximal observed LHCR grade was compared with the χ^2-test, and secondary outcomes were analyzed through linear mixed effect models, correcting for time, randomization group, gender, time to complication, and time to liver transplantation.

Statistical analysis were performed using R statistical software (version 3.3.1). This trial is registered at Clinicaltrials.gov; number NTC01421550.

RESULTS

Due to unforeseen circumstances, the study was ended prematurely. Between February 2011 and July 2014, 34 patients were randomly assigned to either the intervention group (n = 16) or the conservative group (n = 18). Baseline characteristics are shown in Table 2. The median time of follow-up was 19.5 months (range 0 to 33.7 months).

24-month morbidity

Eight patients (44.4%) in the conservative group received umbilical hernia repair: five received liver transplantation with simultaneous repair of the umbilical hernia, and three patients had elective or emergency repair due to complaints or incarceration. Of these eight patients, three developed recurrence of the umbilical hernia (16.7%). In the intervention group, only one patient had a recurrence of the umbilical hernia (6.3%). The mean length of stay after umbilical hernia repair was 3.21 days (range 1 to 9 days).

With regard to 24-month morbidity, 22 patients (64.7%) had at least one hernia related complication, totalling 40 events. In the intervention group, eight patients (50%) experienced 18 events. In the wait-and-see group, 14 patients (78%) had 22 events.

Table 2. Baseline characteristics. Numbers given in n (%) or [a] median (interquartile range); [b] mean (standard deviation)

	Intervention (n = 16)		Wait-and-See (n = 18)	
Gender (male, %)	11	68.8%	15	83.3%
Age[a]	57	48.8 – 61.5	58	56.0 – 60.8
BMI[a]	25.8	23.5 – 29.4	22.6	21.7 – 26.8
MELD score[b]	15.5	4.7	16.3	4.5
Hernia width[b]	2.68	2.5	1.94	1.1
Smoking	11	68.8%	6	33.3%
COPD	1	6.3%	2	11.1%
Diabetes	6	37.5%	4	22.2%
Liver failure cause				
Alcoholic Hepatitis	11	68.8%	8	44.4%
PSC	1	6.3%	3	16.7%
PBC	1	6.3%	0	0%
Hepatitis B	0	0%	1	5.6%
Hepatitis C	2	12.5%	2	11.1%
Auto immune	1	6.3%	0	0%
NASH	0	0%	2	11.1%
Other	0	0%	2	11.1%

BMI: Body Mass Index, MELD: Model of End-stage Liver Disease, COPD: Chronic Obstructive Pulmonary Disease, PSC: primary sclerosing cholangitis, PBC: primary biliary cholangitis, NASH: non-alcoholic steatohepatitis

In Table 3, the complications are split up for minor and major complications. Figure 1 is a Kaplan-Meier depiction of the time to first event per study arm. No difference between groups was found in time to first event ($p = 0.663$). From Table 3, the difference in mortality between groups seems rather large, yet no statistical difference was found ($p = 0.0682$). The survival is also graphically depicted in Figure 2. In the intervention group, one death occurred due to the development of spontaneous bacterial peritonitis resulting in multi-organ failure one week after surgery; the other death was due to progression of end-stage malignant disease. In the wait-and-see group, mortality was due to subcapsular bleeding after the placement of a transjugular intrahepatic portosystemic shunt in one patient; the other causes were progression of liver disease, end-stage malignant disease, and non-surgery-related pneumonia. Additionally, no statistical significance was observed between the LHCR grades in the two groups ($p = 0.152$).

When stratified for MELD score, more complications in total ($n = 24$ and $n = 16$, respectively) and more severe complications ($n = 20$ and $n = 13$, respectively) can be found in the group with patients having a score >15, compared to the patient group with MELD score ≤15.

Table 3. Number of patients with complications, total number of complications, and maximum LHCR grade in patients with complications after 24 months.

	Total (n = 34)	Intervention (n = 16)	Conservative (n = 18)
Patients with complication (%)	22 (64.7)	8 (50)	14 (77.8)
1 complication (%)	13 (38.2)	4 (25)	9 (50)
> 1 complication (%)	9 (26.5)	4 (25)	5 (27.8)
Total complications	40	18	22
Minor	7	3	4
SSI superficial/deep	3	1	2
Seroma	1	0	1
Hematoma	2	2	0
UTI	1	0	1
Major	33	15	18
Organ space SSI	1	1	0
Incarceration	7	3	4
Necrosis of the skin	1	1	0
Post-op. leakage	2	2	0
Bacterial peritonitis	1	1	0
Decompens. Cirr.	6	2	4
Unexp. ICU adm.	5	3	2
Death	10	2	8
Maximum LHCR grade			
1	6	4	2
2	5	2	3
3	1	0	1
4	10	2	8

SSI: Surgical Site Infection, UTI: urinary tract infection, Post-op.: post-operative, cirr: cirrhosis, Unexp. ICU adm: unexpected Intensive Care Unit admission, LHCR: Landelijke Heelkundige Complicatie Registratie (National Surgical Complication Registry).

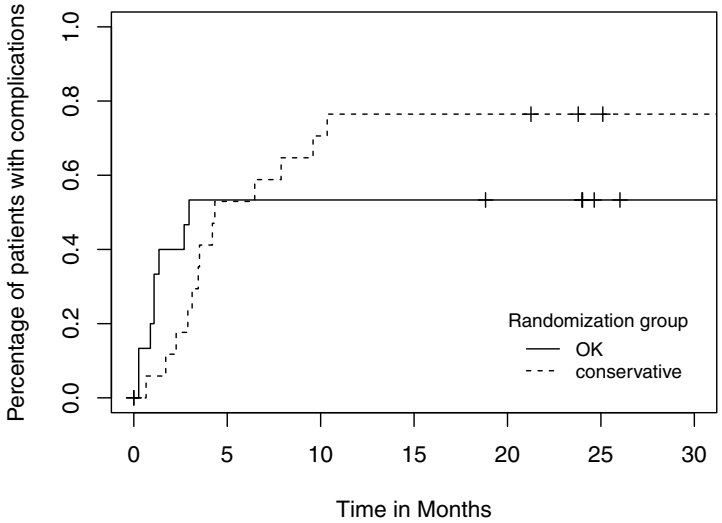


Figure 1. Time to first complication. This complication can be either minor or major (including death). Censored patients are marked with '+'

Secondary outcomes

With regard to the quality of life measured through the SF-36, the coefficients in the linear mixed model show that over time both the physical component score (PCS) and mental component score (MCS) increase for the intervention group, compared to a much smaller increase in the PCS and even a decrease in the MCS for the conservatively treated group (as shown by the negative coefficient for the interaction between time and randomization group in Table 4). The model further reveals that liver transplantation causes patients to score higher on both component scores. Additionally, female patients appear to have a higher MCS than their male counterparts.

Table 4. Coefficients from the created linear mixed models for quality of life expressed through the physical and mental component score, with their respective 95% confidence intervals.

	PCS		MCS	
	Value	**95% CI**	**Value**	**95%CI**
(Intercept)	35.70	29.79 – 41.60	42.46	37.69 – 47.23
Time	0.34	0.09 – 0.59	0.32	-0.01 – 0.65
Wait-and-see group	-9.08	-16.45 – -1.72	-3.63	-9.61 – 2.34
Event at timepoint	0.44	-0.74 – 1.61	0.06	-1.44 – 1.55
LTx at timepoint	5.39	0.59 – 10.20	0.37	-5.40 – 6.13
Female	2.27	-5.61 – 10.16	8.66	3.06 – 14.27
Time:Wait-and-see	-0.25	-0.66 – 0.15	-0.54	-1.05 – -0.03

PCS: physical component score, MCS: mental component score, CI: confidence interval, LTx: liver transplantation

Quality of life measured through the EQ-5D questionnaire showed results similar to the SF-36 questionnaire. The created model showed that over time, quality of life increased (coefficient Time 0.64, 95%CI 0.02 – 1.27). This increase was, however, smaller for the conservative group compared to the intervention group, shown by a negative coefficient (coefficient Time:Wait-and-see -0.32, 95%CI -1.33 – 0.69). Quality of life was at baseline already higher in the intervention group.

For pain outcomes, the coefficients in the created model show that pain decreases irrespective of the randomization group over time (coefficient Time -0.45, 95%CI -0.99 – 0.09). At baseline, the scores were higher for women (coefficient 5.85, 95%CI -12.59 – 24.29), and for patients in the wait-and-see group (coefficient Wait-and-see 25.99, 95%CI 8.68 – 43.32).

Unfortunately, no cost-effectiveness analysis was performed due to the early termination of the study.

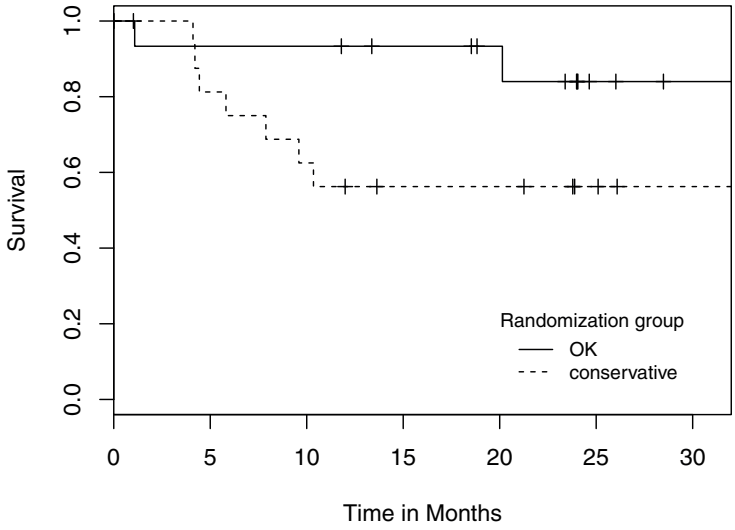


Figure 2. Time to death. Censored patients are marked with '+'

DISCUSSION

In this study, equal numbers of hernia-related complications were observed for elective operation and conservative approach. Additionally, elective repair and wait-and-see treatment were associated with similar quality of life and pain scores. Though underpowered, this suggests that elective repair is safe in patients with liver cirrhosis and can be performed when the patient experiences complaints from his/her umbilical hernia.

In the current study, complication rates were high in both study arms. This is in line with expectations considering the high average MELD score observed in the patient group, as a higher MELD score is associated with higher perioperative morbidity and mortality in various types of elective procedures [17-22]. In the current study, patients with a MELD score ≥15 experienced more incarceration, skin necrosis, unexpected ICU admission, and had a higher mortality rate. Despite the high numbers of complications, this study shows that even in patients with a relatively high MELD score, elective repair of the umbilical hernia is safe. Additionally, a conservative approach can also be accompanied by severe complications; our study showed more incarceration, decompensated cirrhosis and ultimately death for the patients in the conservative treatment group than in the intervention group. Other authors describe a nearly 23% emergency surgery rate due to complications of a hernia during conservative treatment [23].

The most common cause for liver failure in our study was alcoholic liver cirrhosis. Alcoholic liver cirrhosis can cause large amounts of ascites [24], which is associated with com-

plications, including umbilical hernia [25]. This association is applicable for both groups: a large amount of ascites can cause spontaneous bacterial peritonitis in both groups [26], more frequent incarceration and wound problems in the wait-and-see group [8,27,28], and more recurrence and postoperative leakage of ascites in the intervention group [28-30].

However, the results from our study need to be interpreted with caution. The major limitation of this study is the small patient group, due to the premature stop of the study. As a consequence, limited data were available for modelling the secondary outcomes, resulting in large confidence intervals. Especially at later time points, many patients had dropped out of the study due to death or other causes; this was however balanced between the two randomization groups.

Another consequence of the small patient group, is chance for clustering of confounders in the randomization process. This could have caused the difference already present at baseline for quality of life and VAS scores. However, these differences could also have been due to the fact that patients were not blinded for the randomization group they were in. The fact that patients knew they would receive an operation to relieve them of their umbilical hernia might have influenced how those patients filled out their quality of life forms. Nonetheless, the effect of the baseline differences on the secondary outcomes is more than marginal and necessitates careful consideration.

Despite the premature stop of patient inclusion, this study remains a methodologically well-performed randomized controlled trial, providing higher level of evidence than small, retrospective cohorts with their inherent bias. Therefore – unfortunately not providing a definite answer to the management of umbilical hernias in patients with cirrhosis and ascites – this study is a valuable addition to the current body of knowledge on this subject and contributes to providing transparency to the scientific community. In the context of scientific integrity, this data can prove valuable in future meta-analyses, and refraining from reporting the data adds to the burden of publication bias.

Conclusion and implications

Despite not having enough power to show a significant difference between the two groups, this randomized controlled trial suggests that elective repair of an umbilical hernia does not cause excessive morbidity in cirrhotic patients – even with high MELD scores – and thus advisable when the patient experiences complaints of the umbilical hernia. Considering this fact, one could argue that early elective repair when MELD scores are low – even in patients on the waiting list for transplantation, is the safer strategy. The definitive answer to whether elective umbilical hernia repair causes significantly less complications than watchful waiting in patients with liver cirrhosis remains unknown, which leaves room for further study.

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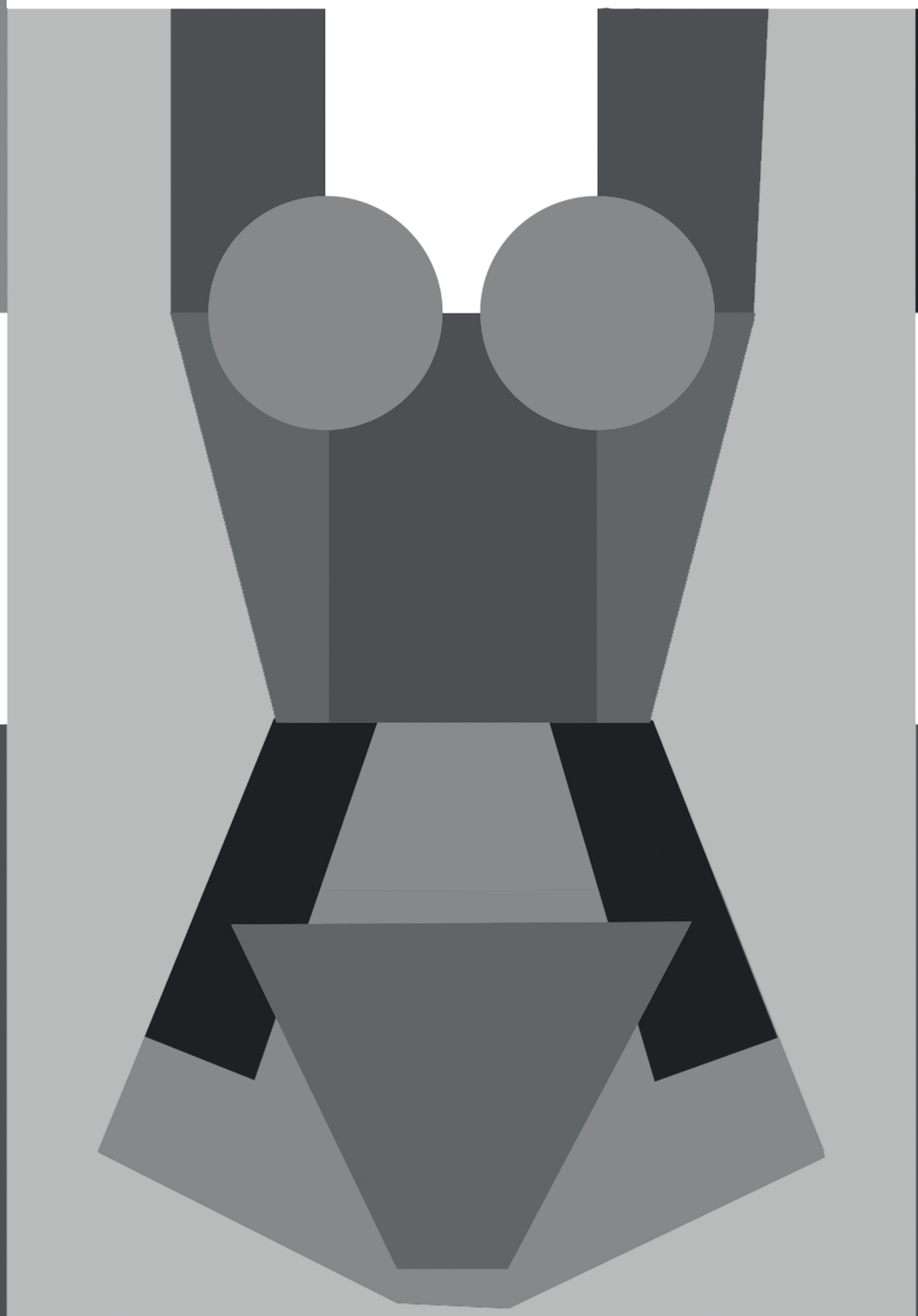
PART III: Incisional hernia treatment with mesh



6 A post-market, prospective, multi-center, single-arm clinical investigation of Phasix Mesh for VHWG grade 3 midline incisional hernia repair: a research protocol

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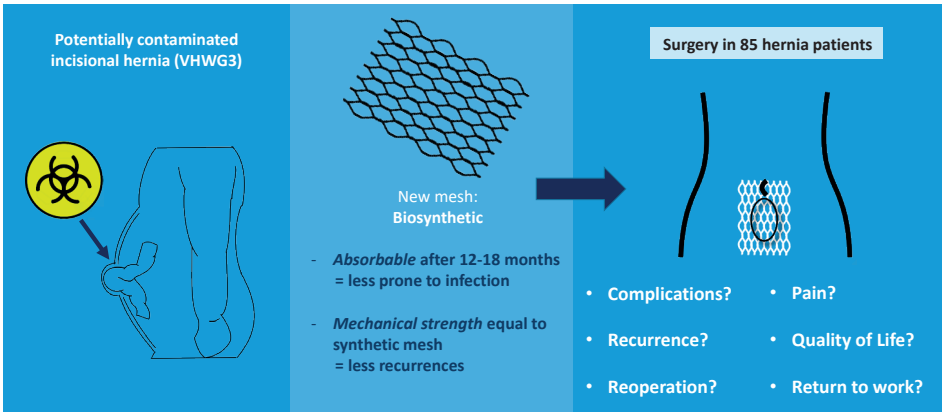

ABSTRACT

Background Incisional hernia is a frequent complication of midline laparotomy. The use of mesh in hernia repair has been reported to lead to fewer recurrences compared to primary repair. However, in Ventral Hernia Working Group (VHWG) grade 3 hernia patients, whose hernia is potentially contaminated, synthetic mesh is prone to infection. There is a strong preference for resorbable biological mesh in contaminated fields, since it is more able to resist infection, and because it is fully resorbed, the chance of a foreign body reaction is reduced. However, when not crosslinked, resorbable mesh products tend to degrade too quickly to facilitate native cellular ingrowth. Phasix™ Mesh is a biosynthetic mesh with both the biocompatibility and resorbability of a biological mesh and the mechanical strength of a synthetic mesh. This multi-center single-arm study aims to collect data on safety and performance of Phasix™ Mesh in VHWG grade 3 hernia patients.

Methods A total of 85 VHWG Grade 3 hernia patients will be treated with Phasix™ Mesh in 15 sites across Europe. The primary outcome is surgical site occurrence, including hematoma, seroma, infection, dehiscence and fistula formation (requiring intervention) through 3 months. Secondary outcomes include recurrence, infection, and quality of life-related outcomes after 24 months. Follow-up visits will be at drain removal (if drains were not placed, then on discharge or staple removal instead) and in the 1st, 3rd, 6th, 12th, 18th and 24th month after surgery.

Conclusion Depending on the results this clinical study will yield, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

Registration The trial was registered on March 25, 2016 on clinicaltrials.gov: NCT02720042

BACKGROUND

Incisional hernia is one of the most frequent complications after midline laparotomy, with incidences varying from 10% to 20%, and even higher percentages occur in high-risk groups [1,2]. Incisional hernia can lead to a high morbidity and reduces quality of life [3,4]. Due to the high incisional hernia incidence rates, hernia repair surgery is one of the most frequently performed surgical procedures [5]. The aim of hernia surgery is to relieve symptoms, to prevent complications, or to resolve acute complications.

There are several options for hernia repair, including simple suture repair, synthetic or biologic material placement, repair with relaxing incisions, component separation and use of musculofascial flaps, utilizing both open and laparoscopic approaches [6-8]. Synthetic mesh repair procedures, either open or laparoscopic, lead to fewer recurrences compared to primary repair; recurrences after mesh are 7.7% compared to 23.8% after primary closure [1,3,9,10]. Improved outcomes are believed to be related to reduced tension on the fascial edges and sutures when mesh is used in hernia repair procedures. Despite reducing hernia recurrence rates, the use of synthetic mesh has been associated with complications in approximately 17% of patients. These complications include infection, pain, adhesions, fistulae and foreign body reactions, including increased inflammation and/or connective tissue deposition [3,11]. Especially complex and large abdominal wall defects continue to pose a challenge to surgeons, which are associated with recurrence rates of up to nearly 40% [12].

It can be stated that synthetic mesh is more prone to infection than primary closure, and this poses a problem in potentially contaminated hernias like Ventral Hernia Working Group (VHWG) Grade 3 hernias [13] (Figure 1). The success of the mesh repair is jeopardized by potential contamination due to complicating factors like previous wound infection, the presence of a stoma or violation of the gastro-intestinal tract.

The use of a biological tissue matrix has been advocated in (potentially) contaminated hernias, because of their ability to resist infection, milder inflammatory response and more orderly collagen deposition than non-resorbable, synthetic meshes [14-16]. Most often, biological meshes are derived from human, porcine, or bovine dermis, and these materials have been processed to acellular sheets of collagen and elastin. The development of resorbable mesh products has faced challenges related to the rate of absorption with complications arising when the mesh product is resorbed too quickly. Rapid resorption does not support sufficient healing if structural reinforcement is diminished during the tissue repair period.

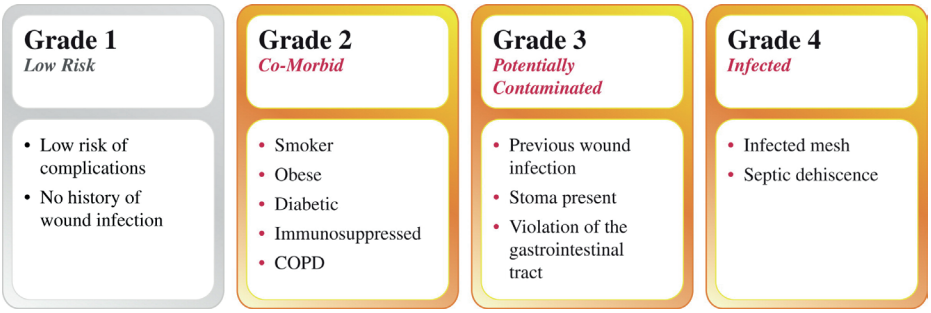

Figure 1. Ventral Hernia Working Group grading system: assessment of risk for surgical site occurrences [13].[b]

Therefore, some meshes contain chemicals to induce additional crosslinking in the graft. This slows down the degradation process, causing the mesh to retain its strength for a longer period of time[17]. However, crosslinking in the mesh reduces its biocompatibility; causing delayed cellular infiltration and neovascularization [17-19]. Ideally, a resorbable mesh should have a high ability to resist infections and retain its functional strength for a sufficient period of time to allow native cellular ingrowth tissue remodelling, maturation of collagen, and gradual shift of mechanical load.

Phasix™ Mesh is a commercially available biosynthetic mesh. It is a slowly resorbable mesh prepared from poly-4-hydroxybutrate which has been studied for use as a biomaterial for different medical applications due its strength and flexibility, biocompatibility, and desirable degradation times [20-22]. Phasix™ Mesh is comparable in performance to traditional polypropylene mesh when using standard measures of mechanical strength (suture pullout, tear and ball burst strength) [23,24]. Preclinical implantation studies indicate that Phasix™ Mesh retains approximately 70% of its original strength at 12 weeks [23]. Absorption of the mesh material will be essentially complete in 12-18 months [24]. Given the long-term strength retention observed in preclinical studies, it is anticipated that Phasix™ Mesh may result in low recurrence and complication rates with minimal pain and discomfort when used for hernia repair.

Rationale

From a general perspective, the current literature still is rather void of evidence-based guidelines regarding optimal choice of mesh. Simple, uncontaminated hernias are usually treated with synthetic mesh; biologic meshes are mostly used in potentially contaminated hernias, since post-operative mesh infection is anticipated.

Until now, Phasix™ Mesh has been studied prospectively in patients with a clean hernia site (CDC class I [25]) and up to VHWG Grade 2 [26-28]. A small retrospective study has also been conducted, showing positive results, but not elaborating on the exact contamination or size of the hernias [29]. Based on the data that will be gained from this clinical study, additional evidence may be provided with a view to optimal selection of hernia repair material in a population of higher risk. Since there is only limited knowledge on the treatment of VHWG Grade 3 patients, additional information is needed on safety and performance of the Phasix™ Mesh. Based on the combination of the features of the Phasix™ Mesh proven in previous clinical and non-clinical investigations, and based on evidence from the clinical study as described in this protocol, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

METHODS

Objectives

The objective of this study is to collect additional data on safety and performance of Phasix™ Mesh in subjects requiring VHWG Grade 3 midline incisional hernia repair. Among others, surgical site occurrence (SSO), hernia recurrence, pain, infection, reoperation and adverse events will be collected from subjects with a VHWG Grade 3 hernia meeting the study inclusion and exclusion criteria.

Design

The study has been designed as a post-market, prospective, single arm, multi-center, open-label study to collect data on performance and safety of Phasix™ Mesh in subjects with a VHWG Grade 3 midline hernia. This study will be conducted in 15 hospitals across Europe, which will each be allowed to include a maximum of 15 patients.

Participants

Subjects with a VHWG Grade 3 incisional hernia scheduled for hernia repair are eligible for this study and will be asked for informed consent at the outpatient clinic. VHWG Grade 3 included, among others, previous wound infection after previous laparotomy (verified in the patient's medical record), small bowel resection with anastomosis, take down of ileostomy with ileocolonic anastomosis, creation of a stoma, stoma presence, jejunostomy, gastrectomy, and cholecystectomy. Patients with active infections, infected mesh, abscesses or active fistulas were not considered among patients with VHWG Grade 3. Patients solely at risk for an incidental enterotomy were not included in the population of which subjects could be drawn from.

Inclusion criteria

All subjects who meet the following criteria can be enrolled in the study:

- Age 18 years or older
- Diagnosis of an incisional midline hernia
- VHWG Grade 3 hernia
- Size of hernia >10 cm^2, measured intraoperatively
- Elective retro-rectus hernia repair
- Signed informed consent

Exclusion criteria

All subjects who meet the following criteria will be excluded from study enrolment:

Regarding the subject:

- Body Mass Index (BMI) > 35 kg/m^2
- Peritonitis
- Use or suspected future use of chemotherapeutic medication during any part of the study
- Known human immunodeficiency virus (HIV) infection
- Cirrhosis of the liver and/or ascites
- Pregnancy, plans to become pregnant during the study period or current breastfeeding
- Alcohol/substance abuse problem or a relapse within 12 months of the screening visit
- Involvement in another interventional clinical study in the last 30 days prior to informed consent signature
- Life expectancy of less than 2 years at the time of enrollment
- Known sensitivity to Phasix™ Mesh or component materials (subjects with known allergies to tetracycline hydrochloride or kanamycin sulfate)
- Any condition that, in the opinion of the investigator, would preclude the use of the study device or preclude the subject from completing the follow-up requirements

Regarding ventral hernia:

- More than 4 previous repairs of the hernia under observation
- The hernia repair requires more than a single piece of mesh
- Intact permanent mesh adjacent to the current hernia to be repaired

Regarding surgery:

- American Society of Anesthesiology class 4 or 5
- Surgical technique requires surgical bridge repair

- Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible
- The hernia repair requires intraabdominal mesh placement

Study procedures

Screening

Subjects with a diagnosis of incisional midline hernia, that requires surgical repair to close the defect, will be considered potential subjects for inclusion and are pre-screened for study eligibility. If inclusion criteria are potentially met and no exclusion criteria are anticipated to be present at the time of pre-screening, the Investigator will invite the subject to participate in the study.

Informed Consent

Subjects will be asked to sign a written informed consent form. A copy of the informed consent will be provided to the subject.

Eligibility

Final eligibility will be determined intraoperatively. Subjects who fail to meet eligibility criteria should be considered screen failures and will be treated per hospital standard of care. Reason for screen failure will be documented. Screen failures are not considered drop-outs, and hospitals will continue to include patients until the required sample size has received surgery.

Intervention

All subjects will undergo an open ventral repair of the hernia. All intraoperative inclusion and exclusion criteria will be verified.

Subjects will be administered perioperative antibiotics according to hospital protocol. Subjects will be prepared to undergo hernia repair with Phasix™ Mesh. The general instructions for the use of Phasix™ Mesh are supplied by the manufacturer.

Surgical technique

The surgical technique will require retro-rectus placement (onlay is allowed as an exception when retro-rectus placement cannot be achieved), using slowly resorbable sutures, with or without Component Separation Techniques (CST). The peritoneum should remain posterior to the mesh upon completion of mesh placement. The mesh may be cut to shape or size desired for each specific application. The mesh is to be positioned so its edges extend beyond the margins of the defect by at least 5 cm. It is recommended that

the mesh is fixated at approximately 5-6 cm intervals (6-12 absorbable sutures) around the periphery of the mesh. Defect closure must be confirmed. All skin incisions will be closed with staples/sutures.

Outcome parameters

Primary outcome

Primary outcome will be surgical site occurrence (SSO) up to and including the 3-month follow-up assessment. SSOs will be assessed by physical examination at each study visit through 3 months. SSO is defined as hematoma, seroma, surgical site infection, wound dehiscence, skin necrosis and fistula, all of which require intervention.

Secondary outcome

Secondary outcomes will be:

- Surgical site occurrence (SSO) after the 3-month follow-up assessment
- Surgical site infection (SSI)[25], which is included in SSOs, but will also be analysed separately
- Hernia recurrence rate (via physical exam, if uncertain via ultrasonography, CT or MRI)
- Pain at every follow-up point, measured with the Visual Analogue Scale (VAS)
- Device related adverse events
- Rate of reoperation due to the index hernia repair
- Quality of Life assessments (Carolinas Comfort Scale™[30a] and EuroQol-5D (EQ-5D)[31])
- Surgical procedure time as measured from incision to closure (skin to skin)
- Return to work
- Length of hospital stay (day of index surgery until day of discharge, LOS)

To measure these outcomes, the following data will be gathered at different points in time, and saved in an electronic case report form:

Pre-operative data

- Demographic data (age, sex, race, ethnicity) and medical history
- Information regarding the inclusion and exclusion criteria
- Height and weight (calculated to a BMI)
- Length and width of hernia
- Wound assessment
    - o signs of infection
    - o status and location of potential previous mesh
    - o signs of necrosis

- Pain medication usage
- Pain (measured with VAS), discomfort (measured with Carolinas Comfort Scale™) and quality of life (measured with EQ-5D)

Peri-operative data

- Information regarding the inclusion and exclusion criteria
- Intra-operative evaluation of wound and abdomen
- Intra-operative assessment and description of hernia
- Intra-operative assessment of complications, e.g. enterotomy
- Surgical procedure
- Mesh details
- Fixation details
- Wound closure

Post-operative data

The following data will be collected at fixed follow-up visits, namely at drain removal (if applicable, otherwise at discharge or at staple removal), 1 month, 3 months, 6 months, 12 months, 18 months and 24 months (Table 1):

- Wound assessment
  - o signs of infection
  - o status and location of potential previous mesh
  - o signs of necrosis
- Hernia recurrence (diagnosed per physical exam, if uncertain via ultrasonography, or via CT/MRI)
- Adverse events
- Device failure/malfunction/defects
- Pain (measured with VAS)
- Discomfort (measured with Carolinas Comfort Scale™)
- Quality of life (measured with EQ-5D)

In addition, pain medication usage will be collected at 12 and 24 months follow-up.

Withdrawal/Early Termination

A subject is considered an Early Termination if discontinuation occurs after study treatment and before 24 months follow-up. The site will attempt to bring the subject back to the hospital to complete all Early Termination visit study procedures: physical examination; assess pain measured with VAS, Carolinas Comfort Scale™,and EQ-5D; and collect adverse events. Reason for subject discontinuation will be documented when possible.

Table 1. Summary of procedures performed per visit.

Study Procedure	Screening and Baseline	Index Surgery	Drain Removal/ Discharge	1, 3, 6 and 18 Month Visit	12 and 24 Month Visit	Early Term
Describe study to potential subject	X					
Obtain informed consent	X					
Collect demographics and medical history	X					
Verify eligibility criteria	X	X				
Physical examination	X		X	X	X	X
Placement of device		X				
Pain Scale (VAS)	X		X	X	X	X
Carolinas Comfort Scale™	X			X	X	X
EQ-5D	X			X	X	X
Collect Adverse Events		X	X	X	X	X
Collect pain medications	X				X	

Sample size consideration

The expected rate of SSO at 3 months is 37% based on historical data (ranging from 21-53%)[32-35]. With 75 subjects, the accuracy of the estimated SSO will be ± 11% (i.e. half of the width of the 95% confidence interval of the estimated rate of SSO is 11%). The study plans to enroll 85 subjects for follow-up. Anticipating on an attrition rate of about 10% after surgery, 75 subjects will be evaluable to assess the primary endpoint of surgical site occurrence (SSO) at 3 months.

Statistical analysis

There will be a modified intention-to-treat population (mITT), which consists of the subjects in whom Phasix™ Mesh has been implanted. The screen failures are not implanted, and will therefore not be used in the analysis. A per-protocol (PP) population may be created if there are subjects who have any major protocol deviations. However, all analyses will be primarily based on the mITT population.

Demographics and baseline characteristics will be summarized using the mITT population. Summary statistics for categorical variables will include frequency counts and percentages, and for continuous variables mean, standard deviation, minimum, median and maximum.

The primary endpoint is the SSO rate up to 3 months (± 14 days) post device placement based on the mITT population. A 95% confidence interval will be reported for the SSO rate.

The SSO rate after 3 months, the hernia recurrence rates and surgical site infection rates until 1, 3, 6, 12, 18 and 24 months post device placement will be reported per visit along with their 95% confidence intervals based on the mITT population as secondary endpoints. Additionally, Kaplan-Meier analyses for the time from surgery to hernia recurrence and for the time from surgery to surgical site infection may be performed.

The secondary endpoints of VAS pain scale, Carolinas Comfort Scale™ and EQ-5D will be summarized based on the mITT population with mean, standard deviation, minimum, median and maximum presented by visit.

The number of subjects with a reoperation due to the index hernia repair will be presented by time intervals (until 1, 3, 6, 12, 18 and 24 months post device placement), surgical procedure duration of the index procedure (calculated as time of skin closure complete minus time of first incision) and length of hospital stay will be summarized descriptively. The time to return to work will be tabulated using summary statistics as well.

No missing value imputation methods will be applied in any of the aforementioned analyses.

Safety

An independent safety monitoring committee will reassess safety of the study protocol and decide about potential adaptations if one of the following criteria are met:

- More than 4 device related serious adverse events within 3 months of Phasix™ Mesh implantation
- More than 1 device related recurrence within 3 months of Phasix™ Mesh implantation

The enrolment and treatment of new subjects are suspended until the impact of the study parameters (e.g. surgical technique, hernia size, mesh size, AE time-course) on the results is assessed. The follow-up for the subjects already treated continues.

Ethics

This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Medical Ethical Committee of the Erasmus Medical Center and the Institutional Review Board of every participating hospital have approved the protocol. Written informed consent will be obtained from all subjects. All study data will be recorded in electronic Case Report Forms provided to the

investigational site. Site and subject numbers will be used to track subject information throughout the study.

The results of the study will be published, regardless of the outcome, either favourable or unfavourable, in a peer-reviewed journal and on clinicaltrials.gov, which is accessible for the public.

DISCUSSION

A major challenge in all hernia studies is the formulation of a clear definition on the severity or grade of the hernia. The difference between grade 3 and 4 hernias is not always clear, since the classification is rather gradual. The definition for Grade 3 hernias used in this study is the same as the one of the Ventral Hernia Working Group in 2010, which excludes presence of infected mesh [13].

A discussion topic in this study is the absence of a control group. No standard treatment is registered for VHWG Grade 3 hernias. The standard treatment per hospital as a control group would not suffice, because 15 hospitals in Europe participate; this would have led to very heterogeneously treated control group with very heterogeneous results, insufficiently valid to compare to the performance of Phasix™ Mesh. Suture closure was considered as a control group, but this would have been disadvantageous for patients because this has been proven to lead to more recurrences [1]. Also non-absorbable synthetic mesh was considered for the control group, because synthetic mesh placement reduces recurrences compared to suture closure or closure with the aid of biological mesh [36,37]. However, synthetic mesh has been hypothesized to lead to a high infection rate due to the potential contamination present in VHWG Grade 3 hernia patients [38,39]. Thirdly, the comparison with biological mesh was also hypothesized to be contra-indicated. Biological mesh has a high salvage rate when infected [40,41], but has a higher recurrence rate than repair with synthetic mesh [37]. This justifies the single-arm design of the study. Therefore, no randomization or blinding has been applied, leading to a possible higher risk of bias. If this study yields positive results, a large randomized controlled trial would be the next step in the exploration of Phasix™ Mesh augmentation in VHWG Grade 3 patients.

Due to the extensive inclusion and exclusion criteria used in this study, and the specific goal of assessing safety and performance, the expected generalizability will be limited. VHWG Grade 3 patients are very specific patients with a high risk of developing an SSO. However, a study has shown that patients with only a history of infection after previous

laparotomy without the other factors determining VHWG Grade 3, have a lower risk of developing an SSO [35]. Therefore, it suggests a modified VHWG Grade 3 scale. It would be useful to analyse the results of the study described in this protocol between patients with only a previous infection after a previous laparotomy, and patients with one or more of the other factors determining VHWG Grade 3. Stratification for other confounders or effect modifiers, such as the presence of a stoma or the CDC wound classification could be of interest as well.

An additional topic for discussion is surgeon skill. Surgeon skill is known to be an important predictor in surgical outcomes. Even though 15 different hospitals with 16 different surgeons participated, all surgeons have more than 10 years of experience in hernia surgery.

Conclusion

This multicenter trial will collect additional data on safety and performance of Phasix™ Mesh in subjects with a VHWG Grade 3 midline hernia requiring surgical repair. Depending on the results this clinical study will yield, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

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Footnotes

[a] The CAROLINAS COMFORT SCALE™ questionnaire was created by and is licensed from the Division of Gastrointestinal and Minimally Invasive Surgery of Carolinas Medical Center, North Carolina

[b] Reprinted from Surgery, 148(3), The Ventral Hernia Working Group, Incisional ventral hernias: Review of the literature and recommendations regarding the grading and technique of repair, 544-558, Copyright (2010), with permission from Elsevier.

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Outcomes of a slowly resorbable mesh (Phasix) in potentially contaminated incisional hernias: a prospective, multi-center, single-arm trial

MMJ van Rooijen
AP Jairam
T Tollens
LN Jørgensen
TS de Vries Reilingh
G Piessen
F Köckerling
M Miserez
ACJ Windsor
F Berrevoet
RH Fortelny
B Dousset
G Woeste
HL van Westreenen
F Gossetti
JF Lange
GWM Tetteroo
A Koch
LF Kroese
J Jeekel

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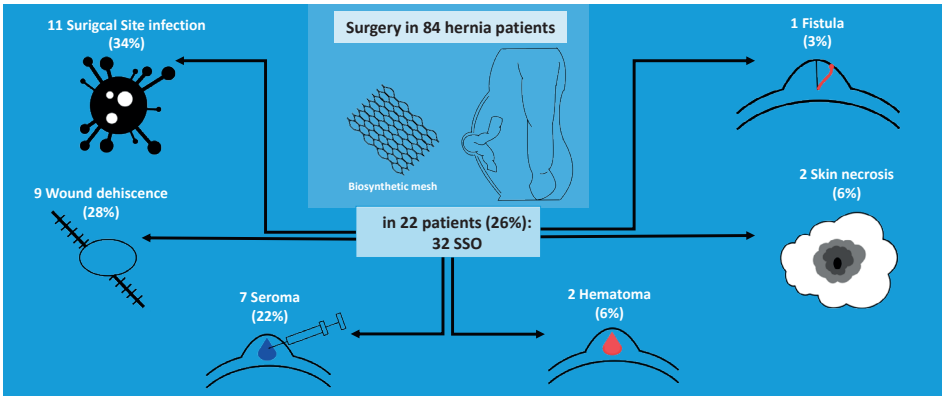

ABSTRACT

Background: Resorbable biomaterials have been developed to reduce the amount of foreign material remaining in the body after hernia repair over the long-term. However, on the short-term, these resorbable materials should render acceptable results with regard to complications, infections, and reoperations to be considered for repair. Additionally, the rate of resorption should not be any faster than collagen deposition and maturation; leading to early hernia recurrence. Therefore, the objective of this study was to collect data on the short-term performance of a new resorbable biosynthetic mesh (Phasix™) in patients requiring Ventral Hernia Working Group (VHWG) grade 3 midline incisional hernia repair.

Materials and methods: A prospective, multi-center, single-arm trial was conducted at surgical departments in 15 hospitals across Europe. Patients aged ≥ 18, scheduled to undergo elective Ventral Hernia Working Group grade 3 hernia repair of a hernia larger than 10 cm^2 were included. Hernia repair was performed with Phasix™ Mesh in sublay position when achievable. The primary outcome was the rate of surgical site occurrences, including infections, that required intervention until 3 months after repair.

Results: In total, 84 patients were treated with Phasix™ Mesh. Twenty-two patients (26.2%) developed 32 surgical site occurrences. These included 11 surgical site infections, 9 wound dehiscences, 7 seromas, 2 hematomas, 2 skin necroses, and 1 fistula. No significant differences in surgical site occurrence development were found between groups repaired with or without component separation technique, and between clean-contaminated or contaminated wound sites. At three months, there were no hernia recurrences.

Conclusion: Phasix™ Mesh demonstrated acceptable postoperative surgical site occurrence rates in patients with a Ventral Hernia Working Group grade 3 hernia. Longer follow-up is needed to evaluate the recurrence rate and the effects on quality of life. This study is ongoing through 24 months of follow-up.

Registration: clinicaltrials.gov (NCT02720042).

INTRODUCTION

Incisional hernia is a frequent complication after abdominal surgery, with incidences varying from 10 to 20% [1], and can be more than 30% in high-risk patients, such as patients with a Body Mass Index (BMI) over 30 kg/m^2 [2,3]. Patients with incisional hernias score lower in the areas of physical functioning, cosmetic, and body image components of health-related quality of life questionnaires [4]. Surgical hernia repair is often needed as a result; some 350,000 ventral hernia repairs are done each year in the Unites States alone [5].

Incisional hernias used to be repaired with sutures only. However, multiple studies have shown that repair with synthetic mesh leads to significantly fewer recurrences compared to primary suture repair [1,6-8]. However, permanent synthetic mesh has also been associated with chronic inflammation, pain, adhesions, and fistulae [6,9]. With a reported infection rate of about 5%, synthetic meshes are more prone to infection than biological tissue-derived materials [10]. This could pose a problem in potentially contaminated hernias like Ventral Hernia Working Group (VHWG) grade 3 hernias (Table 1) [11]. The success of the mesh repair is jeopardized by potential contamination, which is caused by complicating factors such as previous wound infection, the presence of a stoma, or violation of the gasto-intestinal tract.

Table 1. Ventral Hernia Working Group grading system: assessment of risk for surgical site occurrences [11].

Grade 1	Grade 2	Grade 3	Grade 4
Low Risk	*Co-morbid*	*Potentially contaminated*	*Infected*
Low risk of complications No history of wound infection	Smoker Obese Diabetic Immunosuppressed COPD	Previous wound infection Stoma present Violation of the GI tract	Infected mesh Septic dehiscence

COPD: chronic obstructive pulmonary disease, GI: gastro-intestinal

Due to this potential contamination in VHWG grade 3 hernias, it may be desirable that no foreign material remains in the body: that the mesh is resorbed. An alternative to permanent synthetic mesh, such as biological tissue-derived materials, may be considered. It is hypothesized that biological meshes have a higher ability to resist infection, have a milder inflammatory response, and cause more orderly collagen deposition than permanent synthetic meshes [12-14]. However, these biological materials are costly, and have not fulfilled all expectations related to their possible advantages.

A more recent development in surgical prostheses is biosynthetic mesh. Biosynthetic mesh made from poly-4-hydroxybutyrate (P4HB) has the advantage of having mechanical strength comparable to traditional polypropylene mesh [15], and might therefore result in low recurrence rates when used for incisional hernia repair. Additionally, it resorbs over 12 to 18 months [15,16], leaving no foreign material behind in the body. However, this P4HB mesh retains only 70% of its strength after 12 weeks [15,17,18], possibly causing early hernia recurrence due to early breakdown of the mesh. Also its ability to resist infection in potentially contaminated sites (such as VWHG grade 3 hernias) remains understudied. For such a new and promising mesh to be considered for repair, postoperative complication and infection rates should be collected. The objective of this study was therefore to collect additional data on the short-term performance of a P4HB synthetic mesh (Phasix™) in patients requiring VHWG grade 3 midline incisional hernia repair.

METHODS

Study design

This prospective, single-arm, multicenter trial was conducted at surgical departments in 15 hospitals across Europe. The trial protocol has been previously published [19] and can be found on clinicaltrials.gov (NCT02720042). Patients aged 18 years or older and scheduled to undergo elective VHWG grade 3 hernia repair of a midline incisional hernia larger than 10 cm^2 were asked to participate in the trial. Patients with a BMI over 35 kg/m^2, peritonitis, HIV, liver cirrhosis, or chemotherapeutic medication were excluded. An elaborate overview of exclusion criteria has been previously published [19].

The protocol was reviewed and approved by the Institutional Review Boards or Health Authorities of all participating centers. All participants gave written informed consent prior to any study procedures being conducted. The study has been reported following the STROCSS criteria [20].

Procedures

The participants were registered in an online database with a personal, unique trial code. Final eligibility of a patient, with regard to the hernia-specific and intraoperative exclusion criteria, was determined during surgery.

All eligible patients underwent open ventral hernia repair. The Phasix™ Mesh had to be placed in a retro-rectus (sublay) position. Onlay placement was allowed only when retro-rectus placement could not be achieved. The Phasix™ Mesh was fixated with slowly resorbable sutures. The specific type of suture and fixation pattern were left to

the discretion of the surgeon, along with the use of component separation technique (CST), when considered appropriate. The mesh was positioned to overlap the defect on all edges by at least 5 centimeters. It was recommended to the surgeons to fixate the mesh at approximately 5 to 6 centimeter-intervals around the periphery of the mesh. All skin incisions were closed with staples or sutures.

After surgery, patients were treated per hospitals' standard protocol. Patients were invited for follow-up visits on three points in time: after drain removal or at hospital discharge, 1 month after surgery, and 3 months (± 14 days) after surgery. During these follow-up visits – as well as before surgery – patients underwent physical examination by a medical doctor.

Outcomes

The primary outcome was surgical site occurrence (SSO) that required any type of medical or surgical intervention. SSOs were assessed by physical examination at each study visit through 3 months (± 14 days). SSO was defined as hematoma, seroma, surgical site infection (SSI) [21], wound dehiscence, skin necrosis and fistula. As a secondary endpoint, the hernia recurrence rate up until 3 months was assessed.

Statistical analysis

Since VHWG grade 3 hernia patients are rare, it was chosen to use a sample of convenience. Seventy-five patients were deemed sufficient to evaluate the performance of Phasix™ Mesh. This means that at an estimated SSO rate at 3 months of 37% [22-25], the accuracy will be 11% (i.e. half of the 95% confidence interval width of the estimated SSO rate, is 11%). Eighty-five participants were included due to an anticipated attrition rate of approximately 10%.

Data from all patients in whom Phasix™ Mesh was implanted were analyzed, through an intention-to-treat principle. No missing value imputation methods were applied. Patient and hernia characteristics were summarized with frequency counts and percentages, or with the mean and standard deviation (SD). Information on follow-up is given through median and interquartile range (IQR), and the primary endpoint is reported with a 95% confidence interval (CI).

RESULTS

In total, 85 patients were enrolled in the study between March 2016 and April 2017. In one patient, a different type of mesh was implanted. Therefore, 84 patients were included in the analysis. All but 1 patient attended their follow-up visits up to and including the 3-month visit (median follow-up 90 days, interquartile range 85 to 99 days).

Patients and follow-up

Baseline characteristics are listed in Table 2. The mean age in males was 63.3 years (SD 12.8) and in females 61.3 years (SD 11.9). The mean BMI in males was 27.4 kg/m^2 (SD 3.6) and in females 28.3 kg/m^2 (SD 4.6). Twenty-five patients (29.8%) had other significant medical history not listed in Table 3, such as an intersphincteric fistula, Crohn's disease, pancreatitis, depression, hip replacement, cholecystectomy, or post-traumatic stress syndrome, among others.

Table 2. Baseline characteristics.

	N = 84
Gender	
Male (%)	51 (60.7)
Female (%)	33 (39.3)
Age, years (SD)	62.5 (12.4)
BMI, kg/m^2 (SD)	27.8 (4.0)
History of post-surgical infection (%)	60 (71.4)
Hypertension (%)	39 (46.4)
Smoking (%)	39 (46.4)
Cancer history (%)	35 (41.7)
Lung disease (%)	19 (22.6)
Cardiovascular disease (%)	19 (22.6)
Diabetes Mellitus (%)	12 (14.3)
Renal disease (%)	12 (14.3)
Chronic pain (%)	10 (11.9)

kg/m^2: kilogram per square meter, SD: standard deviation, BMI: Body Mass Index.

Hernia and surgery characteristics

Sixty-eight patients (81%) were operated on for a primary incisional hernia, 9 patients (10.7%) were operated for a first-time recurrence, and for 7 patients (8.4%) it was a repair of ≥ second-time recurrence. Of the 16 patients (19.1%) who were operated on for incisional hernia recurrence, 10 (11.9%) had a previously placed mesh that needed to be explanted.

Reasons for VHWG 3 classification were previous wound infections in 51 patients (60.7%), stoma presence in 24 patients (28.6%), violation of gastro-intestinal (GI) tract in 6 patients (7.1%), small bowel resection with anastomosis in 1 patient (1.2%), take down of ileostomy with ileocolonic anastomosis in 2 patients (2.4%), cholecystectomy in 1 patient (1.2%), creation of stoma in 3 patients (3.6%), or other reasons in 4 patients (4.8%). One patient was proven to be contaminated with extended spectrum beta-lactamase bacteria, but did not meet any of the criteria for a VHWG grade 3. After inclusion, two patients were considered to have grade 4 hernias instead of grade 3 due to the presence of an active infection (1; 1.2%) and a fistula (1; 1.2%). However, they remained included in the analyses.

Hernia characteristics can be found in Table 3. One of these characteristics is the CDC wound classification [21]. This is not to be confused with the VHWG grading system; with

Table 3. Hernia characteristics (mean (SD) or n (%)): size, site contamination according to CDC classification, and surgical methods.

	N=84
Hernia defect	
Length in cm (SD)	12.1 (5.7)
Width in cm (SD)	8 (3.5)
Size in cm^2 (SD)	109.2 (87.9)
CDC Wound Class – Preoperative Assessment	
Clean (%)	1 (1.2)
Clean-contaminated (%)	46 (54.8)
Contaminated (%)	37 (44.0)
CDC Wound Class – Assessment at Device Implant	
Clean (%)	35 (41.7)
Clean-contaminated (%)	38 (45.2)
Contaminated (%)	10 (11.9)
Dirty/Infected (%)	1 (1.2)
Surgical details	
Retro-rectus with CST (%)	48 (57.1)
Retro-rectus without CST (%)	35 (41.7)
Onlay, with CST (%)	1 (1.2)
Concomitant procedures (%)	52 (61.9)
In case of CST	
Ramirez/open technique (%)	13 (27.1)
Posterior CST (%)	16 (33.3)
Endoscopic/minimally invasive technique (%)	12 (25.0)
Combination of techniques	7 (14.6)

SD: standard deviation, CST: component separation technique.

the CDC wound classification, the wound site is assessed as either clean, clean-contaminated, contaminated, or infected. The frequency of the use of CST is shown, because CST use in the treatment for incisional hernia repair might lead to more postoperative surgical complications compared to a Rives-Stoppa technique. Concomitant procedures included, among others, lysis of adhesions, relocation of a colostomy, hemicolectomy, removal of excess skin, or Hartmann reversal. All hernias were located in the midline.

SSO rate

The primary outcome measure, SSO rate, is listed in Table 4. In total, 22 patients (26.2%; 95% CI: 17.2% - 36.9%) developed 32 SSOs. Four of the SSOs (12.5%) required hospitalization, 3 required surgical intervention (9.3%), 1 required an ultrasound examination before drainage (3.1%), 1 required a vacuum assisted closure device (3.1%), 2 were resolved by aspiration (6.3%), 1 superficial excision of necrotic tissue took place (3.1%), and twenty SSOs (62.5%) could be managed with either medication, wound care, or drainage alone.

Table 4. SSO rates, split up for the use of component separation technique and preoperative CDC wound class assessment.

	Total (n=84)	with CST (n=49)	without CST (n = 35)	Contam. (n= 37)	Clean-contam. (n=46)
Patients with SSO (%)	22 (26.2)	13 (26.5)	9 (25.7)	9 (23.7)	13 (28.9)
Total SSO	32	20	12	15	17
SSI	11	8	3	6	5
Wound dehiscence	9	6	3	5	4
Seroma	7	4	3	3	4
Hematoma	2	-	2	-	2
Skin necrosis	2	2	-	-	2
Fistula	1	-	1	1	-

SSO: surgical site occurrence, SSI: surgical site infection, CST: component separation technique, Contam.: contaminated, Clean-contam.: clean-contaminated.

Patients with SSOs were stratified for the use of CST and for either contaminated or clean-contaminated wound sites. With regard to the difference of SSO development per sex, among men 19.6% developed an SSO, compared to 36.4% among women.

A total of 90 adverse events (AE) were experienced by 43 patients (51.2%). SSOs were also considered AEs. AEs that were not SSOs, were, for example, postoperative ileus, hypokalemia, or pneumonia. In 2 patients, the AE was considered to be possibly device-related; these were a seroma and a parastomal hernia recurrence. In the other patients the AE was not device-related. Of the 90 AEs, 28 were serious adverse events (SAE), in 16 patients (19.0%), all of which were classified as not device-related. One Phasix™ Mesh had to be explanted due to the patient's development of fecal peritonitis two days after

surgery. No clinical hernia recurrences of the hernias repaired with Phasix™ Mesh occurred within 3 months.

DISCUSSION

Phasix™ Mesh demonstrated acceptable postoperative SSO rates for VHWG grade 3 incisional hernia repair in the short term. An SSO rate of 26% is rather low in this patient population. The reported SSO rate in VHWG grade 3 hernias when synthetic mesh is used, is between 6% and 55% [22,25-29]. The 6% comes from a study in which only 17 patients with VHWG grade 3 were included, and the SSO rate was assessed after 30 days, whereas in this trial, the SSO rate was assessed after 90 days [26]. All other studies reporting an SSO rate in VHWG grade 3 patients treated with synthetic mesh, report rates over 30% [22,25,27-29]. Studies describing the use of synthetic meshes in contaminated settings (not reporting a VHWG grade), observe similar results to ours. One large retrospective study of 100 patients using lightweight polypropylene mesh showed a 26.2% SSO rate in clean-contaminated cases, and 34% in contaminated cases. Also the SSI rate in this study was slightly higher than ours, with 14% within 30 days [30].

Only few studies have reported the SSO incidence in VHWG grade 3 patients after repair with biological mesh. One study reports a 63% SSO rate in patients with either VHWG grade 3 or 4 [31]. Another study compared Permacol®, Surgisis®, and Alloderm®, rendering an SSO rate of 25% to 40% [32]. However, no information on contamination of the hernia site was reported in that study. A recent systematic review on biologic versus synthetic mesh in clean-contaminated hernias found overall surgical site complication rates of 44% in the nonabsorbable synthetic group, and 50% in the biologic group [33].

As described above, comparison of the SSO rate between studies is difficult, since many different factors play a role in studies, such as type of mesh used, the use of a component separation technique, study type (prospective or retrospective), and the timeframe used to detect SSOs. However, the P4HB biosynthetic mesh from this study seems to show acceptable short-term results.

An interesting finding was the difference in SSO development between men and women in the study. Women tended to develop SSOs more often than men (36.4% vs 19.6%). This difference in SSO might be explained by the use of CST between men and women; CST was used in 40% of men and in 75% of women that developed an SSO. There was no difference in contamination of the surgical site between men and women. However,

due to the small study sample, no conclusions can be drawn upon the difference in SSO rate between the sexes.

As we did an intention-to-treat analysis, two patients were included in the analysis while actually having a VHWG grade 4 surgical site. These patients both contributed to the SSO rate, with both developing a postoperative wound infection (SSI) and wound dehiscence. The actual SSO rate in VHWG grade 3 patients would therefore be slightly lower.

From the results, it can also be confirmed that smoking seems to be a risk factor for the development of a superficial or deep infection. Many included patients were smokers, and 7 of the 11 patients that developed an SSI were current or past smokers (63.6%).

Limitations

A methodological limitation of the study is the absence of a control group. However, all comparison options have their own drawbacks. First, no standard treatment is registered for VHWG grade 3 hernias. Because 15 hospitals in Europe participated, it would be insufficient to use the standard treatment per hospital as a control group. This would lead to very heterogeneously treated patients and different results, not suitable for the comparison with the performance of the Phasix™ Mesh. Second, permanent synthetic mesh could have been used in a control group, because it reduces recurrences when compared to suture closure or closure with the aid of biological mesh [34,35]. However, due to the potential contamination in VHWG grade 3 hernias, synthetic mesh could lead to a high infection and potential removal rate [36,37]. Last, using biological mesh in the control group is also not ideal. Biological mesh has the advantage of having a high salvage rate when infected [38,39], but renders a higher recurrence rate than repair with synthetic mesh [35].

Another methodological limitation might be the partially standardized procedure for incisional hernia repair in this study. Multiple centers in multiple countries across Europe participated. Every center or every surgeon has different regulations, habits, and preferences. Because of the patient population, some centers use CST more often than others. CST use in the treatment for incisional hernia repair might lead to more postoperative surgical complications, compared to exclusive use of a sublay technique (24% vs. 11.1%) [40]. However, the SSO rates for both patients treated with and without CST were not significantly different in the present study. This finding might be explained by the fact that all patients were treated in experienced hernia centers across Europe, and that some freedom in the surgical protocol should be allowed to provide the most fitting repair for every individual patient.

Conclusion and implications

Phasix™ Mesh demonstrated acceptable post-operative surgical site occurrence rates for VHWG grade 3 incisional hernia repair. These results on infection and complications rates are valuable for the surgeon in the decision to use this new and promising type of mesh for hernia repair in this high-risk patient group. However, it remains to be studied whether hernia repair with Phasix™ Mesh causes lower recurrence rates and is more cost-effective than the use of biologics or permanent synthetics. Due to the high rate of obesity and comorbidities present in the studied population, the anticipated recurrence rate is high [2,3,41]. A low recurrence rate after longer follow-up would stimulate surgeons to consider the use of a biosynthetic mesh in potentially contaminated hernias. Cost-effectiveness analysis could also be valuable when long-term results are available, as recurrence and reoperation are both costly, but occur frequently later than only 3 months after surgery. Aside from complications, surgical site occurrences, and recurrences, the course of quality of life in patients receiving repair with Phasix™ Mesh should also be assessed. In short, information on the long-term performance of Phasix™ Mesh should be collected to make real recommendations regarding its use, but the early results are promising. This study is ongoing through 24 months of follow-up.

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8 Slowly resorbable biosynthetic mesh: 2-year results in VHWG grade 3 hernia repair

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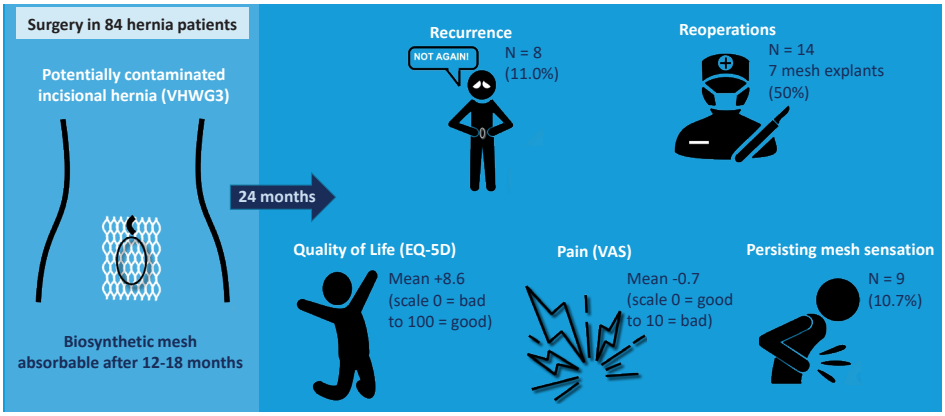

ABSTRACT

Introduction: Information on the long-term performance of biosynthetic meshes is scarce. This study analyses the performance of biosynthetic mesh (Phasix™) over 24 months.

Methods: A prospective, international European multi-center trial is described. Adult patients with a Ventral Hernia Working Group (VHWG) grade 3 incisional hernia larger than 10 cm2, scheduled for elective repair, were included. Biosynthetic mesh was placed in sublay position. Short-term outcomes included 3-month surgical site occurrences (SSO), and long-term outcomes comprised hernia recurrence, reoperation, and quality of life assessments until 24 months.

Results: Eighty-four patients were treated with biosynthetic mesh. Twenty-two patients (26.2%) developed 34 SSOs, of which 32 occurred within 3 months (primary endpoint). Eight patients (11.0%) developed a hernia recurrence. In 13 patients (15.5%), 14 reoperations took place, of which 6 were performed for hernia recurrence (42.9%) and in which 7 the mesh was explanted (50%). Compared to baseline, quality of life outcomes showed no significant difference after 24 months. Despite theoretical resorption, 10.7% of patients reported presence of mesh sensation in daily life 24 months after surgery.

Conclusion: After 2 years of follow-up, hernia repair with biosynthetic mesh shows manageable SSO rates and favorable recurrence rates in VHWG grade 3 patients. No statistically significant improvement in quality of life or reduction of pain were observed. Few patients report lasting presence of mesh sensation. Results of biosynthetic mesh after longer periods of follow up on recurrences and remodeling will provide further valuable information to make clear recommendations.

Registration: clinicaltrials.gov (NCT02720042).

INTRODUCTION

Incisional hernias occur in up to 20% of patients after midline laparotomy [1]. In case of complaints, such as pain and reduced quality of life (QoL), operative repair is indicated [2]. This repair traditionally took place with permanent synthetic meshes, as these have proven to reduce the risk of recurrence compared to primary closure [1,3-5]. However, permanent synthetic meshes remain in the body as foreign material, increasing the risk of seromas, infections, enterocutaneous fistulas, and chronic pain [3,6,7]. This has led to the development of resorbable biologic meshes, which would not cause foreign material to be left in the body, and which were hypothesized to be more infection-resistant [8].

However, resorbable biologic meshes have faced problems in resorption rate; too quick resorption does not support abdominal wall regeneration and will consequently lead to higher recurrence rates. To tackle the problem of too rapid resorption, slowly resorbable biosynthetic meshes have been developed recently for the field of abdominal wall reconstruction [9], among which products made from poly-4-hydroxybutyrate (P4HB). Due to the resorption of these products, no foreign material remains behind, yet this slow resorption process is only essentially complete after 12 to 18 months, providing initial mechanical strength comparable to polypropylene mesh to support the native abdominal wall for cellular ingrowth and remodelling [10,11]. The gradual mesh resorption allows natural forces to put gradual strain on the abdominal wall muscles and aponeuroses, which could restore and reshape the functional tissue structure. This "use it or lose it" concept is known from the remodelling of bone, and might also be applicable to the abdominal wall during recovery after hernia repair [12,13]. All above described characteristics of P4HB meshes are especially desirable in (potentially) contaminated surgical fields, such as Ventral Hernia Working Group (VHWG) grade 3 hernias [14].

Currently, research is focused on whether these biosynthetic meshes live up to their expectations, as they are more costly than synthetic meshes. Our early results suggest that these meshes perform comparable to synthetic mesh on the short-term in high-risk patients [15]. However, information on long-term performance is scarce [16]. It has yet to be discovered whether biosynthetic meshes do indeed cause adequate abdominal wall remodelling and cause less incisional hernias to recur, especially in a high-risk population. Therefore, the objective of this study was to collect additional data on the long-term performance of P4HB mesh in patients requiring VHWG grade 3 hernia repair.

METHODS

Study design

We conducted this prospective single-arm trial in 15 European hospitals. Adults scheduled for elective VHWG grade 3 incisional hernia repair were included. VHWG grade 3 comprises hernias in a surgical site in which there has been previous wound infection, on which a stoma is present, or in which violation of the gastro-intestinal tract takes place. Additional inclusion criteria with regard to the hernia were a midline position and a size of more than 10 cm^2. An elaborate overview of the exclusion criteria has been previously published [15,17].

The research protocol was approved by the institutional review board or health authority of every participating center, has been previously published [17], and is registered at clinicaltrials.gov (NCT02720042). All included patients gave written informed consent prior to any study procedure.

Procedures

Final eligibility of patients was determined during surgery, after which open ventral hernia repair was performed. A P4HB biosynthetic mesh (Phasix™ Mesh, C.R. Bard, Inc., Warwick, RI) was placed retro-rectus as fascia augmentation, overlapping all edges of the defect by 5 centimeters. When this could not be achieved, onlay placement was allowed. Component separation techniques (CST) were used when considered appropriate by the surgeon. The mesh was fixated with slowly resorbable sutures at 5 to 6-centimeter intervals.

Postoperatively, patients received the standard care of their treating center. Follow-up took place after 1, 3, 6, 12, 18, and 24 months, during which patients underwent physical examination by a medical doctor, and were asked to fill out QoL-questionnaires: Carolinas Comfort Scale (CCS) [18], EQ-5D [19], and Visual Analog Scale (VAS). The CCS measures severity of mesh sensation and pain with a score from 0 (no complaints) to 5 (disabling symptoms). The EQ-5D assesses 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and allows patients to rate their "Health Today" on a scale from 0 to 100 [19]. Pain was assessed through the VAS, anchored by "no pain" (score 0) and "worst imaginable pain" (score 10) on a 10-centimetre scale. Patients were censored in case of death or when they ended follow-up.

Outcomes

The short-term, primary outcome was surgical site occurrence (SSO) up to 3 months after surgery, that required medical or surgical intervention. Hematoma, seroma, surgical site infection (SSI) [20], wound dehiscence, skin necrosis, and fistula were all considered

SSOs. Additionally, the surgical procedure time, the length of hospital stay, and the time to return to work were outcomes of interest.

The long-term, secondary outcome was the recurrence rate determined per physical examination, and if uncertain, per ultrasound examination, CT-scan, or MRI. Other long-term outcomes of interest were reoperation rate, SSO rate up to 24 months, and QoL and pain outcomes (CCS, VAS, and EQ-5D).

Sample size and statistical analysis

Seventy-five patients were deemed sufficient to evaluate the performance of Phasix™ Mesh. Anticipating an attrition rate of 10%, the aim was to include 85 patients. Data from all included patients implanted with Phasix™ Mesh were analyzed. Baseline characteristics were summarized with frequency counts and percentages, or with mean and standard deviation (sd). Follow-up is summarized through median with range. Short-term and long-term endpoints are reported as proportions or means with a 95% confidence interval (95%CI) or as medians with range or interquartile range (IQR). The long-term endpoint of recurrence was assessed through time-to-event analysis. No missing value imputation methods were used. Analysis was through an intention-to-treat principle, with Statistical Analysis System (SAS), Version 9.3 and R version 3.3.3.

RESULTS

Between March 2016 and April 2017, 84 patients were included for analysis. Patient and hernia characteristics are presented in Table 1. The median follow-up was 24 months (734 days; range 9–834 days).

Short-term outcomes

Within 3 months, 22 patients (26.2%; 95%CI: 17.2%-36.9%) had developed 32 SSOs. Four patients with SSOs required hospitalization (12.5%) and three patients required surgical intervention (9.4%). The majority – 11 (34.4%) – of these SSOs were SSIs. All but one SSI arose within the first month after surgery. An extended overview of the short-term outcomes has been published previously [15].

The median surgical procedure time from incision to closure was 163 minutes (range: 60-696 minutes). After surgery, the median length of stay was 8 days (range: 3-38 days). Twenty patients (23.8%) spent part of their hospital stay in the intensive care unit (ICU), with a maximum duration of 18 days (median: 2.0 days, IQR: 1-4 days). Of the 26 patients that were employed during the study, the median number of days for returning to work was 55 (range: 7-785 days).

Table 1. Baseline patient and surgical characteristics presented as n (%) or mean (sd).

	N = 84
Patient characteristics	
Gender (%)	
Male	51 (60.7)
Female	33 (39.3)
Age, years (sd)	62.5 (12.4)
BMI, kg/m^2 (sd)	27.8 (4.0)
Obesity (BMI >30 kg/m^2) (%)	22 (26.2)
Hypertension (%)	39 (46.4)
Smoking (%)	39 (46.4)
Lung disease (%)	19 (22.6)
Diabetes (%)	12 (14.3)
Corticosteroid use (%)	3 (3.6)
Cancer history (%)	35 (41.7)
Chronic pain (%)	10 (11.9)
Reason VHWG 3 (%)	
Previous wound infection	49 (58.3)
Stoma present	16 (19.0)
Creation of a stoma	5 (6.0)
Violation of the GI tract	1 (1.2)
Combination of above	8 (9.5)
Other	5 (6.0)
Surgical characteristics	
Hernia defect (sd)	
Length, cm	12.1 (5.7)
Width, cm	8.0 (3.5)
Area, cm^2	109.2 (87.9)
Incisional hernia (%)	
Primary incisional hernia	68 (81.0)
First recurrence	9 (10.7)
>1 recurrence	7 (8.4)
Explant of previous mesh (%)	10 (11.9)
Use of CST (%)	49 (58.3)

BMI: Body Mass Index, sd: standard deviation, CST: Component Separation Technique.

Long-term outcomes

Over the course of 24 months, 15 patients (17.9%) did not complete their 24-month follow-up visit, due to being incapacitated or lost to follow-up (n=7), death (n=3), withdrew from participation (n=1), or had the biosynthetic mesh explanted (n=4; of which 3 due to recurrence). Of these 15 patients, 4 experienced a hernia recurrence. An additional 4 recurrences occurred in the group (n=69) that did complete 24-month follow-up. Therefore, 8 patients out of a total of 73 (11.0%) developed a recurrence of

their incisional hernia (95%CI: 3.8%-18.1%). The hernia recurrences and censored patients over time are depicted in Figure 1.

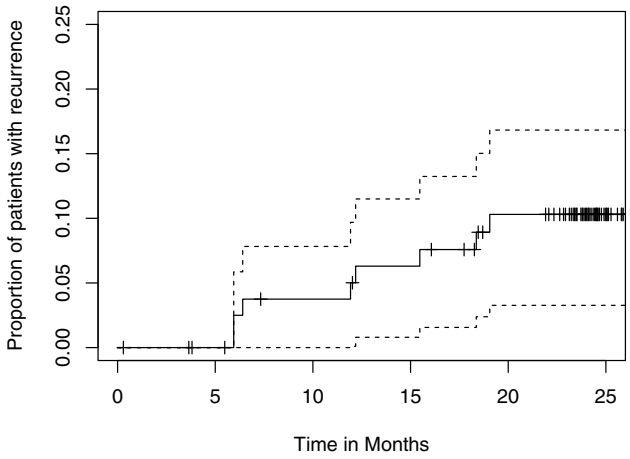

Figure 1. Hernia recurrences over time (solid line) with 95% confidence interval (dotted lines). Censored subjects are marked with "+".

In 13 patients of all 84 (15.5%; 95%CI: 8.5%-25.0%), 14 reoperations took place. Six were performed for hernia recurrence (42.9%, of which one with a concomitant mesh infection), three for mesh infection (21.4%), one each for subcutaneous hematoma, ileus, and subcutaneous abscess (each 7.1%), and two for other reasons (14.3%). During 7 of these 14 reoperations (50%), a full or partial explant of the biosynthetic mesh was deemed necessary. Of the reoperations for mesh infection, two mesh infections were secondary to active infection present at the time of index procedure (VHWG grade 4), and one infection was secondary to faecal peritonitis postoperatively.

With regard to the SSOs up to 24 months, only two more developed after the short-term results of 3 months. The division of the cumulative 34 SSOs is shown in Table 2. Of note – though not significant – 19.6% of men experienced SSOs, compared to 36.4% of women.

With regard to the QoL measurements up to 24 months, the VAS-score dropped 0.7 on average (sd: 2.45). The course of the mean VAS-score over time is depicted in Figure 2. The EQ-5D measure of "Health Today" is similarly depicted in Figure 3.

Pertaining the health domains researched in the EQ-5D questionnaire, the proportion of patients reporting no problems in each domain increases over time. This is also shown in Table 3.

Table 2. Surgical Site Occurrence (SSO) development within 24 months. SSI: Surgical Site Infection.

	Total (n=84)
Patients with SSO, n (%)	22 (26.2)
Total SSO	34
SSI	11
Wound dehiscence	9
Seroma	7
Hematoma	2
Skin necrosis	2
Fistula	3

Results of the CCS questionnaire can be viewed in Figure 4. Proportions of patients reporting a sensation of the mesh during the activities of daily living (ADL) show a downward trend for the 12-month, 18-month and 24-month follow up point. At these time points, the mesh is expected to have been fully resorbed by the body. At 12 months, 20.2% of patients still reports mesh sensation during ADL, and at 24 months, this feeling remains in 9 patients. In comparison, 23 patients (27.4%) report to have sensation of the mesh during ADL one month postoperatively.

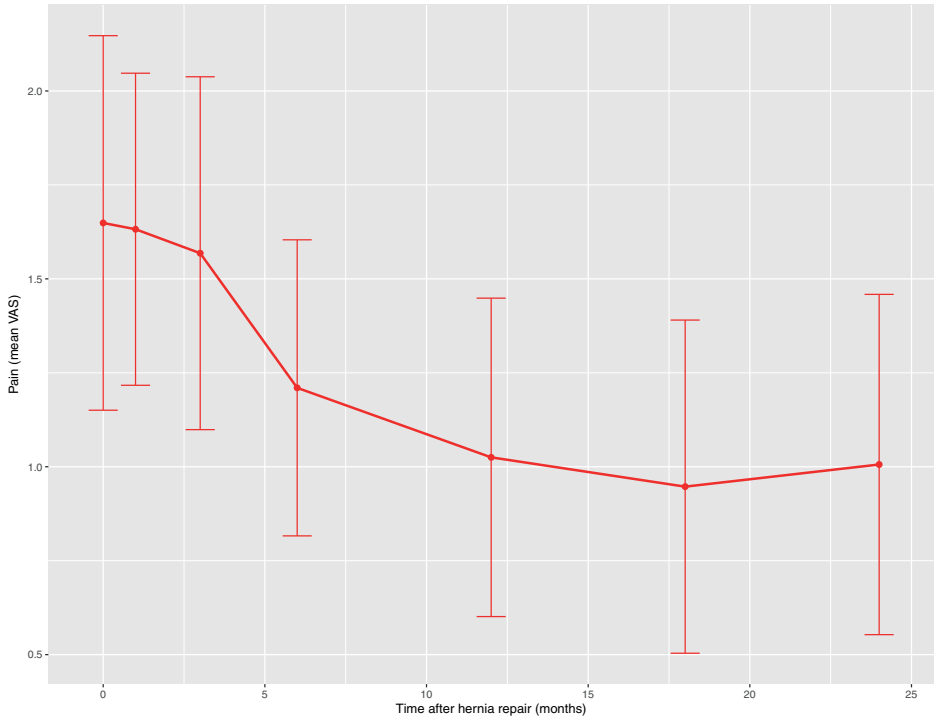

Figure 2. Mean VAS score for pain over time including 95% confidence intervals. VAS: visual analog scale.

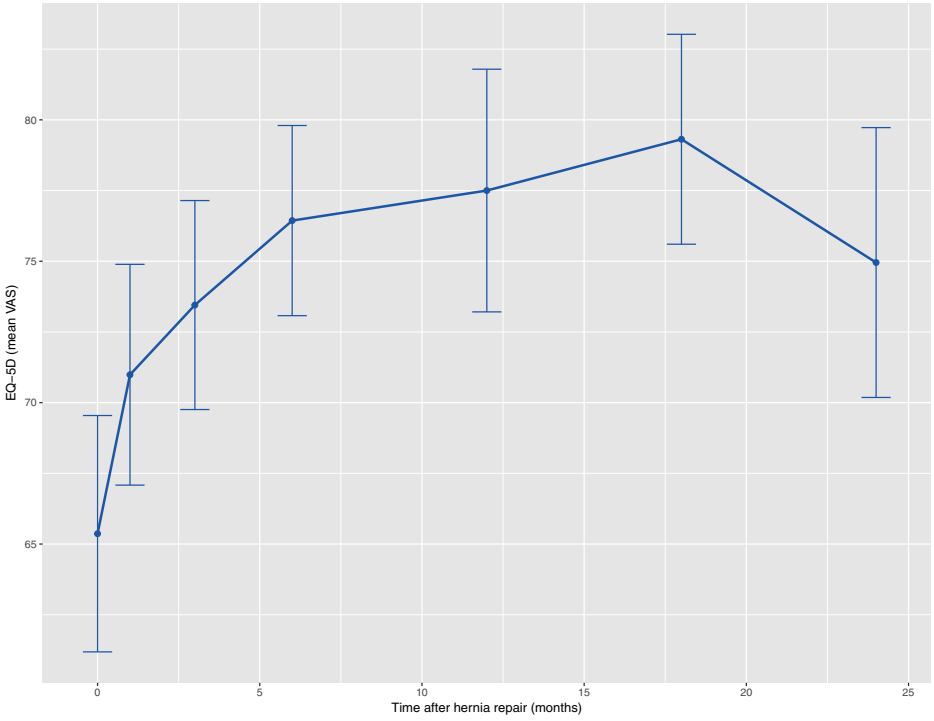

Figure 3 Mean EQ-5D VAS score ("Health Today") over time, including 95% confidence intervals. EQ-5D VAS is a self-reported score on a scale from 0 to 100, with higher values representing a higher quality of life.

Table 3. The five dimensions of the EQ-5D questionnaire per time point. Number and percentage of patients reporting no problems in mobility, self-care, or usual activities, and reporting no pain or no anxiety.

	Baseline	1 mo	3 mo	6 mo	12 mo	18 mo	24 mo
n	84	82	83	80	77	71	69
Mobility (%)	57 (68)	51 (62)	64 (77)	63 (79)	62 (81)	57 (80)	56 (81)
Self-care (%)	67 (80)	59 (72)	70 (84)	71 (89)	71 (92)	63 (89)	64 (93)
Usual activities (%)	48 (57)	41 (50)	60 (72)	65 (81)	61 (79)	56 (79)	55 (80)
No pain/ discomfort (%)	37 (44)	37 (45)	47 (57)	45 (56)	51 (66)	44 (62)	47 (68)
No anxiety/ depression (%)	56 (67)	60 (73)	59 (71)	63 (79)	61 (79)	61 (86)	56 (81)

mo: month.

DISCUSSION

During two years of follow-up, 22 patients developed 34 SSOs (26.2%), and a recurrence rate of 11.0% was observed, demonstrating reasonably good results. Other studies with P4HB mesh reported similar findings: in a small study of 25 patients treated with P4HB

mesh for ventral or incisional hernias, 2 hernias recurred (8%), at 12 and 24 months respectively [21]. In a prospective study of 121 VHWG grade 2 hernia patients, 11 patients (9%) had developed a recurrence after 18 months of follow-up [22].

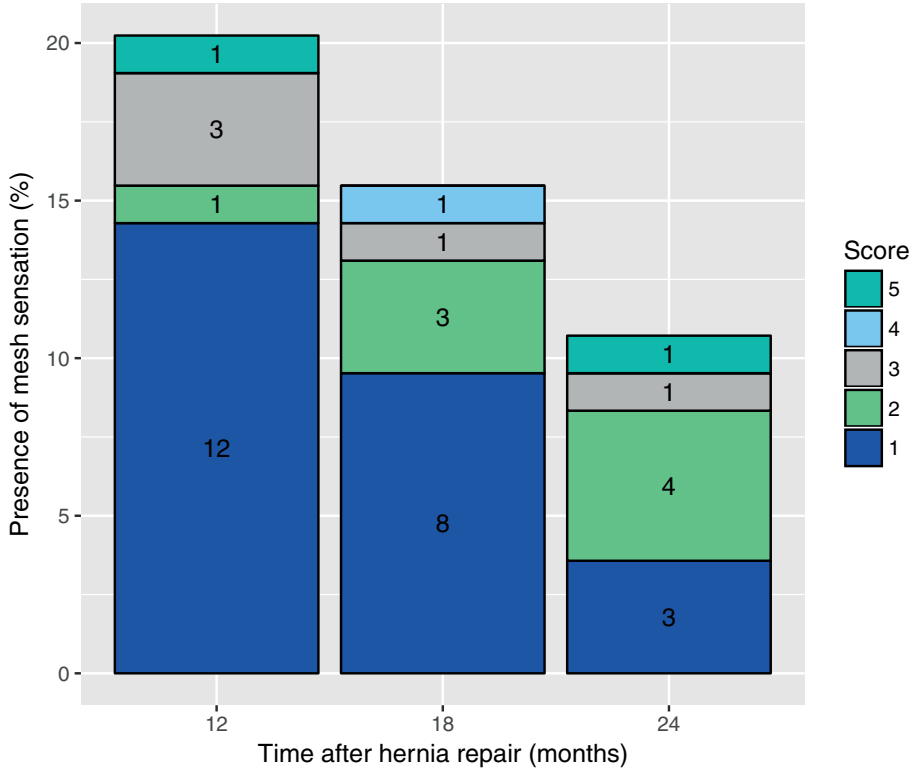

Figure 4. Patients reporting a sensation of the mesh during activities of daily living in the CCS questionnaire at timepoints at which the Phasix™ mesh should have been fully resorbed. Absolute numbers are depicted within the stacked bars.
Score: 5 = disabling; 4 = severe; 3 = moderate and/or daily; 2 = bothersome but not daily; 1 = mild but not bothersome.

Especially in researched high-risk patient group, the recurrence rate is relatively low in comparison with current literature. Reported recurrence rates in *VHWG grade 3 hernias* after an average follow-up of 12 to 28 months vary from 18.5% with permanent synthetic mesh [23], to around 16% with biologic mesh [24,25], to 32.5% in a combined cohort of biologic and permanent synthetic mesh [26]. A recent study showed equally positive results to ours with the use of permanent synthetic mesh *in contaminated fields*. In this retrospective analysis of 402 patients, 14.2% had an SSI and 10.5% had a recurrence after a median follow-up of 30 months [27]. However, comparison between studies is difficult, since many researched factors differ such as type of mesh, operative technique, study

design (prospective or retrospective), and follow-up time. Nonetheless, 11% recurrence in this prospective study seems overall a good result.

This good result is highlighted further when taken from patient perspective. Resorbable materials seem preferential over permanent meshes that remain in the body, reducing fear and anxiety, possibly reducing chronic pain development and sinus formation due to the occasionally described shrinkage of permanent synthetic mesh products [28], and preventing the risk of developing the (rare) complication of enterocutaneous fistula [29-31]. Additionally, due to being resorbed, biosynthetic meshes might possibly be more suitable in contaminated wound sites or high-risk patients. Despite studies tentatively suggesting this too [32], further research is required to provide a conclusive answer to this hypothesis.

The QoL scores over time showed no significant difference from baseline. These findings could have been positively biased over time, as censored patients are more likely to have worse scores. Although hernia repair can increase QoL on the long term [33,34], QoL is affected short-term postoperatively; the majority of SSOs occurred within one month after surgery (91.2%) and more patients report physical problems at one month of follow-up (Table 3). This implicates that hernia repair surgery should be carefully considered in this high-risk patient group, also as nearly a quarter of patients had to spend some nights on the ICU after surgery.

The reoperation rate of 15.5% is relatively high. However, as shown through the presence of many comorbidities and the rate of patients admitted postoperatively to the ICU, this is most likely a high-risk patient group. Previous malignant disease, previous hernia repair, and bowel resection are risk factors for postoperative complications [35], and are ample present in this patient population. As VHWG grade 3 hernias with a potentially contaminated surgical field were treated, three reoperations related to mesh infection are not unexpected.

A remarkable finding is the presence of mesh sensation during ADL in 20.2% and 10.7% of patients after 12 and 24 months, respectively. At these time points, the P4HB biosynthetic mesh is expected to have been fully resorbed. Several explanations for these findings can be considered: either patients filled out the CCS questionnaire incorrectly; or patients had a strong belief they still felt mesh without it actually being there; or incomplete resorption or inadequate remodeling has taken place, in which scar tissue and adhesions cause a sensation of something "being there". Unfortunately, the true cause of these findings cannot be unveiled.

Limitations

Our study has some limitations. Multiple centers in multiple countries across Europe participated in the study, with inter-surgeon difference in hernia repair as a result. However, all centers are experienced hernia centers with abdominal wall specialists performing the surgery.

The use of questionnaires is also associated with limitations. Despite widespread popularity of the used (translated) questionnaires, these have not been validated in all languages. Especially in translated instruments, the question or intention of the instrument can be unclear for patients, resulting in erroneous completion of the questionnaire. Moreover, this is an international study, in which culture can have influenced patients' reporting; this can possibly minimize comparability between answers, and it stresses the subjectivity of questionnaires.

Implications and conclusion

Overall, P4HB biosynthetic mesh seems to be safe and effective in hernia repair up to 2 years after surgery, and results in a favorable recurrence rate. However, further research is desirable into the performance of the biosynthetic mesh over an even longer period of time. Present study focused on the clinical applicability and outcomes of P4HB mesh, but further research with radiological measurements is warranted to answer remaining questions on long-term recurrence and abdominal wall remodeling.

Although not assessed in present study, cost-benefit analyses should also be conducted. P4HB mesh is often 2.5x more expensive than traditional permanent synthetic mesh, but one study indicates that its use might reduce healthcare costs with approximately 770 euros per incisional hernia repair [36]. However, more research on (long-term) clinical outcomes, reoperations, and work incapacity should be conducted to assess cost-utility.

In conclusion, P4HB biosynthetic mesh is safe for incisional hernia repair with regard to SSOs and infection rate, and results in a recurrence rate of 11.0% after 2 years in potentially contaminated hernia sites. Longer follow-up data on abdominal wall remodeling and recurrences are needed to draw definite conclusions on the use of P4HB mesh.

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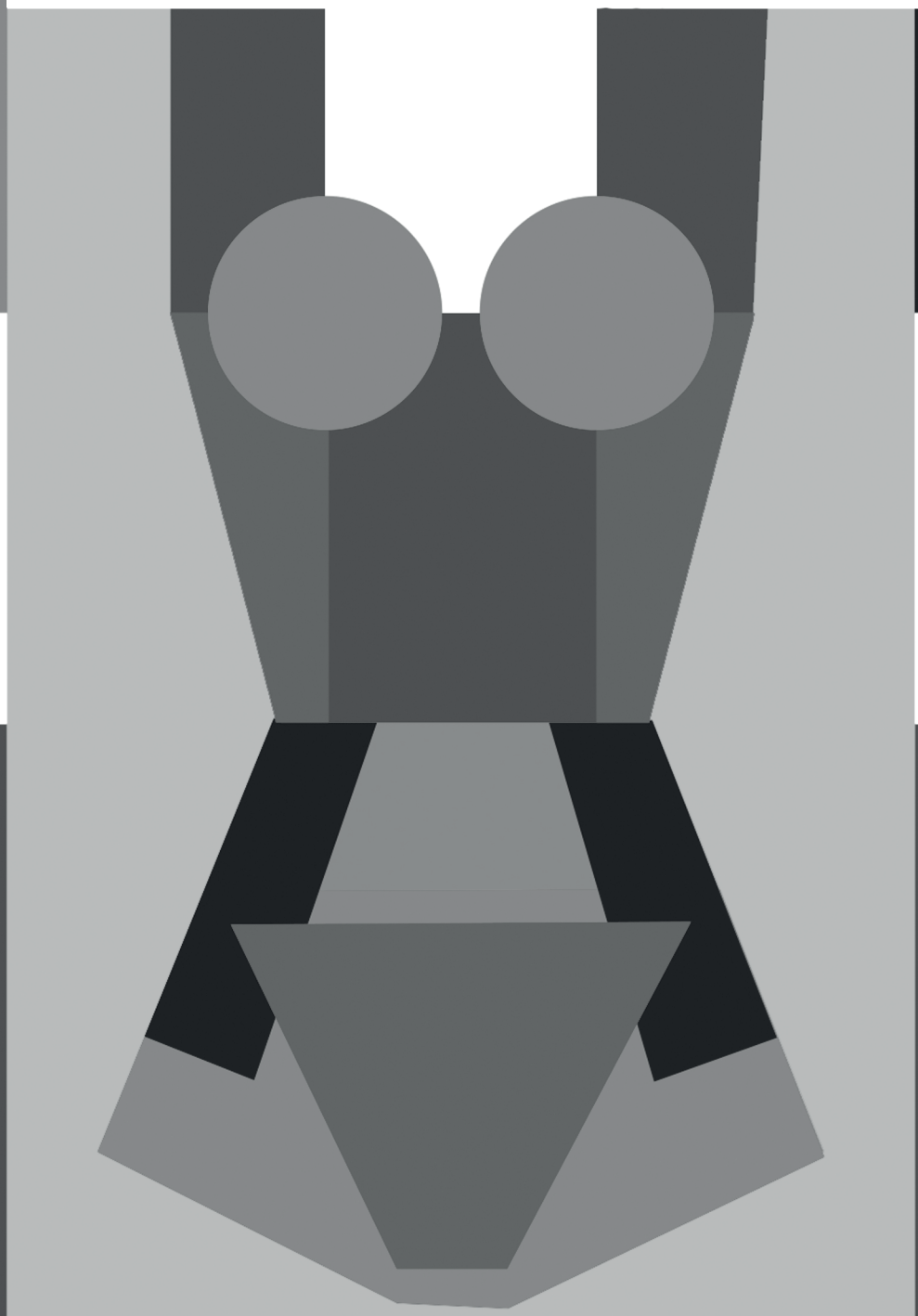
PART VI: Future perspectives on incisional hernia treatment, prevention and research



9 Preventing incisional hernia – closing the midline laparotomy

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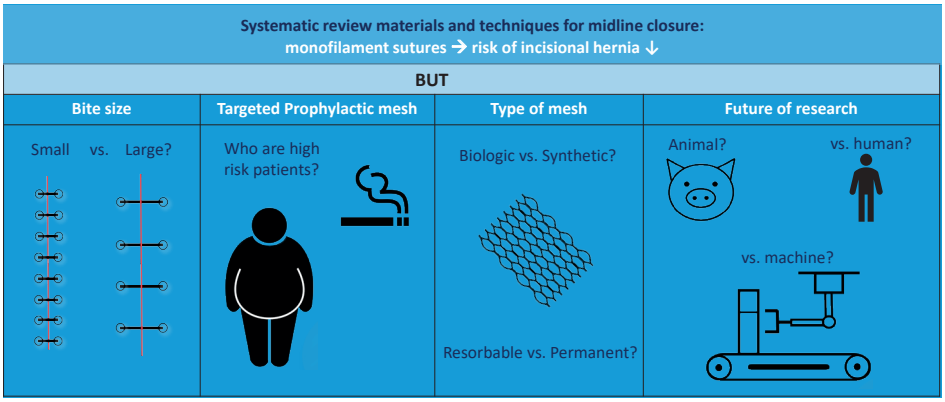

Understanding how to prevent incisional hernia after midline laparotomy is paramount for surgeons, gynaecologists, and urologists. When closure after midline laparotomy fails, several complications can occur. Most importantly, the patient will develop an incisional hernia, accompanied by a reduction in quality of life and potential reoperation with additional costs. To prevent patients from experiencing complications, available materials and techniques should be elaborately considered and evaluated, as was done in the Cochrane review by Patel et al. [1].

A number of important factors, however, are not reported in the included studies of this current review. Firstly, the primary outcome of incisional hernia was only measured at 1 year. As shown by a number of authors, nearly half of incisional hernias occur later than in the first year after surgery [2-4]. Therefore, the review provides insufficient evidence on the long-term effects of the researched materials and techniques. Secondly, the studies included in the review had considerable heterogeneity. In the primary analysis, all information is taken together: no distinction was made between emergency and elective procedures, and although a subgroup analysis was done for midline incisions, this was not done for paramedian or other incisions. The follow-up was done either clinically, by ultrasound, or both, while small incisional hernias can easily be missed clinically. Additionally, the review shows no adjustment for patient risk factors, such as age, BMI, or COPD. This heterogeneity leads to diluted effects, making it difficult to draw definite conclusions about single patient groups.

Lastly and most importantly, the review is titled "closure methods", but it overlooks some important factors of closing the midline, definitely influencing the development of incisional hernia.

First of all, regarding suturing techniques, in large randomized trials of more than 500 patients, several authors have shown that small bite size sutures – as fist published by Israelsson [5] – can reduce the development of incisional hernias [6,7]. Small bites have shown a higher bursting pressure than large bites: if the tension on the wound is distributed over a large number of stitches, the tension on each stitch will be low [8].

Secondly, the use of mesh reinforcement has not been addressed in this review. In high-risk patients, for example obese patients or patients with an abdominal aneurysm of the aorta (AAA), there is ample clinical evidence now that prophylactic mesh augmentation after midline laparotomy can decrease incisional hernia development, regardless of whether it is placed sublay or onlay [9]. Both patient groups suffer from compromised collagen synthesis; patients with AAA are at risk for incisional hernia due to a possible underlying connective tissue disorder, and obesity is associated with wound healing

complications due to a decreased vascularization of the adipose tissue and an increase of proinflammatory tissue factors. However, two questions still remain on the use of mesh reinforcement. One is whether prophylactic mesh augmentation should become standard practice in all patients, and the second one is what kind of mesh material to use. Regarding the first question, the risk of complications with mesh (e.g. seroma, infection) should be weighed against the benefit of preventing incisional hernia in every single patient. Regarding what kind of material should be used, mostly the choice is between (slowly) resorbable or permanent mesh. Resorbable mesh, which can be biologic or synthetic, has faced challenges in the resorption rate. A too rapid resorption does not support sufficient healing and might insufficiently prevent the development of incisional hernia. Non-resorbable synthetic mesh, however, is more prone to infection. The latest development is represented by the slowly-absorbable synthetic mesh, hypothesized to "remodel" the abdominal wall. However, as for now, too little is known on this type of mesh, and more research is necessary into the effectiveness and safety of this material.

Since infection is a risk factor for incisional hernia, the prevention of infection in midline wounds is important, especially in high-risk patients. The prophylactic use of negative pressure wound therapy might play an important role, yet too little has been researched on the effectiveness of this method as a preventative measure.

All these abovementioned factors can influence the development of incisional hernia. Research into these topics should be continued; however, investigating new techniques and materials is difficult. Clinical studies are expensive and per se unsuitable for investigating new methods, whereas preclinical experiments with animals render limited evidence, since the abdominal wall anatomy is considerably different from humans. A relatively newly developed artificial abdominal wall simulator is the AbdoMAN, representing a physical model that mimics the internal and external forces on the abdominal wall quite realistically. On this model, several suturing techniques and materials can be tested. This can offer advantages for midline repair research, as no patients or animals are needed in the exploration of the biomechanics of new theories, techniques, and materials [10].

So what can be said about augmentation materials and suturing techniques in midline laparotomies? As the Dutch surgeon Hans Jeekel already stipulated: "Closure time is no coffee time." Closing a laparotomy should be taken as seriously as all prior operative steps, and it should be performed by a dedicated surgeon, who incises only the linea alba, in order to avoid muscle tissue from becoming necrotic by sutures. From the evidence presented in the review [1], patients could profit from the use of monofilament sutures. However, patients could perhaps benefit even more from the small bite size

technique and from prophylactic mesh augmentation. Depending on the patient risk factors and the contamination of the wound, the most suitable mesh material needs to be considered. The current march of slowly-resorbable synthetic mesh research will show whether this material lives up to its promises. The role of prophylactic negative pressure wound therapy seems promising but remains unclear until now. Although the serious complication of incisional hernia can never be fully prevented due to factors such as surgeon experience and patient risk factors, more research into old and newly developed materials and techniques still remains necessary.

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10 General discussion and future perspectives

Over the past decade, hospitals have put more and more focus on value based healthcare. This is pursued by delivering care aimed to improve the outcomes that matter for patients suffering from a specific disease, taking into account the costs of achieving those outcomes [1]. In hernia care, these outcomes entail not only recurrences, complications, and postoperative outcomes, but also patient reported outcome measures. In order to create value for hernia patients, surgeons should employ a tailored approach by considering individual risk factors, the complexity of the hernia, and the available surgical techniques.

For targeting individual aspects of patients and/or hernias, preoperative risk factors should be further researched. Sarcopenia has been assessed as a risk factor in this thesis, but minimal predictive value for the development of incisional hernia and postoperative complications was found. In addition, sarcopenia is labor-intensive to determine. Other more commonly acknowledged risk factors such as high Body Mass Index (BMI) [2-4] or smoking [3,5] would be easier to target in clinical practice for preoperative patient optimalisation. However, the low predictive values found in Chapter 2 of this thesis suggest that more – still unknown – risk factors exist for the development of an incisional hernia, which could possibly be targeted prior to hernia repair.

Other techniques that can be applied for further patient optimalisation prior to the repair of complex incisional hernias are the use of preoperative Botulinum Toxin A (BT) injections or a progressive pneumoperitoneum (PP). Both techniques can facilitate fascial closure – which reduces the risk of developing a hernia recurrence [6,7] – and are not associated with significant postoperative morbidity. BT qualifies for low-threshold use, whereas PP should be more carefully considered by the surgeon before employment because of the more frequent and sometimes severe complications during its use. Further indications for both methods should be explored and their comparative value assessed to other surgical (perioperative) techniques such as component separation techniques and mesh placement techniques at different locations. Optimal selection of surgical techniques should take place, in which only what is needed is used, as more manipulations increase the risk of complications and drive up the costs of care delivery.

A true tailored approach also comprises the choice of whether to perform surgery at all. Depending on the complexity of patient factors and hernia factors, a choice for or against surgery should be made. The surgeon – in partnership with the patient – should not only consider the direct outcomes of the surgery, but also what can be gained for the patient, *i.e.* quality of life. Hernia repair can increase quality of life [8]. In this thesis, outcomes after a proactive approach of elective umbilical hernia repair were compared to a conservative "wait-and-see" approach in patients with liver cirrhosis and ascites. Such

a conservative approach increases the chance of needing emergency surgery, with its subsequent higher risk of complications and higher costs of care. In both groups, equal 24-month morbidity was found, with patients that were electively treated showing a trend towards a higher quality of life. These results suggest that umbilical hernia repair should not be delayed until liver transplantation, but can be performed earlier when patients are experiencing complaints from their hernia. This shows that to create value – health outcomes that matter to the patient, relative to monetized inputs – choices regarding surgery should be made for individual patients based on their experienced symptoms.

If surgery is indeed decided upon, preoperative abovementioned techniques such as BT and PP can be used to prepare the patient, as well as trajectories for weight loss, muscle building, and smoking cessation. However, also perioperative decisions need to be made.

Ample research has shown that the use of mesh can largely prevent incisional hernia occurrence [9,10]. However, many different materials are available, in many different price ranges. The ideal choice for a mesh product should be for one that is strong and retains its strength for a sufficient amount of time, can withstand the conditions that the body creates in its foreign body reaction to the mesh, but dissolves as soon as its function becomes superfluous. For now, no consensus exists on the "golden material", yet a movement initiated by medical device companies towards the creation of biosynthetic meshes can be observed. These biosynthetic products come with a considerable price tag, but are hypothesized to possess all above advantages, therefore resulting in satisfying patient outcomes. In this thesis, both the research protocol for a study into such a biosynthetic mesh and its outcomes are described, showing that hernia repair with a biosynthetic mesh renders equal results to permanent synthetic mesh, with a manageable complication rate and a relatively low recurrence rate. Quality of life does not increase significantly from baseline with the use of biosynthetic mesh, but comparison to other types of mesh is lacking. The main advantage is that the biosynthetic mesh is absorbed by the body over time, therefore reducing the risk of developing chronic pain, foreign body sensation, and fistula formation. Longer follow-up with medical imaging of these patients treated with biosynthetic mesh should take place. A study for four further years of follow-up is being set up. This would generate valuable information on long-term patient satisfaction, functionality, displacement of the mesh, remodeling of the abdominal wall, and – with these outcomes – therefore also on cost-effectiveness.

In the paragraphs above, matters that could be beneficial for the treatment of (incisional) hernia patients have been addressed, such as preoperative treatment of patient

risk factors and choosing adequate mesh materials. However, many challenges remain in surgical research. One of these challenges is the further exploration of suture techniques for midline closure. It has been shown that the suture-length-to-wound-length ratio should at least be 4:1 [11,12], but further research might shed light onto fitting bite sizes that lead to optimal force distribution– possibly even varying bite sizes depending on the stitch's relative position to the wound edge. Also more research is needed into the use of prophylactic mesh. Prophylactic mesh placement after midline laparotomy in patients with obesity or an aneurysm of the abdominal aorta can prevent incisional hernia occurrence [13]. However, the complications that can occur due to mesh placement (e.g. seroma, infection) should be weighed against the benefit of preventing incisional hernia in every single patient individually.

Investigating such new techniques and materials is difficult. On the one hand, clinical studies are expensive and not always suitable for investigating new methods, but on the other hand, animal experiments or preclinical fundamental research render limited evidence, for the setting and conditions are different to the human body. Nonetheless, basic understanding of the physics of the abdomen and its underlying biomechanical mechanisms is of great importance to innovative surgeons developing new methods.

All these topics of research contribute to care optimization for hernia patients, and therefore leading to progress in developing a tailored approach, ultimately resulting in outcomes that matter for the patient; *id est* value creation.

Future perspectives

With the current ageing population, focusing on value based healthcare is of paramount importance. In the near future, less doctors will be available for the increasing number of patients that live longer and have multiple comorbidities. The focus should first be on a high quality of life for this ageing group, despite the comorbidities, but also on keeping the healthcare expenditure in check. To pursue this twofold goal, collaboration in the broadest sense of the concept is needed.

The first step in multidisciplinary collaboration is with the epidemiology department. To obtain more information on patient risk factors and incisional hernia risk factors, further research through the use of prediction models can be conducted. This will provide information that can be used to determine which factors can be targeted in individual patients. Collaboration with epidemiologist to create further prediction models would therefore prove itself useful and valuable. These models can be created from large databases on hernia surgeries, and such studies would therefore be non-invasive for patients. Moreover, database-studies will deliver vast amounts of information on predictors, con-

founders and associated factors in the development of incisional hernia. In the future, surgeons will also require help from epidemiologists to apply artificial intelligence on their records, to further personalize hernia care and achieve optimal outcomes.

Other fields that qualify for collaboration with the field of abdominal wall hernia surgery are physics and chemistry. Physics has shown to be useful with the progressive pneumoperitoneum (PP), but possibly other concepts and theories can be applied too to benefit surgery. A product of progress in the field of chemistry is the use of Botulinum Toxin A (BT) in the abdominal muscles – also sometimes described as "chemical component separation". Possibly a specific category of patients with smaller hernias might be treated without mesh, using only BT preoperatively. Other insights from physics and chemistry could also be useful in the practice of medicine. Therefore, close collaboration with students from technical universities, to develop new multidisciplinary tools and methods, could reduce the experienced burden of patients with abdominal wall or incisional hernias.

Collaboration with mechanical engineering and industrial design departments of technical universities would also support further research and development in the growing field of health technology. Especially in developing innovative products and improving mesh properties, surgeons could learn from technical experts who approach similar problems from different angles. However, not only the development of new medical devices, but also evaluation of their clinical effectiveness requires further research. Questions that need answering are, for example, on a biomechanical level, whether mesh properties can influence the ratio of collagen I to collagen III formation in scar tissue, and whether desirable remodeling of the abdominal wall takes place. On a clinical level, answers can be found to questions of whether mesh type can influence the development of chronic pain and reduce the chance of mesh deformation, such as creep and bulging. More insight in hernia treatment options can be gained from investing surgical interest and research – in collaboration with engineers – in health technology.

In addition, surgeons, but also hospitals in general, could resort to the expertise of communication and marketing specialists, and even medical influencers. Social media platforms can be more effectively used for the dissemination of research outcomes, and for the creation of further multidisciplinary cooperation. As results from studies are accessed easier worldwide, more opportunities for international collaboration occur. Additionally, social media platforms should also be used to inform patients: results from research can be communicated in simple language and the implications of those results for individual patients or patient groups can be further elaborated. More specifically, hernia surgeons can relate their results to specific incisional hernia types or patient

groups, to further streamline the decision process in hernia care delivery. Moreover, using new digital platforms and developing shiny apps can also help involve younger generations of medicine students and doctors who can tackle problems with a fresh pair of eyes.

All these considerations could be better addressed, if more dedicated specialized surgical teams were created and deployed in the care of abdominal wall hernias (including incisional hernias). Currently, hernia care is still considered a secondary focus of the surgeon's practice, yet gradually "herniology" is proving its relevance.

Lastly, incisional hernia research should put much more emphasis on the analysis of cost-effectiveness. Value in healthcare is defined as patient outcomes divided by the costs to achieve those outcomes [1]. Physicians lack a general sense of how much treatments cost [14,15], and new products tend to have a price tag as equally big as their hypothesized advantages. Hernia surgeons should be aware that one cannot create a protocol for "*the* hernia patient", as there is no standard hernia patient, neither is there a surgical "one size fits all" approach. New meshes for (incisional) hernia surgery might be superior to older ones in certain aspects in high risk patients, but the additional costs of these new meshes might be disproportional in patient groups of lower risk. Costs usually form the drive for hospital policies, and if costs are not analyzed by researchers, new products or techniques will never become employed or implemented in clinical practice. Cost-effective decisions should be made per individual patient, in which the focus is also on value, not on outcomes alone.

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11 Summary
Nederlandse samenvatting

SUMMARY

In this thesis, focus has been on the preparation and treatment of abdominal wall hernias in different high-risk patient groups.

Chapter 1 provides a general introduction to the topic.

In ***PART I***, risk factors for incisional hernias have been addressed.

In **Chapter 2**, sarcopenia, *id est* the progressive loss of muscle mass, is explored as a possible risk factor for the development of an incisional hernia. In total, CT scans of 283 patients were assessed for muscle mass and the skeletal muscle index (SMI), which was calculated by dividing the surface of muscle on the level of the third lumbar vertebra by the patient's height (squared). Subsequently, three logistic regression models were created using the SMI as a continuous measure (model 1), using a cut-off from literature for the SMI to define sarcopenia (model 2), and using the lowest gender-specific quartile as a definition for sarcopenia (model 3). None of the models showed a significant value for sarcopenia in the prediction of the development of incisional hernia. Despite other commonly known risk factors that were included in the model, the Area Under the Curve from the models was below 0.7, suggesting that further research should be done into hernia risk factors.

In ***PART II***, preoperative preparation and choice of treatment in high-risk hernia patients has been described.

Chapter 3 describes a cohort of 23 patients with a giant ventral hernia, that have been prepared preoperatively with either Botulinum Toxin A (BT) injections, a progressive pneumoperitoneum (PP), or both. Primary fascial closure was possible in 82% of all patients. After a median follow-up of 19.5 months (range: 10-60 months), 16 patients (73%) developed 23 surgical site occurrences. Despite these manageable outcomes, the use of PP resulted in complications in 5 patients, of whom one died. Therefore, PP requires critical consideration before its employment in patients.

A systematic review, including a meta-analysis, of the preoperative BT and PP techniques is presented in **Chapter 4**. Twenty studies, out of 905 hits from the search, were included. With regard to the perioperative efficacy of both methods, a pooled fascial closure rate of 94% was calculated. Indications for the use of PP or BT varied widely, and PP resulted in frequent and sometimes severe complications. Therefore, BT qualifies for

low-threshold use whereas PP should be employed cautiously, yet further (comparative) research is needed to permit possible recommendations for the future use of both aides.

In **Chapter 5**, elective umbilical hernia repair in patients with liver cirrhosis and ascites is compared to a "wait-and-see" policy. During this wait-and-see, patients are at higher risk of needing emergency surgery if the hernia were to incarcerate. In this study, 16 patients were randomly assigned to elective repair, and 18 to conservative treatment. Of those 18 patients in the latter group, 3 needed surgery due to incarceration or complaints. After a median follow-up of 19.5 months, equal morbidity related to the hernia or its repair were found, with 8 patients in the elective repair group (50%) and 14 patients in the conservative treatment group (77.8%) experiencing complications. Also quality of life scores showed no significant differences. Therefore, hernia surgeons should consider the elective repair of an umbilical hernia in patients with liver cirrhosis and ascites when they are experiencing complaints.

PART III consists of chapters describing the use of a new type of mesh in the treatment of incisional hernia.

In **Chapter 6**, a study protocol for the use of a new biosynthetic mesh in potentially contaminated incisional hernias is outlined. In general, a strong preference for resorbable products exists under such circumstances, yet the mesh should retain its strength for a sufficient period of time to support local cellular ingrowth and wound remodeling – meaning it should not degrade too quickly. Phasix Mesh is hypothesized to have all these abovementioned advantages as a biosynthetic mesh, and will be the subject of this international, multicenter trial. The primary outcomes of interest are safety and performance, measured through the 3-month surgical site occurrence rate that requires intervention, and recurrences and quality of life outcomes after 24 months of follow-up.

Chapter 7 covers the short-term outcomes after the use of above described biosynthetic mesh. In total, 84 patients with a Ventral Hernia Working Group grade 3 (potentially contaminated) hernia were treated with the Phasix Mesh in a sublay position. Twenty-two of these patients (26.2%) developed 32 surgical site occurrences within 3 months. These included 11 surgical site infections, 9 wound dehiscences, 7 seromas, 2 hematomas, 2 skin necroses, and 1 fistula. At three months, there were no hernia recurrences. These are acceptable short-term postoperative results, yet further follow-up is needed to evaluate recurrences and quality of life outcomes.

This further follow-up is subsequently described in **Chapter 8**. As the mesh should have been resorbed after 12 to 18 months, recurrences and quality of life are of specific

interest. Eight patients (11.0%) developed a hernia recurrence after 24 months. In 13 patients (15.5%), 14 reoperations took place in which the mesh was explanted 7 times. Quality of life outcomes showed no significant increase or decrease after 24 months after surgery, yet 10.7% of patients reported a presence of mesh sensation in daily life. The surgical site occurrences increased to a total of 34. These are manageable complication and recurrence rates, yet even further follow-up is needed to determine whether remodeling takes place and to make definitive recommendations regarding the use of biosynthetic mesh.

PART IV covers future perspectives on treatment, prevention, and research.

In **Chapter 9**, a short comment is made on a previously published systematic review on midline closure techniques and materials. Additional factors to consider during midline closure, such as bite size and the use of prophylactic mesh, are suggested, and some topics for the future of abdominal wall research are highlighted.

Chapter 10 recapitulates all above chapters and provides a general discussion on the covered topics around incisional hernia. In addition, it features some future perspectives for incisional hernia care and research.

NEDERLANDSE SAMENVATTING

In dit proefschrift ligt de nadruk op de voorbereiding en behandeling van buikwandhernia's in verschillende hoog-risicogroepen.

In **Hoofdstuk 1** wordt een algemene introductie over het onderwerp gegeven.

In ***DEEL 1*** worden risicofactoren voor littekenbreuken geadresseerd.

In **Hoofdstuk 2** is sarcopenie – progressief spiermassaverlies – onderzocht als een mogelijke risicofactor voor het ontwikkelen van een littekenbreuk. In totaal werden op CT-scans van 283 patiënten de spiermassa en de skeletspier-index (SMI) bepaald. De SMI werd uitgerekend door het spieroppervlak op het niveau van de derde lumbale wervel te delen door de lengte van de patiënt (in het kwadraat). Vervolgens werden drie logistische regressiemodellen gemaakt, waarbij de SMI als continue waarde werd gebruikt (model 1), waarbij een afkapwaarde uit de literatuur werd gebruikt voor de SMI om sarcopenie te bepalen (model 2), en waarbij het laagste geslacht-specifieke kwartiel werd gebruikt als definitie voor sarcopenie (model 3). Geen van de drie modellen toonde een significante waarde voor sarcopenie in het voorspellen van een littekenbreuk. Ondanks dat andere bekende risicofactoren voor het ontwikkelen van een littekenbreuk in de modellen waren geïncludeerd, was de oppervlakte onder de grafiek minder dan 0.7; dit suggereert dat verder onderzoek gedaan moet worden naar risicofactoren voor deze hernia's.

In ***DEEL II*** zijn de voorbereiding voor de operatie en de keuze voor behandeling bij hoog-risico herniapatiënten beschreven.

In **Hoofdstuk 3** wordt een cohort van 23 patiënten beschreven met een extreme buikwandhernia, die voor de operatie behandeld is met ofwel Botuline Toxine A (BT) injecties, ofwel een progressief pneumoperitoneum (PP), ofwel beide. Primaire buikwandsluiting was mogelijk in 82% van de patiënten. Na een mediane evaluatie van 19,5 maanden (bereik: 10-60 maanden), ontwikkelden 16 patiënten (73%) na de operatie 23 complicaties. Ondanks het feit dat deze complicaties in het algemeen behandelbaar waren, kregen 5 patiënten complicaties gedurende het gebruik van PP, van wie 1 patiënt is overleden. Om deze reden moet PP kritisch overwogen worden alvorens het in patiënten toe te passen.

Een systematische beoordeling en meta-analyse van de literatuur over preoperatieve BT- en PP-technieken worden in **Hoofdstuk 4** gepresenteerd. Twintig studies van de

905 die naar voren kwamen uit de zoektermen, werden geïncludeerd. Het effect tijdens de operatie van beide preoperatieve methoden werd berekend in het integrale buikwandsluitingscijfer van 94%. Indicaties voor het gebruik van PP en BT verschilden aanzienlijk, en PP resulteerde in frequente en af en ook ernstige complicaties. Om deze reden kwalificeert BT zich voor laagdrempelig gebruik, terwijl bij het gebruik van PP terughoudendheid geadviseerd wordt. Echter, meer vergelijkend onderzoek is nodig om aanbevelingen over het toekomstig gebruik van beide methoden te kunnen maken.

In **Hoofdstuk 5** wordt electief navelbreukherstel vergeleken met een afwachtend beleid bij patiënten met levercirrose en ascites. Tijdens een afwachtend beleid liepen patiënten een hoger risico op een spoedoperatie als de hernia beklemd zou raken. In de studie werden 16 patiënten gerandomiseerd in de operatieve behandelgroep, en 18 in de conservatieve behandelgroep. Van de 18 patiënten in deze laatste groep hadden er drie vanwege beklemming of ernstige klachten een operatie nodig. Na een mediane evaluatie van 19,5 maanden werd een gelijke morbiditeit, gerelateerd aan de hernia en/of de herniaoperatie, gezien. Hierbij kregen 8 patiënten in de operatieve behandelgroep (50%) complicaties, tegenover 18 patiënten (77,8%) in de conservatieve behandelgroep. Daarbij toonden kwaliteit-van-levenscores geen significante verschillen. Het wordt daarom aanbevolen dat herniachirurgen electief herstel van een navelbreuk overwegen in patiënten met levercirrose en ascites, als die klachten ondervinden van hun hernia.

DEEL III bestaat uit hoofdstukken die het gebruik van een nieuwe soort mat beschrijven bij de behandeling van littekenbreuken.

In **Hoofdstuk 6** wordt een onderzoeksprotocol geschetst voor het gebruik van een nieuwe biosynthetische mat in potentieel verontreinigde littekenbreuken. Over het algemeen bestaat er onder dergelijke omstandigheden een sterke voorkeur voor oplosbare producten, maar daarbij moet de mat wel lang genoeg zijn sterkte behouden om lokale ingroei van cellen en wondherstel mogelijk te maken – de mat mag dus niet té snel oplossen. Van de Phasix mat wordt verondersteld dat deze alle bovengenoemde voordelen heeft, het zijnde een biosynthetische mat, en wordt daarom onderzocht in deze internationale studie in meerdere centra. De primaire uitkomstmaten zijn veiligheid en prestatie, welke gemeten worden aan de hand van de wondcomplicaties na 3 maanden, waarvoor interventie nodig is. Ook recidieven en kwaliteit-van-leven uitkomsten na 24 maanden worden onderzocht.

In **Hoofdstuk 7** zijn de korte termijn resultaten na het gebruik van bovenbeschreven biosynthetische mat behandeld. In totaal zijn 84 patiënten met een Ventrale Hernia Werkgroep (VHWG) graad 3 hernia (mogelijk verontreinigd) geopereerd met de Phasix

mat onder de rectusspier. Tweeëntwintig van deze patiënten (26,2%) ontwikkelden 32 wondcomplicaties, waaronder 11 wondinfecties, 9 dehiscenties, 7 vochtcollecties, 2 bloedingen, 2 huidnecrose en 1 fistel. Drie maanden na de operatie waren er geen recidieven van de hernia's. Dit zijn acceptabele korte termijn resultaten, maar verdere evaluatie is nodig om ook de recidieven en de kwaliteit van leven te onderzoeken.

Deze evaluatie op lange termijn is in **Hoofdstuk 8** beschreven. Omdat de mat na 12 tot 18 maanden opgelost zou moeten zijn, zijn in het bijzonder de recidieven en de kwaliteit van leven interessant. Na 24 maanden ontwikkelden acht patiënten (11,0%) een recidief van hun littekenbreuk. Bij 13 patiënten (15,5%) vonden 14 heroperaties plaats, waarbij bij 7 patiënten de mat verwijderd moest worden. Kwaliteit-van-leven uitkomsten toonden geen significante stijging of daling 24 maanden na de operatie, maar wel rapporteerde 10,7% van de patiënten de mat in het dagelijks leven te voelen. Het aantal wondcomplicaties steeg tot een totaal van 34. Bovengenoemde zijn beheersbare complicatie- en recidiefcijfers, maar nog verder vervolg van deze patiënten is nodig om te bepalen of remodellering plaatsvindt en om definitieve aanbevelingen met betrekking tot het gebruik van een biosynthetische mat te doen.

DEEL IV beslaat toekomstige perspectieven op behandeling, preventie en onderzoek.

In **Hoofdstuk 9** wordt een eerder gepubliceerde systematische beoordeling van de literatuur over het sluiten van de middellijn van de buikwand becommentarieerd. Bijkomende factoren om tijdens buikwandsluiting te overwegen worden geopperd, zoals de afmetingen van de hechtingen en het gebruik van een mat als profylaxe. Verder wordt een aantal onderwerpen voor de toekomst van buikwandonderzoek belicht.

In **Hoofdstuk 10** worden alle bovenstaande hoofstukken gerecapituleerd en een algemene discussie over de behandelde onderwerpen rondom littekenbreuken wordt gegeven. Bovendien worden in het hoofdstuk toekomstige perspectieven voor zorg en onderzoek van littekenbreuken aangegeven.

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RESEARCH PORTFOLIO

Courses		
Course name	**Year**	**ECTS**
Scientific Integrity	2020	0.3
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2018	1.5
Scientific Writing	2017	2.0
Introduction to Bayesian Methods in Clinical Research (ESP68)	2017	1.4
Missing Values in Clinical Research (EP16)	2017	1.7
Courses for the Quantitative Researcher (SC17)	2017	1.4
Repeated Measurements (CE08)	2017	1.7
Advanced Topics in Decision Making in Medicine (EWP02)	2017	2.4
Systematic Literature Retrieval	2017	0.5
Workshop Endnote	2017	0.2
Biostatistical Methods II: Clinical Regression Models (EP03)	2016	4.3
Biostatistical Methods I: Basic Principles (CC02)	2016	5.7
Study Design (CC01)	2016	4.3
The Practice of Epidemiologic Analysis	2016	0.7

Conferences, masterclasses & research meetings		
Oral presentations	**Year**	**ECTS**
Chirurgendagen NVvH 2019	2019	1.0
54th International Meeting of the European Society for Surgical Research (ESSR) 2019	2019	1.0
Science Day from the Erasmus MC Department of Surgery 2019	2019	1.0
Chirurgendagen NVvH 2018	2018	1.0
52nd International Meeting of the European Society for Surgical Research (ESSR) 2017	2017	1.0
Investigator meetings	**Year**	**ECTS**
International Hernia Symposium (IHS) London 2018	2018	0.3
Masterclasses	**Year**	**ECTS**
Phasix Masterclass Brussels	2017	0.1

Total		**33.5**

CURRICULUM VITAE

Machteld van Rooijen was born on February 11th, 1995 in Woerden. After finishing secondary school in 2013 (Grammar school with Latin) at the Minkema College, she started studying Medicine at the Erasmus University Rotterdam.

During her first year, she became a member of the faculty Honours Class, and in her second year she took part in the university-wide interdisciplinary Honours Programme "Crossing Borders" (Over Grenzen). In addition, she was a member of the student rowing association "Skadi" during her studies, where she was a coxswain of a Women's 8+. She also participated in several extracurricular activities in the department of Anatomy (Erasmus Anatomy Research Project, EARP) and department of Anaesthesiology (Advanced Student Anaesthesiology Project, ASAP), and did an internship Global Health in Indonesia.

Before commencing the Master-phase of the study Medicine, she started the master Clinical Research at the Netherlands Institute of Health Sciences (NIHES), and she obtained a master's degree in Health Care Management. Subsequently, during her clinical rotations, she extended her research activities– under supervision of prof. Lange, prof. Jeekel, and prof. Kleinrensink from the REPAIR group – into a PhD trajectory.

Part of her clinical rotations she performed in Germany, and she arranged a clinical rotation at the Board of Directors of the Erasmus MC. She finished her studies in Medicine in January 2021, after her senior clinical rotation at the Ministry of Health, Welfare and Sport.

PREPARE AND REPAIR