Early clinical outcomes following laparoscopic inguinal hernia repair

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STUDY I
Tolver MA, Strandfelt P, Forsberg G, Hjorne FP, Rosenberg J, Bisgaard T. Determinants of a short convalescence after laparoscopic transabdominal preperitoneal inguinal hernia repair. Surgery 2012; 151:556-63.

STUDY II
Tolver MA, Strandfelt P, Rosenberg J, Bisgaard T. Pain characteristics after laparoscopic inguinal hernia repair. Surg Endosc 2011; 25:3859-64.

STUDY III
Tolver MA, Rosenberg J, Juul P, Bisgaard T. Randomized clinical trial of fibrin glue versus tacked fixation in laparoscopic groin hernia repair. Surg Endosc 2013; (Epub ahead of print).

STUDY IV
Tolver MA, Strandfelt P, Bryld EB, Rosenberg J, Bisgaard T. Randomized clinical trial of dexamethasone versus placebo in laparoscopic inguinal hernia repair. Br J Surg 2012; 99:1374-80.

INTRODUCTION
The first laparoscopic operation of inguinal hernia repair was performed in 1982 [1]. Today the two favorable laparoscopic techniques are transabdominal preperitoneal hernia repair (TAPP) and total extraperitoneal hernia repair (TEP) [1]. In Denmark, around 10.000-12.000 inguinal hernia repairs are performed annually (5.5 million inhabitants) [2] with the conventional open approach such as Lichtenstein being the most frequent hernia repair [3]. Nevertheless, an increasing number of repairs are being performed by the laparoscopic technique. Thus, 16% of inguinal hernia repairs in DK were done by TAPP in 2008 compared with 5% in 2003 [3]. Because of tradition, the TEP approach is almost never used in DK and there may not be any difference in outcomes between TAPP and TEP [4, 5].

The increasing popularity of laparoscopic inguinal hernia repair is, in part, due to the clinical potentials with less postoperative pain and a shorter duration of convalescence compared with an open hernia repair technique [6-8]. Thus, to gain the full clinical benefits of laparoscopic inguinal hernia repair procedure-specific analyses of the early postoperative clinical outcomes and evaluation of convalescence after laparoscopic inguinal hernia repair with non-restrictive recommendations are needed. This is also a prerequisite for optimization of the early postoperative period.

Postoperative pain is an important determinant of duration of convalescence after inguinal hernia repair and in other ambulatory surgical procedures [9-11]. Consequently, reduction of pain is essential. Furthermore, severe postoperative pain after surgery may influence fatigue, discomfort, nausea and vomiting in the early postoperative period [12]. Optimization of these outcomes may be achieved by reducing pain intensity. Prior to the initiation of this PhD a few randomized studies indicated analgesic advantages of mesh fixation using fibrin sealant in TAPP compared with titanium tack fixation [13, 14]. However, results were not uniform [15]. Furthermore, the glucocorticoid dexamethasone had shown analgesic benefits after several surgical procedures [16-20] but had not been studied in patients undergoing laparoscopic inguinal hernia repair.

Based on this knowledge, the overall aim of the present PhD thesis was to study the characteristics of early clinical outcomes after laparoscopic inguinal hernia repair and to optimize the postoperative period by improving clinical outcomes.

METHODOLOGICAL CONSIDERATIONS
All registrations are based on self-assessment by patients apart from recurrence, which is registered by reoperation rate and clinical recurrence.

Assessments
Pain
Pain is a subjective experience and intensity of pain was measured by two unidimensional scales in the included studies: a visual analog scale (VAS) and a verbal rating scale (VRS). These scales are extensively used in acute pain research [21-23]. VAS consists of a 100 mm horizontal line with endpoints labeled "no pain" (0 mm) and "worst possible pain" (100 mm) and is sensitive

to changes in pain intensity [22, 23]. Its shortcomings are the need for considerable instructions from the investigator [23]. In the present studies VAS was used for estimation of pain during rest and movement-evoked pain (pain during coughing). The latter is found to be more intense than pain during rest in the first 3 postoperative days [24]. VRS may consist of a four-point category scale (1=none, 2=light, 3=moderate, 4=severe) and is less sensitive to changes in pain intensity compared with VAS [23]. Its advantages are that patients find VRS easy to use compared to VAS and only sparse instruction is needed from the investigator [23]. Its disadvantages are that the gaps are probably not identical and patients may not find that their pain experience fit into any of the categories [23]. VRS was used to assess overall pain intensity.

Discomfort

VAS is also used for assessing other subjective feelings such as general well-being [25] or discomfort. The scale is not validated for this purpose and the outcome has not been assessed in previous RCTs after laparoscopic inguinal hernia repair. However, it has been used after laparoscopic cholecystectomy [26] and laparoscopic ventral hernia repair [27]. VAS was used to monitor discomfort in the present studies.

Fatigue

Postoperative fatigue is a common phenomenon after abdominal surgery [28] and is a complex of symptoms consisting of an increased desire for sleep, muscle weakness, and psychological changes [29, 30]. Fatigue is estimated on a 10-point numerical rating scale (NRS) with "anchor" descriptors for point 1=fit, 4=slightly tired, 7=tired, and 10=fatigued [31]. These descriptions are followed by brackets with examples of decreased performance in daily activities and increased need for sleep with increasing score on the scale [31]. It has been argued that this scale is ambiguous since it combines two dimensions: subjective feeling (tiredness) and muscle weakness (performing daily activity) [32]. However, the scale has been found applicable in a number of studies with patients undergoing abdominal surgery [17, 26, 31, 33-37]. NRS was used to evaluate fatigue in the present studies.

Nausea and vomiting

Nausea is a subjective patient sensation [38]. For comparison, vomiting involves expulsion of stomach contents through the mouth and is a brainstem reflex [38]. Thus, even though nausea and vomiting are often related they may occur on their own [38] and this is why nausea and vomiting is registered separately. Nausea was assessed with VRS (1=none, 2=light, 3=moderate, 4=severe) as recommended by others [38]. Vomiting was registered as the number of vomiting episodes covering the preceding defined time period [39].

Psychological factors

Anxiety and depression may be predictors of prolonged convalescence after different procedures [40-43]. To assess these outcomes the Hospital Anxiety and Depression Scale (HAD) was used. The scale was developed in 1983 [44] and has been translated into Danish [45]. It has been validated in multiple foreign trials and found reliable in both somatic, psychiatric, and general population [46]. HAD has also been used in earlier studies in patients undergoing open and laparoscopic inguinal hernia surgery in the investigation of persistent postoperative pain [47-49].

It consists of anxiety and depression subscales. See Appendix 1 for internal consistency of the Danish translation of HAD.

Pain catastrophizing is a psychological predictor of pain and can be defined as exaggerated negative orientation toward noxious stimuli [50]. The outcome is assessed by the Pain Catastrophizing Scale (PCS) developed and first validated in 1995 and consists of 13-items with 3 subscales (rumination, magnification, and helplessness) [51]. PCS has not been validated in Danish. See Appendix 1 for translation and internal consistency of PCS.

Functional status

In the present PhD thesis it was hypothesized that preoperative functional status could predict postoperative duration of convalescence and intensity of pain. For this purpose Activity Assessment Scale (AAS) was used [52]. The AAS scale was developed in 2005 and found reliable and valid in assessing patient functioning after hernia surgery. It consists of 13-items with 3 subscales (sedentary activities, ambulatory activities, work and exercise activities). AAS has not been validated in Danish and the English version was translated prior to study I, and internal consistency investigated. See Appendix 1 for details.

Convalescence

Factors to determine duration of convalescence are multiple [10, 53]. However, the effect of different surgical and analgesic factors on convalescence cannot be assessed accurately unless recommendations are specified and uniform [10]. Convalescence was defined as the number of postoperative days away from work or main leisure activity [34]. Thus, convalescence was 1 day if operated on a Monday and back to work or leisure activity the following Tuesday (POD 1). Non-restrictive recommendation of 1 day of convalescence regardless of workload and level of leisure activity was given in study I, II, and IV. The recommendation was given orally, in writing, and through a study-dedicated 10-minute video [54]. Patients registered prospectively the actual date of resumption of activities. Duration of convalescence was not evaluated in study III because of differences between recommendations at Aleris-Hamlet Private Hospital and Køge Hospital.

Recurrence

Patients were seen for clinical examination for hernia recurrence. If in doubt an ultrasonography was performed. Recurrence was not an outcome parameter but should be considered a safety parameter. The studies did not have sufficiently long follow-up and were not powered to investigate the risk of recurrence.

Statistics

VAS and NRS have a finite range with many observations in the extremes (0-100 mm or 1-10) and the distribution is not symmetric. Therefore, the assumption of normal distribution was not fulfilled and non-parametric Friedman, Wilcoxon signed rank test, and Mann-Whitney U-test were used for these continuous variables. Log-rank test was used to compare duration of convalescence between work and leisure activity. Univariate and multivariate linear regression analyses (parametric methods) were performed in order to identify independent variables to explain duration of convalescence and total (cumulative) postoperative pain. Analysis of co-variance with adjustment for preoperative value was used to correct the difference between groups for potential bias in case of baseline imbalance.

Fisher´s Exact test was used for comparing binary or categorical outcomes across groups (including VRS). McNemar´s test was

used to compare prevalence of different pain components. Bonferroni correction was used to avoid mass significance. Cronbach´s alpha coefficient (α) of internal consistency [55] was used to measure the reliability of HAD, PCS, and AAS.

Data were analyzed according to per-protocol or intention-to-treat principles. P-values < 0.05 were considered to be statistically significant.

Study design

The present PhD thesis was based on prospective studies with pre-specified study protocols and collection of data in a forward manner from the start of the studies. This is in contrast to retrospective studies where data refers to registrations of non-planned past events. Randomization means that patients are allocated to different treatments at random. The purpose is to minimize the risk of difference between patients, which could introduce bias [56]. Blinding is used to keep investigator and/or patient in ignorance of the treatment given. Thus, their judgment will not be affected. All studies were performed in single-centers.

Surgical procedure

TAPP involves perforation of the abdominal wall by trocar insertion [57] and creation of pneumoperitoneum causing distension of the peritoneum [58]. Bladeless disposable trocars (Ethicon Endo-Surgery Inc., Johnson & Johnson, Cincinnati, Ohio, USA) were used. Local anesthetics (bupivacaine 0.5%, 20 ml) were used at port incisions. The peritoneal flap was created and an Ultrapro™ mesh 10 x 15 cm (Ethicon Inc., Johnson & Johnson, USA) was inserted. Ultrapro™ mesh is composed of a weave of lightweight polypropylene (nonabsorbable fibers) and poliglecaparone (absorbable fibers) [59]. ProTacks™ fixation devices (Auto Suture, Tyco Healthcare, Norwalk, Connecticut, USA) were used for fixation of mesh applying 4 to 6 tacks in the mesh and adapting the peritoneum using another 4-6 tacks with precautions taken not to damage vessels in the triangle of doom and nerves in the triangle of pain [57]. In study III depending on randomization Tisseel® fibrin sealant (BioSurgery, Baxter, Deerfield, Illinois, USA) was used for fixation of mesh and adaptation of peritoneum.

Analgesic treatment

Postoperatively, it was not possible to give the same analgesic treatments at the two centers because of different standardized analgesic routines. Hence, all patients at Køge Hospital (study I, II, and IV) received paracetamol 1 g orally x 4 daily (starting 4 hours after premedication) for 4 days and ibuprofen 600 mg orally x 3 for 4 days (POD 0 – POD 3). A routine use of postoperative opioids was avoided due to side effects such as nausea, vomiting, and somnolence [60]. Intravenous oxycodone 5 mg was only given at VAS>60 mm on POD 0 (maximum (max) 30 mg) and at discharge, three capsules oxycodone 5 mg were handed out for use when needed. At Aleris-Hamlet (study III) patients received paracetamol 1 g orally x 4 daily (starting 4 hours after premedication) for 4 days, and diclofenac 50 mg orally x 3 daily for 4 days. IV or capsule oxycodone 5-10 mg was given on request (max 30 mg) and tramadol 100 mg on request (max 400 mg).
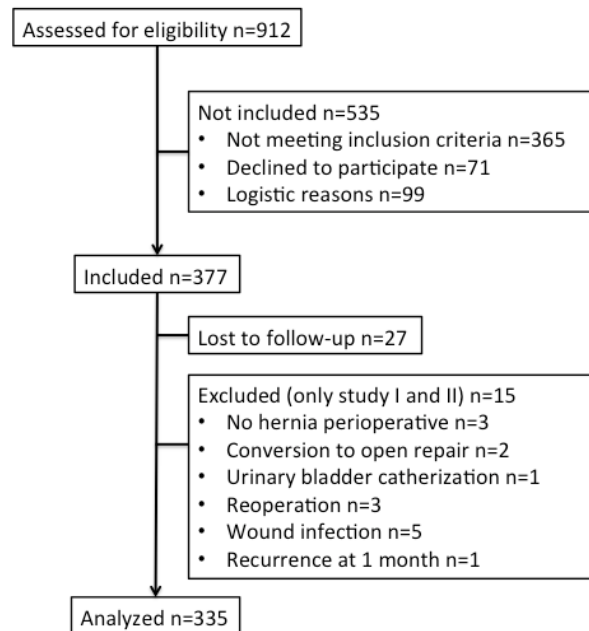
RESULTS

Patients

Overall, 912 patients were assessed for eligibility and 377 men were included in study I-IV (Figure 1). The study profile is shown in Table 1. Twenty-seven patients were lost to follow-up (7%) and 15 patients excluded (4%) (only exclusion of patients in studies I and II). Thus, 335 patients were analyzed (Figure 1). Overall, patients were a homogeneous group of men with the majority being healthy (ASA I), middle-aged (median 55 years), and employed.

Figure 1

Overall flow-chart of participants in studies I-IV.

Overall results from clinical studies (Study I-IV)

Duration of convalescence from work and leisure activity was 3-5 days after TAPP in patients receiving specific and short recommendations. The intraabdominal pain component dominated over incisional pain, which again dominated over shoulder pain. In two randomized studies fibrin sealant for fixation of mesh proved advantages compared with tacks fixation, whereas preoperative dexamethasone did not show any advantages apart from reduced use of antiemetics compared with placebo.

Table 1: Overall study profile

Included patients	377 men
Age (years)*	55(20-85)
Body mass index (kg/m^2)*	25(18-45)
ASA** grade	
• I	279
• II	98
• III	0
Hernia type	
• Primary	321
• Recurrent	56
• Unilateral	363
• Bilateral	14
Employed patients	256

*Values are median (range). **ASA=American Society of Anesthesiologists.

STUDY I

Determinants of a short convalescence after laparoscopic transabdominal preperitoneal inguinal hernia repair.

Aim: The main aim was to identify the duration of convalescence (days) from work and leisure activity after TAPP with non-restrictive recommendations, and to identify determinants of short convalescence and postoperative pain. Additionally, the aim was to investigate early clinical outcomes (pain, discomfort, fatigue, nausea and vomiting) in the postoperative period.

Methods: The intervention was preoperative non-restrictive recommendations of 1 day of convalescence. Participants were excluded from the study if the following events/complications occurred peri- or postoperatively until 1 month after operation (conversion to open repair, urinary bladder catherization, wound infection, reoperation, and recurrence).

Results: Between August 2009 and August 2010, 185 patients were enrolled and 162 patients were available for analysis. Convalescence from work and leisure activity was median 5 days (range 1-40) and 3 days (1-49), respectively (p=0.34, Fig. 2). Preoperative expectation of prolonged convalescence from work was the only determinant of prolonged convalescence (p<0.0001). Bilateral hernia (vs. unilateral), high levels of postoperative discomfort, employed status, and moderate/strenuous degree of leisure activity was determinants of prolonged duration of convalescence from leisure activity. Planned sick leave, complaints of postoperative pain, and fatigue were the 3 dominant, self-reported reasons for not resuming work and leisure activity within POD 1-3. Pain during coughing (Figure 3), discomfort, and fatigue changed during the study period (p<0.0001) but were normalized on POD 3 compared with preoperative parameters (all p-values≥0.12). Age was the only determinant of postoperative pain in an inverse relationship (p=0.00045). Number of patients reporting moderate/severe pain was 67 (41%), 63 (39%), and 16 (10%) on POD 0, POD 1, and POD 3, respectively. Fourteen (9%) patients reported moderate/severe nausea, and 11 (7%) patients vomited on POD 0.

Conclusion: Patients undergoing TAPP had 3-5 days of convalescence from work when recommended 1 day of convalescence. Preoperative expectation of prolonged duration of convalescence was an important reason for convalescence from work beyond 1 day.

Figure 2
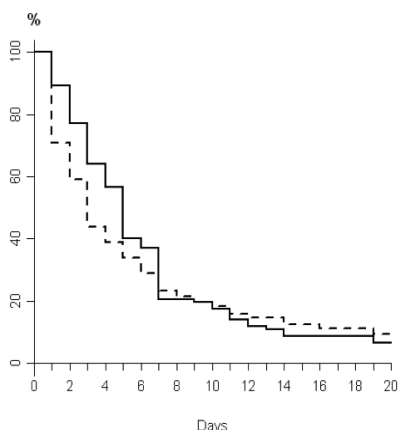
Convalescence. Kaplan-Meier survival plot showing the percentages of patients not returned to work (solid line, n=92) and leisure activities (dashed line, n=162), respectively. Reproduced with permission from Surgery [162].

Study limitations: The major limitation was that the sample size was not based on a power calculation and thereby may be underpowered to detect determinants of convalescence and pain

(type II statistical error). Additionally, there was a risk of confounding factors affecting the results. Information bias may also be present because we kept close contact with patients throughout the study period, increasing the risk of losing external validity of the results. Furthermore, when focusing on the uncomplicated laparoscopic hernia repair and not analyzing the results as intention-to-treat, again there is a risk of losing external validity. This study had the limitations of a descriptive study because the results were not compared with a control group who did receive restrictive recommendations. Only a single centre participated in the study, and standardized anesthetic and analgesic regimen was used, which strengthens the result in terms of internal and external validity.

Figure 3
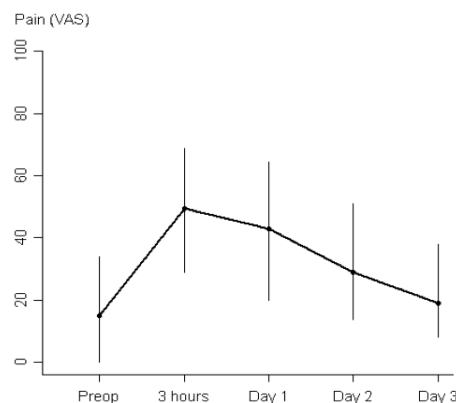
Pain during coughing was measured with a visual analog scale (VAS, 0-100 mm) preoperatively (preop) and on POD 0-3 (n=162). Median and interquartile ranges are shown. Reproduced with permission from Surgery [162].

STUDY II

Pain characteristics after laparoscopic inguinal hernia repair.

Aim: The aim was to perform a detailed procedure-specific analysis of the early postoperative pain after TAPP, and to compare pain at different sizes of port incisions.

Methods: Patients were also included in study I. Pain was categorized into four different measures of pain during coughing: intraabdominal pain (visceral pain), incisional pain (somatic pain), shoulder pain (referred pain), and overall pain intensity. Patients were explained that intraabdominal pain was a deep abdominal pain including the groin area. Incisional pain was a superficial pain localized in the wound/abdominal wall. Shoulder pain was defined as a sensation of pain in the shoulder(s). Furthermore, pain at the three different trocar incisions was recorded in POD 0-3.

Results: Between November 2009 and May 2010, 50 patients were enrolled and 46 patients were available for analysis. Pain during coughing and rest peaked 3 hours after TAPP on POD 0 and declined to preoperative levels on POD 3. Furthermore, pain during coughing was more intense compared with pain during rest (p<0.001). Intraabdominal pain scores (POD 0-3) were significantly higher compared with incisional pain scores, which again were significantly higher than shoulder pain (Fig. 4) (all p-values <0.001). The prevalence of moderate/severe intraabdominal pain during coughing was also significantly higher compared with incisional pain (p=0.004), which again had a higher prevalence than shoulder pain (p=0.002). Pain at port incision 1 (5 mm), 2 (12 mm), and 3 (5 mm) were not significant different: 1 vs. 2, p=0.39;

1 vs. 3, p=1.00; 2 vs. 3, p=0.12. Intravenous opioids were required by 22 out of 46 patients (median dose 5 mg (range 5-20 mg) on POD 0.

Figure 4
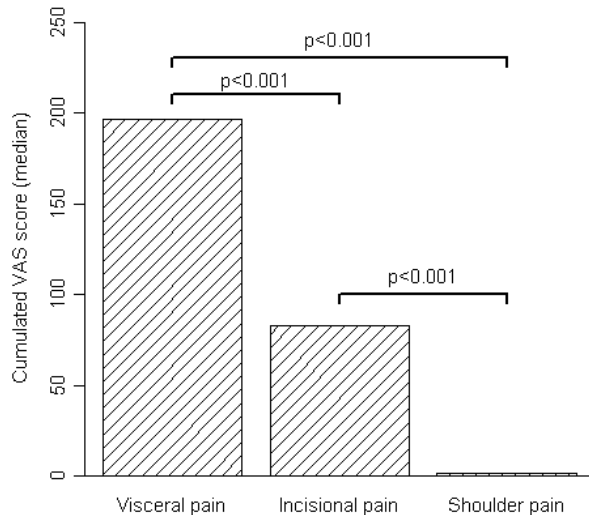
Cumulated pain scores (median) for the 3 pain components (intraabdominal, incisional, and shoulder pain) assessed by visual analog scale (VAS) during coughing on POD 0-3 (n=46). All p-values <0.001 for pairwise comparisons between pain components. Reproduced with permission from Surgical Endoscopy [163].

Conclusion: Pain was most intense 3 h after TAPP on POD 0 and normalized to preoperative levels on POD 3. Intraabdominal pain was the most dominating pain. Almost 50% of patients required intravenous opioids.

Study limitations: This study was an explorative and hypothesis generating study. The sample size was not based on a power calculation. Excluding patients with complications increased the risk of losing external validity.

STUDY III

Randomized clinical trial of fibrin glue versus tacked fixation in laparoscopic groin hernia repair.

Aim: The main aim was to compare fibrin sealant versus tacks fixation's effect on early postoperative pain after TAPP. Primary outcome was pain during coughing on POD 1.

Methods: One-hundred and twelve patients were randomized. The allocation ratio was 1:1, with 56 envelopes for fibrin glue and 56 envelopes for tacks. The surgeon, the anesthetist, and the nurses at the operating theatre were for obvious reasons not blinded. The patient, the investigator, and nurses attending to the patient postoperatively were all blinded towards the intervention.

Sample size calculation was based on an earlier study in patients undergoing TAPP [61]. VAS pain was mean 36.2 mm with standard deviation (SD) 20.2 mm 24 hours postoperatively [61]. We designed the present study to detect a minimal relevant difference (MIREDIF) of 13 mm in VAS-pain on day 1. Statistical Type I error was set to 5% and type II to 20% resulting in a sample size of n=46 patients in each arm. We included 50 patients in each arm (100 patients in total). In case of dropouts additional patients

were included by new randomization blocks of 4 to obtain primary endpoints from a minimum of 100 patients.

Results: Between September 2009 and August 2011, 112 men were enrolled out of 306 eligible patients and randomized into two arms: fibrin sealant (n=56) and tacks (n=56). Twelve patients were lost to follow-up or withdrew consent. The fibrin group had lower pain scores during coughing (p=0.020) and during rest (p=0.001) on POD 1 compared with the tacks group. When adjusting for potential bias due to baseline imbalance significance was maintained on POD 1 between groups. There was a lower incidence of moderate/severe pain on POD 1 in the fibrin group compared with the tacks group (p<0.001). Cumulated pain scores (POD 0-3) were significantly lower in the fibrin group compared with tacks group during coughing (p=0.007) and during rest (p=0.004). Discomfort and fatigue scores were significantly lower in the fibrin group compared with the tacks group on POD 1 and cumulated POD 0-3. There were no differences in incidence of moderate/severe nausea (p=1.00) and vomiting (p=1.00) between groups. Furthermore, there was no difference in seroma formation (p=0.715) and haematoma (p=0.056) on POD 10 between groups. The incidence of foreign body sensation was significantly lower in the fibrin sealant group at 1 month (p=0.006) compared with the tacks group. There was no difference in early recurrence between groups at 6 months (p=0.241).

Conclusion: Fibrin sealant for mesh fixation significantly reduced early postoperative pain, discomfort, fatigue, and incidence of foreign body sensation after laparoscopic groin hernia repair compared with tacks fixation.

Study limitations: Baseline imbalances can happen by chance in a randomized study. In the present study patients were randomized and the study was conducted in agreement with the protocol. Still, slight imbalances could be suspected between the treatment groups in pain during coughing at baseline. However, an adjustment for potential bias due to baseline imbalance was performed to ensure that postoperative differences were not just caused by differences at baseline. Additionally, findings were uniform for all outcomes in favor of fibrin sealant.

Missing data from 12 patients (11%) caused by lost to follow-up or withdrawn consent was evenly divided between the two groups. The missing data was judged to be missing completely at random so the absence of data did not bias the estimated outcomes. However, there was a loss of power when omitting these patients with missing data as done in the present study.

STUDY IV

Randomized clinical trial of dexamethasone versus placebo in laparoscopic inguinal hernia repair.

Aim: The main aim was to compare the effect of dexamethasone versus placebo on early postoperative pain and duration of convalescence after TAPP. Primary outcome was pain during coughing on POD 1.

Methods: The allocation ratio was 1:1 with 40 patients randomized to 8 mg of intravenous dexamethasone (Fortecortin®) and 40 patients randomized to placebo (intravenous saline). The patient, the surgeon, the anesthesiologist, the nurses in the operating room and the PACU, and the investigators were blinded for the nature of the injected solution.

Sample size calculation was performed by using data from the first 28 male patients with unilateral inguinal hernia participating in study I. On POD 1, pain during coughing as estimated by VAS was mean 40.1 mm with a SD of 18.8 mm. With a power to detect a minimal relevant difference (MIREDIF) between the two groups

of patients of 40 per cent (16 mm) and a type 1 and 2 error of 0.05 and 0.20, respectively, 22 patients in each group would be needed. To compensate for dropouts from the study, the protocol specified an inclusion of 40 patients in each arm.

Results: Between August 2010 and August 2011, 80 men were consecutively enrolled in the study. Time between injection of dexamethasone or placebo solution and skin incision did not differ between the two groups (37 vs. 32 min, p=0.335). The mean dose of dexamethasone was 0.1 mg/kg. No serious adverse drug reactions occurred.

Pain during coughing, rest, discomfort, and fatigue on POD 1 showed no differences between groups of patients (p-values>0.05). Furthermore, cumulated pain scores during coughing, rest, cumulated discomfort, and cumulated fatigue on postoperative days 0-3 were not significantly different between the two groups (p-values>0.05). There was no difference between groups in duration of convalescence from work and leisure activity (p-values>0.05). The need for analgesics in the postanesthesia care unit (PACU) was not significantly different between the two groups. Furthermore, there was no difference in incidence of nausea or episodes of vomiting between groups (p>0.05). However, in the placebo group there was a more frequent use of antiemetics in the PACU compared with the dexamethasone group (p=0.026).

Conclusion: A single dose of 8 mg of dexamethasone prior to TAPP did not alter early postoperative pain, discomfort, or fatigue after TAPP. However, dexamethasone significantly reduced use of antiemetics in the PACU.

Study limitations: Although the study was randomized, it had potential weaknesses, which could, in part, explain the negative findings. Firstly, the interval between administration of dexamethasone and skin incision may have been too short causing a delayed biologic action of dexamethasone on the inflammatory stress response to surgery. Secondly, the dose of 8 mg dexamethasone may not have been adequate in patients with high body mass index. Thirdly, the sample size calculation was based on finding a potential difference in pain on POD 1 between groups. Thus, the negative findings of the other outcomes may be due to low statistical power.

DISCUSSION

This PhD thesis basically found that duration of convalescence from work and leisure activity was 3-5 days after TAPP in patients receiving 1-day recommendation for duration of convalescence. Intraabdominal pain dominated over incisional pain, which again dominated over shoulder pain. Fibrin sealant fixation of mesh had clinical advantages to tacks fixation, whereas preoperative 8 mg intravenous dexamethasone did not show any advantages apart from reduced use of antiemetics in the PACU compared with placebo.

Postoperative pain

Different laparoscopic procedures may have their own individual pain pattern underlining the importance of procedure specific analgesic treatment [62]. The procedure-specific characteristic of early postoperative pain pattern after TAPP was not described in detail prior to start of the included studies in this thesis.

The etiology of postoperative pain after laparoscopic surgery includes patient-related factors [63], surgical-related factors [58, 64], and inadequate perioperative analgesic treatment [58, 62]. Although postoperative pain intensity has large inter-individual

variation, overall pain intensity peaked postoperatively on POD 0 after TAPP (study I and II) in accordance with previous studies [63]. However, results are not uniform and in a number of studies pain intensity peaked on POD 1 or 2 after TAPP [14, 65, 66]. Reasons for this difference may be caused by a large gap between analgesic treatment on POD 0 in hospital and after discharge in some studies. Pain decreased in the following postoperative days (study I and II) [63]. Sixty-seven patients (41%), 63 (39%), and 16 patients (10%) reported moderate or severe pain on POD 0, 1, and 3, respectively (study I). Pain intensity declined to preoperative levels on POD 3 in studies I and II. However, a number of earlier studies reported that pain persisted until day 7 or longer [63].

Intraabdominal pain (including groin pain) dominated in the early postoperative period over incisional pain, which again dominated over shoulder pain after TAPP (study II). Comparable findings are seen after laparoscopic incisional hernia repair [27]. Certain similarities also exist between the two procedures (hernia repair of abdominal wall and fixation of mesh) so it seems rational that the mutual relationships between pain components after these two procedures are alike.

Preoperative identification of early postoperative high pain responders may be important to initiate differentiated prophylactic analgesic treatment. The present PhD thesis identified age as the only independent predictive variable of postoperative pain. Thus, age was a determinant of early postoperative pain in an inverse relationship. Similar findings have been reported in earlier studies on patients undergoing TAPP [67], TEP [67, 68], Lichtenstein, mesh plug repair [67], and other surgical procedures [69-73]. Furthermore, previous studies found a positive correlation between anxiety, psychological distress, preoperative pain, pain catastrophizing and postoperative pain in patients undergoing different kind of surgical procedures [73]. The incidence of these conditions was not high in the population of hernia patients (study I). Thus, the study may have been underpowered to detect a potential link between these conditions and postoperative pain. Bilateral TAPP repair (vs. unilateral repair) and recurrent inguinal hernia (vs. primary hernia) did also not lead to higher postoperative pain intensity in the first postoperative week in previous studies investigating TAPP or TEP [63]. No relationship was identified between no. of tacks used and postoperative pain (n=162, median 10 tacks used (7-17)) in study I. However, the study may have been underpowered to detect an association. An earlier prospective study in laparoscopic ventral hernia repair (n=32, median 59 tacks used (23-90)) also found no correlation between no. of tacks used and postoperative pain within postoperative first week [27]. Another prospective study in TAPP (n=331) identified that use of > 10 tacks was an independent predictor of postoperative pain at 1 month [74]. One RCT (n=360) assessed the association between chronic pain incidence (>6 months after operation) and no. of tacks used during TEP and found an association when > 6 tacks were used [75].

In summary, early postoperative pain peaked on POD 0 and declined in the following days. Already on POD 3 pain intensity was back at preoperative levels. Intraabdominal pain (including groin pain) was the most dominating pain component in the first four PODs after TAPP. Age was inversely related to early postoperative pain and older patients had a lower risk of postoperative pain compared with younger patients.

Convalescence

Duration of convalescence after inguinal hernia repair have socio-economic and patient interest. The length of convalescence may depend on patient-related factors [37, 76, 77], surgical-related factors including analgesic treatment [17, 78, 79], as well as socio-cultural factors such as given recommendations and workers' compensation [9, 10, 80-82]. Convalescence from work and leisure activity with non-restrictive recommendations was 5 days (range 1-40) and 3 days (1-49), respectively, in study I. Previous studies on TAPP or TEP in RCTs or comparative nonrandomized trials (vs. open hernia repair), or non-comparative trials (n≥20) were highly heterogeneous regarding given recommendations of convalescence and varied widely from no recommendations/not described in article [61, 66, 83-108], to non-restrictive recommendations for 1 days convalescence/to resume work/activities as soon as possible [65, 67, 76, 77, 109-123], and up to 14 days with restriction of strenuous activities [124-126]. Duration of convalescence from work ranged between 5-35 days (n=5802) [61, 65-67, 76, 83, 85-95, 97-112, 114, 115, 118-121, 123, 125] and convalescence from leisure activities (domestic activities, physical activity) ranged from 2-36 days (n=6393) [61, 65, 67, 83, 85, 86, 88, 91, 95-97, 100, 102-104, 106, 110-113, 115, 116, 118-120, 122, 125, 126]. However, this may not reflect the "true" duration of convalescence after uncomplicated laparoscopic inguinal hernia repair for the following reasons. Firstly, there is a risk of information bias causing prolonged convalescence when no standardized recommendations or restrictive recommendations of multiple days or weeks are given. Secondly, many studies introduced recall bias by assessing convalescence in interviews performed at follow-up weeks or months after ended convalescence or in retrospective questionnaires [61, 66, 67, 76, 83-87, 92-98, 100, 103, 104, 108, 109, 111, 113-117, 119-122, 124-126]. Thirdly, the definition of leisure activities varied in studies between light physical activities to strenuous physical activities making the outcome very heterogeneous. Lastly, numerous studies also included patients with perioperative complications or concomitant procedures and thereby prolonged convalescence period [61, 65-67, 76, 83-88, 90, 91, 93-100, 102-104, 106-117, 119-126]. In study I, standardized non-restrictive recommendation was used, convalescence was prospectively assessed, and only patients with uncomplicated courses were included in the final analyses (162 patients out of 185).

Self-reported contributory factors for not following the given recommendations in study I were planned sick leave, complaints of postoperative pain, and fatigue. By using recommendations of 1 day of convalescence limiting factors of short convalescence were exposed. Planned sick leave and postoperative pain were also identified as limiting factors of short convalescence after open inguinal hernia repair [9, 10].

This thesis found that patients' preoperative expectations of prolonged postoperative convalescence after TAPP were the only independent predictive variable for convalescence from work. This finding has also been seen in earlier studies investigating open inguinal hernia repair [127] and cholecystectomy [34]. Bilateral hernia, high levels of postoperative discomfort, employed patients, and moderate/strenuous degree of leisure activity were determinants of prolonged duration of convalescence from leisure activity in study I. A previous comparative study did not find any difference in duration of convalescence from leisure activities after TEP between patients with bilateral vs. unilateral hernia [128]. Even though the study had a larger sample size (n=206) and the study was of good quality [129], the duration of convalescence was assessed retrospectively during follow-up and patients with complications or having concomitant procedures were included in the analysis.

In summary, only 3-5 days of convalescence after TAPP is possible for most patients. Earlier knowledge on duration of convalescence is not of ideal quality with no given recommendations or restrictive recommendations, or with retrospective investigation of convalescence. Patient expectation of prolonged duration of convalescence is an important determinant of convalescence after TAPP and other abdominal surgical procedures. Patients reported pain and fatigue as limiting factors of short duration of convalescence underlining the need to reduce the severity of postoperative pain and fatigue after TAPP.

Port incisions and pain intensity

Although incisional pain was not the most severe pain component after TAPP and no differences in pain at different port incisions (12 mm and 5 mm) were found (study II), downsizing the trocars could theoretically further reduce incisional pain as it has been shown in randomized controlled trials in laparoscopic cholecystectomy [35, 130]. TAPP is traditionally performed using one 12 mm trocar and two 5 mm trocars (study I, II, and IV). One trocar with minimum size of 5 mm is required for allowing the introduction of the mesh [131, 132]. On the other hand, use of 2-3 mm trocars has been reported to cause difficulties with dissecting and grasping because of the small jaws of the instruments, and bending of instruments [130, 133]. Case series found needlescopic TAPP (5 mm and 3 mm trocars) safe and feasible [132-134] but only one comparative trial (n=40) investigated the analgesic effect and effect on duration of convalescence by downsizing trocars in TAPP. The authors concluded that patients in the needlescopic group (2x5 mm and 1x3 mm) had significantly reduced use of analgesics postoperatively compared with the traditional trocar group but no difference between groups regarding duration of convalescence [131]. However, the study was non-randomized, poorly blinded, and small-scaled. Another comparative but retrospective trial evaluated radially expanding trocars (n=39) with cutting trocars (n=104) during TAPP and found significantly reduced use of analgesics and shorter length of convalescence with use of radially expanding trocars [79]. Unfortunately, the date of ended convalescence and use of analgesics was retrospective registered by an unblinded investigator leading to increased risk of recall bias and the investigator affecting the patient. Reducing the number of trocars to a transumbilical one-port (single incision laparoscopic surgery (SILS)) in TAPP has only been assessed in case series [135, 136] and case reports [137-140] but stated a conversion rate of 0% to traditional TAPP [135-140] and a fine cosmetic result [135, 136, 139, 140]. Disadvantages of SILS were clashing of instruments and lack of triangular formation of instruments [133, 137]. Cosmetic results and also risk of trocar site hernia should also be accounted for when choosing trocar size in TAPP. Not surprisingly, downsizing trocars contributes to better cosmetic results [131]. Additionally, trocar size ≥10 mm may increase the risk of trocar site hernia [141].

In summary, downsizing to 3 x 5 mm trocars in TAPP is feasible (was used in study III) and may improve cosmetic results and decrease risk of trocar site hernia. The analgesic effect of downsizing trocars, using radially expanding trocars, and SILS needs to be further evaluated in randomized controlled clinical trials. Further technical development of the 2 and 3 mm trocars and instruments are needed before routine use.

Fibrin sealant versus tacks fixation of mesh

Fixation of mesh is performed to minimize risk of recurrence in laparoscopic inguinal hernia repair. Pain caused by tacks fixation remains a potential problem. Because of concern for tissue injury and nerve entrapment alternative fixation methods of mesh and closing the peritoneum has been suggested. Fibrin sealant is one such alternative being a non-invasive and degradable fixation device. Fibrin is a coagulation cascade protein with adhesive and hemostatic properties and is converted from fibrinogen by thrombin, calcium chloride and factor XIII [142, 143]. After application of the commercially available fibrin sealant during hernia repair the degradation of the fibrin clot is prolonged up to 9-10 days by aprotinin [143, 144]. Since equal tensile strength was demonstrated in 2001 between tacks and fibrin sealant with TEP in a pig model [142], and the technique has shown to be safe and feasible, the use of fibrin sealant in laparoscopic inguinal hernia repair has become increasingly popular [144, 145]. However, fibrin sealant has limitations in large direct hernias (defect >3-4 cm) surrounded by suboptimal adhesive surfaces such as pubic bone and Cooper´s ligament resulting in increased risk of recurrence caused by mesh migration [146]. In these situations tacks may be a better alternative [146]. Furthermore, meshes differ in the biomechanical structure and this may affect the adhesion behavior when fibrin is used. Actually, Ultrapro™ mesh as used in study III has shown poor adhesion with fibrin sealant because of its large pores (3-4 mm) compared with other lightweight meshes with smaller pores (1.0-2.5 mm) [147].

Previous data on early postoperative pain within POD 30 comparing fibrin sealant with tacks fixation are inconsistent. One RCT [15] in TEP and 4 RCTs [13, 14, 148, 149], and one prospective comparative study [146] in TAPP has investigated the subject prior to study III. Fibrin sealant reduced pain in 4 studies on POD 1-15 [14] or POD 4 [146], POD 7 [13, 146], and POD 30 [149] compared with tacks. On the contrary, pain was not reduced in the fibrin group on POD 0-6 in TEP [15], on POD 0-10 [148] and on POD 30 in TAPP [13]. However, the use of analgesics was lower in the fibrin sealant group in TEP compared with the tacks group [15]. Study III confirmed that fibrin sealant reduced early postoperative pain on POD 0-3, and the difference between groups had disappeared on POD 10. Fibrin sealant did not reduce the postoperative use of analgesics compared with tacks. Study III showed that fibrin sealant also reduced other early postoperative clinical outcomes such as discomfort, fatigue, and incidence of foreign body sensation. Thus, the use of non-invasive and degradable fibrin sealant positively affects several early clinical outcomes, which may help to shorten patient restitution and thereby shorten duration of convalescence. However, convalescence as an outcome was not evaluated in study III because patients at Aleris-Hamlet Private Hospital received recommendations with restriction on activity as part of the hospital policy. Earlier RCTs on TAPP [14, 149, 150] or TEP [15] have conflicting results regarding duration of convalescence between patients with fixation of mesh with tacks vs. fibrin sealant. Half of the studies identified a shorter duration of convalescence from work or normal activities in the fibrin sealant group compared with tacks group [14, 149]. These studies were also large-scaled and one of them used non-restrictive recommendation [149].

It has earlier been proposed that fibrin incited a stronger inflammatory reaction which increased exudation and thereby seroma formation. This was shown in a pig model using human-derived fibrin and findings may have been species-related [142].

The majority of earlier RCTs in TAPP or TEP did not find any difference in incidence of seroma when using fibrin sealant compared with tacks [13, 149, 150] while one RCT stated higher incidence of seroma in the fibrin sealant group [15], and another RCT found the highest incidence of seroma in the tacks group [14]. The invasive nature of tacks with risk of bleeding during fixation has been hypothesized to increase the risk of haematoma formation compared with the hemostatic fibrin sealant. Nevertheless, two RCTs found no difference in incidence of haematoma between patients with tacks or fibrin sealant at clinical follow-up [149, 150]. Two other RCTs found a larger proportion of haematoma in the patients with tacks fixation [13].

In summary, fixation of mesh with fibrin sealant may reduce early postoperative outcome after laparoscopic inguinal hernia repair compared with tacks but the effect may diminish within the first two weeks.

Dexamethasone

Inflammation caused by surgical tissue injury may contribute to early postoperative pain [151] and fatigue [152]. However, perioperative administration of glucocorticoids such as dexamethasone exerts an anti-inflammatory response by genomic and nongenomic mechanisms [153, 154]. Glucocorticoid alters protein synthesis by binding to intracellular receptors and thereby changing gene transcription and translation. The result is suppressed synthesis of proinflammatory proteins and increased expression of antiinflammatory and regulatory proteins [154]. The genomic mechanisms are time-consuming and the onset of biologic action on tissue and organ level is 1-2 hours after administration [153, 155]. The nongenomic mechanisms have a rapid onset of effect within 15 minutes and consist of interaction with cellular membranes and actions via receptors [153]. However, the role of the nongenomic mechanisms is still unclear [153, 154]. Thus, the timing of glucocorticoid administration may seem important to diminish the inflammatory response of surgical tissue injury [155]. Preoperative administration seems preferable compared with intraoperative administration of glucocorticoid [156]. However, the optimal timing of administration is still uncertain [20, 156].

Only one randomized controlled study (study IV) has investigated the analgesic effect and effect on other early clinical outcomes after TAPP using a preoperative, single dose of 8 mg intravenous dexamethasone. A dose of 8 mg was chosen because it was sufficient in earlier trials to prevent postoperative pain, opioid consumption, nausea and vomiting, and duration of convalescence from recreational activities [17, 18, 157, 158]. No effects on any early clinical outcomes were seen in study IV apart from reduced use of antiemetics. However, a recent meta-analysis of 24 RCTs including 2,751 patients undergoing different surgical procedures evaluated the dose-dependent analgesic effects of perioperative dexamethasone and the authors concluded that a mean dose > 0.1 mg/kg reduced postoperative pain and opioid consumption [156]. In study IV the dose was only mean 0.1 mg/kg, which may in part explain the negative findings. It is already known that dexamethasone reduces the incidence of nausea and vomiting [159, 160]. The only positive finding in study IV was that dexamethasone reduced the use of antiemetics while no difference was found in incidence of nausea and vomiting between groups and this may be explained by a type II statistical error.

In summary, a single dose of 8 mg intravenous dexamethasone administered around 30 min before TAPP gave no

important clinical benefits compared with placebo, apart from reduced use of antiemetics in the PACU.

CONCLUSION AND FUTURE PERSPECTIVES

The present PhD thesis has provided evidence to support non-restrictive recommendations for early resumption of normal activities after laparoscopic inguinal hernia repair (TAPP). Prior to surgery patients should be recommended to resume work and leisure activities one day after operation and should be informed that approximately 50% of patients will have 3-5 days away from work and leisure activities. Patients should be informed that primarily pain and fatigue might prolong the convalescence period. Early postoperative pain may be most intense in the groin area compared with wounds and shoulders. Pain, fatigue, and discomfort are most intense on the day of operation and will be reduced within 1-3 days.

Optimization of the early clinical outcomes can be obtained by using fibrin sealant for fixation of mesh and peritoneum while preoperative 8 mg intravenous dexamethasone may not have any effect on early clinical outcomes after TAPP apart from reduced use of antiemetics. Future studies on early postoperative outcomes after laparoscopic inguinal hernia repair should focus on reduction of the intraabdominal pain rather than incisional and shoulder pain. Furthermore, investigation of port incisions effect on pain should be performed in a large-scaled study, and future outcome studies focusing on duration of convalescence should use non-restrictive recommendations. Another important aspect is the risk of chronic pain after TAPP, which has not been studied in the present PhD. This should be studied in future trials.

Fibrin sealant used as fixation method of mesh and adaptation of peritoneum during TAPP significantly optimized the early postoperative period. Long-term follow-up of a larger sample size of patients with fibrin fixation must be performed in the future to evaluate chronic pain and risk of recurrence.

Preoperative single dose of 8 mg intravenous dexamethasone had no significant effect on early clinical outcomes apart from reduced use of antiemetics with the given dose and time of administration compared with placebo. At this state, preoperative dexamethasone cannot be recommended as routine in patients undergoing laparoscopic inguinal hernia repair. Future randomized studies are needed with dexamethasone dose according to weight (>0.1 mg/kg) compared with placebo. Furthermore, time of administration of dexamethasone should be investigated.

SUMMARY

Laparoscopic inguinal hernia repair (TAPP) has gained increasing popularity because of less postoperative pain and a shorter duration of convalescence compared with open hernia repair technique (Lichtenstein). However, investigation of duration of convalescence with non-restrictive recommendations, and a procedure-specific characterization of the early clinical outcomes after TAPP was lacking. Furthermore, optimization of the postoperative period with fibrin sealant versus tacks for fixation of mesh, and the glucocorticoid dexamethasone versus placebo needed to be investigated in randomized clinical trials. The objective of this PhD thesis was to characterize the early clinical outcomes after TAPP and optimize the postoperative period.

The four studies included in this thesis have investigated duration of convalescence and procedure-specific postoperative pain and other early clinical outcomes after TAPP. Furthermore, it has been shown that fibrin sealant can improve the early postoperative period compared with tacks, while dexamethasone

showed no advantages apart from reduced use of antiemetics compared with placebo. Based on these findings, and the existing knowledge, 3-5 days of convalescence should be expected when 1 day of convalescence is recommended and future studies should focus on reducing intraabdominal pain after TAPP. Fibrin sealant can optimize the early clinical outcomes but the risk of hernia recurrence and chronic pain needs to be evaluated. Dexamethasone should be investigated in higher doses.

APPENDIX 1

Cronbach´s alpha coefficient (α) [55] of internal consistency was used to measure the reliability of HAD, PCS, and AAS. Internal consistency means that the items included in the scale are homogeneous. For example, two persons with similar degree of depression answer "yes" or "no" to the same questions and achieve a similar total score. Thereby, making it possible to interpret the results [55]. Cronbach´s alpha should ideally be between 0.60 and 0.90 [46, 55]. The Danish HAD translation used in study I was for subscale $HAD_{anxiety}$ α = 0.82 and $HAD_{depression}$ α = 0.75. Cronbach´s alpha coefficient for $HAD_{anxiety}$ in earlier studies were reported to vary between 0.68 to 0.93 (mean α = 0.83), and for $HAD_{depression}$ to vary between 0.62 to 0.90 (mean α = 0.82) [46]. Thus, the present translation seems reliable with acceptable correlation between items, and useable in a male population with inguinal hernia.

The English version of PCS was prior to study I translated in accordance with guidelines [161]. Three native-speaking Danish translators performed independent translations of PCS from English to Danish (forward translations). The translations were compared with one another and an earlier translation made by Aasvang et al. [49]. Discrepancies were discussed and a first version of Danish PCS was created. Backward translation [161] (Danish to English) of the first consensus version was done by two native-speaking Danish translators to identify potential translation problems. Based on these exercises a final PCS version was created. Cronbach´s alpha coefficient of internal consistency was estimated to α = 0.91 for total PCS and subscales (Rumination, α =0.88; Magnification, α = 0.75; Helplessness, α = 0.80) in study 1. Thus, the translation seems reliable, especially regarding the three subscales.

The English version of AAS was also prior to study I translated (see PCS translation above). Internal consistency of the Danish version of AAS was estimated to be α = 0.87 in study I, which seems reliable.

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