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CONTROLLED CLINICAL TRIAL

Chronic pain after inguinal hernia repair with the ONSTEP versus the Lichtenstein technique, results of a double-blinded multicenter randomized clinical trial

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Abstract
Purpose The open new simplified totally extraperitoneal (ONSTEP) technique for the repair of inguinal hernia was presented some years ago with promising initial results regarding chronic pain. We conducted a randomized clinical trial investigating the ONSTEP technique versus the Lichtenstein technique with focus on postoperative pain. The aim of this paper was to report the results regarding chronic pain from follow-up at 6 and 12 months for the participants in the ONSTEP versus Lichtenstein trial.
Methods This study was conducted as a randomized double-blinded clinical trial in male participants with primary unilateral hernias, having surgical repair of their hernia at one of five participating general surgical departments. At surgery, participants were allocated (1:1) to the ONSTEP or the Lichtenstein technique for inguinal hernia repair. Participants were followed up with questionnaires at 6 and 12 months. The primary outcome was the proportion of patients with substantial pain-related impairment of daily functions at 6- and 12-month follow-ups.
Results From April 2013 to May 2014, 290 male patients were included in the study. Regarding follow-up for pain, a total of 259 patients (89%) completed the 6-month follow-up and a total of 236 patients (81%) completed the 12-month follow-up. Regarding pain at the 6- and 12-month follow-ups, no difference was found between groups. Two patients operated with Lichtenstein technique developed severe disabling chronic pain postoperatively, which was not seen in the ONSTEP group.
Conclusion The ONSTEP technique was not superior to the Lichtenstein technique regarding chronic pain following repair of primary inguinal hernias in males.
Trial registration https://clinicaltrials.gov NCT01753219

Keywords Inguinal hernia · ONSTEP · Lichtenstein · Chronic pain · Randomized clinical trial

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Introduction

Inguinal hernia is a common disease, with increasing risk of surgical repair throughout life [1]. The optimal repair of inguinal hernias has been sought for centuries, and before the introduction of mesh-based repairs, the major problem following inguinal hernia repair was recurrence [2]. After the introduction of mesh-based methods, focus for clinicians, as well as researchers, has shifted towards other complications and sequelae, primarily chronic pain [3]. Today, two different approaches to the inguinal canal are recommended, when repairing inguinal hernias, laparoscopic or Lichtenstein repair [4, 5]. The methods have

problems regarding pain or costs [6, 7]. Due to the problems with pain after Lichtenstein repair and the cost of the laparoscopic repair, new methods for repair are being invented and tested in order to offer patients a lower risk of chronic pain, while still keeping the recurrence rate and cost of the procedure at an acceptable level. A potential new promising method called the open new simplified totally extraperitoneal (ONSTEP) technique for the repair of inguinal hernia was presented a few years ago [8]. The first presentation of the method was a series of almost 700 patients with 0% chronic pain and a recurrence rate of only 0.6% [8]. We tested the ONSTEP method in a small series in our own department and found it promising and worthwhile of investigating in a larger setting [9]. Therefore, we conducted a randomized clinical trial investigating the ONSTEP versus the Lichtenstein technique for the repair of primary inguinal hernia in men [10].

The aim of this paper was to report the results regarding chronic pain at 6- and 12-month follow-ups for the participants in the ONSTEP versus Lichtenstein trial.

Material and methods

This study was designed as a superiority, two-arm, blinded, randomized (1:1), clinical trial with blinding of participants and personnel handling questionnaires. The study was conducted as a multicenter trial with patients from five general surgical departments in Denmark and reported according to the CONSORT statement [11]. The protocol has been published previously [10].

Patient eligibility was male patients older than 18 years of age with a primary inguinal hernia that required surgical intervention. Patients had to be eligible to undergo both Lichtenstein and ONSTEP procedures and were not included if they had chronic pain or American Association of Anesthesiologist (ASA) score of more than three or did not speak or understand Danish. A full list of in- and exclusion criteria can be found in the protocol [10]. Participants were enrolled in the study when visiting the outpatient clinic for assessment of their hernia either by dedicated study personnel or by the physician in the clinic.

The five surgical departments participating in this trial all had to have surgeons that were experienced with inguinal hernia repair. In order for surgeons to operate patients for this trial, they had to have performed at least 40 Lichtenstein repairs and 10 ONSTEP repairs. They had to have completed a standardized training with proctoring for learning the ONSTEP technique [12]. The Lichtenstein repair was used as the control group and had to be performed in accordance with published guidelines from the Danish Hernia Database [4]. The method under investigation in this trial was the ONSTEP repair and had to be performed according to the description published by the inventors of the technique [8]. The ONSTEP method is an open repair of inguinal hernias, where the mesh is placed partly preperitoneally and partly between the internal and external obliques. The mesh has a memory ring, and therefore fixation of the mesh is avoided as opposed to the Lichtenstein technique where the mesh needs fixation [8, 13]. All patients were operated under general anesthesia, since it was the standard method for open inguinal hernia repair in most participating departments.

The measurements in this study were the patient-reported outcomes with the use of questionnaires. Patients were asked to fill out questionnaires preoperatively, during the first 10 days postoperative, and at 6- and 12-month follow-ups. Preoperative data and questionnaires and questionnaires during the first 10 days were collected by the operating surgical department. The questionnaires included the Activities Assessment Scale (AAS) [14], the Inguinal Pain Questionnaire (IPQ) [15], and the Carolinas Comfort Scale [16]. Questionnaires at 6 and 12 months were collected by the coordinating center at Herlev Hospital. Short-term outcome from the first 10 days after surgery has been reported previously [17].

For this report (6- and 12-month follow-ups), two primary outcomes were predefined [10]: One was the proportion of patients with substantial pain-related impairment of function at 6-month follow-up (defined as an AAS > 8.3) and the other was the proportion of patients with pain that impaired daily function at 12-month follow-up.

The sample size calculations showed that 130 patients were needed in each group for the 6-month follow-up and 115 were needed in each group for the 12-month follow-up [10]. These calculations were based on the assumptions that in the Lichtenstein group, 16 and 12.9% would experience pain at 6- and 12-month follow-ups, respectively. The corresponding assumptions for the ONSTEP group for 6 and 12 months were 4 and 3%, respectively. Secondary outcomes included patient's pain assessed with the IPQ and comfort assessed by the CCS.

The randomization list was created through www.randomization.com and was divided into blocks of six. This was done in order to stratify on center level by giving each center a unique randomization list. The allocation to treatment was concealed by envelopes that were opaque and packed by persons not otherwise involved in the study. After induction of anesthesia, the envelope for that particular patient was opened and patients were allocated to ONSTEP or Lichtenstein repair [10].

At follow-up, patients were mailed the questionnaires both 6 and 12 months postoperatively. The envelope contained the questionnaires and a prestamped return envelope. If they failed to return the questionnaires, they received reminding phone calls.

Data from questionnaires were entered into a premade Excel sheet by persons not aware of treatment allocation. Thereafter, data were transferred to SPSS statistics for Windows (Version 20.0 IBM Corp., Armonk, NY). Categorical data were compared between groups using the chi-square test or Fisher's exact test depending on expected counts in each cell. Continuous data were visually examined for normal distribution by the use of histograms, Q-Q plots, and the Shapiro-Wilk test. If regarded as normally distributed, comparison between groups was done by the use of Student's *t* test, and for data not normally distributed, the Mann-Whitney *U* test was used. For Carolinas Comfort Scale, the results were analyzed according to the Carolinas Comfort Scale—User Guide. Furthermore, if a patient had a mean score larger than one, they were regarded as having a symptomatic repair.

Registration on clinicaltrials.gov (NCT01753219) was done prior to inclusion of patients. The ethics committee of the Capital Region of Denmark gave permission to the study (H-3-2012-175) as well as the Danish Data Protection Agency (HEH-2013-006). Prior to inclusion in the study, all patients were informed both in writing and verbally and signed an informed consent form.

Results

From April 2013 to May 2014, a total of 290 patients were included in the study (Table 1). Regarding follow-up for pain, a total of 259 patients (89%) completed the 6-month follow-up and a total of 236 patients (81%) completed the 12–month follow-up (Fig. 1). No statistical significant differences were found in baseline characteristics between the groups. Information regarding perioperative data and baseline characteristics has been published in details elsewhere [17].

Regarding pain at 6- and 12-month follow-ups, no differences were found between groups (Tables 2 and 3). At 6-month follow-up, 10.9% of patients in the ONSTEP group had substantial pain-related impairment of their function compared with 13.7% of patients in the Lichtenstein group, $p = 0.49$. Likewise, there was no difference at 12-month follow-up.

VAS score at rest or during movement showed no difference between the groups at either follow-up (Tables 2 and 3). No differences between groups were found using the Carolinas Comfort Scale, analyzed both as number of patients with symptomatic repair, comparison of overall mean, and comparison of mean within the three domains of the questionnaire: sensation of mesh, pain, and movement limitation (Tables 2 and 3). The IPQ was investigated, and no differences between groups were found for any of the items in the questionnaire (data not shown).

At 6-month follow-up, two patients were identified from the Lichtenstein group with severe disabling chronic pain. One was a 25-year-old blue-collar worker, who after surgery was unable to work and still had disabling pain at 6-month follow-up, from the operated groin. The other patient was a 53-year-old blue-collar worker that also suffered from chronic pain to a degree that made him unable to work. Both patients were referred to a specialized pain center and have been reoperated with mesh removal and neurectomy. The 53-year-old was pain-free and had returned to work 1 year after index hernia repair and 3 months after mesh removal. The younger patient also experienced improvement in symptoms after mesh removal, but he was still unable to work due to pain two and half years after index hernia repair and 6 months after mesh removal. No patients in the ONSTEP group experienced these disabling symptoms. Even though being of utmost clinical relevance, the difference of two versus zero was not statistically significant.

In total, six recurrences (6/125) was found in the ONSTEP group 4.8% (95% CI 1.8–10.2) and five recurrences (5/124) was found in the Lichtenstein group 4% (95% CI 1.3–9.4), $p = 0.78$. In the ONSTEP group, three recurrences occurred before day 30, one before the 6-month follow-up, and two before the 12-month follow-up. In the Lichtenstein group, one recurrence was before day 30 and the remaining four were between 6- and 12-month follow-ups.

Table 1 Demographics of patients included for analysis of pain at 6 months. Similar demographics were found for the group completing 12-month follow-up

Allocation	ONSTEP ($n = 129$)	Lichtenstein ($n = 130$)
Age, mean (SD) (years)	54 (15)	55 (14)
BMI, mean (SD) (kg/m^2)	24.6 (2.7)	24.9 (2.6)
VAS at rest, median (IQR)	2 (0–4)	3 (0–7)
VAS at movement, median (IQR)	3 (1–11)	6 (2–19)

VAS visual analog scale (0–100 mm), *IQR* interquartile range

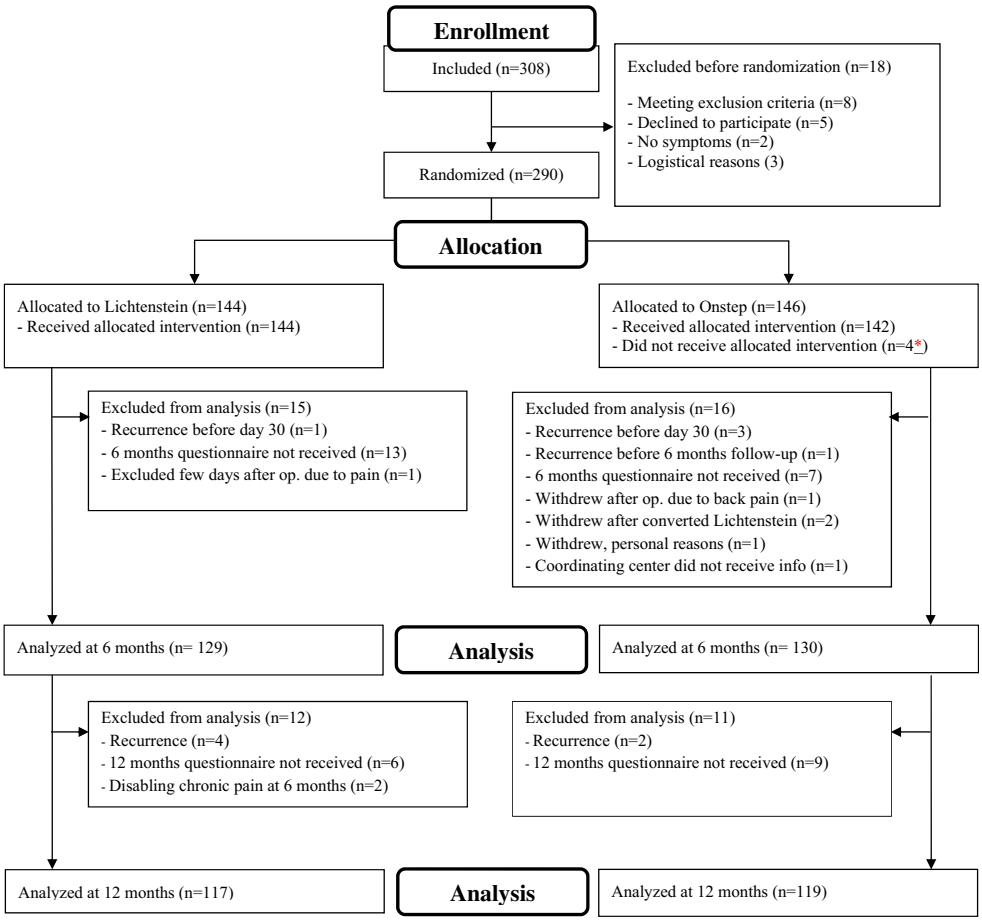

Fig. 1 Study flow diagram. *Asterisk* indicates that two patients had too much subcutaneous fat making the ONSTEP difficult, one had had a prostatectomy and therefore too much scar tissue in the preperitoneal space, and the fourth had a large and complicated hernia that could not be managed through the ONSTEP incision

Discussion

This study found no difference between the ONSTEP and the Lichtenstein repairs of primary inguinal hernia in men regarding chronic pain. Both the number of patients with impairment of daily function measured by AAS and comparison of VAS for pain during rest and movement showed no differences between groups. Two patients from the Lichtenstein group and none in the ONSTEP group were diagnosed with disabling chronic pain.

Our results differ from the results presented by the inventors of the ONSTEP technique [8]. There might be several explanations for this. In our study, patients were randomized to one of two treatments, unaware of the method of repair, and were followed up using standardized questionnaires. These were filled out at home without influence from caretakers or surgeons to favor or disfavor the technique with which they were operated. Furthermore, patients for this study were

Table 2 Results at 6-month follow-up

Procedure conducted	ONSTEP	Lichtenstein	*p* value
AAS score > 8.3, *n* (%)	14 (10.9)	18 (13.7)	0.49
VAS at rest, median (IQR)	0 (0–2)	0 (0–2)	0.67
VAS at movement, median (IQR)	0 (0–2)	0 (0–2)	0.31
Carolinas comfort scale, symptomatic patients			
Overall *n* (%)	5 (4.4)	4 (3.6)	1.00
Sensation of mesh *n* (%)	8 (7.1)	7 (6.2)	0.77
Pain *n* (%)	7 (6.3)	7 (6.2)	0.98
Movement limitation *n* (%)	4 (3.5)	3 (2.7)	0.71

AAS activity assessment scale, *VAS* visual analog scale (0–100 mm), *IQR* interquartile range

Table 3 Results at 12-month follow-up

Procedure conducted	ONSTEP	Lichtenstein	*p* value
AAS score > 8.3, *n* (%)	15 (11.9)	9 (7.6)	0.18
VAS at rest, median (IQR)	0 (0–2)	0 (0–1)	0.10
VAS at movement, median (IQR)	0 (0–2)	0 (0–1)	0.16
Carolinas comfort scale, symptomatic patients			
Overall *n* (%)	4 (4.1)	1 (0.9)	0.14
Sensation of mesh *n* (%)	16 (16.3)	12 (11.3)	0.29
Pain *n* (%)	6 (6.1)	4 (3.8)	0.52
Movement limitation *n* (%)	3 (3.1)	0 (0.0)	0.10

AAS activity assessment scale, *VAS* visual analog scale (0–100 mm)

operated by surgeons in departments that are not specialized in hernia repair, and therefore our results might be more representative of the ONSTEP technique when introduced to a general surgical department, thus showing the external validity of the method. The standardized questionnaire might also explain why a higher incidence of chronic pain and discomfort was found compared to the initial report, since a whole range of questions were asked compared to a clinical interview where pain might be dichotomized: "present" or "absent."

The difference in number of patients with disabling symptoms was not significant. However, it is worthwhile to pay attention to this complication. Disabling pain following inguinal hernia repair is a devastating situation for the patient but difficult to study because of the low incidence [18]. A much larger randomized clinical trial would be needed in order to investigate the difference in disabling pain between ONSTEP and the Lichtenstein repair. However, the ONSTEP group of 119 patients was followed up for 12 months and none of the patients experienced disabling symptoms. Furthermore, no other centers in Europe have reported disabling pain in patients after ONSTEP repair. A clinically important difference between ONSTEP and Lichtenstein techniques could therefore be disabling pain.

A study using nationwide data from the Danish Hernia Database found that the reoperation rate within the first year of a Lichtenstein repair was around 1% [19]. This is slightly lower than our findings with a lower border of the confidence interval for Lichtenstein repair at 1.3%. However, our study identified recurrences, which previously have been shown to be about 40% higher than the reoperation rate [20]. Therefore, our results in the Lichtenstein group are comparable to general practice. The recurrence rate in the ONSTEP group was 4.8% and comparable to the Lichtenstein group. Therefore, the recurrence rates identified in this study are not alarming but need to be followed closely in other prospective studies and on a nationwide level with the use of the Danish Hernia Database. The recurrences were identified based on symptoms and suspicion of recurrence from the patients. There is a risk that this approach might have overlooked some recurrences that could have been found with the use of ultrasound. However, based on the questionnaire, recurrences causing a bulge, pain, or discomfort were most likely identified. The recurrence mechanisms following an ONSTEP procedure have been presented and discussed elsewhere [21].

The strength of this study is that we have used standardized, validated questionnaires to investigate pain and discomfort. Patients were blinded and filled out the questionnaires at home, without the influence of surgeons or researchers interested in proving superiority of one technique over the other. The limitation of the study is that we might have operated patients when surgeons were still at the learning curve, and therefore better results could occur after a longer period of using the ONSTEP technique.

The perspectives of this study could be a recommendation to consider the ONSTEP, when deciding appropriate methods for the repair of primary inguinal hernias in men. It is worthwhile to notice that our results are comparable to the Lichtenstein repair, even for a new technique with which the surgeon had somewhat limited experience. We found severe disabling pain only in the Lichtenstein group, although not statistically different between groups, and the ONSTEP technique is faster than the Lichtenstein technique [17]. Thus, we found no reason not to use the ONSTEP technique instead of the Lichtenstein technique regarding patient-reported outcomes. Further studies need to investigate the learning curve and the most appropriate methods for introducing the ONSTEP technique.

Conclusion

The ONSTEP technique was not superior to the Lichtenstein technique regarding chronic pain following repair of inguinal hernias. Further studies are needed to clarify the learning curve and most appropriate methods for introducing and teaching the ONSTEP technique.

Author's contribution KA contributed to the conception and design of the work, the acquisition of data, the analysis of data, and interpretation of data for the work, and the drafting of the work.

J Burcharth contributed to the conception and design of the work, the analysis of data and interpretation of data for the work, and the drafting of the work.

SF contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

LH contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

JPR contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

SD contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

DW contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

MBE contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

RT contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

DH contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

FSS contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

J Bjerg contributed to the acquisition of data and interpretation of data for the work and revised the draft critically for important intellectual content.

JR contributed to the conception and design of the work, the analysis of data and interpretation of data for the work, and the drafting of the work.

Compliance with ethical standards

Conflict of interest KA reports nonfinancial support from Bard, Davol, during the conduct of the study. JR reports grants from Bard, during the conduct of the study; grants from Johnson & Johnson, personal fees from Bard, and personal fees from Merck, outside the submitted work. SF, LH, JPR, SD, DW, MBE, RT, DH, and FS declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Permissions The ethics committee of the Capital Region of Denmark gave permission to the study (H-3-2012-175) as well as the Danish Data Protection Agency (HEH-2013-006). Prior to inclusion in the study, all patients were informed both in writing and verbally and signed an informed consent form.

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