

Clinical outcomes after elective repair for small umbilical and epigastric hernias

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The PhD thesis includes the following articles

I. Christoffersen MW, Olsen BH, Rosenberg J, Bisgaard T. Randomized Clinical Trial on the postoperative use of an abdominal binder after laparoscopic umbilical and epigastric hernia repair. *Hernia* 2015;19:147-153.

II. Christoffersen MW, Westen M, Assadzadeh S, Deigaard SL, Rosenberg J, Bisgaard T. The clinical effects of closure of the hernia gap after laparoscopic ventral hernia repair: protocol for a randomised controlled trial. *Dan Med J* 2014 ;61:A4865.

III. Christoffersen MW, Helgstrand F, Rosenberg J, Kehlet H, Bisgaard T. Lower reoperation rate for recurrence after mesh versus sutured elective repair in small umbilical and epigastric hernias. A nationwide register study. *World J Surg* 2013;37:2548-52.

IV. Christoffersen MW, Helgstrand F, Rosenberg J, Kehlet H, Strandfelt P, Bisgaard T. Long-term recurrence and chronic pain after repair for small umbilical or epigastric hernias: a regional cohort study. *Am J Surg* 2015;209:725-732.

INTRODUCTION

Background

Elective repair for an umbilical or epigastric hernia is one of the most frequently conducted gastrointestinal surgical procedures with approximately 1,500 repairs annually in Denmark and more than 350,000 repairs annually in the United States (1,2). A recent epidemiological Danish study found a prevalence of umbilical hernia repair of 0,53% in males (age of 60-70 years) and of 0,09% for epigastric hernia repair in females (age of 40-50 years) (3).

The repair technique for an umbilical or epigastric hernia can be open (sutured repair or mesh repair) or laparoscopic depending on the surgeon's appraisal, expertise, and the size of the hernia defect. Even though evidence-based guidelines regarding laparoscopic ventral hernia repair techniques exist (4) the choice of repair technique is not always based on scientific evidence and by many referred to as a "tailored approach". Although, the operation is regarded as a minor surgical procedure there is little consensus, especially in small umbilical or epigastric hernias (≤ 2 cm), on the optimal repair technique. Moreover, several clinical challenges remain to improve outcomes after a repair for elective umbilical and epigastric hernia, some of which will be addressed in this thesis. First, the readmission rate is surprisingly high at the level of 10% (1) mainly due to postoperative pain (1,5,6) and wound-related complications (seroma, haematoma, surgical-site-infections) (1,5,7,8). Secondly, data on long-term recurrence and chronic pain are limited (9–16). Finally, the literature does not provide clear evidence of whether a laparoscopic or open technique should be applied in small hernias (17,18).

The literature

Laparoscopic repair for ventral hernias (including umbilical or epigastric hernias) has become increasingly popular due to its minimally invasive technique. The laparoscopic technique is potentially with less risk of surgical site infection, shortened convalescence, and comparable risk of recurrence compared with open repairs (17–20). There are, however still unsolved surgical questions regarding the laparoscopic ventral hernia technique (4). Unsolved questions include type of mesh and fixation device, how to handle the hernia sac, to close or not to close the hernia defect (21). Furthermore, methods to reduce seroma formation, bulging of the mesh, and optimization of early and late postoperative pain are needed (5,21–25). Several intraoperative and postoperative interventions have been proposed to improve these outcomes after ventral hernia repair. One of these is the use of an abdominal binder to decrease pain, seroma formation, abdominal discomfort, and recurrence (22,26–29). However, there is no procedure-specific evidence of the clinical effects (or possible side-effects) using an abdominal binder after ventral hernia repair (30).

Classically, laparoscopic ventral hernia repair has been performed in a tension-free manner with a mesh covering the un-closed hernia defect. Yet, closure of the hernia defect with substantial tension before mesh reinforcement has become more or less the routine procedure. This novel technique may (or may not) lower recurrence rates (31–34), provide better abdominal wall function, and postural support by re-approximating the abdominal muscles (26,35,36). The technique may also decrease seroma formation

(26,34), improve the cosmetic result, and overall patient-satisfaction (35,37). Up till now outcome data are primarily derived from observational, non-controlled studies (26,32,33,35,37-42), and one systematic review (34). Based on pooled data the authors reported less recurrences, less bulging of the meshes, and less seroma formations after closure of the hernia defect compared with a non-closure technique (34). In another prospective cohort-study the authors stated that closure of the hernia defect did not influence rate of seroma formation, postoperative pain, protrusion of the mesh, or recurrence (43).

An open sutured repair with or without mesh reinforcement is the standard procedure in patients with small (≤ 2 cm) umbilical or epigastric hernias (4). Data from 9 retrospective observational studies (44-52), two randomized controlled trials (RCTs) (9,48), and two meta-analyses (11,15) have demonstrated lower recurrence rates using mesh reinforcement in open repair for an umbilical or epigastric hernia. In a meta-analysis it was shown that recurrence rate increased from 2.7% ($n = 17$) after mesh repair to 8.2% ($n = 94$) after sutured repair ($P < 0.001$) (11). The size of the hernia defects and definition of recurrence (reoperation and/or clinical recurrence) were not clearly specified (15). Despite the above mentioned positive mesh results surgeons have remained reluctant to use mesh reinforcement in small umbilical or epigastric hernias, mainly due to fear of wound complications and chronic pain (53,54). A meta-analysis found comparable risk of wound complications in patients undergoing suture and mesh repairs without statistical differences (15). Unfortunately, the included studies were highly heterogenic with respect of reported complications seroma formation, haematoma, and surgical-site infection. These specific type of complications were pooled as "wound complications" in the meta-analysis (15). Another meta-analysis reported surgical site infection and seroma formation separately. Surgical site infection and seroma formation was predominant in the mesh group compared with the sutured group (7.3% ($n = 31$) vs. 6.6% ($n = 43$) ($P < 0.02$) and 7.7% ($n = 32$) vs 3.8% ($n = 21$) ($P < 0.004$), respectively) (11).

As in groin hernia surgery (55), chronic pain have attained increasing focus after ventral hernia repair (5) but have been sporadically investigated in mainly retrospective studies (12,14,16,50,52). Risk factors for chronic pain, impact on daily living, quality of life, and other patient reported outcomes are described but not systematically investigated. Few retrospective studies using different definitions of chronic pain found a 4-20% incidence of chronic pain after umbilical or epigastric hernia repair (12,14,52) with no important differences regarding different surgical techniques.

Aim

For the above mentioned reasons this PhD thesis aimed at analysing early and late clinical outcomes in patients undergoing repair for umbilical or epigastric hernias.

The primary objective was to reduce early postoperative pain and seroma formation after laparoscopic umbilical or epigastric hernia repair. Furthermore, the thesis aimed to establish long-term recurrence rate (reoperation for recurrence and clinical recurrence) in patients undergoing open repair for small umbilical or epigastric hernias with sutured or a mesh repair. The secondary objective was to describe the incidence of chronic pain in patients undergoing open repair for an umbilical or epigastric hernia with or without mesh reinforcement.

The following four H0-hypotheses was addressed

1. An abdominal binder provides no difference in postoperative pain, seroma formation, or quality of life after elective laparoscopic umbilical or epigastric hernia repair (Study I) (56).
2. A closure of the hernia defect provides no difference in postoperative pain, seroma formation, quality of life, or cosmesis after elective laparoscopic umbilical or epigastric hernia repair (Study II) (57).
3. Long-term risk of reoperation for recurrence is comparable after sutured vs. mesh repair in open, elective repair for small (≤ 2 cm) umbilical or epigastric hernias (Study III) (58).
4. Long-term risks of reoperation for recurrence, clinical recurrence, and chronic pain are comparable after sutured vs. mesh repair in open, elective repair for small (≤ 2 cm) umbilical or epigastric hernias (Study IV) (59).

Methodological considerations

General

Study design. Randomised controlled trials (RCTs) and meta-analyses based on RCTs provide the highest level of evidence for the effects of treatment (60-62). RCT results aim to describe the effect of an optimized, standardized intervention in selected patients (high internal validity) (63). However, for several reasons surgical research questions, including hernia surgery, cannot always be answered through RCTs. First, the external validity in RCTs are often low due to a highly selected group of included patients. Second, randomisation cannot rule out the heterogeneity of each individual surgical case (64). Especially patients with more complex ventral hernias (compared with patients with small umbilical or epigastric hernias) show high patient heterogeneity, and can often not be referred to as standard surgical patients. Last, the causation between intervention and outcome measures may often be multifactorial and is not sufficiently covered by simple assumptions (64). On the other hand well-organised clinical databases may provide large-scale long-term clinical data with a high follow-up rate (64) revealing small but important differences in outcomes after different surgical strategies. Register-based cohort studies tend to reflect the daily clinical practice (high external validity) but can be criticized due to risk of selection bias and possible confounding (63). The present thesis included one RCT and one protocol for a running RCT (Study I and II) and two register-based cohort studies (Study III and IV). The RCTs investigated clinical effects of well-defined interventions in controlled settings providing data from highly selected groups of patients. The cohort studies investigated long-term clinical outcomes in patients recruited from the Danish Ventral Hernia Database (DVHD), providing reliable clinical data reflecting the outcomes from the present surgical practice. The inherent risk of selection bias and confounding was sought reduced by performing multivariate analyses.

The DVHD is a nationwide register covering approximately 80% of all ventral hernia repairs in Denmark since 2007 (65) with high agreement between data in the database and hospital files (89-99%) (66). The DVHD provides specific intraoperative information about the hernia repair such as the defect size, suture and/or mesh material, mesh fixation material, recurrent or primary hernia repair etc. However, the DVHD provides no specific information on preoperative patient-related factors such as preoperative

symptoms or health status. Nor provide the DVHD information about surgeon expertise, specific suture technique, anesthesia, analgesic treatment, or postoperative complications. In Study III and IV information on reoperation for recurrence and reoperation for complications was provided by matching data with data from the Danish National Patient Registry (DNPR). The DNPR offers complete data on all emergency and elective surgical procedures performed in public and private hospitals in Denmark. The registration rate is as high as 98-100% and is regarded as a highly reliable data source (67–69).

Laparoscopic repair

Patients included in Study I and II underwent laparoscopic umbilical or epigastric hernia repair. Two experienced laparoscopic hernia surgeons at each center performed the procedures using intraperitoneal onlay mesh technique (IPOM). The abdominal cavity was insufflated to 12 mmHg by Verres needle placed under the left costal margin and, two 12 mm -trocars and one 5 mm trocar were placed in the lateral left side in a vertical line downward. Adhesiolysis was performed as needed and the defect was cleared for fatty tissue. The maximum diameter of the defect was measured under a 6-8 mmHg intraperitoneal pressure. A Physiomesh (Ethicon, NJ, USA) was placed with at least 5 cm overlap of the defect. The defect was either left open (56) or closed (57), and the mesh was fixated with double crown technique using non-absorbable titanium tacks (Protack™; Covidien, CN, USA) with 1-2 cm distance between tacks. Ten ml bupivacaine 0.5% were administered into the trocar-sites at the end of the hernia repair.

Open repair

Patients included in Study III and IV underwent open, elective sutured repair or mesh repair for small (≤ 2 cm) umbilical or epigastric hernias. Repairs were performed by surgeons of varying expertise. The sutured repairs were either performed with fast absorbable (e.g. polyglactin), slowly absorbable (e.g. polydioxanone), or non-absorbable suture (e.g. polypropylene), and the mesh repairs were performed with varying types of polypropylene meshes and the positioning of the mesh was inlay/plug, sublay, onlay, or intraperitoneal.

Anesthesia, analgesia, and anti-emetics

Before each laparoscopic repair (Study I and II) the patients received 16 mg methylprednisolone succinat i.v. and 1500 mg cefuroxime i.v. The patients were anesthetized using propofol 3-5 mg/kg/hour and remifentanyl 1 microgram/kg/hour. At the end of the procedure sufentanil 0.15 microgram/kg i.v. and ketorolac 30 mg i.v. were administered. Postoperative pain was controlled with morphine (0.1 mg/kg) administered until VAS was < 20 in the postoperative care unit. Postoperative nausea and vomiting (PONV) was treated with ondansetron 4 mg i.v. Unfortunately, we have no specific information about the open repairs.

Early postoperative outcomes

Patient-reported outcome measures (PROMs) are increasingly used in clinical research to assess the impact of treatments from the patient perspective (70,70,71). Unlike other clinical outcome measures, such as mortality, morbidity, and complications PROMs provide assessment by the patients, and thus minimize the interference by the researcher (72,73). In Study I and II patients were asked to assess PROMs such as pain, fatigue, general well-being, movement limitation, quality of life (QoL), PONV, patient's satisfaction, and the cosmetic result. Whether or not the chosen

PROMs were relevant and actually reflected the patients' complaints before and after hernia repair has not been investigated (validated) in previous studies. Accordingly, we had no evidence of the relevance of our chosen outcome measures.

Pain. Early postoperative pain is an important limiting factor for short duration of convalescence, and an important reason for early readmissions (1). Postoperative pain may affect quality of life up to six months or more after laparoscopic ventral hernia repair (5,6). Primary outcome in Study I and II was pain during activity the first postoperative day (24 hours after the hernia repair). We used a 100 mm one-dimensional visual analogue scale (VAS) (anchors labelled 0 = no pain, 100 = worst imaginable pain) for this purpose. VAS pain measurements were supplemented with registrations on a Verbal Rating Scale (VRS) (no pain, little pain, moderate pain, severe pain). VAS was used to assess pain intensities over time (74–76), while VRS assessed incidence of pain. VAS has been criticized for being difficult to use especially when used by elderly patients, which may compromise registration compliance and validity (76). To account for this limitation patients in Study I and II were carefully instructed how to use the VAS. The VRS is an easy applicable assessment instrument, but may be less sensitive than VAS (76).

Seroma. Seroma formation after ventral hernia repair may induce pain and discomfort, and may result in readmittance of the patient (1). Seroma formation is a frequent complication with incidences of 13 - 95% (21,29,77–79) depending on timing and assessment methods (7,21). In the present thesis seroma formation was secondary outcome in Study I and II. We used transabdominal ultrasonography scan for assessment of seroma (incidence and volume estimation) in Study I (as done previously (79)), and we used clinical examination at day 30 in Study II.

QoL, PONV, cosmesis, and patient's satisfaction. In Study I and II QoL was assessed using VAS and the American validated hernia-specific QoL questionnaire "Carolina Comfort Scale" (CCS) (80). The CCS has not been validated in Danish patients, but we translated the CCS from English to Danish and back again as described in details elsewhere (81). For obvious reasons CCS was not applicable in the preoperative course due to questions regarding "sensation of mesh" (82). Thus, assessments with CCS could not assess whether the hernia repair actually improved the patients' QoL compared with preoperative levels. PONV were evaluated during the first 24 hours as described elsewhere (83). The cosmetic result can be of pronounced concern for many patients. Complications such as seroma formation and bulging of the mesh through a non-closed defect may compromise the cosmetic result. In the present thesis patients registered their degree of satisfaction with the cosmetic outcome using a numeric rating scale (0-10) and two VRSs, as used in previous literature (84). In Study I, patients were asked to rate their satisfaction regarding the abdominal binder (benefits or discomforts) with two VRSs (1= no benefit, 2= little benefit, 3= moderate benefit, 4= maximal benefit) or (1= no discomfort, 2= little discomfort, 3= moderate discomfort, 4= severe discomfort).

Late postoperative outcomes

Recurrence. The primary outcome in Study III and IV was long-term cumulated recurrence rate (85). In Study III we used reoperation for recurrence as a proxy for recurrence. However, a recent study from our research group found that reoperation for recurrence as a proxy for recurrence severely underestimated

clinical recurrence (86). Accordingly, Study IV was conducted to assess both reoperation for recurrence as well as clinical recurrence. A structured questionnaire was sent by regular mail to identify patients with clinical recurrence. The questionnaire was previously validated with sufficient specificity (78%) and sensitivity (86%) to identify recurrence in Danish patients undergoing ventral hernia repair (86). The questionnaire data were supplemented with data from the DNPR regarding reoperation for recurrence. Patients who noted suspicion of recurrence in the questionnaire underwent clinical examination by the same surgeon visiting local hospitals or patients in their private homes all over the Region of Zealand. A clinical recurrence was defined as a palpable fascial defect with protrusion of bowel or lump (85,86). In case of uncertain clinical examination a CAT scan was performed. The questionnaire also included questions regarding levels of persisting chronic pain at the site of the hernia/ previous hernia (described below). For this purpose we used VRS (none = 1, mild = 2, moderate = 3, severe = 4 pain).

Chronic pain. The incidence of moderate or severe chronic pain was secondary outcome in Study IV. Chronic postoperative pain may influence patients' QoL and daily living (5,55,74,87,88). Chronic pain is a common complication after several specific surgical procedures such as groin hernia repair (89), breast surgery (90), thoracic surgery (91), leg amputation (92), coronary artery bypass (93), and caesarean section (94). The incidence of chronic pain after umbilical or epigastric hernia repair has not been well-investigated, but may be 4-20% and possible risk factors for chronic pain remain to be established (12,14,16,50,52). Chronic pain is defined as persisting postoperative pain for longer than 3-6 months after the surgical procedure (74). However, for logistic reasons we were not able to assess chronic pain at three or six months postoperatively because patients were recruited from the DVHD. Instead, chronic pain was assessed after median 3 years with a large range of follow-up time (59).

Statistics

The studies in the present thesis were analysed with non-parametric statistics. The number of included patients in the RCTs was based on statistical sample size calculations. Data were analysed by intention-to-treat. The cohort studies were explorative and not based on sample size calculation. The cumulated risk of recurrence was evaluated using Kaplan-Meier survival analysis (85), and results were presented as hazard functions. The level of significance was Bonferroni-corrected to account for multiple testing in Study III. In Study IV we performed multivariate logistic regression and Cox regression to adjust for possible confounders and bias by selection.

RESULTS

This PhD included analysis of 6,235 patients undergoing repair for an umbilical or epigastric hernia (Table 1 and Figure 1). In Study I, we included patients scheduled for elective, laparoscopic hernia repair for primary or recurrent umbilical or epigastric hernias at Hvidovre Hospital University. The study period was from 1st of October 2012 to 1st of October 2013. Study II was a multi-centre study (Hvidovre, Herlev, and Køge University Hospitals of Copenhagen) including patients with similar

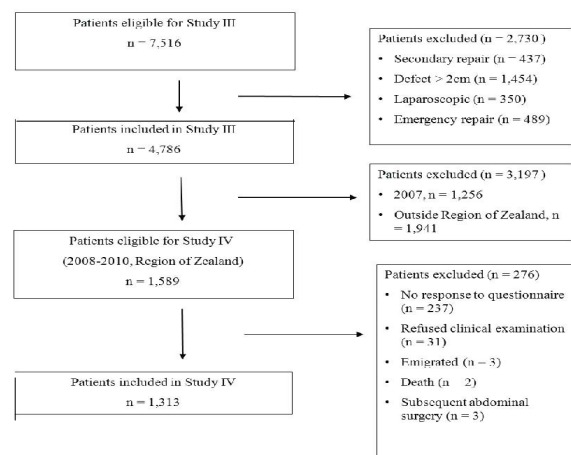
characteristics as described for Study I. Inclusion began in November 2013 and is expected to end in October 2015. In the present PhD thesis Study II is represented by our now running RCT (57). The patients in Study I and II were men and women, at age between 18-80 years with an umbilical or epigastric hernia (defect size of 2-6 cm) undergoing laparoscopic repair. A total of 7,516 patients who underwent open, elective repair for small umbilical or epigastric hernias (≤ 2 cm) from 2007-2010 registered in the DVHD were screened for inclusion for Study III (Figure 1). A subgroup of the patients in Study III (those who underwent repair in the region of Zealand from 2008-2010, n=1,587 patients) were included for analysis in Study IV (Figure 1). There were data overlap in 76 patients between Study III and IV.

Table 1

Study	Database	n	Design	Primary outcome
Study I	2012-2013	503	RCT	Level postoperative pain
Study II	2013-2015	903	RCT	Level postoperative pain
Study III	2007-2010	7,516	Register based cohort study	Litulated reoperation for recurrence
Study IV	2008-2010	1,313	Register based cohort study with clinical re-evaluation follow up	Litulated reoperation for recurrence and clinical recurrence

Overview of the included studies in the thesis. Study designs, and primary outcomes of the present thesis based on Study I, II, III, and IV. n = number of patients studied, RCT = randomized con-trolled trial.

Figure 1



Patients undergoing umbilical or epigastric hernia repair in Denmark 2007-2010 registered in the Danish Ventral Hernia Data-base. Detailed information on inclusion and exclusions of patients reported in Study III and IV.

Study I (56)

Background. Abdominal binders may be used to prevent seroma, decrease pain, and to enhance mobilization after ventral hernia repair (22,28). However, the clinical effects of using an abdominal binder have been investigated only in patients undergoing laparo-

tomy (95–98) and not after ventral hernia repair. One RCT found a significant analgesic effect of the abdominal binder after laparotomy (98) and another RCT found enhanced recovery after laparotomy in the abdominal binder group measured by improved walking distance (95).

This study was undertaken to evaluate the pain and seroma reducing effect of one-week abdominal binder after elective laparoscopic umbilical or epigastric hernia repair.

Aim. To investigate if a postoperative abdominal binder could reduce postoperative pain, seroma formation, and improve quality of life after elective laparoscopic umbilical or epigastric hernia repair compared with no abdominal binder.

Methods. Randomised clinical, outcome-assessor blinded trial. Patients were randomly allocated 1:1

to wear an abdominal binder or not for 7 days and nights after their repair. The primary outcome was VAS pain and secondary outcomes were seroma, QoL, and other PROMs assessed with self-registrations as described above. Based on sample size estimation and accounting for drop-outs 2 x 30 patients (n = 60) were to be randomized.

Results. 2x28 patients were included for analysis. There was no difference in pain, seroma, QoL or other PROMs between the two groups (Figure 2). However, patients in the abdominal binder group reported subjective beneficial effects (moderate or maximal benefit) of wearing the binder in 24 of 28 patients.

Conclusion. There were no effects of an abdominal binder on pain, seroma, QoL, or any other PROMs, but most patients claimed a subjective beneficial effect of using their abdominal binder.

Study limitations. It may be argued that a major study limitation was a too optimistic statistical sample size calculation. We chose a minimum relevant difference (MIREDIF) in VAS pain scores between the intervention and control group to be 20 mm (33% reduction). The chosen MIREDIF was, in part, inspired by a validation study that found that a MIREDIF of 13 mm on a VAS represented a clinically significant change in acute pain (99). However, it is likely that the present study may have been statistically underpowered with a substantial risk of statistical type II error. The majority of patients noted a beneficial effect of the abdominal binder, which opposed to the findings of no significant intergroup differences in our chosen outcomes. Another explanation could simply be that an abdominal binder had no important effects during the postoperative period and thus, the subjective beneficial effect of the abdominal binder could have been a result of intervention bias. Obviously, it was not possible to control for this bias by the use of a placebo -abdominal binder. During ultrasonography examination it was sometimes possible to squeeze the

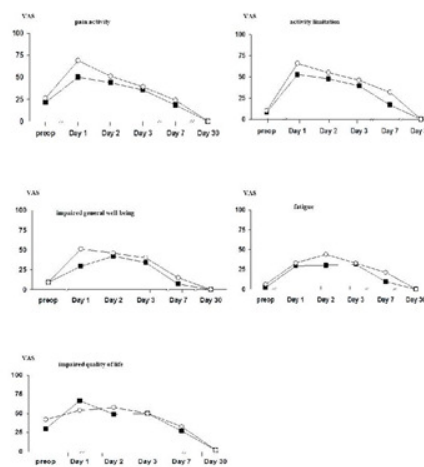
seroma into the abdominal cavity through the open hernia defect and mesh. This may have decreased ultrasonic accuracy of the volume estimation. However, this possible inaccuracy should be expected equally distributed between the two groups due to randomisation.

Study II (57)

Background. Laparoscopic ventral hernia repair is usually performed by fixation of the mesh without closing the defect. Hereby, a tension-less repair is obtained. Despite the dogma of tension-free ventral hernia repair a closure of the defect has gained increasing acceptance among hernia surgeons (26,32–35,37). Closure of the defect can be with intracorporeal sutures (31,36) or transcutaneous sutures (26,32,33,35,37,42) followed by mesh reinforcement. Outcomes may or may not be beneficial.

Preliminary observational and retrospective non-randomised trials have suggested decreased seroma formation (26), improved cosmetic result, patient-satisfaction (35,37), abdominal wall function, and postural support by this novel technique (35,36). Furthermore, closure of the defect may lower recurrence rates (31–33) compared with a non-closure technique. On the contrary, one cohort study concluded that defect closure was associated with a higher overall complication risk and with no long-term benefits (43). The effects of closing the defect on early pain, seroma, cosmesis, and long-term recurrence have not been investigated in a RCT setting (34).

Figure 2



Patient-reported clinical outcomes (PROMs) from patients with abdominal binder vs. no abdominal binder after laparoscopic umbilical or epigastric hernia repair. Visual analogue scale (VAS) scores of pain during activity, activity limitation, impaired general well-being, fatigue, and impaired quality of life in 56 patients analysed in Study I.

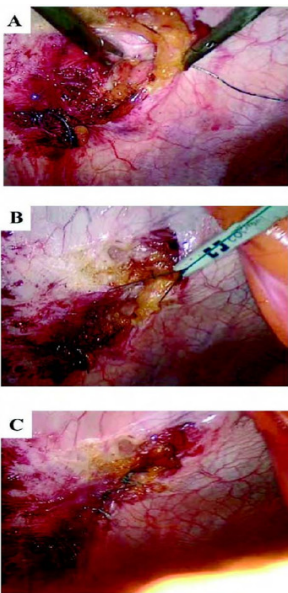
Aim. To investigate the effects on pain, seroma formation, QoL, and cosmesis after closure of the hernia defect vs. non-closure in patients undergoing laparoscopic umbilical or epigastric hernia repair.

Methods. Protocol article for a running randomized, controlled, double-blinded, multi-center study, which by now have 60 patients included (aim 80 patients). Patients are randomized to closure (intervention) or non-closure of the defect (control) before standard on-lay mesh fixation. Closure of the defect is performed by intracorporeal suturing with non-absorbable sutures (Figure 3). Primary outcome is VAS pain and secondary outcomes are QoL, cosmesis, and other PROMs assessed with self-registrations as described above. Clinically detectable seroma, morbidity, complications, readmissions, and other possible side-effects are registered at a clinical follow-up. Based on sample size estimation and accounting for drop-outs 2 x 40 patients should be randomized. Details about the statistical analysis plan and how results will be presented are outlined in the published protocol article (57).

Results. Inclusion of patients is on-going, and 60 patients are currently randomized (27th of February). The study is expected to end in October 2015. Preliminary blinded results (group A vs. group B) will be presented at the PhD defense.

Study limitations. The present study may be regarded as exploratory, since differences in early pain levels between closure and non-closure of the defect has not been investigated previously. Furthermore, the sample size calculation may be criticized. In Study II all patients receive a surgeon-administered transabdominal transvers abdominis plane (TAP) block before end of surgery, but the sample size calculation was based on pain levels from Study I, where patients did not receive TAP block. However, the analgesic effect of a TAP-block may be low 24 hours postoperatively (100), and TAP-block may not affect postoperative pain levels during movement (100). A suggested benefit of closing the defect should be reduced recurrence rate, but a minimum of two years follow-up is required to investigate hernia recurrence. Thus, the present running study cannot conclude on long-term effects, and accordingly a 2-year follow-up study will be launched.

Figure 3



Laparoscopic umbilical hernia repair with closure of the defect (Study II). A) Hernia defect with one suture and the second suture incorporating the hernia sac. B) Knot tied with a laparoscopic knot-pushing instrument. C) Closed hernia defect.

Study III (58)

Background. Open repair for umbilical or epigastric hernias can be performed with sutured repair or mesh repair. Mesh repair may be superior to sutured repair with regard to recurrence but data are

mainly derived from retrospective and observational studies (8,44–49) and two systematic reviews based on these studies (11,15). Large-scaled nationwide data have not been previously reported.

Aim. To investigate long-term risk of reoperation for recurrence after open sutured repair or mesh repair in patients with a small umbilical or epigastric hernia.

Methods. National, register-based cohort study with prospectively registered intra-operative data from patients recruited from the DVHD. Complete long-term follow-up on reoperation for recurrence was obtained from the DNPR. The follow-up period was defined as time from the primary operation until reoperation

for recurrence, death, emigration, or end of study period December 31st, 2010.

Results. A total of 4,786 patients were analysed. The hernia defect was median 1 cm. Patients were followed for median 21 months (range 0-47 months). Reoperation rates for recurrence were 2.2% for the mesh group and 5.6% for the sutured group ($P = 0.001$). Subgroup-analyses of different suture material and different mesh positions revealed no differences in reoperation rates for recurrence.

Conclusion. Reoperation for recurrence rate was significantly lower after mesh repair compared with sutured repair.

Study limitations. First, the study was not randomised. Second, we had no information on patients with possible clinical recurrence, who did not undergo reoperation for different reasons. Moreover, we had no information on long-term complaints in terms of pain and discomfort. These facts encouraged us to conduct Study IV. A third limitation was the lack of patient-specific information such as work and leisure activities, preoperative symptoms, BMI, or smoking/alcohol habits, which could have influenced the surgeon's choice of using a mesh or not.

Study IV (59)

Background. The risk of reoperation for recurrence is significantly reduced by using mesh reinforcement compared with a sutured technique (11,15,58). However, the total recurrence rate (reoperation for recurrence and clinical recurrence) and the incidence of chronic pain after repair for small-sized umbilical or epigastric hernias with or without mesh reinforcement is not clear. Reoperation for recurrence may underestimate total recurrence (reoperation for recurrence and clinical recurrence) by three to four-fold (86). Also, mesh repair may increase the risk of wound complications (8,11) and induce chronic pain (12,14,16).

Aim. The primary aim was to investigate long-term risk of reoperation for recurrence and clinical recurrence after sutured repair vs. mesh repair in patients with small umbilical or epigastric hernias. Secondary outcomes were to investigate the incidence of chronic pain and identify risk factors for recurrence and chronic pain.

Methods. Regional register-based cohort study with prospectively collected data from the DVHD. A structured questionnaire regarding recurrence and chronic pain (as described above) was sent to the patients registered in the DVHD undergoing a sutured repair or mesh repair for small umbilical or epigastric hernias in the Region of Zealand in Denmark from 2008-2010. Suspicion of recurrence led to a clinical examination by the same surgeon visiting the local hospital or the patients in their private homes. **Results.** 1,313 patients responded our questionnaire (83% response rate). The total cumulated recurrence rate after 55 months was 21% for sutured repair and 10% for mesh repair ($P = 0.001$). Subgroup analysis regarding defect size and risk of recurrence found that patients with defects >0-1 cm had 12% vs. 21% ($P = 0.033$), and patient with defects size >1-2 cm had: 8% vs. 17% ($P = 0.036$) (Figure 4a+b).

Subgroup analysis regarding specific suture materials and the different

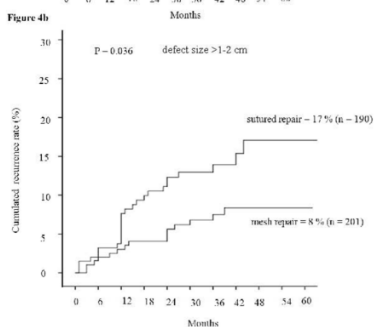
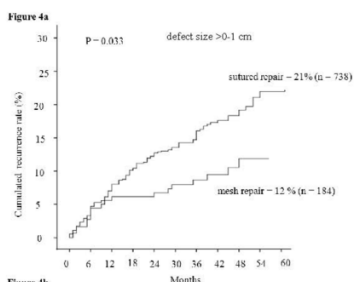
specific mesh positioning showed no significant differences between different suture materials or mesh positioning. Incidence of moderate or severe chronic pain was similar in both surgical groups (5% vs. 6%, $P = 0.711$). There were no significant differences in risk of reoperation for complications between the sutured and mesh repair groups (3% CI: 1-5% vs. 1%, CI: 0-2%).

Conclusion. Mesh repair halved the long-term risk of recurrence compared with sutured repair in patients undergoing repair for small umbilical or epigastric hernias, but without increasing the risk of chronic pain or reoperation for complications.

Study limitations. In this non-randomized database cohort study with prospective clinical follow-up there was a risk of selection bias. However, we sought, in part, to compensate by statistical multivariate analyses. We collected information about BMI and smoking habits retrospectively, which could have led to recall bias. Patient characteristics were not evenly distributed in the suture and mesh group. An epigastric hernia was an independent risk factor for recurrence and thus, the presence of more epigastric hernias in the sutured repair group could have biased our results. However, the possible bias could be counterbalanced by the fact that the mesh repair group had larger hernia defects (higher risk of recurrence) and longer follow-up time (allows more recurrences to be diagnosed). Both would possibly enhance the findings of lower recurrence rate in the mesh repair group.

Chronic pain could be caused by a variety of other factor than the surgical technique (sutured/mesh repair) but other possible influencing factors were not addressed in this study. Moreover, the impact of chronic pain on daily living was another important factor, which was unfortunately not addressed in Study IV.

Figure 4



Kaplan-Meier hazard plot illustrating the cumulated recurrence rate for open, elective repairs for small umbilical or epigastric hernias >0-1 cm and >1-2 cm (Study IV), n = numbers of patients

DISCUSSION

The present thesis consisted of 1 RCT, 1 protocol for an on-going RCT, and 2 register-based cohort studies with questionnaire and clinical follow-up. This thesis found that the use of abdominal binders after laparoscopic umbilical or epigastric hernia repair did not significantly decrease pain or seroma formation. The possible clinical effects of closing the hernia defect are awaited until final results are available from the second RCT. The use of mesh rein-

forcement significantly halved the long-term risk of recurrence from 21% to 10% and mesh repair did not significantly increase the risk of chronic pain or reoperation requiring complications. Indications for elective repair for umbilical or epigastric hernias should be definite and based on evidence. In this context clinical outcome studies should aim at assessing PROMs covering patients' concerns and expectations as well as relevant postoperative complaints using validated assessment methods (82,101). Currently, there is no literature on patient-reported symptoms or expectations from patients with an umbilical or epigastric hernias. Also, there is only sparse literature on evidence-based indications for elective repair of uncomplicated hernias. Accordingly, prior to the present PhD study, we had no systematic data to support our choice of PROMs. In Study I, we chose to assess pain, fatigue, general well-being, movement limitations, PONV, seroma, and QoL, but only pain and QoL were affected preoperatively. One study investigated indications for incisional hernia repair and found that pain and activity limitations were considered as the most important indications for incisional hernia repair among surgeons (102). These symptoms may, however, not apply to patients with small umbilical or epigastric hernias, and the study was based on the surgeon's opinion alone.

The possible analgesic effect of an abdominal binder after ventral hernia repair has not been

investigated in previous studies. Study I found that an abdominal binder did not reduce postoperative pain or seroma formation, and did not improve scores of QoL. On the other hand most patients claimed a subjective beneficial effect when using an abdominal binder. The lack of detectable clinical effects measured by a variety of clinical scorings may, in part, be explained by a statistical type II error due to possible statistical under powering of the study. One previous study suggested that abdominal binders reduced psychological distress during the first days after laparotomy (95). Thus, the effect of an abdominal binder on psychological distress after ventral hernia repair should be evaluated. In Study I, seroma volume was assessed using transabdominal ultrasonography. The incidence of seroma was found to be 96% vs. 93% in the abdominal binder group and intervention group, respectively ($P = 0.611$), and the volumes were likewise comparable. However, patients with seromas were often without any symptoms or further complications. We concluded that ultrasonography may have been too sensitive to use in a clinical study setting, detecting seromas that were not symptomatic. Accordingly, we changed the timing and method of assessment for Study II to a clinical detectable seroma on postoperative day 30.

Study II aimed to evaluate early PROMs after defect closure technique vs. standard non-closure technique in a RCT setting and final conclusions are pending. The closure technique has gained increasing popularity, although existing clinical studies have provided only low levels of evidence for the proposed effects (26,32-41). These former studies have suggested several positive effects, but a closure of the defect may increase tension on the abdominal wall and thus, may induce early and chronic pain. Only one previous study has addressed the impact of closure of the defect on 2-months postoperative pain (43). No difference was found in postoperative pain regardless of closure or non-closure of the hernia defect. However, this study was retrospective with small number of patients ($n = 36$ primary ventral hernias) and early pain was not evaluated (43). Study II is exploratory, hypothesising that a closure of the hernia defect provided no differences in postoperative pain compared with non-closure technique. Accordingly, our sample size calculation may be speculative, and a prior pilot study could preferably have been conducted. However, innova-

tive elective surgical techniques should be closely monitored in controlled trials in order to achieve valid controlled results that are compared with the current golden standards.

In Study III and IV recurrence and chronic pain was studied. Recurrence after hernia repair may affect quality of life (51) and induce chronic pain even after repair for small incisional, umbilical, or epigastric hernias (14,50). It is well-established that mesh repair significantly lowers recurrence rates after large ventral and incisional hernia repairs (11,15,103). Nonetheless, surgeons remain reluctant to use a mesh in small-sized umbilical or epigastric hernias due to fear of complications, such as surgical-site-infection, fistulation, and chronic pain (53,54). Study III and IV found that mesh repair more than halved recurrence rate with equal incidences of chronic pain and 30-day reoperation for surgical-site-infection. This effect of mesh repair on recurrence was still evident when patients were subdivided into groups of hernia defects sizes of >0-1 cm and >1-2 cm. Other subgroup analyses of different suture material and different mesh positions revealed no differences in recurrence rates, but these sub-groups may have been too small to show a difference (type II error). The present findings suggested that these repairs should all be with mesh to avoid recurrence, but final conclusions should optimally be confirmed in a large multicenter RCT. Until then evidence supports mesh reinforcement even in small umbilical or epigastric hernias.

Previous investigations of chronic pain after umbilical or epigastric hernia repair found incidences of 4-20% (12,14,16,50,52) but studies were with substantial methodological heterogeneity and were retrospective with inherent risk of bias. In Study IV we found that 5-6% of patients complained of moderate or severe chronic pain after open, elective repair for small a umbilical or epigastric hernia without significant impact of mesh reinforcement or not. The incidences are lower than reported by most other studies. However, one retrospective study found an incidence of chronic pain at rest of 4% three months after the repair without differences between mesh and sutured repair (50). The authors reported significant difference in chronic pain in patients who underwent re-operation for recurrence compared with the non-recurrence patient group (50). In study IV recurrence was the only independent risk factor for chronic pain as observed in an earlier retrospective study from our group (14). These findings underline the importance of performing a primary repair with lowest possible risk of recurrence. Results in Study IV may be biased by selection and the causality and patient-related risk factors for chronic pain remain to be established. Besides the choice of technique, chronic postoperative pain could be caused by a variety of preoperative factors that we did not analyze.

Future research

Within the area of this PhD thesis, future studies should focus on interventions to improve early postoperative outcomes, such as pain and wound complications. Consensus on relevant PROMs after umbilical or epigastric hernia repairs should be made. Patient-reported preoperative symptoms as well as expectations should be adequately compared with postoperative symptoms in well-conducted prospective studies.

The clinical effects of an abdominal binder in patients undergoing incisional hernia repair with a large surgical trauma should be conducted with relevant and validated PROMs. We are awaiting RCT results after closing the defect in umbilical or epigastric hernia and our findings should probably be confirmed (or the opposite) by more RCTs within the same patient category and in pa-

tients undergoing repair for small to moderate-sized incisional hernias. The prevalence of severe chronic pain after umbilical or epigastric hernia repair (and after incisional hernia repair) should be further studied in nationwide populations to understand causality and patient-related risk factors for chronic pain and the impact on daily living.

Although not studied in the present PhD indication for repair and the risk of emergency repair should be studied in patients with a small umbilical or epigastric hernia within a watchful waiting protocol (104). Future studies should establish which patients would benefit from an open, and which would benefit from a laparoscopic repair for an umbilical or epigastric hernia by means of combining nationwide clinical database data and well-designed multi-centre RCTs with strict outcomes.

Identification of potential risk factors for chronic pain, such as surgical technique is needed. Focus should be on the benefit of mesh reinforcement vs. risk of surgical site infections and seroma. Lastly, evidence-based recommendations for physical restrictions and duration of sick leave and convalescence after ventral hernia repair are warranted.

CONCLUSIONS

A postoperative abdominal binder had no effect on early pain, seroma, or QoL after laparoscopic umbilical or epigastric hernia repair. However, patients reported subjective benefits of wearing the abdominal binder. We await the effects of closing the hernia defect on early pain, seroma, and cosmesis from the present and other running RCTs. The risk of long-term recurrence after open repair for small umbilical or epigastric hernias was halved by using mesh repair. The incidence of chronic pain was 5-6% with no significant differences between sutured repair and a mesh repair. Mesh repair did not increase the risk of reoperation for complications.

These results suggest that mesh repair improves long-term outcomes, and thus, mesh repair should be used as standard in patients undergoing elective repair for even a small umbilical or epigastric hernia.

SUMMARY

Repair for an umbilical or epigastric hernia is one of the most frequently conducted gastrointestinal surgical procedures. Although, it is a minor procedure, there is no consensus on the optimal repair technique. The readmission rate is surprisingly high due to postoperative pain, wound-related complications, and long-term results in terms of recurrence and chronic pain is not well investigated. The overall objective of this thesis was to improve early and long-term postoperative outcomes after repair for umbilical or epigastric hernias. The present thesis consisted of 1 RCT, 1 protocol article for a running RCT, and 2 register-based cohort studies. An abdominal binder had no analgesic effects or impact on seroma formation. We await early and late postoperative outcomes from a running RCT studying clinical effect of closing the hernia defect (inclusion is expected to end in October 2015). The two cohort studies included in the present theses found that mesh repair halved the long-term risk of recurrence compared with sutured repair. Mesh repair did not increase the risk of chronic pain or rate of reoperation for complications.

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