ANTERIOR PREPERITONEAL INGUINAL HERNIA REPAIR

G.G. Koning

Anterior Preperitoneal Inguinal Hernia Repair

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2013

About the covering photographs©

A ***B***

In this model the tube bulges out through the weakened outer tire because of the pressure from inside the inner tube, illustrating the pathophysiological mechanism of an inguinal hernia (Photo A).
The position of the mesh, between the inner and outer tire, represents the sutureless preperitoneal mesh position in man after inguinal hernia repair according to the transinguinal preperitoneal (TIPP) technique (Photo B).
This model was designed and created by G.G. Koning. The setting and materials for the photographs were, free of charge, provided by Jan Kooij 2wielers Nijmegen. The original mesh with memory ring of the TULIP trial was used in this model.

Colofon

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Aan mijn ouders

Voor Petra, Annemijn & Olivier

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Abbreviations used in this thesis

TEP	totally extraperitoneal (endoscopic)
TAPP	transabdominal preperitoneal technique (laparoscopic)
TIPP	transinguinal preperitoneal technique
TREPP	trans rectussheath preperitoneal technique
LoE	level of evidence (level 1-5*)
TULIP	Trial acronym: The **T**ilb**u**rg double blind randomised controlled trial comparing inguinal hernia repair according to **Li**chtenstein and the transinguinal **p**reperitoneal technique
PPS	preperitoneal space
Lichtenstein	global reference technique (guideline technique for primary inguinal hernia repair)
Mesh	prosthesis used for inguinal hernia repair to reinforce the inguinal canal
TSA	trial sequential analyses
SD	standard deviation
SEM	standard error of mean
QALW	quality adjusted life week
RCT	randomised controlled trial
CI (Dutch: BI)	confidence interval (betrouwbaarheidsinterval)
GRADE	grading of recommendations assessment, development and evaluation
CONSORT	consolidated standards of reporting trials
SAE	severe adverse event
MeSH term	descriptor for searching online databases
ISRCTN	international standard randomised controlled trial number
VAS	visual analogue scale
ASA	American society of anesthesiologists
PROM	patient reported outcome measure
EHS	European hernia society
TSMB	trial sequential monitoring boundaries
BMI	body mass index
OPD	outpatient department

For a complete overview of frequently used techniques for inguinal hernia repair (in past and present) see also Chapter 8 Table 1 (page 132)

**Keus F, Wetterslev J, Gluud C, van Laarhoven CJHM (2010), Evidence at a glance: error matrix approach for overviewing available evidence. BMC: 10-90.*

Chapter 1

Introduction, objective & outline of this thesis

G.G. Koning

Introduction

An inguinal hernia occurs when soft tissue - usually part of the intestine - protrudes through a weak point or tear in the lower abdominal wall. The resulting bulge can be painful - especially when coughing, bending over or lifting a heavy object. Not necessarily dangerous by itself, an inguinal hernia does not get better or go away on its own. An inguinal hernia can lead to life-threatening complications. For this reason, it is likely to recommend surgical repair of an inguinal hernia that is painful or becomes larger. Inguinal hernia repair is a common surgical procedure.[1] However, in the European Hernia Society (EHS) Guideline 'watchful waiting' is concluded to be an acceptable option for patients with minor complaints.[2]

In the Netherlands approximately 30.000 inguinal hernia repairs are performed each year.[3] The Lichtenstein technique (or tension-free mesh repair) is the present reference technique for inguinal hernia treatment.[4,5] The Lichtenstein has reduced the incidence of the recurrent inguinal hernia to 2-5% compared to anterior non-mesh techniques.[6] Unfortunately, postoperative chronic pain after Lichtenstein's repair is the main complication presently, and is estimated to occur between 15-40% in several studies.[7-10] Chronic pain is defined by the International Association for the Study of Pain as: 'pain which lasts for more than three months'.[11] Chronic pain after inguinal hernia repair is probably caused due to manipulation and dissection of the inguinal canal per-operatively (nerve damaging or stretching) or may be related to interaction of the mesh and the inguinal nerves.

Since the introduction of the mesh (prosthesis) the problem of recurrences has been successfully managed but a main postoperative complication, chronic pain, became more and more present after using a mesh. Efforts have been put into strategies to reduce postoperative chronic pain (e.g. surgical approach of the hernia, type of mesh, or mesh position). The crucial steps in the evolution of the preperitoneal approaches to the groin have been described extensively in an historical review.[12] Finally leading to scopic preperitoneal procedures. The totally extraperitoneal repair (TEP) and the laparoscopic transabdominal preperitoneal technique (TAPP) have been introduced. Randomised trials suggest less chronic pain due to the preperitoneal position of the mesh by using these techniques. Some studies reported 'superiority' of the endoscopic TEP for hernia repair. However, this 'superiority' has not been unequivocally demonstrated.[13,14]
The most important drawback of endoscopic hernia repair is the considerable proportion of severe adverse events such as bladder injury, iliac vessel damaging, major bleeding, recurrence. [13,14] Other disadvantages of procedures using an endoscope are the extensive learning curve, the need for general anesthesia, and higher costs.[15,16]
Pélissier introduced the transinguinal preperitoneal (TIPP) hernia repair with a soft mesh with memory ring[17,18] which may very well combine the safe anterior approach with the 'promising'

preperitoneal soft mesh position. This anterior (or `open´) technique has been suggested as alternative for Lichtenstein, and is associated with less postoperative chronic pain, and a short learning curve.[19]

Aim & outline of this thesis

The aim of this thesis was to evaluate anterior (open) inguinal hernia repair techniques with a preperitoneal positioned mesh, focusing on patients with postoperative chronic pain and other severe adverse events after TIPP. Chronic pain was defined as any form of pain on the visual analogue scale (VAS), lasting for more than 3 months after surgery. This definition was defined by the International Association of the Study of Pain.[11] The Lichtenstein tension-free inguinal hernia repair was the control intervention, as it is the standard technique advocated by national and international guidelines.[2,4,5]

Outline

A protocol for a systematic review with meta analyses and trial sequential analyses to compare the TEP method and the Lichtenstein technique was written and published prior to the start of the systematic review process (available at: www.ctu.dk). This systematic review (**chapter 2**) was protocol based, with meta analyses and trial sequential analyses and in line with the suggestions and methods described in the Cochrane Handbook of Systematic Reviews.[20] The aim of the systematic review was to assess the benefits and harms of the endoscopic TEP method compared with the Lichtenstein technique for inguinal hernia repair.

Recent reports suggest that a preperitoneal mesh, either by TEP or by the laparoscopic TAPP method, results in less postoperative chronic pain. The conceptually more logic TEP is advocated in the Dutch guideline for inguinal hernia repair when expertise is present, especially in bilateral inguinal hernias. However, a considerable proportion of severe adverse events seems to be present using TEP after analyzing data taken from a Cochrane study [13], fuelling the need for a technique that combines the anterior approach from the Lichtenstein with a preperitoneal mesh position as in TEP.

The study described in **chapter 3** aimed to evaluate three years of transinguinal preperitoneal mesh repair (TIPP) and Lichtenstein experience in the Hernia Center Brabant. The results of this step-up study provided the basis for a randomised controlled clinical trial (the TULIP trial). **Chapter 4** presents the study protocol of the TULIP trial in which primary and secondary outcome measures are defined and power calculations are described to compare the TIPP versus the Lichtenstein technique. The protocol was published prior to the launch of the trial. The TULIP trial tried to find an answer to reduce the main complication: the amount of patients with postoperative chronic pain. The methods of this trial were critically evaluated according to the recommendations for trials with a low risk of bias, the GRADE working group, and the CONSORT statements during designing and writing of the protocol.[20,21,22]

The aim of the study described in **chapter 5** was to evaluate the primary and secondary outcomes of the trial. Patients with postoperative chronic pain after the transinguinal preperitoneal technique (TIPP) and Lichtenstein repair were evaluated in the first postoperative year. The visual analogue scale (VAS) was used for this purpose next to physical examination, and follow-up was scheduled until 1 year. The TIPP is a technique wherein a soft mesh with memory ring is positioned in the preperitoneal space, using the transinguinal approach and the internal ring. The Lichtenstein technique is the reference technique for inguinal hernia repair globally.

Because of the adequate blinding components of the TULIP trial the patients were not aware of the operation technique that was used for their inguinal hernia correction during the follow up period of one year. Blinding was performed successful because of the identical scars (and wound position) of both techniques.

In **chapter 6** a study alongside the trial was undertaken to assess the health status of patients after TIPP and Lichtenstein procedures in the first postoperative year. The eight scales (dimensions) of the short form questionnaire (SF-36) are interpreted and described after the TIPP and Lichtenstein procedures. In the study described in **chapter 7** an economic evaluation alongside the TULIP trial was carried out using some of the data of the trial comparing the two modalities (TIPP and Lichtenstein) in the first postoperative year. Two scenario's, a hospital - and a societal perspective, are presented.

The search for "the best" inguinal hernia repair technique is an ongoing evolution globally, aiming to keep the low recurrence rates of the Lichtenstein and to prevent the main complication of postoperative chronic pain in patients. The combination of the favourable TIPP results with other reported inguinal hernia techniques led to yet another, conceptually promising, approach. The transrectus sheath preperitoneal mesh repair (TREPP). A retrospective TREPP study is described in **chapter 8**. The results of the TREPP study were used as step-up for a new randomised clinical trial (the ENTREPPMENT trial) comparing TREPP with TIPP of which the study protocol has been accepted for publication. [23] The results of all studies are summarized and discussed, and future perspectives are provided at the end of **chapter 9**. The Dutch summary is provided in **chapter 10**.

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Chapter 2

The totally extraperitoneal method versus Lichtenstein's technique for inguinal hernia repair: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials

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Abstract

Background

Lichtenstein´s technique is considered the reference technique for inguinal hernia repair. Recent trials suggest that the totally extraperitoneal (TEP) technique may lead to reduced proportions of chronic pain. A systematic review evaluating the benefits and harms of the TEP compared with Lichtenstein´s technique is needed.

Methods

The review was performed according to the 'Cochrane Handbook for Systematic Reviews'. Searches were conducted until January 2012. Patients with primary uni- or bilateral inguinal hernias were included. Only trials randomising patients to TEP and Lichtenstein were included. Bias evaluation and trial sequential analysis (TSA) were performed. The error matrix was constructed to minimize the risk of systematic- and random errors.

Results

Thirteen trials randomised 5404 patients. There was no significant effect of the TEP compared with the Lichtenstein on the number of patients with chronic pain in a random-effects model risk ratio (RR 0.80; 95% confidence interval (CI) 0.61 to 1.04; p=0.09). There was also no significant effect on number of patients with recurrences in a random-effects model (RR 1.41; 95% CI 0.72 to 2.78; p=0.32) and the TEP technique may or may not be associated with less severe adverse events (random-effects model RR 0.91; 95% CI 0.73 to 1.12; p=0.37). TSA showed that the required information size was far from being reached for patient important outcomes.

Conclusion

TEP versus Lichtenstein for inguinal hernia repair has been evaluated by 13 trials with high risk of bias. The review with meta-analyses, TSA and error matrix approach shows no conclusive evidence of a difference between TEP and Lichtenstein on the primary outcomes chronic pain, recurrences, and severe adverse events.

Introduction

Inguinal hernia repair is one of the most frequently performed procedures in surgery and many different techniques have been suggested. Techniques vary essentially by: using a mesh or not, the position of the mesh (onlay, inlay or sublay), the approach of the hernia (anterior or posterior), and the technique being open or endoscopic. It has been shown that the use of a mesh is associated with a reduced number of patients with recurrence.[1]

Both a systematic review and a meta-analysis without a systematic review have been published.[1,2] In these, combinations of different techniques are compared in one intervention group versus combinations of other techniques as a control group. However, one specific technique for inguinal hernia repair cannot be claimed to be superior based on the comparisons of heterogeneous intervention groups.[3]

Guidelines in many West European countries consider the Lichtenstein technique as the reference standard.[4] Recent reports suggest that a preperitoneal mesh, by the endoscopic totally extraperitoneal (TEP) method, results in a reduction of chronic pain and a quicker recovery.[2] Conceptually, the TEP rather than the transabdominal preperitoneal (TAPP) approach seems a logic choice as it avoids entering the abdominal cavity.

A systematic review of randomised trials comparing only the TEP technique versus only the Lichtenstein technique is needed. Available evidence needs to be evaluated in the perspective of the three dimensions of possible risks of errors: the systematic error (bias), the random error (`the play of chance´), and the design error (the outcome measure chosen).

The objective was to conduct a systematic review of the benefits and harms of the TEP technique compared with the Lichtenstein technique for inguinal hernia repair.

Methods

This review was conducted according to the prior published protocol following the recommendations of the *Cochrane Handbook for Systematic Reviews* [3] and reported according to the PRISMA statement (at: www.prisma-statement.org). The protocol [5] of this review is available online at http://www.ctu.dk.

Criteria for considering studies for this review.

Studies

Only randomised trials were considered for inclusion irrespective language, blinding, publication status, or sample size. It was intended not to include quasi-randomised trials regarding assessment of benefits, but it was intended to include regarding assessment of harms.[3]

Patients

Only adult patients were considered. Patients with primary uni- or bilateral inguinal hernias were included, but patients with hernia repair for recurrent hernias were excluded since proportions of patients with chronic pain may differ.

Interventions

Trials using the TEP technique by endoscopy and any type of mesh for inguinal hernia repair were included. Trials using the transabdominal preperitoneal (TAPP) technique were excluded. Trials using both the TEP and TAPP technique were included only if the vast majority of more than 80% of interventions were performed with the TEP technique.

The Lichtenstein technique using any type of mesh was considered the control intervention; trials using any other open technique were excluded.

Outcomes

The outcome measures were graded according to the patients' perspective (GRADE working group 2004).[6]

Primary outcomes were all-cause mortality, chronic pain defined as persisting pain for longer than three months, recurrences, and severe adverse events (SAE). The composite outcome measure of SAE outlined in the protocol in advance, was constructed summarizing all severe complications including chronic pain, deep wound infections, vascular injuries, visceral injuries, and recurrences.[5] It was recognized that the number of complications may have been summarized rather than the number of patients with one or more SAE. Therefore, double counts may have occurred. Since severe complications in elective hernia repair are rather rare, it is expected that double counts will be limited to less than 5%.

Secondary outcomes were conversions, time until return to usual activity, length of hospital stay, and duration of operation.[5] Other secondary outcomes were reported according to availability of data.

Search strategy

Searches included MeSH descriptors ("Clinical Trials", "Randomised Controlled Trials", "TEP", "TEPP", "totally, extraperitoneal", "Lichtenstein", "Liechtenstein", "laparoscopic", "Laparoscopy", "preperitoneal", "endoscopic", "inguinal hernia", "Hernia, Inguinal") and

were performed in CENTRAL on The Cochrane Library (Issue 1 2012), The National Library of Medicine (MEDLINE/PubMed) (1966–January 2012), and The Intelligent Gateway to Biomedical & Pharmacological Information (EMBASE) (1980–January 2012) for randomised trials (Attachment 1). Additional relevant trials were looked for by checking the reference lists of identified reviews and randomised trials.

Data collection and analysis

Two authors independently identified trials for inclusion and extracted the following data: year and language of publication, country in which the trial was conducted, duration of the trial, single- or multicenter design, and in- and exclusion criteria. Further, baseline imbalance and early stopping of trials were registered. All trial authors were requested for additional information lacking in their reports. Any differences in opinion were resolved through discussion.

Assessment of bias risk

The risk of bias of the trials was assessed by two authors independently, without masking of trial names, following the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions*.[3] According to empirical evidence [7-10], risk of bias components were scored as low, unclear, or high. The following risk of bias components were extracted from each trial: generation of the allocation sequence, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other bias risks such as academic bias and source of funding bias. Trials were classified as trials with low risk of bias only if all risk of bias components were scored as low. Otherwise, if one or more of the bias components were scored unclear or with high risk of bias, the trial was considered to have a high risk of bias.

Error matrix approach

Data on the outcomes of all trials were assessed for the risk of bias (measured by the level of evidence), the risk of random error measured by standard error (SE), and the design error measured by grading the outcomes.[11] Data were presented in a three-dimensional Manhattan error matrix which may facilitate the overview of available evidence at a glance and may identify possible lacunae.

Statistical analysis

Meta-analyses were performed according to the *Cochrane Handbook for Systematic Reviews of Interventions* [3] using Review Manager version 5.1.[12] For a dichotomous variable, the risk ratio (RR) with the 95% confidence interval (CI) was calculated if there were two or more trials for an outcome. For events occurring less than 5% the odds ratios (OR) with their 95% CI were calculated. The proportion of patients with the outcome in each group and the *p*-value for the

comparison between the groups was reported. For continuous variables, the mean difference (MD) or the standardized mean difference (SMD) with 95% CI were calculated. For both dichotomous and continuous outcomes a *p*-value of less than 0.05 was considered statistically significant.
A random-effects model [13] and a fixed-effect model [14] were used for meta-analysis in the presence of two or more trials included under the outcomes. In case of discrepancy between the two models, both results were reported. Considering the anticipated abundant clinical heterogeneity the random-effects model was emphasized except if one or two trials dominated the available evidence. Heterogeneity was explored by Cochran´s test. Significance was set at *p*-value 0.10, and the quantity of heterogeneity was measured by I^2.[3,15] The analyses were performed on an intention-to-treat basis whenever possible. Otherwise, the `available-case analysis´ was adopted.[3] No data for the post-randomisation drop-outs for any of the continuous outcomes was imputed.[16]

Sensitivity analyses
In sensitivity analyses the standard deviation was imputed from *p*-values according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* and the median was used for the meta-analysis when the mean was not available.[3] If it was not possible to calculate the standard deviation from the *p*-value or the confidence interval, the standard deviation was imputed as the highest standard deviation noted for that group under that outcome.

Subgroup analyses
It was intended to perform the following subgroup analyses: Trials with low risk of bias (all bias components scored as low risk) compared to trials with high risk of bias (one or more of the bias components scored as unclear or high risk). Trials were divided in two groups based on the time of publication. Results of an initial first group were compared to the results of the second (last) group to evaluate whether results have improved over time. Only subgroup analyses showing statistical significant test of interaction ($p<0.05$) provided evidence that the intervention effect may depend on the subgroup.

Bias exploration
It was planned to use a funnel plot to explore small trial bias [17,18] and to use asymmetry in funnel plot of trial size against treatment effect to assess this bias.

Trial sequential analysis
Cumulative meta-analyses may increase type-I errors due to sparse data and repeated significance testing when updated with new trials.[19,20] To minimize the risk of type-I errors, trial sequential analysis (TSA) was used. TSA combines an estimation of the required information size for a meta-analysis (meta-analysis sample size) with an adjusted threshold for statistical significance of the meta-analysis.[19-21] The latter, called trial sequential monitoring boundaries (TSMB), reduce the

risk of type-I errors. In TSA the addition of a new trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed or not. The idea in TSA is that when the cumulative *z*-curve crosses the TSMB, a sufficient level of evidence has been reached and no further trials may be needed. If the *z*-curve doesn´t cross one of the boundaries for benefit, harm or futility and the required information size has not been reached, there is insufficient evidence to reach a conclusion.[19,20,22,23] Information size was calculated as diversity-adjusted required information size [24] based on an a priori anticipated [5] relative risk reduction of 20% and by the relative risk reduction of the intervention effect suggested in a meta-analysis of the included trials. TSA was performed on all primary outcomes and on all secondary outcomes showing statistically significant differences between the two interventions. The required information size was calculated according to an overall type-I error of 5% and a power of 80%.[24] The analyses were performed using the TSA program and manual, developed by The Copenhagen Trial Unit (CTU, Center for Clinical Intervention Research, Denmark). The TSA software and manual are available at: www.ctu.dk/tsa.

Results

Altogether the search resulted in 16.902 hits. In each step of selection, the publication was included in case of any doubt. A total of 884 hits remained after manual screening of the titles. All abstracts were reviewed independently by two authors. Double publications of trial results were considered as one trial. Based on titles and abstracts 812 publications could be excluded. A total of 72 publications remained for full text evaluation from which 55 were excluded based on the protocol criteria. Finally, seventeen publications describing 13 randomised trials were included (Figure 1). Additional data of each trial was requested by contacting the investigators. None of the included trials used quasi-randomised design.

Patient characteristics and trial designs

All 13 trials used similar inclusion criteria. The specifications of the exclusion criteria varied. From one of the trials information was only available as a poster.[25] Arguments for imbalances in baseline characteristics regarding age, gender, BMI, or ASA classification were not found (Table 1). One study [26,27] consisted of three trials; only the trial comparing TEP versus Lichtenstein was selected. All other trials used a two-arm parallel-group design.[25,26,28-41]

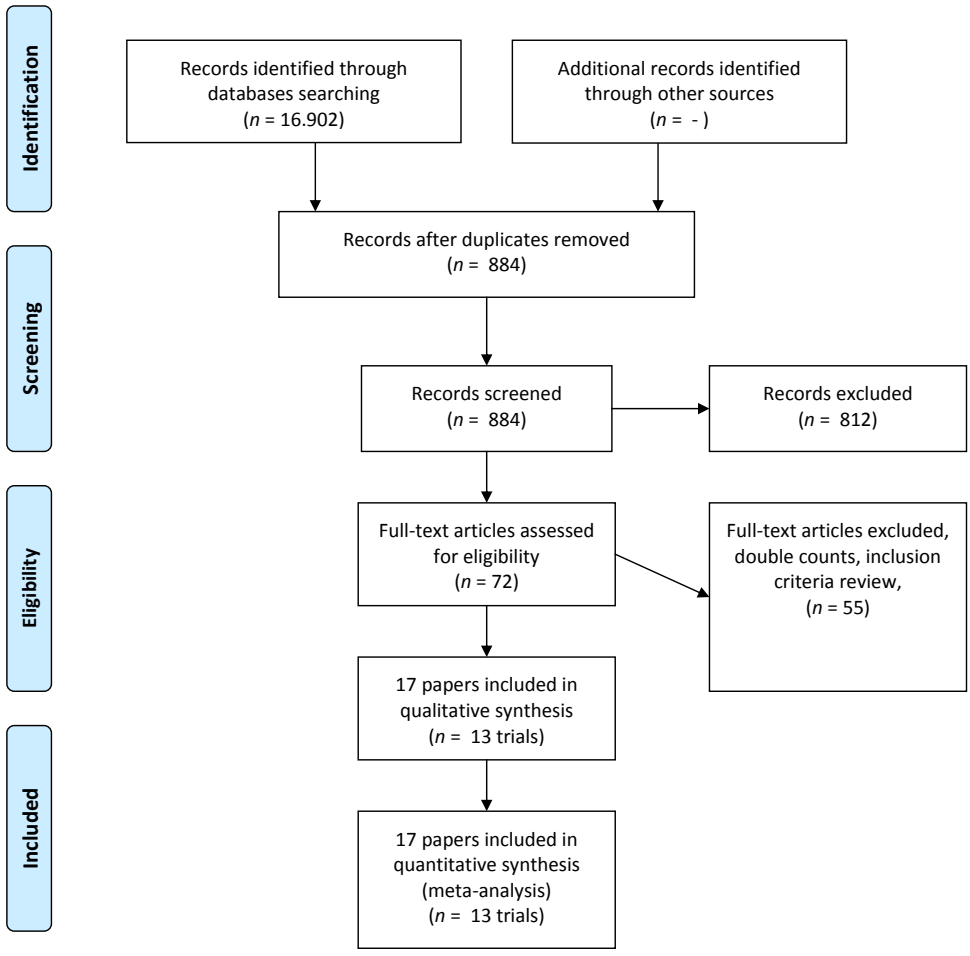


Figure 1: Flow diagram summarizing the search process and results of each phase of the systematic review.

Table 1

Author	Included patients (*n*)	Included patients (*n*)	Multi/Single Center	Age (yr)		Gender		ASA Classification	(I / II / III / IV)
	TEP	*Lichtenstein*		*TEP*	*Lichtenstein*	*TEP*	*Lichtenstein*	*TEP*	*Lichtenstein*
Andersson 2003 [28]	81	87	S	50.0 (SD9)	49.0 (SD9)	M	M	C	C
Colak 2003 [29]	67	67	S	49.4 (R21-78)	51.6 (R16-77)	M57/F10 pts	M62/F5 pts	C	C
Eklund 2006 [30-33]	665	706	M	53.0 (SD10)	52.0 (SD10)	M	M	584/66/5/0 pts	633/57/5/0 pts
Gokalp 2003 [34]	61	62	S	47.0 (R18-59)	45.0 (R18-60)	M	M	72/28/0/0%	64.5/35.5/0/0%
Heikkinen 1998 [26]	23	22	S	44.0 (R21-65)	46.0 (R22-58)	M	M	68/32/0/0%	70/30/0/0%
Hildebrandt 2003 [35]	72	66	S	54.5(SD13.6)	60.0 (SD12.7)	M51/F4 pts	M57/F9 pts	Mean ASA 1.82	Mean ASA 1.49
Merello 1997 [25]	60	60	S	Median 53	Median 51	U	U	C	C
Moreno 1999 [36]	50	50	S	55.0 (R21-80)	60.0(R24-73)	M47/F3 pts	M44/F6 pts	U	U
Neumayer 2004 [37]	1077	1087	M	58.6 (SD12.8)	58.4 (SD12.7)	M	M	34.7/46.8/18.5/0%	33.6 /47.7/18.7/0%
Lal 2003 [38]	25	25	S	36.7(SD12.1)	37.8 (SD12.4)	M	M	C	C
Langeveld 2010 [39]	336	324	M	Median 55	Median 56	M99%	M98%	Mean 1	Mean 1
Lau 2006 [40]	100	100	S	55 (SD15.5)	56 (SD13.1)	M	M	C	C
Wright 1996 [41]	67	64	M	63.0 (R46-71)	68.0 (R51-77)	M56/F4 pts	M59/F1 pts	37/22/1/0 pts	29/28/3/0 pts

Baseline characteristics of randomized TEP- and Lichtenstein patients of all included trials.Author= first author of trial, year and reference, S= single center, M= Multicenter, SD= standard deviation, R= range, M= male, F=female, pts=patients(*n*), C=comparable as mentioned in text, U= unknown, ASA I/II/III/IV= American Society of Anesthesiologists classification.

Surgical interventions

In all trials the TEP hernia repair was performed as published by Voeller.[42] The Lichtenstein technique was performed as described by Amid.[43,44] One trial had a mixed group of TEP and TAPP procedures.[37] However, this trial was included since 90% of the patients were operated with the TEP technique according to personal communication with the author. Open procedures in all trials were Lichtenstein repairs.

Risk of bias

The risk of bias of the included trials was assessed (Figure 2).[3,12] Many bias risk components were unclear. None of the trials used any form of blinding, especially no blinding of outcome assessment. In all trials three or more out of eight bias components were scored as unclear or high risk of bias. Therefore, all trials were classified as high risk of bias trials.

Error matrix approach

In clinical research there are 3 dimensions that have widely been recognized to be important. The included trials were assessed for risks of errors: the risk of bias measured by the level of evidence, the risk of random error measured by standard error, and the design error measured by grading the outcome measures according to GRADE.[6,11]

The outcome measures were graded according to the patients' perspective (Figure 3). All-cause mortality, chronic pain, recurrences, and severe adverse events were considered critical for decision making. Other secondary outcomes were graded important, but not critical for decision making. All trials were assessed as trials with high risk of bias (level of evidence 1d [11]). The standard errors of the meta-analytic estimate were calculated (Table 2). Figure 4a&b shows the three-dimensional 'Manhattan' error matrix consisting of the standard error (SE), the level of evidence and the outcome measures.

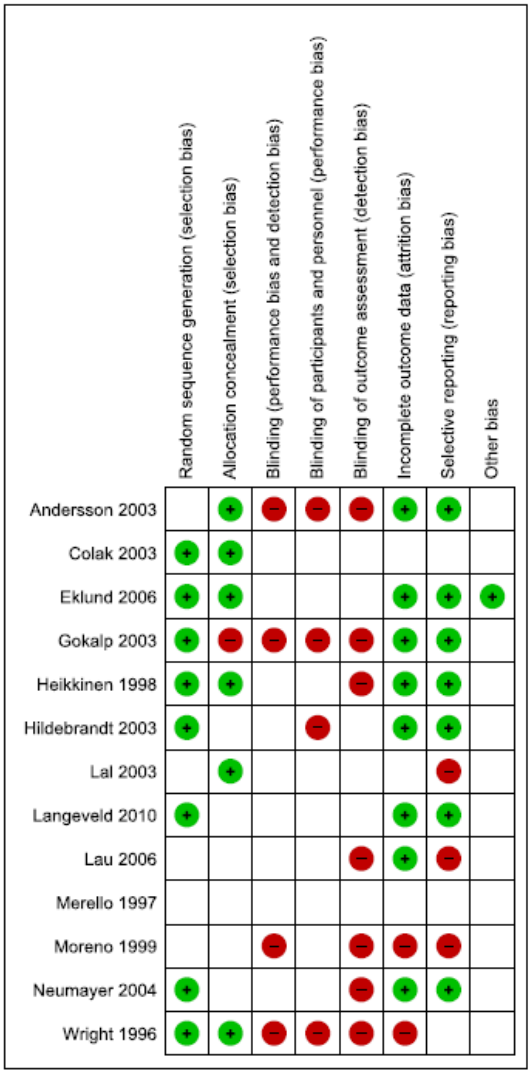
The systematic error distinguishes studies based on their risk of bias. Trials with low risk of bias and data on mortality are absent. At a glance it is noticed that chronic pain was assessed with low risk of random error; in five trials the SE's were between 0.12 and 0.18.

Recurrences are associated with considerable risk of random error (only one trial has SE of 0.17 and all other trials have SE's > 0.50). SAE were also assessed with low risk of random error as five trials had SE's between 0.09 and 0.18.

Effect of interventions

Thirteen trials randomised 5404 patients for inguinal hernia repair between the TEP technique (2684 patients) and Lichtenstein´s technique (2720 patients).

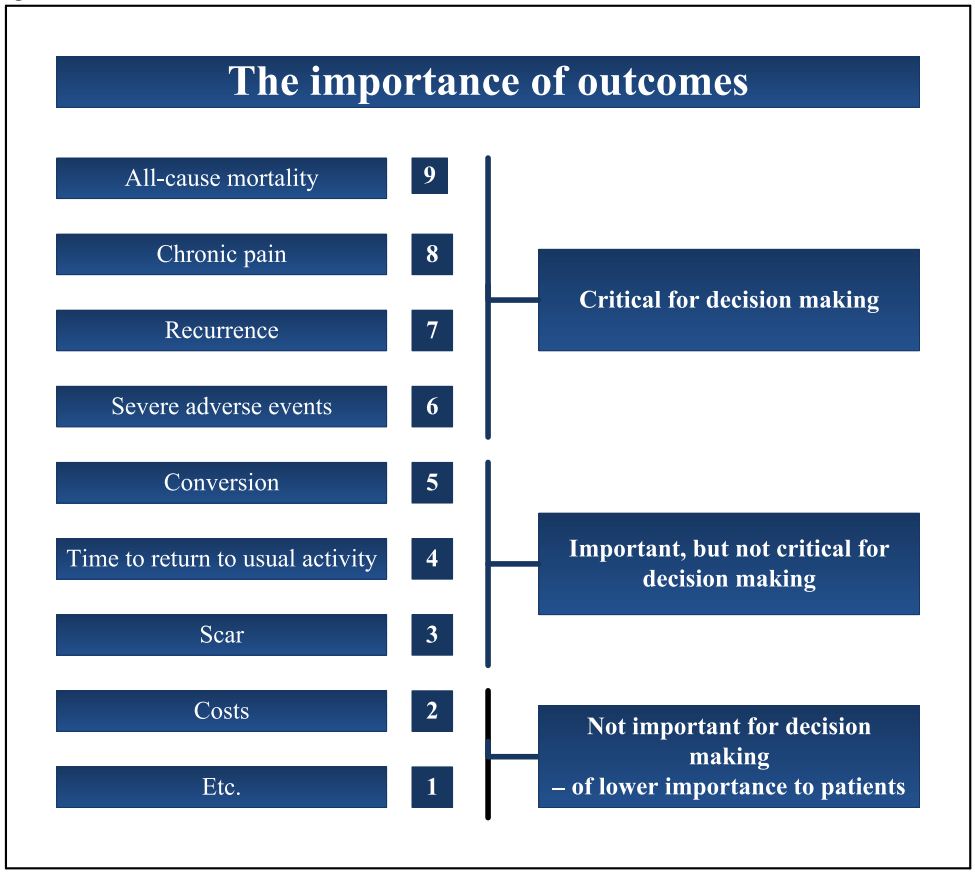
Figure 2



Risk of bias summary of all included trials, the eight criteria on the X-axis. Name of first author and year of trial on Y-axis.

\+ (green) = adequate
\- (red) = inadequate
Blanc (white) = unclear

Figure 3



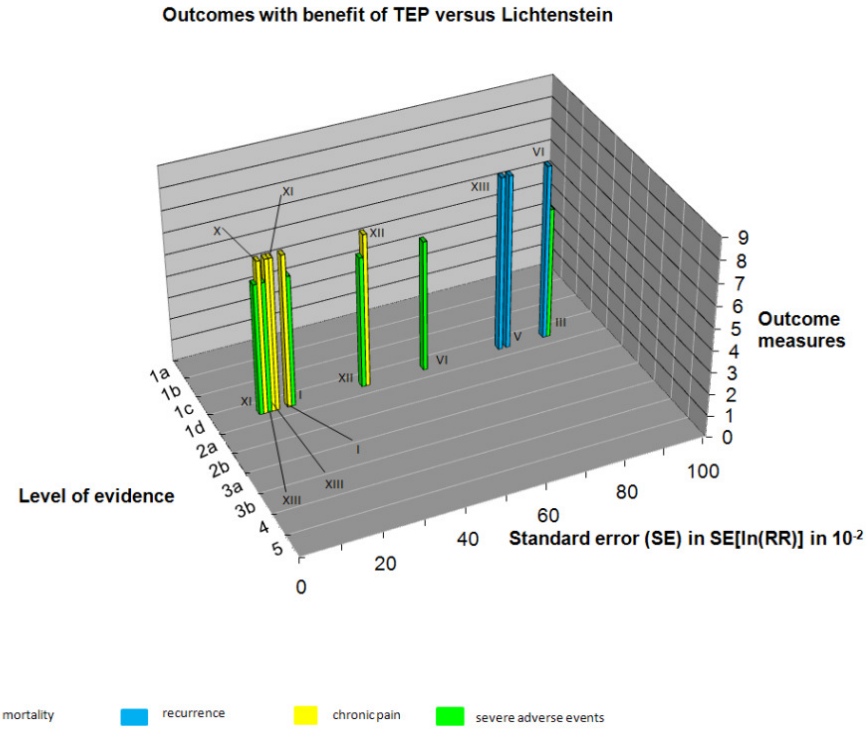
Hierarchy of outcomes according to importance to patients undergoing inguinal hernia repair (GRADE 2004). Some outcome measures may be correlated (e.g. recurrence is included in severe adverse events).

Table 2

Trial		Level of evidence	All cause mortality	Recurrence		Standard error Chronic pain		Severe adverse events	
I	Wright 1996 [41]	1d	n/a	n/a	-	0.18	b	0.18	b
II	Merello 1997 [25]	1d	n/a	z	e	n/a	-	z	e
III	Heikkinen 1998 [26,27]	1d	n/a	z	b	z	b	0.86	b
IV	Moreno 1999 [36]	1d	n/a	z	e	n/a	-	z	e
V	Andersson 2003 [28]	1d	n/a	0.75	b	0.18	h	0.16	h
VI	Colak 2003 [29]	1d	n/a	0.85	b	0.74	h	0.53	b
VII	Gokalp 2003 [34]	1d	n/a	z	e	z	h	z	h
VIII	Hildebrandt 2003 [35]	1d	n/a	z	h	z	h	z	h
IX	Lal 2003 [38]	1d	n/a	z	e	z	h	z	h
X	Neumayer 2004 [37]	1d	z	0.17	h	0.12	b	0.09	h
XI	Eklund 2006 [30-33]	1d	n/a	0.50	h	0.15	b	0.12	b
XII	Lau 2006 [40]	1d	n/a	z	e	0.38	b	0.37	b
XIII	Langeveld 2010 [39]	1d	n/a	0.73	b	0.14	b	0.13	b

Ordering of the available evidence according to levels of evidence (systematic error), standard error (random error) and outcome measures (design error) in TEP versus Lichtenstein patients. b=benefit, h=harm, e=equal, z=zero events in one or both intervention arms. n/a= no data available.

Figure 4a

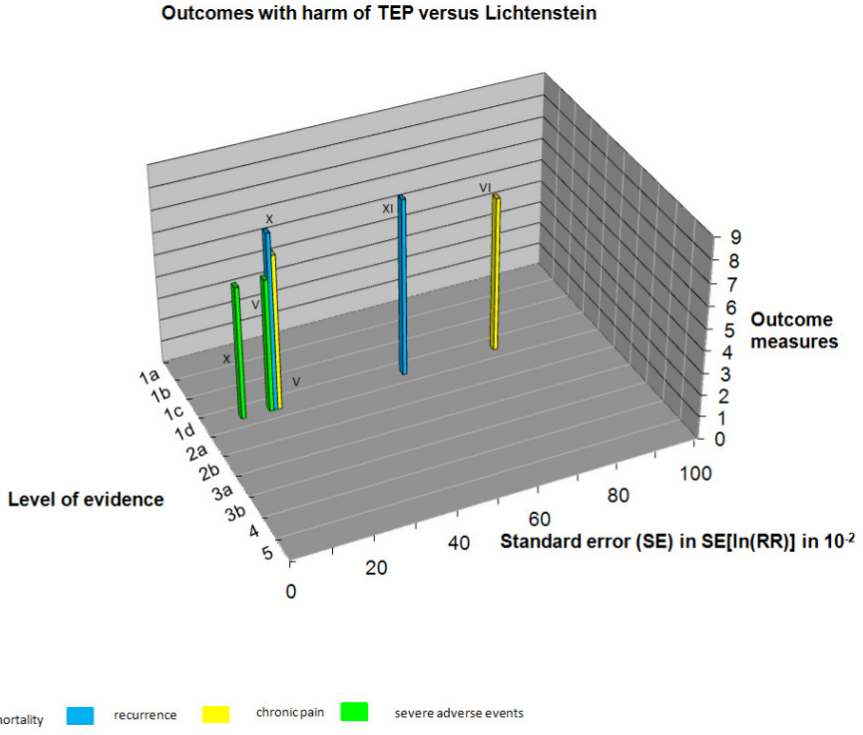


Trials and their outcomes with benefit according to the three dimensions; standard error (SE), graded from patients perspective (0-9) and level of evidence (1a-5). See legenda for references to trial numbers I-XIII.

Legenda for figure 4a and b

No:	Trial:
I	= Wright 1996
II	= Merello 1997
III	= Heikkinen 1998
IV	= Moreno 1999
V	= Andersson 2003
VI	= Colak 2003
VII	= Gokalp 2003
VIII	= Hildebrandt 2003
IX	= Lal 2003
X	= Neumayer 2004
XI	= Eklund 2006
XII	= Lau 2006
XIII	= Langeveld 2010

Figure 4b



Trials and their outcomes with harm according to the three dimensions; standard error (SE), graded from patients perspective (0-9) and level of evidence (1a-5). See legenda for references to trial numbers I-XIII.

Primary outcomes

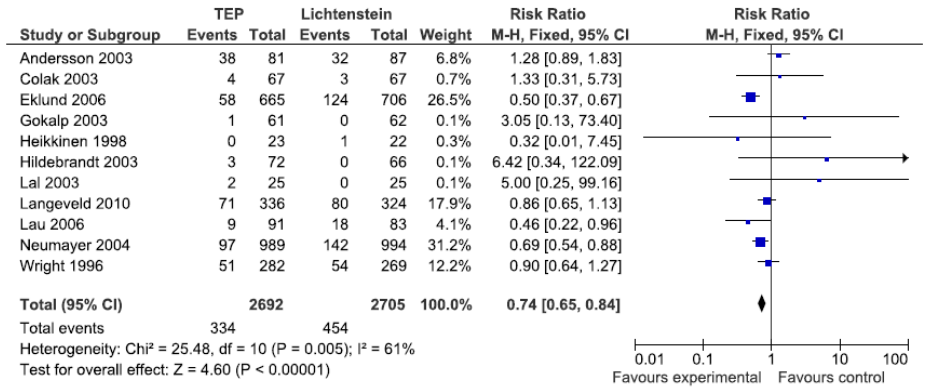
Mortality

No meta-analysis of all-cause mortality was performed as only one trial reported mortality with merely two deaths in the TEP group.[37]

Chronic pain

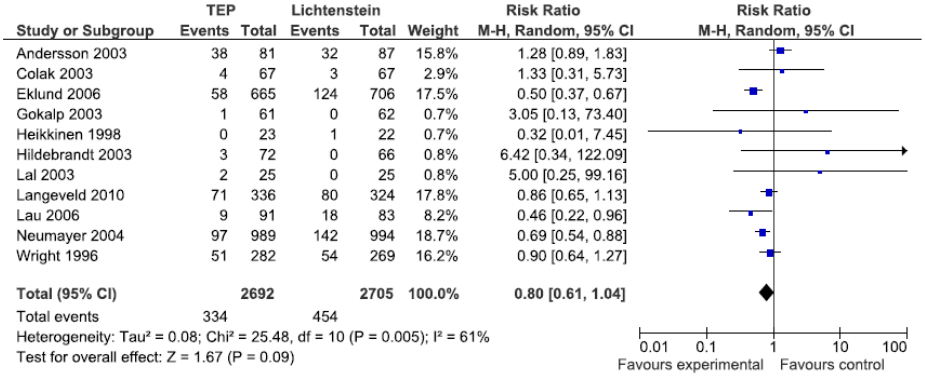
Eleven trials reported on chronic pain defined as persisting pain for longer than three months, in 334 patients (12.4%) in 2692 patients in the TEP group versus 454 patients (16.8%) in 2705 patients in the Lichtenstein group. However, substantial heterogeneity was present (I^2 61%; p=0.005), and the random-effects model showed no statistically significant differences between the TEP and Lichtenstein group (RR 0.80; CI 0.61 to 1.04; p=0.09). Meta-analysis using the fixed-effect model showed significant less chronic pain using the TEP technique (RR 0.74; CI 0.65 to 0.84; p<0.00001) (Figure 5a&b).

Figure 5a



Forest plot on chronic pain. Fixed-effect model.

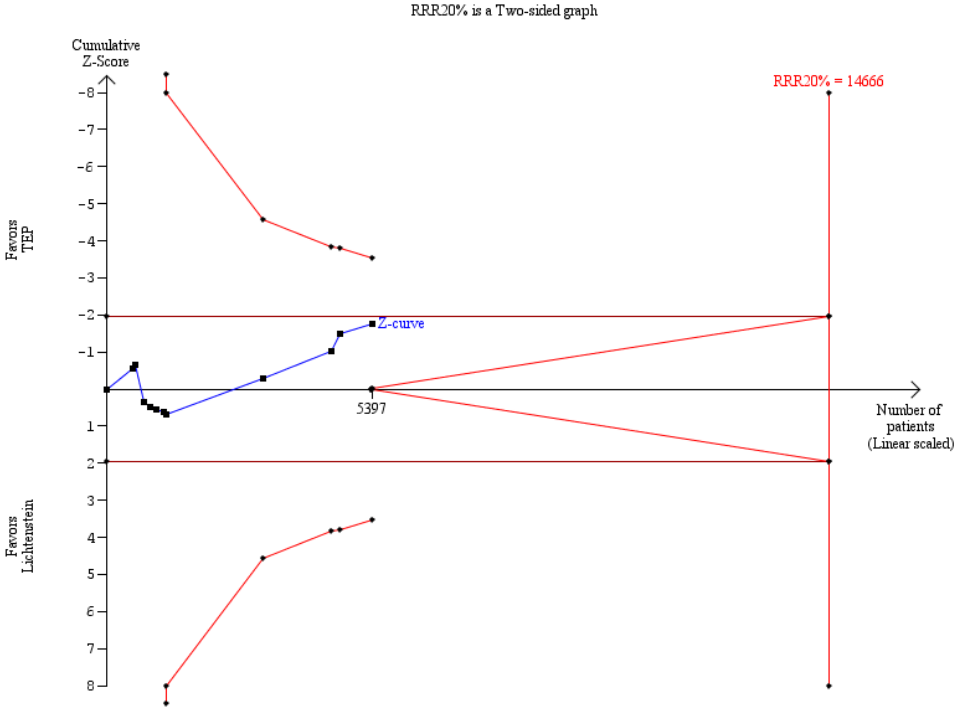
Figure 5b



Forest plot on chronic pain. Random-effects model.

The TSA, assuming a control event rate of 17%, an anticipated intervention effect of 20% relative risk reduction (RRR), and a power of 80%, shows a cumulative *z*-curve without crossing the TSMB (Figure 6). Moreover, the *z*-curve does not even cross the conventional p=0.05 boundary, showing lack of evidence to conclude on the superiority (or futility) in the comparison of the techniques considering chronic pain.

Figure 6



TSA on chronic pain data.
Trial sequential analysis of the effect of TEP vs. Lichtenstein anticipating a realistic relative risk decrease of chronic pain of 20% with TEP compared to Lichtenstein assuming a control event proportion of 17% and a type 1 error risk of 5% and a type 2 error risk of 20% (power=80%). Even in a traditional random-effects meta-analysis the intervention effect is not statistically significant and therefore the cumulative z-curve does not cross the TSMB for harm, constructed for a diversity-adjusted required information size of 14.666 participants either suggesting lack of evidence for TEP reducing the proportion of patients with recurrence.

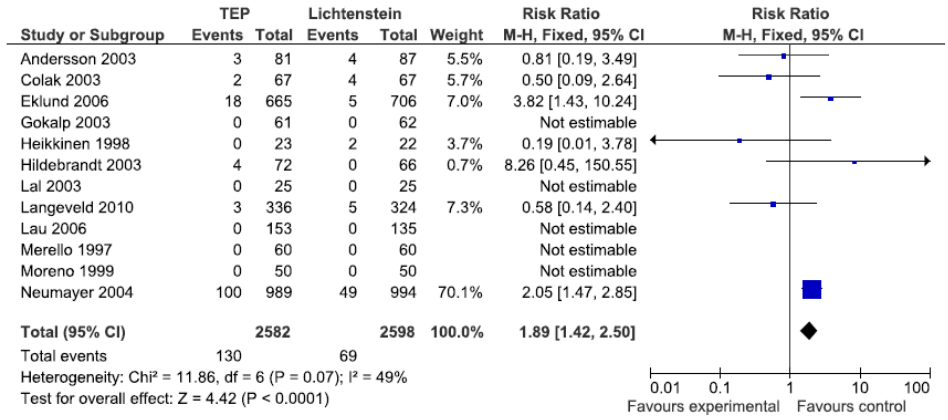
Recurrences

All 13 trials reported on recurrences with 130 recurrences (5.0%) out of 2583 patients in the TEP group versus 72 recurrences (2.7%) out of 2598 patients in the Lichtenstein group.

Meta-analysis using the fixed-effect model showed significant more recurrences in the TEP group (RR 1.89; 95% CI 1.42 to 2.50; p=0.0001).

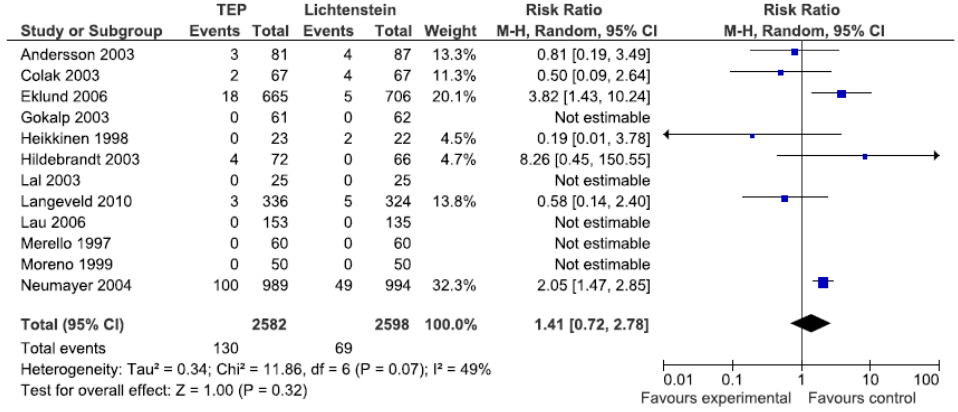
Random-effects meta-analysis showed no statistically significant difference (RR 1.41; 95% CI 0.72 to 2.78; p=0.32) I^2=49% (Figure 7a,b). Calculations using OR did not show noticeable difference.

Figure 7a



Forest plot on recurrence. Fixed-effect model.

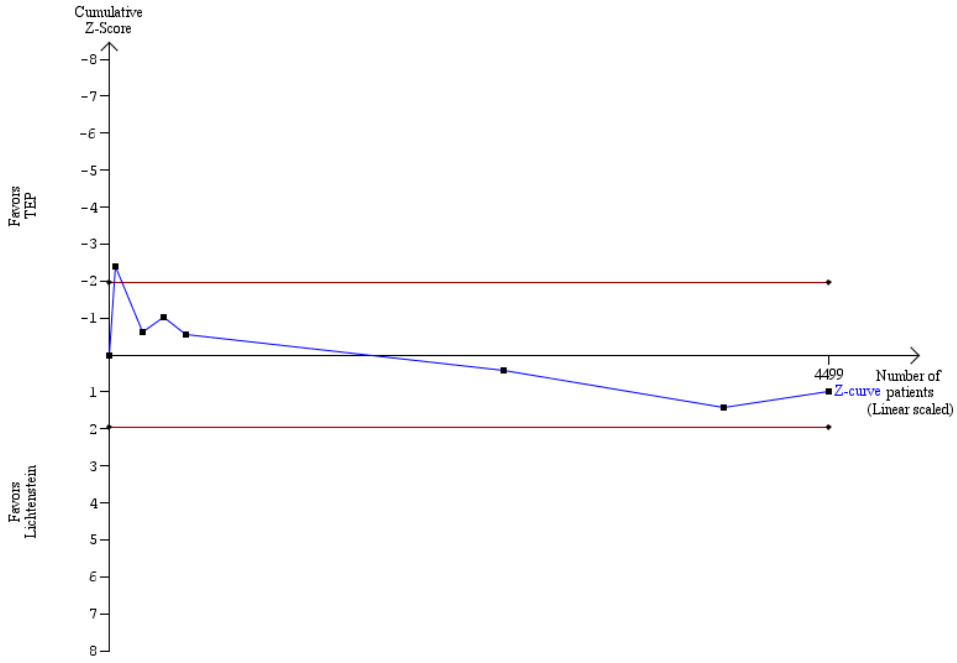
Figure 7b



Forest plot on recurrence. Random-effects model.

TSA assuming a control event proportion of 3%, an anticipated intervention effect of 20% RRR, and a power of 80% showed no crossing of either the TSMB, the conventional boundary, or futility boundaries (Figure 8). TSA showed that many more randomised patients are needed before firm evidence can be reached as the diversity adjusted information size is incalculable.

Figure 8



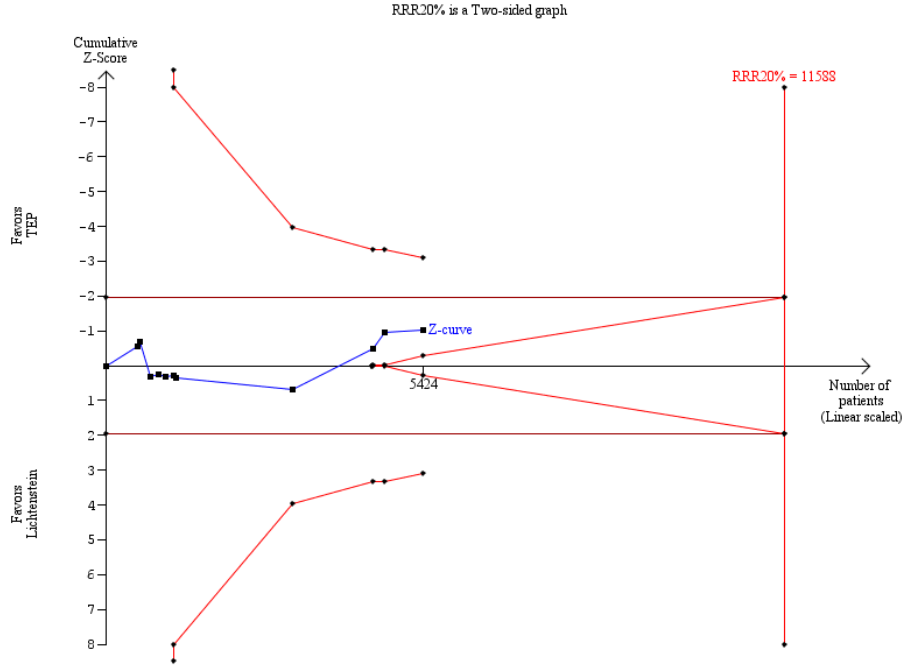
TSA on recurrences TEP versus Lichtenstein.
TSA of the effect of TEP vs. Lichtenstein anticipating a realistic relative risk increase of recurrence of 20% with TEP compared to Lichtenstein assuming a control event proportion of 3%, a type 1 error risk of 5%, and a type 2 error risk of 20% (power=80%). Even in a traditional random-effects meta-analysis the intervention effect is not statistically significant and therefore the cumulative z-curve does not cross the TSMB for harm. The required information size is incalculable due to too little information available, suggesting lack of evidence for TEP reducing the proportion of patients with recurrence.

Severe adverse events

All 13 trials reported on the composite outcome measure of severe adverse events (SAE) including all serious complications. There were 509 patients (18%) with SAE out of 2811 patients in the TEP group versus 559 patients (20%) with SAE out of 2833 patients in the Lichtenstein group. Meta-analysis using both the random-effects models (RR 0.91; CI 0.73 to 1.12; p=0.37) (I^2=58%) and the fixed-effect model (RR 0.92; CI 0.83 to 1.02; p=0.12) showed no statistical significant difference between the TEP and the Lichtenstein technique.

TSA assuming a control event proportion of 20%, an anticipated intervention effect of 20% RRR and a power of 80% showed that the cumulative z-curve did not cross neither the TSMB the conventional, nor the futility boundaries (Figure 9).

Figure 9



TSA on severe adverse events, TEP versus Lichtenstein.
TSA of the effect of TEP vs. Lichtenstein anticipating a realistic relative risk reduction of severe adverse event of 20% with TEP compared to Lichtenstein and assuming a control event proportion of 20% and a type 1 error risk of 5% and a type 2 error risk of 20% (power=80%). Even in a traditional random-effects meta-analysis the intervention effect is not statistically significant and therefore the cumulative z-curve does not cross the TSMB constructed for a diversity-adjusted required information size of 11.588 participants suggests lack of firm evidence that TEP reduces the proportion of patients with severe adverse events when the analysis adjusts the significance level for considering sparse data and repetitive testing on accumulating data.

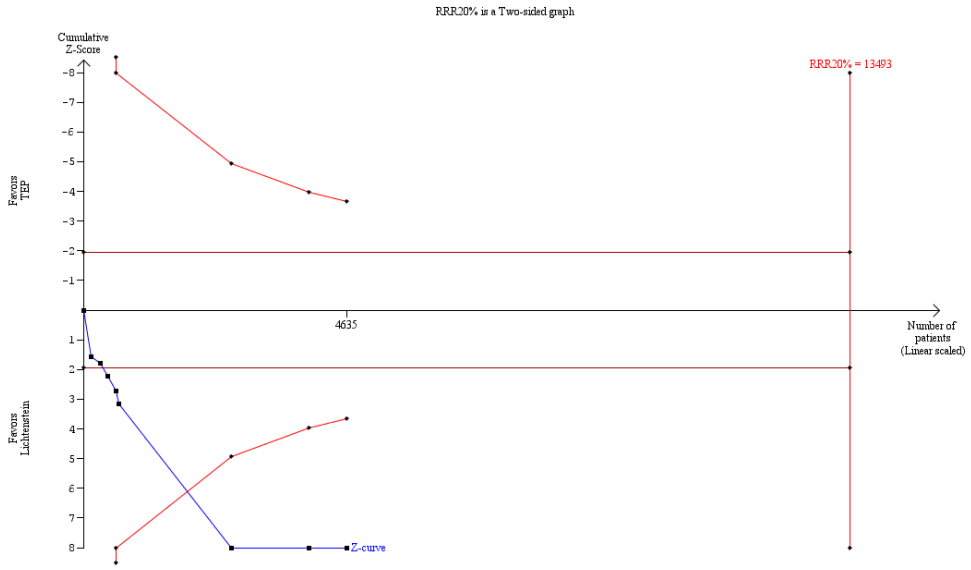
Secondary outcomes

Conversions

Ten of the 13 trials reported conversion. There were 168 patients with conversions (7%) in 2425 patients in the TEP group versus 22 patients with conversions (1%) in 2455 patients in the Lichtenstein group. Meta-analysis using both the fixed- and random effects models showed significantly more conversions in the TEP group (fixed-effect model, RR 6.96; 95% CI 4.58 to 10.58; p=0.00001). No heterogeneity was present (I^2=0%).

TSA assuming a control event proportion of 5%, an anticipated intervention effect of 20% RRR and a power of 80% showed that the z-curve did cross the TSMB showing firm evidence that TEP is associated with substantially more conversions compared to the Lichtenstein technique (Figure 10).

Figure 10



TSA shows more conversions for TEP compared to Lichtenstein.

Time to return to usual activity, hospital stay and operative time

There was a huge variation in return to usual activity (I^2=78%), hospital stay (I^2=81%), and operative time (I^2=96%) in the included trials. Therefore, pooling of data was not performed.

Other outcomes: persisting numbness

Eight trials reported persisting numbness. There were 70 patients (4.3%) with persisting numbness out of 1616 patients in the TEP group versus 205 patients (12.5%) out of 1639 patients in the Lichtenstein group. The random-effects model (I^2=37%) showed significant less persisting numbness when using the TEP technique (RR 0.32; 95% CI 0.21 to 0.49).

TSA assuming a control event proportion of 12%, an anticipated intervention effect of 20% (RRR), and a power of 80% showed that the *z*-curve did cross the TSMB indicating firm evidence, notwithstanding the high bias risk, that TEP is associated with less persisting numbness compared to Lichtenstein.

Subgroup analyses

As none of the trials had low risk of bias and trial reports did not clearly mention different anaesthesia techniques, the pre-planned subgroup analyses could not be conducted. No indications were found that the year of publication was associated with any of the outcome results. The funnel plots (Attachment 2) showed no clear arguments for small trial bias including publication bias [chronic pain: Begg's test: p=0.53 (2-tailed); Egger's test: p=0.35 (2-tailed) and SAE: Begg's test: p=0.76 (2-tailed); Egger's test: p=0.60 (2-tailed)].

Discussion

This systematic review with meta-analysis included thirteen trials randomizing 5404 patients comparing the TEP with the Lichtenstein technique. So far, there is no conclusive evidence of differences in proportions of patients with chronic pain and recurrences between the two techniques. Data have been evaluated according to the three dimensions of risk of error: bias, `play of chance´, and design. Trials fall short on the bias protection, the included numbers of patients, and the chosen outcomes. Trial sequential analysis (TSA) and the error matrix approach were used in addition to conventional meta-analytic techniques to reach these conclusions, favouring one technique over the other, based on firm evidence, cannot be drawn yet. There is neither evidence that one technique favours the other nor for a 20% non-inferiority comparing the two techniques.

All trials must be classified as having high risk of bias, as they all scored unclear or high risk of bias in three or more of the eight bias risk components (Figure 2). Therefore, the meta-analytic effect estimates in our analyses may eventually appear to overestimate the effect when trials with low risk of bias emerge.[21–23] In this review proportions of SAE are high, 18% and 20%, respectively, in the TEP and Lichtenstein group. These percentages are higher than the maximally reported in other reviews that include non-randomised cohorts.[1] However, this is in concordance with methodological studies showing linkage between unclear / inadequate bias control and risk of significant overestimation of beneficial effects and underestimation of adverse effects.[45]

There is substantial risk of random error regarding the primary outcomes of chronic pain, recurrences, and severe adverse events (Table 2 and Figure 4a,b). TSA shows that many more randomised patients may be needed, e.g. 9269 and 6164 respectively, considering chronic pain and SAE before a conclusion on effect or lack of effect can be reached. Recurrence seems to be so rare that the required number of patients needed to identify an effect is incalculable.

In this review the outcome measures were graded from the patients' point of view according to GRADE, focusing on the patient important outcomes critical for decision making.[6,11] Chronic pain, recurrence and SAE were considered as such critical outcomes.[5]
Before the use of a mesh became standard (e.g. Bassini´s technique), recurrence was regarded as the most important outcome in inguinal surgery. After non-mesh repair using Bassini´s technique at least 8% of patients may experience recurrence.[46] However, after introduction of the mesh the number of patients with recurrence is reported as low as 2% with Lichtenstein's technique.[47] Reduced numbers of patients with recurrence and mesh-associated pain have drawn the attention towards another primary outcome: chronic pain. Up to 40% of patients having chronic pain has been reported recently after the Lichtenstein's technique.[48]

It is uncertain whether low-weight or 'soft' meshes decrease the number of patients with chronic pain, however, sufficient data on the type of mesh was not available from trials included in this review.

This review focuses on primary outcomes, graded as critical for decision making.[6,11] Secondary outcomes were not considered to be equally important. Inguinal hernia repair is largely a day-case procedure.[49] Budget restrictions, logistic arguments, surgeon´s habits, or organizational procedures may be involved in different cultural situations making comparison and pooling of outcomes like hospital stay and operative time unreliable. Moreover, in the meta-analyses (clinical as well as statistical) heterogeneity appears to be high. Therefore, from the patients' perspective, outcomes like hospital stay and duration of operation should probably be avoided for deciding whether one technique should be preferred for another as long as critical outcomes have not been sufficiently evaluated (Figure 3).

Previous reviews suggest lower proportions of chronic pain associated with TEP.[1] However, these reviews did consider heterogeneous groups of interventions (TEP and TAPP) and they conducted a multitude of post hoc subgroup analyses making conclusions premature and unreliable. Moreover, the superiority of one technique cannot be claimed based on comparisons of heterogeneous groups of interventions. There is still a considerable risk that the advantage of the TEP procedure suggested by the fixed-effect model, ignoring the large heterogeneity, may turn out to be the combined result of bias and random-error.

The included trials did not consider any learning curve effect on both techniques. However, learning curve effects probably do influence effect estimates. The learning curve of the TEP technique may be less steep compared to the Lichtenstein technique, and therefore results of the TEP technique may have been less favourable than expected. It may be that highly experienced and dedicated hernia surgeons in large volume centres produce more favourable results with TEP, regarding the important outcomes from patients' perspective. Residents or non hernia-dedicated surgeons participating in the trials may have produced the heterogeneous results. Therefore, common clinical practice and the number of patients with complication ought to be followed up through clinical databases and compared with benchmark values.[3]
After completing this review, it is concluded that chronic pain continues to remain an important issue after hernia surgery. Both techniques (TEP and Lichtenstein) are associated with considerable rates of chronic pain. It has to be established whether the suggested point estimate of the relative risk reduction of approximately 20% of pain and SAE with TEP is actually "free" of bias and random error.

A priori, a composite outcome measure of SAE including chronic pain, deep wound infections, vascular injuries, visceral injuries and recurrences was constructed.[5] This summary outcome may have included patients counted twice since complications are summarized rather than considering the total number of patients with one or more SAE. Although all trial authors were contacted repetitively for additional data, their response rate was low. However, since the vast majority of patients recover without any SAE it was hypothesized that this sampling error only occurred occasionally.

Future trials and studies should be well argued before they are launched. However, even though databases may provide large numbers of patients, and, given they inform on consecutive cohorts of patients and may provide some answers of the actual status on benefits and harms, they will always be prone to the huge risk of bias introduced by the choice of intervention by indication. None of the trials included in this review are large trials in the sense that they statistically have the power to detect or exclude even rather large intervention effects on important outcomes. Therefore, future studies should plan to check their position along the 3 dimensions of possible errors: bias, `the play of chance´ and the choice of outcomes. It has been proven extensively that trials with low risk of bias produce more reliable results compared with trials with high risk of bias. [3,10]

Despite how provocative it may seem and based on the above considerations, it is proposed to conduct a new large trial (or several trials) with low risk of bias and with outcomes critical for decision making.

These future trials should focus on comparing techniques each using a preperitoneal mesh position [42,47,49], and use the present reference technique as comparator (Table 3).

Table 3

Item	Recommendation
To avoid bias	The trial report should be able to fulfill the CONSORT statements.[50]
To minimize risk of random error	The sample size should be exceed e.g. 2000 patients. It may not be just one trial, but at least the total number of patients accrued in future trials exceed 2000.
To avoid design error	*One* technique, no mixed groups (e.g. just TEP).
Comparator intervention	*One* reference technique (e.g. just Lichtenstein).
Comparison	Outcome measures critical for decision making according to the GRADE.[6]
To get the evaluation of serious adverse advents (SAE) right	**Count the patients** with one or more SAE, and not just the total number of SAE. This will lead to less multiple counts and avoid sampling error when the outcome is evaluated. This outcome may very well be the most important at the end of the day.
Mesh position	Preperitoneal (sublay) position.

Checklist of recommendations for future randomised clinical trials, comparing the TEP with the Lichtenstein technique. In an attempt to bridge the information gap a new trial should at least comprise as many patients as the hitherto largest and that preferably several new trials will be needed with at least as many patients as it takes to produce a boundary break through (boundary for benefit, harm or futility) in the TSA, or in the worst case scenario; to close the gap between the required and the presently accrued information size.

Attachment 1: Search Strategy

PubMed/MEDLINE:
("Clinical Trials as topic" [MeSH Terms] OR "Randomised Controlled Trials as Topic" [MeSH Terms] OR random* OR trial) AND (TEP OR TEPP OR (total* AND extraperiton*) OR lichten* OR *liechten* OR laparosc* OR "Laparoscopy" [MeSH Terms] OR preperiton* OR (endosc* AND (inguinal hernia OR "Hernia, Inguinal" [MeSH Terms])))

MeSH terms used: Clinical Trials, Randomised Controlled Trials, Totally extraperitoneal, transabdominal preperitoneal, Lichtenstein, Liechtenstein, laparoscopy, endoscopy, preperitoneal, inguinal hernia, hernia, inguinal.

CENTRAL (Wiley):
(Inguinal hernia or groin hernia) in Title, Abstract, Keywords, OR Hernia, Inguinal in MeSH descriptor in Trials in the Cochrane Central Register of Controlled Trials (http://www.thecochranelibrary.com).

EMBASE (OvidSP):

1 tep.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: totally extraperitoneal

2 tepp.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: totally extraperitoneal

3 (total* and (extraperiton* or extra periton*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: totally extraperitoneal, extraperitoneal

4 (lichtenst* or liechtenst*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: Lichtenstein, Liechtenstein

5 laparosc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: laparoscopy

6 (pre periton* or preperiton*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: pre peritoneal, preperitoneal

7 (endosc* and inguinal hernia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: endoscopy, inguinal hernia

8 1 or 2 or 3 or 4 or 5 or 6 or 7

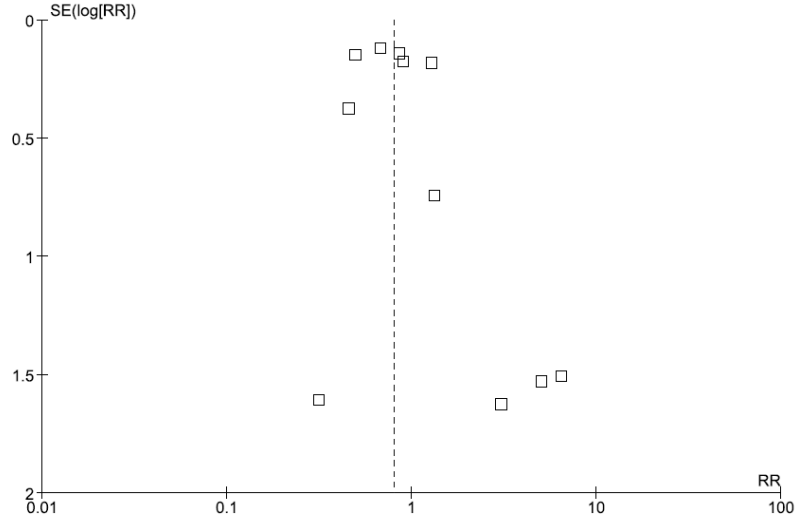
9 (random* and trial).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Terms: randomised trial, randomised trial

10 8 and 9

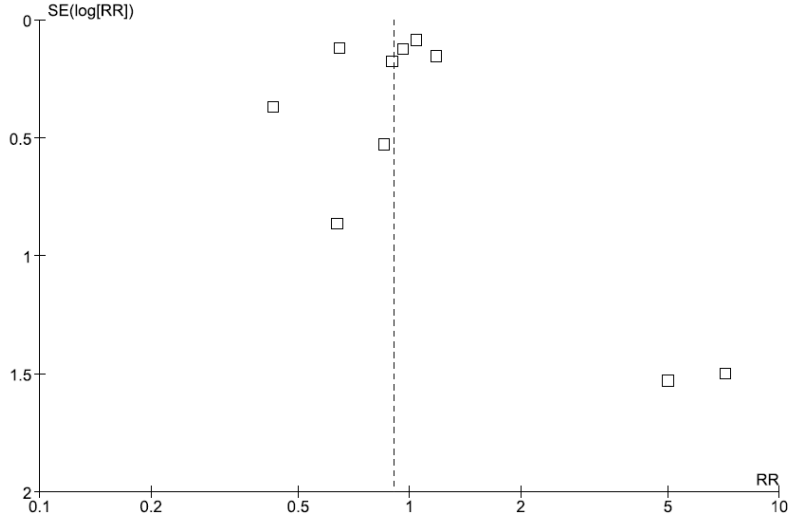
Terms used: Clinical Trials, Randomised Controlled Trials, Totally extraperitoneal, transabdominal preperitoneal, Lichtenstein, Liechtenstein, laparoscopy, endoscopy, preperitoneal, inguinal hernia, hernia, inguinal.

Attachment 2: Funnel plots

The funnel plot on **chronic pain** (Begg's test: p=0.53 (2-tailed); Egger's test: p=0.35 (2-tailed)).



The Funnel plot on **severe adverse events** (SAE) (Begg's test: p=0.76 (2-tailed); Egger's test: p=0.60 (2-tailed)).



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Chapter 3

The transinguinal preperitoneal hernia correction versus Lichtenstein's technique: is TIPP top?

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According to the article in Hernia 2011;15:19-22

Abstract

Background

Chronic pain is the main drawback of the Lichtenstein procedure for inguinal hernia repair, with a reported incidence of 15–40%. The transinguinal pre-peritoneal (TIPP) technique seems to be associated with less chronic pain, comparable to the total extra peritoneal (TEP) technique. The aim of this study was to evaluate 3 years of TIPP and Lichtenstein experience since the start of our Hernia Center Brabant in January 2006.

Methods

Patient records of unilateral primary inguinal anterior hernia corrections (TIPP and Lichtenstein) performed since the opening of Hernia Center Brabant (2006–2008) were evaluated in a retrospective study. ASA class 4 and 5, <18 years, recurrences and bilateral hernias were excluded. In the TIPP technique, a Polysoft™ Hernia Patch was placed into the preperitoneal space using an anterior protocol led approach. The Lichtenstein technique was performed as described by Amid [Amid et al (1996)] and modified with a soft mesh. One of the hernia surgeons decided peroperatively which technique to perform. Baseline characteristics and postoperative complications were assessed retrospectively. The attempted follow up period was 6 months. Chronic pain was assessed in both groups as mild (VAS 1–3), moderate (VAS 4–6) or severe (VAS 7–10). Chronic pain was defined in both groups as any pain sensation lasting longer than 3 months postoperatively, or when local injection of analgesia was necessary. Patients who did not come back because of chronic pain after regular follow up were regarded as free of pain.

Results

A total of 496 patients were included in this study; 225 TIPP and 271 Lichtenstein anterior inguinal hernia operations were analyzed. Data from one TIPP-patient were lost. Both groups were comparable with regard to baseline characteristics regarding age (p = 0.059), gender (p = 0.478) and ASA-classification (p = 0.104).

TIPP group: mean age 52.7 years, ASA-classification I: 54%, II: 36% and III: 5.3%. A total of 7.6% complications were assessed; recurrence (n = 1), bleeding (and re-operation) (n = 4); chronic pain (n=10; 4.4%). Persisting sensation loss (numbness) occurred in 0.9%.

Lichtenstein group: mean age 57.3 years, ASA-classification I: 51%, II: 38% and III: 11%. A total of 8.5% complications were assessed; recurrence (n = 3), bleeding (and re-operation) (n = 3); chronic pain (n=11;4.1%). Persisting sensation loss occurred in 2.2%. Limitations of this retrospective study were incomplete follow up (31.3% had only one post operative visit 14 days after surgery) and these patients were further regarded as free of pain. Therefore, possible under-reporting of chronic pain could be present. The study was not double blind.

Conclusion

This retrospective unmatched cohort study revealed no significantly better results for the TIPP procedure as compared to the Lichtenstein technique. The incidence of chronic pain in this study was low in both groups. These results, and acknowledged possible biases inherent to the study design, form the basis for a prospective randomised controlled trial comparing the TIPP and Lichtenstein techniques.

Introduction

Tension-free mesh inguinal hernia repair has reduced the incidence of recurrence of hernia to 2–5% [1]. The gold standard technique (Lichtenstein) is the typical mesh repair technique. Nowadays chronic pain, with a reported incidence of 15–40%, is the main complication and is associated with the Lichtenstein procedure [2, 3]. The transinguinal pre-peritoneal (TIPP) technique seems to be associated with less chronic pain, comparable to the total extra peritoneal (TEP) technique [4]. Chronic pain has significant effects on all daily activities, including walking, work, sleep, relationships with other people, mood and general enjoyment of life [3, 5]. Thus, much effort has been put into strategies to reduce chronic pain. Specialized hernia centers have reported excellent results after endoscopic repair. This "concentration of care" principle may be associated with less complications, steep learning curves and a higher quality of life for patients after operation. In line with assumed improvement due to this "concentration of care" since January 2006, all hernia repairs of the St. Elisabeth Hospital and the TweeSteden Hospital in Tilburg, the Netherlands, were performed in The Brabant Hernia Center (www.liesbreukcentrumbrabant.nl).
The aim of this study was to evaluate 3 years of TIPP and Lichtenstein experience since the opening of this hernia center.

Methods

Patient records of unilateral primary inguinal hernia corrections (TIPP or Lichtenstein) performed in the Hernia Center Brabant from January 2006–December 2008 were evaluated in a retrospective unmatched cohort study (Level of evidence 3b). Patients with ASA class 4 and 5, younger than 18 years, operated for recurrences or bilateral hernias were excluded from analyses. Cases where preperitoneal surgery had been previously performed were also excluded. Combined sessions (e.g., inguinal hernia repair, radical prostatectomy or vasectomy) were excluded from analyses. Only TIPP and Lichtenstein techniques were analysed. Hernias were not classified according to a defined hernia classification system (such as described by the EHS) at that time. In this study population, groin hernia was corrected according to Lichtenstein as described by Amid et al. [6], i.e., adapted to present-day insights; the use of a soft mesh (Soft Mesh™, BARD, Benelux, Belgium). The other technique used in this population was the TIPP technique with a Polysoft™ Hernia Patch (BARD, Benelux, Belgium). This technique involves a standard anterior approach, with high dissection of the sac reducing the preperitoneal space (PPS) through the internal ring. Blunt dissection in the PPS was carried out using one finger or large dissection gauze through the internal orifice, and was then extended deep towards epigastric vessels and transverse fascia in the direction of the pubic spine. The hernia patch was introduced in the PPS via the internal orifice. The patch has a memory ring and unfolds easily. Because only regional or local anaesthesia was used, the patient was asked to strain or cough, which allows correct

anatomical spreading of the mesh after removal of the gauze. External oblique aponeurosis repair superficial to the cord was performed to restore normal anatomy. Hernia surgeons changed their standard technique (Lichtenstein) to TIPP after its introduction in Tilburg. After 3 years, data of this the unmatched cohort of TIPP and Lichtenstein patients were analyzed. Baseline characteristics and postoperative complications were assessed. The follow up data in the patient record files were assessed for a period of 6 months postoperatively. Chronic pain was assessed in both groups as mild (VAS 1–3), moderate (VAS 4–6) or severe (VAS 7–10) retrospectively, based on descriptions in patient records. Chronic pain was defined in both groups as any form of pain sensation lasting longer than 3 months postoperatively, or when local injection of analgesia was necessary. Patients who did not come back after operation because of chronic pain after regular follow up were regarded as free of pain. To prevent recall bias, the TIPP and Lichtenstein patients were not questioned by telephone in this study. There was no defined protocol for standardized follow up. Case record forms were searched only for available data concerning chronic pain.

Results

A total of 689 unilateral hernia corrections of all kinds were performed in the Hernia Center during the study period. Reasons for exclusion (n = 193; 28%) were: children, recurrences from other hospitals, previous surgery in PPS or bilateral hernias (TEP). 496 patients with a primary inguinal hernia were included in this study.

225 (32.7%) were TIPP and 271 (39.3%) Lichtenstein procedures. Data from one TIPP-patient were lost. Both groups were comparable with regard to baseline characteristics in terms of age (p = 0.059), gender (p = 0.478) and ASA classification (p = 0.104).

Transinguinal pre-peritoneal repair: mean age 52.7 years, ASA-classification I: 54%, II: 36% and III: 5.3%. A total of 7.6% complications were assessed; recurrence (n = 1), bleeding (and re-operation) (n = 4); chronic pain (n=10; 4.4%) (mean VAS 4.6, range 1–6). Persisting sensation loss (numbness) occurred in 0.9%.

Lichtenstein repair: mean age 57.3 years, ASA-classification I: 51%, II: 38% and III: 11%. A total of 8.5% complications were assessed; Hernia recurrence (n = 3), bleeding (and re-operation) (n = 3); chronic pain (n=11; 4.1%) (mean VAS 5.3, range 3–9). Persisting sensation loss occurred in 2.2% (Table 1).

Table 1

Baseline characteristics	Lichtenstein	TIPP	p value
Patients (n)	271	225	-
Mean age (years)	57	53	0.059
Gender (M/F)	257/14	210/15	0.478
ASA 1	139 (51%)	121 (54%)	
ASA 2	103 (38%)	82 (36%)	0.104
ASA 3	29 (11%)	12 (5.3%)	
Mean duration of operation (min)	45	41	0.004
Bleeding	3 (1.1%)	4 (1.8%)	0.707
Chronic pain	11 (4.1%)	10 (4.4%)	0.832
Mean VAS score (range)	5.3 (3-9)	4.6 (1-6)	0.653
Persisting sensation loss	6 (2.2%)	2 (0.9%)	0.302
Recurrence	3 (1.1%)	1 (0.4%)	0.630
Total complications	23 (8.5%)	17 (7.6%)	0.868

Baseline charateristics of transinguinal pre-peritoneal repair (TIPP) and Lichtenstein repair groups.

Discussion

Tension-free mesh repair has reduced the incidence of recurrence and direct post operative pain in inguinal hernia repair. The incidence of recurrences is 2–5% [1, 6]. However, chronic pain after inguinal hernia repair is an underestimated problem [2]. The exact incidence of chronic pain is unknown. Well conducted, large and unselected epidemiological studies suggest that about 20% of patients are affected with chronic pain [3–5, 7]. Chronic pain has significant effects on all daily activities, including walking, working, sleep, relationships with other people, mood and general enjoyment of life [7]. Thus, much effort has been put into strategies to reduce chronic pain. Specialized hernia centers have reported excellent results after endoscopic repair. This "concentration of care" principle is possibly associated with less complications, steep learning curves and a higher quality of life for patients after operation.

Chronic pain is the main problem associated with the Lichtenstein procedure, with a reported incidence of more than 15% [7]. Suggestions to reduce chronic pain include the three-nerve-recognizing Lichtenstein procedure or triple neurectomy. Disadvantages of damaging the inguinal nerves are the loss of sensation in the affected dermatome. In our series, this inadvertently persisting sensation loss during regular procedures affects a considerable proportion of patients treated with the Lichtenstein procedure (Table 1), and underreporting of these sensory loss findings is possible.

The TIPP technique, as described by Pélissier, seems to be associated with less chronic pain, comparable to the total extra peritoneal (TEP) technique [8–10] The drawback of endoscopic hernia repair over the open approach is the added cost, particularly when disposable instruments are used [11]. The other disadvantages of endoscopy, compared with open hernia repair, are general anaesthesia [12] and TEP may be associated with a long learning curve. Complications of endoscopic hernia repair are rare but can be severe.

Since January 2006 all hernia repairs at the St. Elisabeth Hospital and the TweeSteden Hospital in Tilburg, the Netherlands, have been performed in the Brabant Hernia Center (www.liesbreukcentrumbrabant.nl). TIPP and Lichtenstein are performed according to standardized protocols based on initial descriptions of these procedures by Pélissier and Amid. The Lichtenstein procedure was modified with a soft mesh instead of the previously used "harder" mesh. The aim was to evaluate 3 years of TIPP and Lichtenstein experience since the opening of the Hernia Center Brabant. All six dedicated hernia surgeons use the same techniques for the TIPP or Lichtenstein procedures.

Details of each step in both operations were standardized after discussion. During the operation schedule, approximately eight patients per operating room (n = 2) are treated in the center. Patients visit the outpatient department after 14 days to check wound healing and to evaluate their experience. All findings are entered into the electronic patient files. These case record forms were analysed retrospectively.

Considering the methodological quality of this study, the following shortcomings and biases need to be addressed and the limitations of this retrospective study include incomplete follow up.

Conclusions on the results should be taken cautiously because of:

Selection bias
The retrospective nature of the study, the low rate of inclusions in analysis versus the total amount of operated patients, the unmatched (non-randomised) groups, and the fact that no (uniform) classification was used.

Treatment bias
The expert surgeon may have decide to use e.g. Lichtenstein in more difficult cases?

Follow up bias
Only 31.3% visited once the outpatients´ postoperatively, it is unknown if the follow up was equally divided among both groups.
There may very well be under-reporting of chronic pain, as 31.3% had only one post-operative visit 14 days after surgery, and these patients were further regarded as free of pain because they did not return to the outpatient department.

Blinding bias
Surgeons were not blinded which may have influenced the overall outcome. The observer was not blinded either.

With the biases in mind, a true comparison of the results of both techniques cannot be made safely; and warrants a prospective, double blinded and randomised controlled trial with low risk of bias. This study, however, shows that concentration of care, with either technique, renders acceptable low complication (chronic pain, adverse events) and low recurrence rates (Table 1), although, with the impaired follow up and under reporting in mind the results may not be in line with large studies like those reported by Amid.

In conclusion the presented results form the basis for a prospective randomised controlled trial comparing the TIPP and Lichtenstein techniques: the TULIP Trial, ISRCTN93798494.

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Chapter 4

Protocol TULIP trial

The Tilburg double blind randomised controlled trial comparing inguinal hernia repair according to Lichtenstein and the transinguinal preperitoneal technique

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According to the article in Trials 2009 Sep 25;10:89. doi: 10.1186/1745-6215-10-89

Abstract

Background

Anterior open treatment of the inguinal hernia with a tension free mesh has reduced the incidence of recurrence and direct postoperative pain. The Lichtenstein procedure rules nowadays as reference technique for hernia treatment. Not recurrences but chronic pain is the main postoperative complication in inguinal hernia repair after Lichtenstein's technique. Preliminary experiences with a soft mesh placed in the preperitoneal space showed good results and less chronic pain. In line with our conclusions of a retrospective, unmatched cohort study on this topic and with the knowledge gap in literature, a prospective randomised controlled trial was designed in order to validate the possible advantages of the transinguinal preperitoneal (TIPP) repair compared with Lichtenstein´s technique.

Methods

The TULIP is a double-blind randomised controlled trial in which 300 patients will be randomly allocated to anterior inguinal hernia repair according to Lichtenstein or the transinguinal preperitoneal technique with soft mesh. All unilateral primary inguinal hernia patients eligible for operation who meet inclusion criteria will be invited to participate in this trial. The primary endpoint will be direct- and postoperative chronic pain. Secondary endpoints are recurrence, operation time, postoperative complications, hospital stay, costs, and return to daily activities (e.g. work). Success rate of hernia repair and complications will be measured as safeguard for quality. To demonstrate that inguinal hernia repair according to the transinguinal preperitoneal (TIPP) technique reduces postoperative pain to <10%, an assumed difference of at least 10% to Lichtenstein´s technique with an α=0.05 and power of 80%, a total sample size of 300 patients was calculated.

Discussion

The TULIP trial is aimed to show a reduction in postoperative chronic pain after anterior hernia repair according to the transinguinal preperitoneal (TIPP) technique, compared to Lichtenstein. In our hypothesis the TIPP technique reduces the amount of patients with postoperative chronic pain, compared to Lichtenstein.

Trial registration: ISRCTN 93798494

Background

Inguinal hernia is a common surgical problem. In the Netherlands about 30.000 unilateral inguinal hernia repairs are performed each year [1]. Tension free mesh repair has reduced the incidence of recurrence and direct post operative pain. The incidence of recurrences are 2-5% [2]. However, chronic pain after inguinal hernia repair is an underestimated problem [3]. The exact incidence of chronic pain is unknown. Well conducted, large and unselected epidemiological studies suggest that about 20% of patients are affected with chronic pain [4-7]. A randomised controlled trial comparing Shouldice, Lichtenstein and endoscopic preperitoneal repair showed that 31% of patients had some form of chronic pain after Lichtenstein repair [8]. Patients are classified as having chronic pain if postoperative pain lasts for more than three months [9]. Chronic pain may vary from subtle discomfort to disabling pain. In general, three chronic groin pain syndromes have been defined: somatic, neuropathic, and visceral pain [10]. Somatic pain is localized to the pubic tubercle and is a result of periosteal damage during stapling of prosthetic mesh or incorporation of the peri-osteum into the most medial stitch of an open anterior repair. Neuropathic pain usually develops in the sensory distribution of the injured nerve and can present days to weeks after the repair. Chronic neuralgia results from nerve trauma secondary to partial or complete division, stretching, contusion, crushing, electrical damage, suture compression, and adjacent inflammation from mesh or suture material [11,12]. The most commonly offended nerves after open inguinal hernia repair include the ilioinguinal-, iliohypogastric-, and genital branch of the genitofemoral nerve [13]. Visceral pain usually presents as pain during ejaculation [14].

To assess the objectivity of pain the visual analogue scale (VAS score) is frequently used nowadays [15]. VAS has been a proven instrument to score postoperative pain in inguinal surgery. Chronic pain has significant effects on all daily activities including walking, work, sleep, relationships with other people, mood and general enjoyment of life [16]. So much effort has been put in strategies to reduce chronic pain. Endoscopic hernia repair has been postulated to result in less chronic pain due to the preperitoneal placed position of the mesh.

Several studies have been performed to investigate if endoscopic repair resulted in less chronic pain. A large mesh is placed in preperitoneal position to cover the myopectineal orifice after reduction of the hernia sac. Liem et al. concluded a lower incidence of pain after endoscopic hernia repair compared to open non-mesh repair [17]. Grant et al. however found in a randomised trial after 5 years that the incidence of chronic pain was still 27% at one year compared with 36% chronic pain in the Lichtenstein group. Groin numbness was significantly reduced (18% vs 40%) [18]. Specialized hernia centres reported excellent results after endoscopic repair. Wright failed to prove reduced pain after endoscopic approach (13% vs. 10%) in a randomised controlled trial with 5 years follow up. This study showed that testicular pain was more frequent after endoscopic repair and groin pain more common after open repair [19]. A review of randomised

controlled trials comparing endoscopic with open mesh hernia repair showed that the endoscopic approach was associated with less persisting pain [2]. One of the drawbacks of endoscopic hernia repair over the open approach are the added costs, particularly when disposable instruments are used [20]. The other disadvantage of laparoscopy compared with open hernia repair is that general anaesthesia is necessary. Finally, the endoscopic learning curve is long [21]. The principal reasons for the long learning curve are the surgeon's lack of familiarity with the preperitoneal anatomy and the time it takes to develop the skills to operate in a confined space. Complications of endoscopic hernia repair are scarce but might be severe [22].

Rationale for the mesh and type of mesh

No recent systematic review or meta-analysis regarding postoperative pain after inguinal hernia repair has been performed. Endoscopic preperitoneal approach in order to reduce pain is expensive and has several other disadvantages, but a cost-effectiveness meta analysis has to be performed yet. Since pain is often related to neuralgia and recurrences occur at the myopectineal orifice an alternative mesh was developed to be placed in the preperitoneal space, but with anterior approach. Preliminary experience with a preperitoneal placed mesh showed a recurrence rate of 0,7% with a median follow up of 63 months [23]. After adding a memory ring to the mesh to allow easy placement in the preperitoneal space, preliminary studies showed low recurrence rates and low postoperative pain rates [24,25].

Different meshes have been developed and tested to reduce the chronic pain after inguinal hernia repair. A randomised clinical trial comparing the Prolene Hernia System, mesh plug repair and Lichtenstein method for open inguinal hernia repair showed that 39,7% of patients had some form of pain after three months. No difference could be detected between type of mesh used [26].

These studies let to the concept of the transinguinal preperitoneal (TIPP) technique with soft mesh which combines the anterior approach according to Lichtenstein with the preperitoneal position of the mesh as known from the endoscopic total extra peritoneal technique (TEP).
In line with our conclusions of a retrospective, unmatched cohort study on this topic and with the knowledge gap in literature, a prospective randomised controlled trial was designed in order to validate the possible advantages of the transinguinal preperitoneal (TIPP) repair compared with Lichtenstein´s technique.

Methods

Study objectives

Two techniques, Lichtenstein and TIPP, for inguinal hernia patients will be compared in a prospective randomised double blind controlled trial. Patients will be included at the outpatient departments of both hospitals by surgeons and supervised residents. Dedicated hernia surgeons will always supervise and/or perform the operations. Objective success: the percentage of operations with successful inguinal hernia reduction and direct postoperative - and chronic pain incidence lower than 25%.

Primary endpoint

The primary endpoint is the incidence of direct postoperative pain and chronic pain after inguinal hernia repair according to Lichtenstein or TIPP using the visual analogue scale (VAS).

Secondary endpoints

The secondary endpoints are recurrence, operation time, hospital stay, complications (e.g. infection), cost-efficiency analyses, and time to return to daily activities/work after TIPP or Lichtenstein procedures.

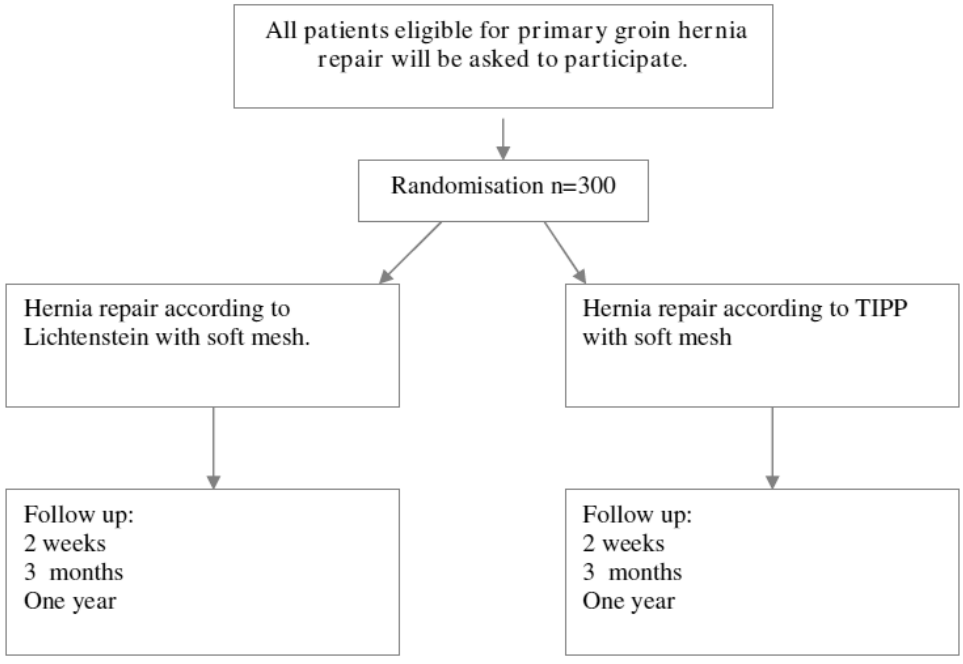
Design

TULIP is a double-blind, randomised controlled trial. Randomisation will be performed by pulling a sealed double blind envelope, based on a digital random table, in the trial centre after contact by telephone prior to incision. Obviously, the surgeons know which technique they are performing during operation. By securing the digital operation report, the investigator assessing the outcome on the outpatient department will be blinded.
The patient is not informed on which procedure has been performed because it is written down on paper and not mentioned in theatre.

Patients

A total of 300 patients, with a unilateral primary groin hernia, visiting the outpatient clinics at the St. Elisabeth Hospital or TweeSteden Hospital in Tilburg will be randomised (figure 1). Analyses of inguinal hernia patients in the past showed a number of approximately 600-700 per year in both hospitals, equally divided. This number is the sum of both hospitals and includes recurrences, children/elderly, incarcerated and bilateral inguinal hernia's. An inclusion rate of 30-50% of eligible patients is being foreseen (1.5years). Data will be collected by VAS-diary and SF36-list (Health Status). Forms will be filled in by the patients at 14 days, 3 months and one year after surgery during follow up (figure 1).

Figure 1



Flow chart of the trial

Inclusion criteria

- Primary unilateral groin hernia
- Age >18 <80 years
- ASA classification 1-3
- Signed informed consent letter

Exclusion criteria

- Recurrent hernia
- Age <18 or >80 years
- Scrotal hernia(s)
- ASA classification >4
- Acute incarcerated inguinal hernia(s)
- Psychiatric disease or other reason (other causes of chronic pain) making follow up or questionnaires unreliable
- Previous preperitoneal surgery (e.g. radical prostatectomy)

Ethics, informed consent

This study is conducted in accordance with the principles of the Declaration of Helsinki and "Good Clinical Practice Guidelines". The independent ethics committee of both participating hospitals approved the final protocol. Oral and written informed consent in form is obtained from the patient before inclusion in the trial. The TULIP Trial is registered at: http://www.controlled-trials.com/ISRCTN93798494.

Surgical Techniques

All patients will be operated via anterior approach with a skin incision two centimetres above the Poupart ligament. In half of the study population the groin hernia will be corrected according to Lichtenstein, as described by Amid et al. [27]. This is the reference treatment advised by the Dutch Society of Surgeons [28]. The Lichtenstein technique will be attempted to present-day insights; a soft mesh will be used instead of the polypropylene mesh [29]. The other 150 inguinal hernia patients will be operated by the transinguinal preperitoneal (TIPP) technique with Polysoft™ mesh as described by Pélissier et al. [26]. In this technique the same inguinal incision is made, the external oblique aponeurosis is divided and the cord lifted with a tape. The cremaster muscle is divided around the internal orifice, but not striped, and the sac is dissected. The technique of placement of the Polysoft™ mesh into the preperitoneal space adapts anatomically to the type of hernia. Type of hernia will be assessed using the European Hernia Society groin hernia classification [30]. This classification is simple and easy to remember. The size of the hernia orifice is registered as 1 (≤ 1 finger), 2 (1-2 fingers) or 3 (≥ 3 fingers) accompanied with L (lateral), M (medial) or F (femoral). All the hernia's will be primary (P) classified according to the inclusion criteria so recurrent (R) will not be assessed in our population. Example; a lateral inguinal hernia with an orifice of 2 fingers and a primary origin will result into L2P. In indirect hernias high dissection of the sac is performed and the sac is thus reduced in the pre peritoneal space (PPS) through the internal ring. Blunt dissection is carried out in the PPS, through the internal orifice and is then extended deep to epigastric vessels and transverse fascia, in the direction of the pubic spine, beyond its level. The patch is introduced in the PPS via the internal orifice. In regional or local anaesthesia asking the patient to strain allows correct anatomical spreading of the mesh, which is applied to the deep aspect of the fascia. The assessment is done by asking the patient to strain and to cough. External oblique aponeurosis was repaired superficial to the cord to restore the normal anatomy.

In direct hernias, after division of the cremasteric fibers so as to check the internal orifice for an indirect sac, the transverse fascia is divided circularly around the hernia bulge and the sac is reduced. Blunt dissection is carried out in the PPS, medially in the direction of the pubic spine and laterally behind the epigastric vessels in direction of the iliac spine. The patch is introduced through the transverse fascia opening and spread in the PPS so as to cover all the weak inguinal area. When an indirect sac, even if it is small, is associated to the direct one, both sacs are dissected and reduced.

Escape medication

A standardized general anesthesia/spinal anesthesia protocol will be used in both groups in combination with a standardized post operation regimen, based on VAS scores for pain and nausea. These regimes are based on current and acceptable practice and the standardization serves to avoid unnecessary bias. The choice of anesthesia technique will be left, in principle, to the

preference of the patient. All patients will be seen, pre-operatively at the pre-operative screening outpatient clinic at one of the two locations. Standardized pre and postoperative medication will be handed out to the patients to be used each day, up to 5 days postoperatively, including any part of this period that the patient may already have been discharged. This includes, but is not limited to, paracetamol 1 gram four times daily and diclofenac 50 mg 3 times daily and as rescue medication tramadol 50 mg 3 times daily when regular painkillers are not satisfying.

Statistical analysis

The analysis will be performed on the basis of intention to-treat principles. It is anticipated that the use of TIPP technique with soft mesh at least will lead to a reduction in postoperative chronic pain to 10%. The sample size calculation is based on $\alpha = 0.05$ and a power of 80%. This leads to a required sample size of 300 patients. Taking into account a 5% loss-to-follow up, a total of 2 × 158 patients will be randomised. There are three postoperative follow up visits at the outpatient department at two weeks, three months and one year for both groups (Lichtenstein and TIPP). The expected study end is December of 2010 (after 1,5 years inclusion period).

Randomisation

The randomisation list was generated by using the website randomisation.com http://www.randomisation.com. According to this list a random allocation of Lichtenstein and TIPP method was performed. Randomisation will take place by pulling a sealed envelope after phone call to the trial centre prior to incision at the theatre. Operation forms are blinded in the electronic patients files and not available for the independent outpatient clinic researcher.

Conclusion

The TULIP is a double blind randomised controlled trial that aims to show a reduction in direct postoperative- and chronic pain after anterior inguinal hernia repair with placement of a soft mesh either in the inguinal canal (Lichtenstein) or in the preperitoneal space (TIPP).
Hypothetically the TIPP technique reduces chronic pain substantially compared to Lichtenstein because of the placement of the soft mesh in the preperitoneal space.

Competing interests

The authors declare that they have no competing interests. Objective analyses will be performed on the TULIP data. There will be no violating of this study protocol.

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Chapter 5

Randomised clinical trial of chronic pain after the transinguinal preperitoneal technique compared to Lichtenstein's method for inguinal hernia repair

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Abstract

Background

Preliminary experience has suggested that preperitoneal mesh positioning causes less chronic pain than Lichtenstein's technique for inguinal hernia repair. Therefore, a randomised controlled trial was conducted with the aim of evaluating the incidence of postoperative chronic pain after transinguinal preperitoneal (TIPP) mesh repair *versus* Lichtenstein's technique.

Methods

Patients with a primary unilateral inguinal hernia were randomised to either TIPP or Lichtenstein's repair in two teaching hospitals. The primary outcome was the number of patients with chronic pain after surgery. Secondary outcomes were adverse events. Follow-up was scheduled after 14 days, 3 months and 1 year. Patients and outcome assessors were blinded.

Results

A total of 302 patients were randomised to TIPP (143) or Lichtenstein (159) repair. Baseline characteristics were comparable in the two groups. Some 98·0 per cent of the patients were included in the analysis (141 in the TIPP group and 155 in the Lichtenstein group). Significantly fewer patients in the TIPP group had continuous chronic pain 1 year after surgery: five patients (3·5 per cent) *versus* 20 patients (12·9 per cent) in the Lichtenstein group (p = 0·004). An additional 12 patients (8·5 per cent) in the TIPP group and 60 (38·7 per cent) in the Lichtenstein group experienced pain during activity (p = 0·001). There were two patients with recurrence in the TIPP group and four in the Lichtenstein group, but no significant differences were found in other severe adverse events between the groups.

Conclusion

Fewer patients had continuous chronic pain or pain during activity at 1 year after the TIPP mesh inguinal hernia repair compared with Lichtenstein's repair. Registration number: ISRCTN93798494 (http://www.controlled-trials.com).

Introduction

Inguinal hernia repair is one of the most frequently performed surgical interventions globally, and in the Netherlands approximately 30 000 inguinal hernia repairs are carried out each year[1]. The Lichtenstein technique (tension free mesh repair) is currently the reference technique for inguinal hernia treatment both in the Netherlands and worldwide [2,3]. The Lichtenstein repair has reduced the incidence of recurrent inguinal hernia to 2–5 per cent compared with anterior non-mesh techniques[4]. However, chronic postoperative pain, currently the main complication after Lichtenstein repair, has been reported in 15–40 per cent of patients[5–9]. Chronic pain is defined by the International Association for the Study of Pain as: 'any VAS [visual analogue scale] score above zero which lasts for more than three months'[10]. Currently, there are no evidence-based inguinal hernia repair techniques that prevent postoperative chronic pain. Chronic pain may be caused by nerve damage during surgery, or stretching or suturing. It may also be related to the position of the mesh in the inguinal canal. Continuous chronic pain is described by patients as an ongoing awareness of pain.

The surgical community has made major efforts to reduce chronic postoperative pain by exploring various strategies (such as surgical approach, type of mesh, mesh position) in hernia trials. The totally extraperitoneal (TEP) and laparoscopic transabdominal preperitoneal techniques have been introduced suggesting that less chronic pain occurs owing to the preperitoneal position of the mesh[4,11]. Some studies have reported superiority of endoscopic hernia repair, but this has not been demonstrated unequivocally. Furthermore, the issue of chronic pain has not yet been resolved because of conflicting evidence and methodological difficulties in studying this complication after inguinal hernia repair. The most important drawbacks of endoscopic hernia repair are adverse events. In the authors' systematic review, analysis of data in a Cochrane study[4] revealed a severe adverse event rate of 10 per cent in endoscopic hernia repairs, which is higher than previously assumed (http://www.ctu.dk; G.G. Koning, J. Wetterslev, C.J.H.M. van Laarhoven and F. Keus, *accepted for publication PLoS ONE Journal 2012*)). Other disadvantages of endoscopic procedures are the extensive learning curve, the need for general anaesthesia and higher costs[12,13].

Transinguinal preperitoneal (TIPP) hernia repair with soft mesh and memory ring combines the safe anterior approach with a preperitoneal sutureless mesh position, by using the annulus internus as an entrance to the preperitoneal space[14–16]. This open and sutureless technique is associated with a short learning curve and lower costs than the TEP technique[9]. Hypothetically, TIPP may be associated with less chronic postoperative pain than Lichtenstein's technique. Therefore, a double blind randomised trial (TULIP) was conducted to compare TIPP with Lichtenstein repair for inguinal hernia repair, with the incidence of the number of patients with chronic postoperative pain as the primary outcome. The design of the trial also focused on reducing the risk of errors in

the dimensions of bias, random error and the chosen outcome measures[17–19]. The protocol of the TULIP trial has already been published[20].

Methods

Before the start of the trial, the study protocol was written, published and available online (http://www.ncbi.nlm.nih. gov/pmc/articles/PMC2761380)[20], and was registered with Current Controlled Trials (http://www.controlledtrials. com/ISRCTN93798494).

Study design

This trial was designed as a double-blind randomised controlled trial; it started in January 2009 and was completed in June 2011. Two techniques for inguinal hernia repair (TIPP and Lichtenstein) were compared. Patients were included by surgeons and supervised junior doctors at the outpatient departments of the participating hospitals (St. Elisabeth Hospital Tilburg and TweeSteden Hospital, Tilburg/Waalwijk, the Netherlands). Both centres are large (non-academic) teaching hospitals, and the surgeons are experienced in TIPP and Lichtenstein procedures[9]. The hospitals provide a representative example of standard surgical practice in the Netherlands. The Hernia Centre Brabant (a collaboration between the two hospitals) was established by six surgeons (3 from each centre) in 2006, with the aim of teaching junior doctors and concentrating care for patients with inguinal hernia[9].

Before the launch of the trial, group sessions (in the operating theatre and discussions) were held to ensure complete standardization and uniformity of both hernia repair techniques with all participating surgeons. Randomised patients were operated on according to this protocol[20]. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines, as already described[20]. The protocol was approved by the ethics committee.

Patients

Patients with a unilateral primary inguinal hernia, visiting the outpatient department were invited to participate and written informed consent was obtained[20]. Data concerning body mass index, sex and side of hernia were recorded. Inclusion criteria were a primary unilateral groin hernia, age between 18 and 80 years, American Society of Anesthesiologists (ASA) grade I–III, and signed informed consent letter. Exclusion criteria were a recurrent hernia, scrotal hernia, acute incarcerated inguinal hernia, psychiatric illness or other reason making follow-up or questionnaires unreliable, and previous preperitoneal surgery (such as radical prostatectomy)[20].

Randomisation and blinding

Patients were randomised to either TIPP or Lichtenstein repair. Allocation sequence, allocation concealment, blinding and follow-up were done according to the recommendations of the Cochrane Handbook[21]. The allocation sequence was computer-generated. Allocation concealment was achieved using sealed envelopes. Before incision the trial office was contacted by telephone. At the trial office, a sealed opaque envelope was opened. The nurse in the operating room did not mention but wrote down the technique for the surgeon (randomly scheduled; 1 of the 6 hernia surgeons present), so the patient was unaware of the technique used. Operation reports were blinded in the electronic patient files, and the outcome assessor, a junior doctor not involved in the operations, was not allowed access to the operation reports. Patients could ask which procedure they had received after the last follow-up visit, and after completing forms, questionnaires and physical examination.

Anaesthesia and analgesia

Before surgery, all patients visited the anaesthesia outpatient department. A single anaesthesia protocol was used in combination with a standard postoperative regimen (anaesthetist and nurse) guided by the patient's need, based on a visual analogue scale (VAS) score for pain and nausea[20]. These regimens were based on current practice, and standardization served to avoid bias. The first choice of anaesthesia was spinal because of its ease and expedited postoperative recovery, avoiding the risks of general anaesthesia. If the patient declined, general anaesthesia was permitted. The anaesthetists were all very experienced in both spinal and general anaesthesia. Bupivacaine 0·1 per cent was used for inguinal block (5 ml) and also for wound infiltration (5 ml) at the end of all procedures. Rescue medication Tramadol/paracetamol (Zaldiar®; Grünenthal, Aachen, Germany) for pain was also standardized[20].

Intervention

Dedicated hernia surgeons performed the operations, or supervised surgical junior doctors. Skin incisions (8-10cm long) (TIPP and Lichtenstein) were made 2 cm above Poupart's ligament. The inguinal canal was closed with 3/0 Vicryl® (Ethicon, Johnson and Johnson; Somerville, New Jersey, USA). Scarpa's fascia was closed with one stitch of 3/0 Vicryl®. The skin was closed intracutaneously with 3/0 Vicryl® Rapide (Ethicon, Johnson and Johnson) in both techniques.

Transinguinal preperitoneal repair

TIPP repair was carried out as described previously[9,15,16, 20,22]. Nerves were identified and spared. The hernia sac was reduced into the preperitoneal space. A dissection gauze was inserted and subsequently the preperitoneal space was bluntly dissected with a finger. A soft mesh with memory ring (Polysoft™, 16×9·5 cm; Bard, Benelux, Belgium) was positioned in the preperitoneal space after the gauze had been removed. In this way the soft mesh with memory ring was in the same

preperitoneal position as in endoscopic techniques but the approach was anterior without the need for a scope.

Lichtenstein repair (control intervention)
The Lichtenstein technique (current standard and extensively reported) was adapted based on present-day insights with use of a soft mesh (SoftMesh, 6 × 13·7 cm; Bard)[23,24]. Nerves were identified and spared. A 3/0 Prolene® (Ethicon, Johnson and Johnson) suture was used for fixation of the mesh.

Data recording and follow-up
All hernias were classified according to the European Hernia Society (EHS) hernia classification[25]. Follow up including physical examination was scheduled at 14 days, 3 months and 1 year. Patients were blinded to the intervention and were investigated (by a blinded assessor) in the outpatient department. They were asked to keep a VAS pain diary for the first 14 days after surgery [26,27]. The VAS score was determined on a scale from 0 (no pain) to 10 (worst pain imaginable). The pin-prick test on the operated side was used to assess numbness in the dermatomes related to the inguinal nerves. A figure of dermatomes was used for anatomical orientation[28].

Outcome measures
The primary outcome was the proportion of patients with chronic postoperative pain at 1 year[20]. Secondary outcomes were recurrence, adverse events (minor/early complications, such as urinary retention, superficial wound infection), duration of operation, length of hospital stay, time to return to usual daily activities and numbness.

Reporting
The TULIP trial findings were graded to facilitate critical decision-making from the patient's perspective according to Grading of Recommendations Assessment, Development and Evaluation (GRADE)[18]. Study outcomes are reported in concordance with the recently updated Consolidated Standards of Reporting Trials (CONSORT) checklist[29].

Statistical analysis
The analysis was performed on an intention-to-treat basis. It was hypothesized that the TIPP mesh technique would reduce the percentage of patients with chronic postoperative pain from 20 per cent to less than 10 per cent. This reference percentage of 20 per cent was based on the reported 15–40 per cent incidence of chronic pain[5–9,20]. To obtain a representative power and sample size, a 10 per cent reduction in the number of patients with chronic postoperative pain was considered realistic. Based on an absolute risk reduction of 10 per cent in incidence of patients with postoperative chronic pain, with an α of 0·05 and a power of 80 per cent, a required

sample size of 300 patients was calculated. The expected time frame for inclusion was 1·5 years. No interim analyses were allowed.

Binary outcomes were analysed by means of χ^2 test and continuous outcomes using the *t* test. The normality of data was checked. $p < 0{\cdot}050$ was considered statistically significant. Calculations were made with SPSS® version 17 (SPSS, Chicago, Illinois, USA) and SAS® version 9.2 (SAS Institute, Cary, North Carolina, USA).

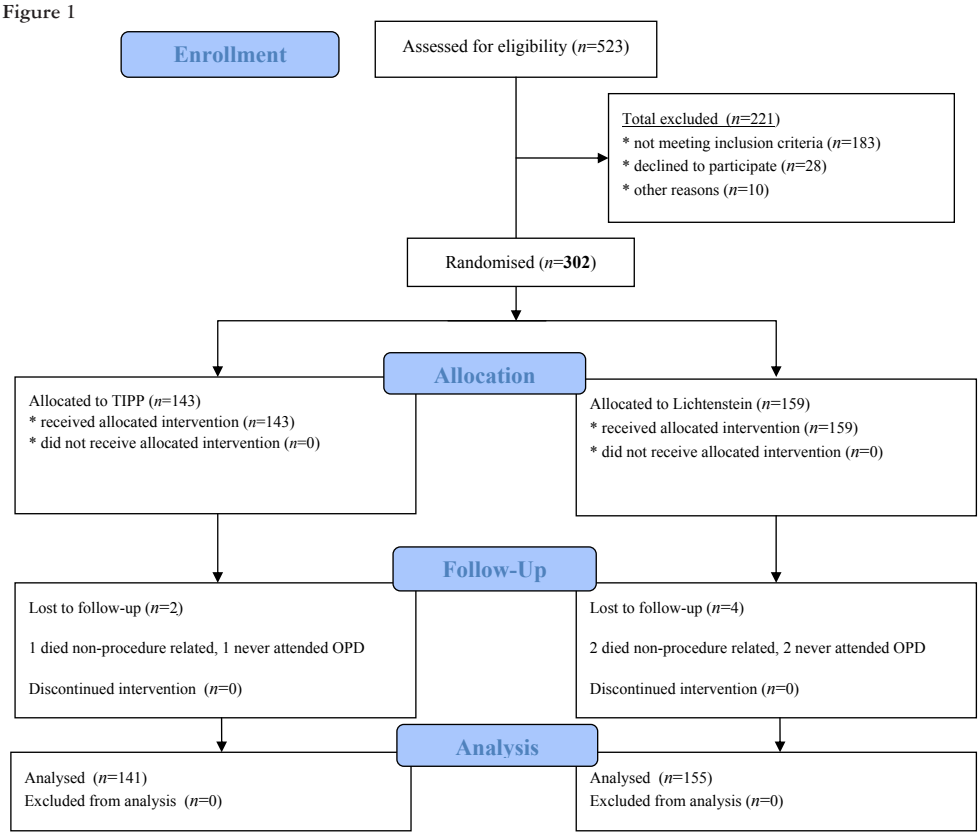
Results

Between 1 January 2009 and 31 March 2010, 523 patients visited the outpatient departments of the hospitals for inguinal hernia treatment. A total of 221 patients were not eligible for trial inclusion for various reasons: refusal to participate, age below 18 years or over 80 years, ASA grade more than III, recurrent hernia, previous preperitoneal operations, psychiatric history or meeting other exclusion criteria. Excluded patients also received the best possible inguinal hernia treatment in accordance with guidelines, but outside this trial. A total of 302 (89%) out of 340 eligible patients were randomised to TIPP ($n = 143$) or Lichtenstein ($n = 159$) repair (*Fig. 1*). Included patients were all treated in accordance with the protocol. No operations were carried out under local anaesthesia. Six patients were excluded after randomisation. There were three non-procedure-related deaths within the trial period, at least 3 months after operation, one in the TIPP group and two in the Lichtenstein group (*Fig. 1*). Causes of death were stroke, progressive cancer during follow-up and newly diagnosed progressive muscle disease. Altogether 98·0 per cent of the patients completed the 1- year follow-up. A total of 296 patients were analysed on an intention-to-treat basis.

Baseline characteristics

Overall 288 men and 14 women were randomised. There were 130 left-sided and 172 right-sided inguinal hernias. Confirming adequate randomisation, there was no difference in age, sex, body mass index, ASA grade and EHS hernia classification between the TIPP and Lichtenstein groups. For some unknown reason, hernias in two patients were not classified during operation (*Table 1*).

Figure 1



Revised CONSORT diagram[29] showing each stage of the TULIP trial.

Perioperative data

The operating teams (resident supervised by surgeon or surgeon assisted by resident) were similar in both groups (and equally divided; ratio 50 : 50).The mean (s.d.) duration of operation (skin-to-skin) was 34·1(9·9) min for the TIPP technique and 39·9(12·0) min for the Lichtenstein procedure. There were no crossovers (conversion of TIPP to Lichtenstein technique or vice versa) and the preperitoneal space was created successfully in all patients allocated to the TIPP technique. Two hundred and sixty eight patients were treated in a day-care setting, with no difference between the two groups. Nine patients in the TIPP group and 29 in the Lichtenstein group had minor complications (not critical for decision-making according to GRADE[17,18]) (p =0·003); these included superficial wound infection, bladder retention, nausea, headache and conversion from spinal to general anaesthesia.

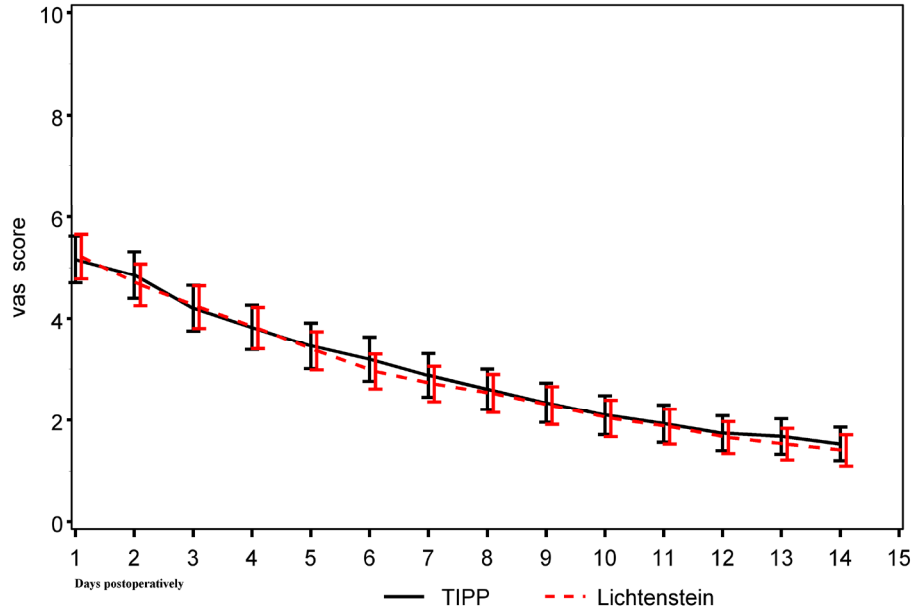
Patients in the TIPP group returned to usual daily activities significantly earlier (*Table 2*). There was no difference in immediate postoperative pain between patients in the TIPP and Lichtenstein groups. The pain diary after surgery showed no differences in VAS scores in the first 14 days after TIPP and Lichtenstein repair (*Fig. 2*). The amount of analgesic medication (paracetamol, diclofenac and the rescue medication (Tramadol/paracetamol) was similarly low in the first 14 days after surgery in both group (*Fig. S1*, supporting information). After 3 months there was still no difference in the proportion of patients experiencing postoperative pain.

Table 1

	TIPP *n*=143	**Lichtenstein** *n*=159
Male	135 (94.4%)	153 (96.2%)
Female	8 (5.6%)	6 (3.8%)
Age (mean +/- SD)	57.0 years (12.1)	56.5 years (13.2)
Side of hernia		
Left	62	68
Right	81	91
ASA classification		
1	81 (56.6%)	99 (62.3%)
2	52 (36.4%)	50 (31.5%)
3	10 (7.0%)	10 (6.3%)
Body Mass Index (mean +/- SD)	25.1 (2.8)	25.4 (2.9)
EHS Hernia Classification[25]		
Primary	142 (100%)	158 (100%)
Lateral size 1	24 (16.9%)	38 (24.1%)
size 2	57 (40.1%)	51 (32.3%)
size 3	15 (10.6%)	15 (9.5%)
Medial size 1	12 (8.4%)	12 (7.6.%)
size 2	14 (9.9%)	17 (10.8%)
size 3	12 (8.4%)	13 (8.2%)
Combination **L** and **M** (pantaloon)	8 (5.6%)	12 (7.6%)
Inguinal hernias without classification	*n*=1	*n*=1

Baseline characteristics of patients randomised to TIPP or Lichtenstein (equally divided and checked for normality of data). Because of the successful randomisation it is not appropriate to provide *p*-values for these data.
Abbreviations: ASA: American Society of Anesthesiologists. Body mass index: calculated as weight in kilograms divided by height in meters squared. EHS: European Hernia Society. *n*: number of patients. SD: standard deviation.

Figure 2



The mean VAS scores of the TIPP and Lichtenstein patients in the first 14 days postoperatively. The error bars illustrate two times the standard error of the mean (2SEM) of both groups.

Outcomes after 1 year

Analysis of the primary outcome showed that five patients (3·5 per cent) in the TIPP group and 20 (12·9 per cent) in the Lichtenstein group had continuous chronic pain after 1 year (p=0·004) (*Table 2*). The pain was moderate (VAS score 4–6) in all five patients in the TIPP group and 18 patients in the Lichtenstein group; two patients were still experiencing severe continuous chronic pain (VAS 7–10) after Lichtenstein repair. An additional 72 patients, 12 (8·5 per cent) in the TIPP group *versus* 60 (38·7 per cent) in the Lichtenstein group (p=0·001) reported that they experienced pain during activity (such as cycling, running, kneeling, walking up stairs, gardening, lifting at work) at the 1-year follow-up visit. The pain disappeared after stopping these activities. Nineteen patients (13·5 per cent) in the TIPP group and 84 (54·2 per cent) in the Lichtenstein group experienced severe adverse events (critical for decision-making[17,18]) in the first year after surgery; these included postoperative chronic pain, activity-related pain and reoperation for recurrence (*Table 2*).

After 1 year significantly fewer patients in the TIPP group had persisting numbness (*Table 2*). Analyses of the pin-prick test at 1 year showed persisting numbness of the corresponding dermatome of the iliohypogastric nerve in four patients in the TIPP group and ten in the Lichtenstein group, in the ilioinguinal nerve in six and 46 patients respectively, and in the branch of the genitofemoral nerve in nine and 53 patients respectively.

Table 2

	TIPP *n*=141	Lichtenstein *n*=155	Statistical analysis (*p*-value)
Mortality **(non procedure related)**	1	2	N/S
Patients with **continuous** chronic pain	5 (3.6%)	20 (12.9%)	0.004*
VAS score 1-3	0	0	-
VAS score 4-6	5	18	0.001*
VAS score 7-10	0	2	0.633
Patients with **activity-related** pain	12 (8.5%)	60 (38.5%)	0.001*
Patients with recurrence of hernia	2 (1.4%)	4 (2.6%)	0.478
Patients with persisting numbness at one year	15 (10.5%)	79 (49.7%)	0.0001*
Patients with 1 night stay postoperative	12 (8.5%)	16 (10.3%)	0.646
Patients with superficial wound infection§	2 (1.4%)	4 (2.6%)	0.478
Patients with other minor§ complication (e.g. bladder retention, urinary tract infection, nausea, headache, hematoma without intervention)§	7 (4.9%)	25 (16.1%)	0.002*
Total of patients with minor§ complication (according to GRADE: not critical for decision making[19])	9 (6.4%)	29 (20.3)%	0.003*
Operation time in minutes (SD)	34.1 (9.9)	39.9 (12.0)	<.0001*
Mean hospital stay in hours (SD)	8.1 (6.5)	9.0 (5.1)	0.151
Time to return to ADL (e.g. work, gardening) in days (SD)	9.9 (11.4)	16.4 (20.5)	0.0014*

Clinical comparison of patients in the first year after the TIPP or Lichtenstein procedure.
* significance assessed
§ minor complication, not critical for decision making according to GRADE
Abbreviations used in table 2
N/S: not significant
VAS: Visual Analogue Scale
SD: standard deviation
ADL: activities of daily life (work, sports, gardening etcetera)

Trial bias indicators

Analysis of bias indicators showed a low risk of bias in all categories (*Fig. S2*, supporting information). There were no protocol violations.

Discussion

The present randomised controlled trial was conducted to investigate whether the TIPP technique reduced the incidence of chronic postoperative pain compared with the Lichtenstein technique in primary inguinal hernia repair. The outcomes favour the TIPP technique as a significantly smaller proportion of patients had chronic postoperative pain or activity-related pain at 1 year after TIPP than after Lichtenstein repair. The TIPP technique was also associated with significantly fewer minor complications (not critical for decision-making). All six recurrences in the trial were clinically proven during physical examination and were re-operated; no femoral hernias were diagnosed.

On an evidence based level 1b (randomised trial with low risk of bias) the TIPP hernia repair proved to be preferable to the Lichtenstein repair for both dedicated hernia surgeons as well as junior doctors in training. As well as reducing the incidence of chronic postoperative pain, the TIPP technique effectively resolved the problem of the inguinal hernia. The preperitoneal space was easily dissected in patients allocated to TIPP and no conversions or crossovers to other inguinal hernia repair techniques were needed. The TIPP technique is not yet widely known, but has been described in literature as an alternative to Lichtenstein repair[22,30]. The results of the present trial strengthen these reported TIPP results.

Some elderly patients may be treated with TIPP under local anaesthesia when their ASA grade is too high for spinal and/or general anaesthesia. However, in this trial no operations were performed under local anaesthesia. Postoperative pain directly after surgery was comparable after TIPP and Lichtenstein repair, and there were no differences after 14 days and 3 months. Retrospectively, it may have been more logical to schedule the second postoperative visit after 6 months (instead of 3 months) because of the definition of chronic pain. Differences in pain may not have been apparent during the first few months after surgery as patients probably tended to adopt a cautious lifestyle. However, the primary outcome of postoperative chronic pain is considered to be critical for decision-making from the patient perspective[17,18]. Based on the trial results, TIPP hernia repair should be considered for all primary inguinal hernias that fulfill the inclusion criteria of this trial.

A probable explanation for the reduction in incidence of chronic pain with TIPP repair is the preperitoneal and sutureless mesh position, outside the inguinal canal. The anterior approach in combination with spinal anaesthesia may provide the most logical explanation for low rates of severe adverse events. Furthermore, experienced anaesthetists were involved in the design of the protocol. Other ways of preventing chronic postoperative pain have been described such as use of lightweight *versus* heavyweight mesh, but no significant reduction in postoperative pain or

discomfort was found[31]. However, a recent systematic review concluded that use of lightweight mesh reduced the incidence of chronic groin pain[32].

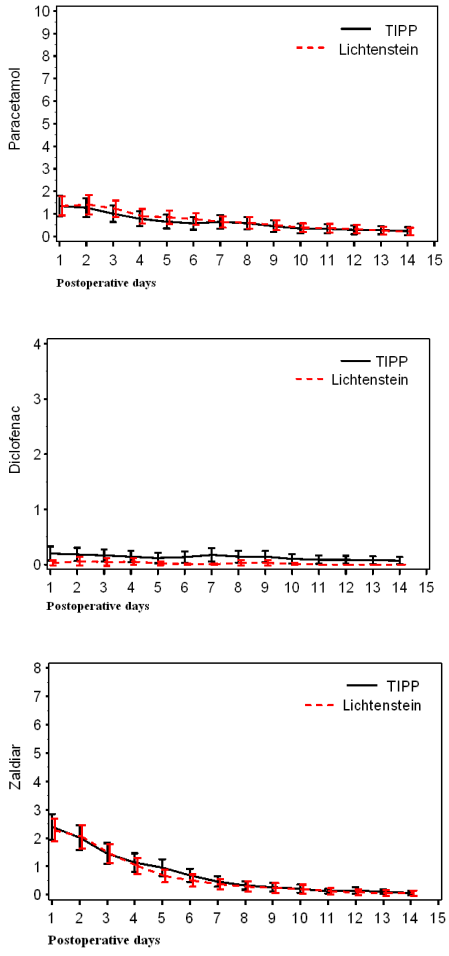
Mesh of similar weight was used in both groups in the present trial so should not have affected the results. Patients in the Lichtenstein group more frequently experienced either chronic pain or activity-related pain. The incidence of chronic pain after Lichtenstein repair was not consistent with the surgical literature. The Groin Pain Trial Group, using a similar definition of chronic pain, reported chronic pain in 4·1 per cent of 733 patients 1 year after Lichtenstein repair[33]. However, that study may have (unintentionally) systematically underestimated harmful effects[21]; a mixed group (Lichtenstein and Trabucco techniques) was used for analyses, and blinding components and other Cochrane Handbook criteria were not described. On the other hand, the rate of chronic postoperative pain after Lichtenstein repair was lower than reported in other studies (15–40 per cent)[6,9]. Other explanations may be trial participation or (hypothetically) the use of a soft mesh.

Chronic pain has significant effects on all daily activities, including walking, working, sleeping, relationships with other people, mood and general enjoyment of life[26]. Direct postoperative pain was uncommon in the present trial, probably because all procedures were performed under spinal anaesthesia, and wounds were infiltrated with local anaesthetic. No differences were found between the groups, and there was no relationship between direct postoperative and chronic pain. This is in contrast to previous findings of a relationship between immediate postoperative pain and other risk factors for developing chronic pain, such as genetic susceptibility and multiple psychosomatic risk factors[34,35].

Persisting numbness was found more frequently in the Lichtenstein group than the TIPP group, despite nerve identification. This fuels a hypothesis for (unintentional) involvement of (one of) the three nerves during Lichtenstein procedures. This complication, however, from the patient perspective, may not be as important as postoperative chronic pain, major bleeding, deep wound infection, recurrence or secondary intervention. The design of this trial focused on reducing the risk of systematic error (bias), random error and design error[17] (outcome measures chosen), and the recommendations outlined in the Cochrane Handbook[21] were used. The risk of bias was low in the domains of generation of the allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias mechanisms[17,21]. It is therefore unlikely that there has been an underestimation of the harmful effects or overestimation of the benefits of the TIPP technique compared with Lichtenstein repair. The data from this trial most likely reflect rates of pain and complications close to the true incidence. However, no scrotal hernias were included, which may have contributed to selection bias. Clinical trials, such as TULIP, are by definition prone to bias because of selection by indication and the chosen outcome measures, and there is always

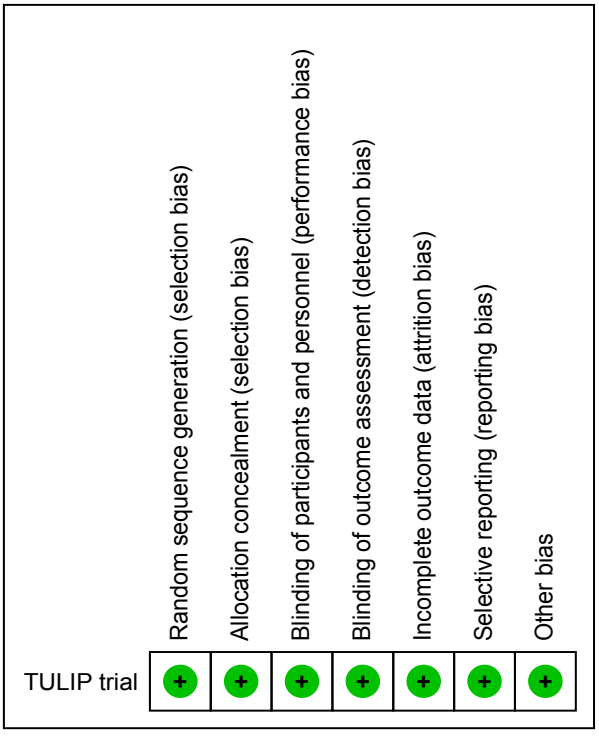
tension between methodological rigour and pragmatism. To determine whether it stands the test of time, long term follow-up of TIPP repair is required and additional good trials evaluating this technique should be conducted to confirm the present results.

Figure S1



Mean analgesics use of the randomised patients in the first 14 days postoperatively after TIPP and Lichtenstein procedures. Analgesics all in tablets: paracetamol (1000 mg), diclofenac (50 mg), and the 'rescue medication' zaldiar (50 mg). Error bars illustrate two times the standard of the mean (2SEM) of both groups. The y-axis represents the number of tablets taken.

Figure S2



Bias risk summary* of the trial.

Legenda:
Green = low risk of bias

Blanc/white = unknown risk of bias (this was not assessed).

Red = high risk of bias (this was not assessed).

*Review Manager (RevMan). Version 5.1 for Windows. (updated to 5.0.25 on 15 September 2010) The Nordic Cochrane Centre, The Cochrane Collaboration: Copenhagen, 2008.

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Chapter 6

Health status one year after TransInguinal PrePeritoneal inguinal hernia repair and Lichtenstein´s method: an analysis alongside a randomised clinical study

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Abstract

Background

The Lichtenstein technique is the treatment of first choice according to guidelines for primary inguinal hernia treatment. Postoperative chronic pain has been reported as complication in 15–40% after Lichtenstein's repair. The postoperative effects on health status after open preperitoneal hernia repair have hardly been examined. Development of an open technique that combines the safe anterior approach of the Lichtenstein with the 'promising' preperitoneal soft mesh position was done; the transinguinal preperitoneal (TIPP) mesh repair. A double-blind prospective randomised controlled trial (TULIP trial, ISRCTN93798494) was conducted to compare different outcome parameters after TIPP or Lichtenstein, one parameter is topic of evaluation in this paper; the health status after TIPP and Lichtenstein for inguinal hernia repair.

Methods

The study protocol has been published. It was hypothesized that the health status of inguinal hernia patients would be better after the TIPP repair compared with the Lichtenstein technique. The size of this study was based on chronic pain as primary outcome measure. Three hundred and two patients were randomised. Patients and the outcome assessors were blinded. Follow-up was scheduled after 14 days, 3 months, and 1 year. The three dimensions of possible errors were warranted.

Results

With regard to health status, significant differences were found in the dimensions 'physical pain' [difference: 6.1 (95% CI 2.3–9.9, p = 0.002)] and 'physical functioning' [difference: 3.5 (95%CI 0.5–6.7, p =0.023)], favouring the TIPP patients after 1 year.

Conclusion

The SF-36 'physical function' and 'physical pain' dimensions after TIPP show significant better patient outcomes at 1 year compared with the Lichtenstein patients in this trial. These differences are in line with reported significant differences in less patients with postoperative chronic pain after TIPP compared with Lichtenstein at 1 year.

Introduction

Approximately 30,000 inguinal hernia repairs are performed in the Netherlands annually [1]. The Lichtenstein technique is the first choice according to guidelines for primary inguinal hernia treatment [2, 3]. The Lichtenstein repair has reduced the incidence of recurrent inguinal hernias compared with non-mesh repairs [4]. However, postoperative chronic pain has been reported as complication in 15–40% after Lichtenstein's repair [5–9].

The postoperative effects on health status have hardly been examined after open (or anterior) preperitoneal inguinal surgery. Several studies have been performed to investigate the health status after inguinal surgery, mainly comparing the totally extraperitoneal (TEP) and Lichtenstein technique. The TEP may conceptually be associated with favourable health status outcomes compared with Lichtenstein [10, 11], but this was not unequivocally demonstrated. Analysis of data from an inguinal hernia study in the Cochrane library showed a considerable proportion of severe adverse events after the 'promising' TEP (10%) [12, 13].

Development of an open technique that combines the safe anterior approach of the Lichtenstein with the 'promising' preperitoneal soft mesh position of the TEP was done by Pélissier [14, 15]. This technique has been described as the transinguinal preperitoneal (TIPP) hernia repair with a preperitoneal mesh with memory ring [9, 16]. Hypothetically, the TIPP is associated with less postoperative chronic pain because no mesh fixation is needed and less nerve involvement may be expected and therefore may result in a better health status than the Lichtenstein technique.
Currently, no health status data are available after TIPP procedures. A double-blind randomised clinical trial (the TULIP trial, ISRCTN93798494) was conducted to compare different outcome parameters after TIPP and Lichtenstein inguinal hernia repair in the first postoperative year. The parameter of health status is topic of this paper using the SF-36 data of the trial [17]. This validated questionnaire has previously been used in studies on inguinal hernia repair [18–24].
Trial funding: none. Trial status: completed.

Methods

The study protocol was written, registered (http://www.controlledtrials.com/ISRCTN93798494), and published prior to the start of the trial [17]. It is available online (www.ncbi.nlm.nih.gov/pmc/articles/PMC2761380).

Design

TULIP was a double-blind randomised controlled trial. Two techniques for inguinal hernia repair were compared (TIPP and Lichtenstein). Patients were included by surgeons and residents who were supervised by the surgeons at the outpatient department (OPD) of the St. Elisabeth Hospital Tilburg and the TweeSteden Hospital, Tilburg, Waalwijk, the Netherlands. Prior to the launch of the TULIP trial, group sessions (in the operating theater and by discussion) for complete standardization and uniformity of both hernia repair techniques with all participating surgeons were performed. Randomised patients were operated on according to this standard. Dedicated hernia surgeons performed the operations or directly supervised the residents. All skin incisions (TIPP and Lichtenstein) were made 2 cm above the Poupart ligament (exactly the same approach). Wound closure occurred by closing the inguinal canal with vicryl 3.0. Scarpa's fascia was closed with 1 stitch vicryl 3.0. The skin was intracutaneously closed with vicryl rapide 3.0 in both techniques.

Patients

Patients with a unilateral primary inguinal hernia, visiting the OPD's at the participating hospitals, were invited to participate, and informed consent was obtained. Inclusion criteria were as follows: primary unilateral inguinal hernia, age >18 to <80 years, American Society of Anesthesiologists (ASA) Classification 1–3, and signed informed consent letter.

Exclusion criteria were as follows: recurrent hernia, scrotal hernia, acute incarcerated inguinal hernia, psychiatric disease or other reasons making follow-up or questionnaires unreliable, and history of preperitoneal space (PPS) surgery (e.g., radical prostatectomy).

Intervention

The TIPP technique has been described in the protocol [17]. In brief, the transinguinal approach was used. Nerves were identified and spared. The sac was reduced into the preperitoneal space. The preperitoneal space was developed with a finger. A soft mesh with memory ring (Polysoft™ 16x9.5cm, Bard Company Benelux, Belgium) was positioned in the preperitoneal space (TIPP) [14–16]. Mesh size was standardized.

Control intervention

The Lichtenstein technique was performed as described by Amid [25] and was adapted to present-day insights with a soft mesh ('light weight') [26] (Soft Mesh 6.9x13.7 cm, BARD Company Benelux, Belgium). The three inguinal nerves (ilioinguinal, ramus genitofemoral and iliohypogastric) were identified and spared. For fixation of the mesh, a Prolene wire 3.0 was used. Using a lightweight mesh was based on a randomised controlled clinical trial [26] as best available level of evidence at the time of writing the protocol. Mesh size was standardized.

Outcome measures

In this paper, the topic of health status of the patients after TIPP or Lichtenstein procedures is reported using the SF-36 data of the trial. Primary outcomes of the trial have been reported [27].

Anesthesia and analgesia

One anesthesia protocol was used in combination with a standardized postoperative regimen based on a combination of the patient's demand, the VAS score, and nausea.

These regimes were based on current and acceptable practice, and the standardization serves to avoid unnecessary bias. Standard anesthesia technique was spinal anesthesia; if the patient refused, general anesthesia was permitted to fulfill the preference of the patient. Inguinal block (5cc) and wound infiltration (5cc Bupivacaine® 0.1%) were used at the end of both techniques. Escape medication for pain was standardized [17].

Randomisation and blinding

Attention was paid to obtain correct generation of the allocation sequence, allocation concealment, blinding, and follow-up [28]. The allocation sequence was computer generated. Allocation concealment was achieved using sealed envelopes. Prior to incision the trial office was contacted by telephone. At the trial office, a sealed blinded envelope (impermeable for intense light) was opened. The nurse in the operating room did not mention but wrote down the technique, so the patient was unaware of the technique. Operation reports were blinded in the electronic patient files, no access to the operation reports was allowed for the outcome assessors.

Data recording and follow-up

All hernias were classified according to the European Hernia Society (EHS) Hernia Classification [29]. The short form 36-item (SF-36) questionnaire is a validated short questionnaire with 36 items that comprise eight multi-item scales: physical functioning (ten items), social functioning (two items), role limitations due to physical problems (four items), role limitations due to emotional problems (three items), mental health (five items) energy and vitality (four items), pain (two items), and general perception of health (five items) [20–22]. For each variable item, scores are coded, added up, and transformed onto a scale from 0–100 [19–22]. Data on health

status were prospectively gathered at the OPD after physical examination. Follow-up was scheduled at 14 days, 3 months, and 1 year postoperatively. After completing the last follow-up visit (including filling in forms and the SF-36 questionnaire), patients were informed about the performed procedure on demand.

Ethics, informed consent

This study was conducted in concordance with the principles of the Declaration of Helsinki. The medical ethics committee approved the study and written informed consent was obtained from all participants. Further details have been described [17].

Analysis and sample size

It was hypothesized that the health status of inguinal hernia patients would be better after the TIPP repair compared with the Lichtenstein technique. The size of this study was based on chronic pain as primary outcome measure. Three hundred and two patients were randomised. No power analysis with respect to health status was performed. No interim analyses were allowed nor performed.

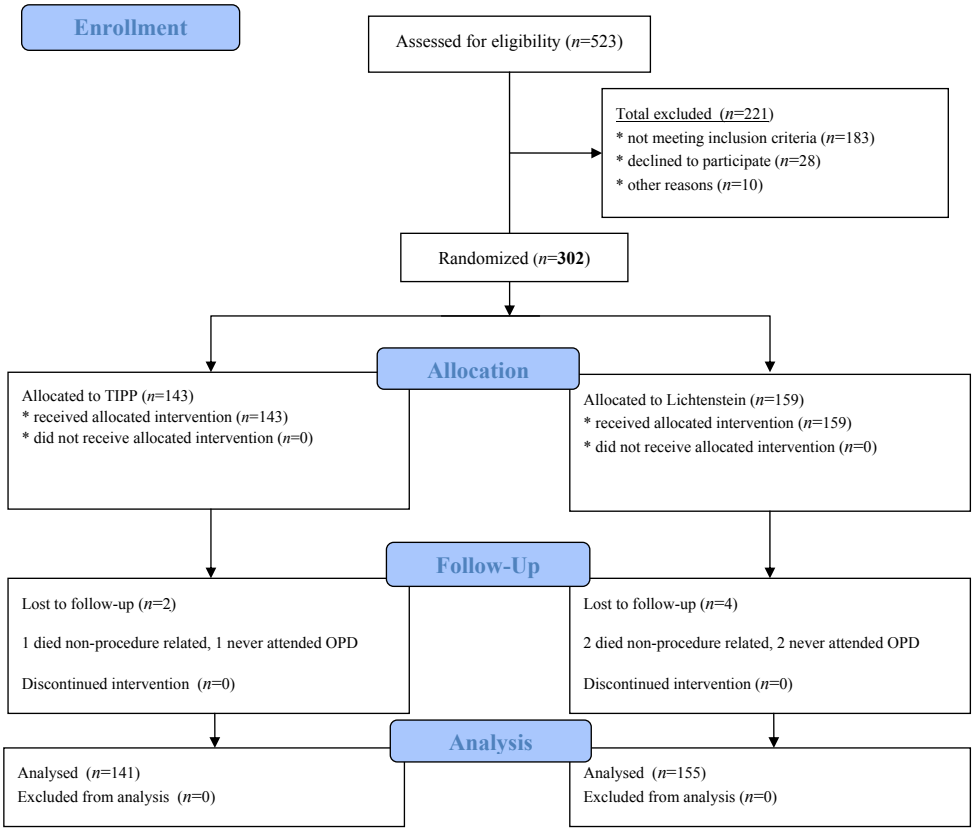
Statistics

The analysis was performed according to the intention-to-treat principle. The primary results, 1 year after treatment, were evaluated using an analysis of variance model with factors treatment and centre. Other results were analyzed in a similar way. Two-sided *p*-values and 95% confidence intervals were calculated. Calculations were made with SPSS® Statistics (version 17.0, 2008), and SAS® (Proprietary Software, version 9.2 (2002–2008), SAS Institute Inc. Cary, NC, USA).

Results

Eligible participants were recruited between January 1, 2009 and March 31, 2010. A total of 523 patients visited the OPD's for inguinal hernia treatment. Many patients were not eligible for inclusion because of various reasons; for example, recurrences from other hospitals, children, previous PPS operations, psychiatric history, or meeting other exclusion criteria, or refused to participate in the trial. Altogether 302 patients met the inclusion criteria and were included in the trial after informed consent was given (Fig. 1). After reminding the patients by telephone and mail to attend to their last follow-up visit at 1 year, 296 patients (98%) visited the OPD. The baseline characteristics of the two trial groups were comparable (fueling adequate randomisation) with regard to age, American Society of Anesthesiologists (ASA) Classification, European Hernia Society (EHS) Classification, body mass index (BMI), and gender (Table 1). Operating teams (resident supervised by consultant or consultant assisted by resident) were equally in both groups (ratio 50–50).

Figure 1



Flow diagram [30] of each stage of the TULIP trial.

Table 1

	TIPP *n*=143	**Lichtenstein** *n*=159
Male	135 (94.4%)	153 (96.2%)
Female	8 (5.6%)	6 (3.8%)
Age (mean +/- SD)	57.0 years (12.1)	56.5 years (13.2)
Side of hernia		
Left	62	68
Right	81	91
ASA classification		
1	81 (56.6%)	99 (62.3%)
2	52 (36.4%)	50 (31.5%)
3	10 (7.0%)	10 (6.3%)
Body Mass Index (mean +/- SD)	25.1 (2.8)	25.4 (2.9)
EHS Hernia Classification[29]		
Primary	142 (100%)	158 (100%)
Lateral size 1	24 (16.9%)	38 (24.1%)
size 2	57 (40.1%)	51 (32.3%)
size 3	15 (10.6%)	15 (9.5%)
Medial size 1	12 (8.4%)	12 (7.6.%)
size 2	14 (9.9%)	17 (10.8%)
size 3	12 (8.4%)	13 (8.2%)
Combination **L** and **M** (pantaloon)	8 (5.6%)	12 (7.6%)
Inguinal hernias without classification	*n*=1	*n*=1

Baseline characteristics of patients randomized to TIPP or Lichtenstein reveal no differences, fuelling an adequate randomization. Abbreviations: ASA: American Society of Anesthesiologists. Body mass index: calculated as weight in kilograms divided by height in meters squared. EHS: European Hernia Society. *n*: number of patients. SD: standard deviation.

With regard to health status significant differences were found in the dimensions physical pain, difference: 6.1 (95% CI 2.3–9.9, p=0.002) and physical functioning, difference: 3.5 (95% CI 0.5–6.7, p=0.023), favouring the TIPP patients after 1 year (Table 2, Fig. 2). Table 2 illustrates that these differences were not yet present after 14 days nor 3 months.

The other six SF-36 dimensions of the TIPP and Lichtenstein patients showed no significant differences at 14 days, 3 months, and 1 year between both groups (Table 2).

Three patients died during the trial because of a stroke, cancer and a progressive muscle disease (newly diagnosed after randomisation). Mortality was not procedure-related.

The differences in health status outcome were influenced by the differences in patients with postoperative chronic pain. Briefly, there were significant less TIPP patients compared to Lichtenstein patients with postoperative chronic pain after 1 year. Additionally, twelve TIPP patients and sixty Lichtenstein patients had activity-related painful episodes [27]. These severe adverse events were critical for decision making according to GRADE [31].

No differences in severe adverse events were present apart from postoperative chronic pain and activity-related pain after 1 year between the TIPP and Lichtenstein patients. Direct postoperative minor complications were graded according to GRADE [13, 31] as not-critical for decision making (e.g., superficial wound infection, hematoma without intervention, nausea, headache, bladder retention (once), and conversion of spinal to general anesthesia). Direct postoperative recovery showed no differences between the groups. There were two patients with recurrences in the TIPP group and four in the Lichtenstein group (p =0.687). The minor complications showed no influence on the health status outcomes.

Table 2

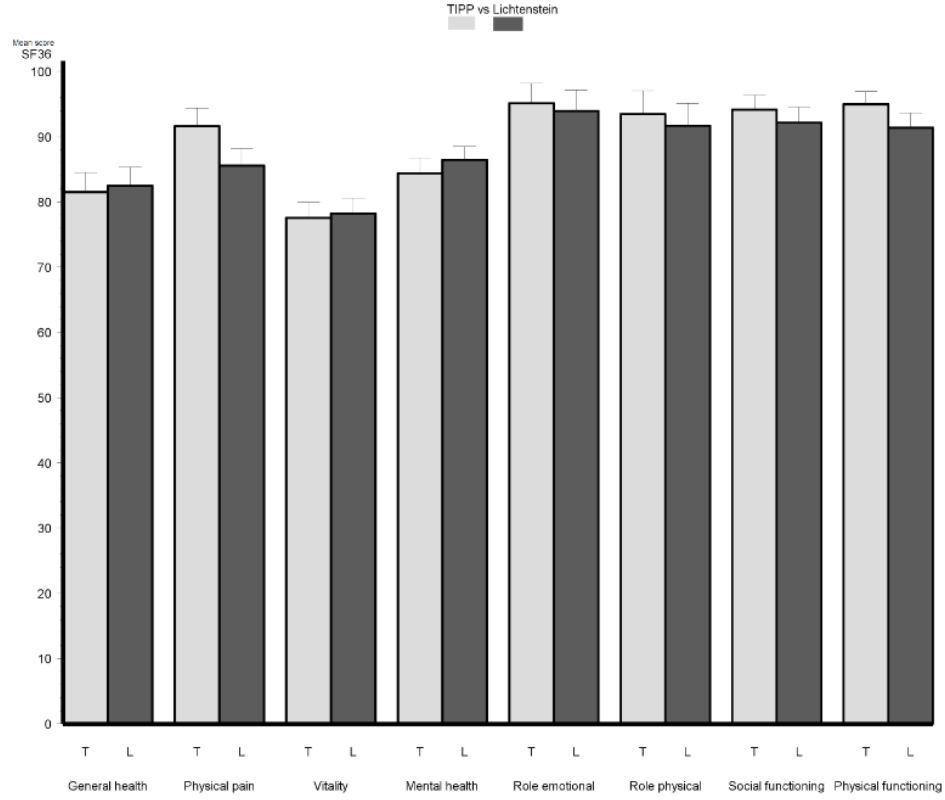
SF-36 dimension	Technique	Postoperative 2 weeks *n*=267	3 months *n*=260	1 year *n*=296	One year 95%CI (*p*-value)
General health	*TIPP*	79.3 (SD 16.9)	80.3 (SD 18.1)	81.5 (SD 18.0)	-5.1 to 3.1 (0.630)
	Licht	80.5 (SD 18.9)	82.5 (SD 17.3)	82.5 (SD 17.9)	
Physical pain	*TIPP*	60.7 (SD 21.7)	87.5 (SD 15.1)	91.6 (SD 16.4)	2.3 to 9.9 (0.002)*
	Licht	58.9 (SD 20.2)	87.0 (SD 16.5)	85.5 (SD 17.0)	
Vitality	*TIPP*	70.2 (SD 19.1)	74.2 (SD 18.1)	77.6 (SD 14.9)	-4.1 to 2.7 (0.696)
	Licht	70.8 (SD 17.9)	77.5 (SD 15.3)	78.2 (SD 15.1)	
Mental health	*TIPP*	81.6 (SD 16.9)	82.2 (SD 17.1)	84.4 (SD 14.7)	-5.2 to 1.1 (0.197)
	Licht	83.8 (SD 14.3)	86.2 (SD 13.0)	86.5 (SD 13.1)	
Role emotional	*TIPP*	77.0 (SD 35.3)	90.0 (SD 26.3)	95.1 (SD 18.5)	-3.3 to 5.7 (0.604)
	Licht	75.2 (SD 38.4)	93.1 (SD 21.6)	93.9 (SD 20.8)	
Role physical	*TIPP*	47.7 (SD 41.0)	85.6 (SD 30.0)	93.5 (SD 21.6)	-3.2 to 6.8 (0.474)
	Licht	43.1 (SD 41.9)	89.2 (SD 26.9)	91.7 (SD 22.1)	
Social functioning	*TIPP*	78.3 (SD 21.4)	89.5 (SD 19.3)	94.1 (SD 13.3)	-1.3 to 5.3 (0.230)
	Licht	77.3 (SD 21.6)	90.5 (SD 17.1)	92.1 (SD 15.4)	
Physical functioning	*TIPP*	79.3 (SD 19.2)	91.0 (SD 16.7)	94.9 (SD 12.0)	0.5 to 6.7 (0.023)*
	Licht	77.4 (SD 21.1)	90.8 (SD 20.8)	91.4 (SD 14.9)	

Indicating the health status of the randomized patients between TIPP or Lichtenstein according to intention-to-treat principle. The health status was assessed by using the SF36-list (mean scores and SD) after 2 weeks, 3 months, and one year. The data response rate varied from 89.6% at 14 days to 98% at one year.

*= significance was assessed

Abbreviations used in table 2: SF-36= short form 36-items questionnaire, TIPP= TIPP patients, Licht= Lichtenstein patients, 95%CI= 95% confidence interval.

Figure 2



The SF-36 dimensions physical pain and physical function, one year after inguinal hernia repair favour TIPP-patients significantly in the TULIP trial. The outcomes should be interpreted as better functional outcome measure. The higher the score, the better the functional outcome is. The other six SF-36 dimensions show no differences between TIPP and Lichtenstein patients after one year. The error bars on top represent the 95% confidence interval (95%CI) of the mean.

Discussion

The aim of this study was to compare the topic of health status of patients after TIPP and Lichtenstein's tension-free inguinal hernia repair after the first postoperative year [17]. It was hypothesized that the health status would be better after TIPP compared with the health status after Lichtenstein. This study shows a significant better health status of TIPP patients in the SF-36 dimensions 'physical pain' and 'physical function' at 1 year (Fig. 2). Figure 2 shows a better functional outcome in the dimension of 'physical pain' after TIPP and therefore should not be interpreted as more pain in the TIPP patients. These differences in TIPP and Lichtenstein patients were not yet present after 14 days or at three-month follow-up. They appear to develop later on in the postoperative period. It may very well be that patients are more cautious in the first months after surgery compared with the period thereafter. These significant health status differences are in line with elsewhere reported differences in less patients with postoperative chronic pain after TIPP compared with Lichtenstein at 1 year [27].

In literature, no data on health status after TIPP repair are presently available due to the recent introduction of TIPP. Therefore, its long-term health status is unknown. The health status after Lichtenstein has been evaluated [10, 11, 32, 33]. The health status of the Lichtenstein patients in the TULIP trial is better than has been reported in other studies. This may be correlated to the concentration-of-care principle [9], or due to trial participation (complete standardization of operation). The majority of previous reports of health status after Lichtenstein can be summarized as studies with high-risk-of-bias, and therefore may have the risk of systematically underestimate harmful effects and overestimate benefits [34]. In other words; the results of these studies may carry the status of "truth". However, there is a high probability that differences between treatments are found because of random errors ('the play of chance'), systematic errors ('bias') and design errors ('wrong design to answer the question posed' or 'wrong context'), and should be cautiously interpreted [35]. Nevertheless, comparing conclusions of low-risk-of-bias studies to higher-risk-of-bias studies may therefore be potential unreliable.
Next to the described methodological short comings, the concepts of 'health status' and 'quality of life' (QoL) may be confusing for readers, especially when both refer to the validated short form 36-item questionnaire. The SF-36 is a widely used and standardized instrument giving subjective insights in the functional 'health status' of a person by measuring eight multi-item scales (dimensions) [19–24] and has been used for inguinal hernia reports [18]. To compare, subsequently, different reports on health status and/or QoL after Lichtenstein may lead to heterogeneous groups, making comparison less reliable [13].

Limitations of this study

No pre-operative SF-36 scores were obtained because the health status was no primary or secondary outcome measure. Power calculations for this study were based on the sample size of patients with postoperative chronic pain in the trial. Nevertheless, health status is logically related to outcomes critical for decision making, such as postoperative chronic pain. The SF-36 results presented are to indicate the first postoperative year of patients after inguinal hernia surgery according to TIPP, compared with Lichtenstein. Although statistically significant differences in scores on 'physical pain' and 'physical function' between the two hernia repair techniques were recorded, closer examination reveals relatively small differences in the absolute scores. Potential weakness of this study, as said, is the lacking power calculation specifically for health status. Nevertheless, the dimensions of physical pain and physical function were significantly favouring the TIPP. The presented favourable physical TIPP results of this study are logical in a sense that these dimensions are influenced greatly by postoperative chronic pain.

Complications

Complications may logically have a direct influence on health status after inguinal hernia surgery. Overall, the amount of patients with non-critical complications was low in the trial. Grading complications from patient's perspective may give other interpretations to the outcomes of this study than other reports. When severe adverse events are present in a trial, one should count the patients with one or more events. It is important to realize that 'complications' instead of 'patients-with-complications' were scored in other studies. These double counts fuel the sampling error when evaluating outcomes [13]. Nevertheless, 'patients with complications' may be the most important outcome at the end of the day, and may very well influence greatly on the patient's health status.

The different position of the mesh in TIPP and Lichtenstein patients should also be considered explaining the physiological differences at 1 year. The preperitoneal position of the mesh in the TIPP technique caused significantly less pain and better functional outcomes. No sutures nor mesh fixation are necessary for TIPP because the mesh is not in contact with the inguinal nerves. Physical movements lead to different forces in the inguinal region, and may therefore demand anatomical 'adaptation' of the mesh. Sutures bring their forces and tractions in the inguinal canal as is done Lichtenstein's repair, and may bring the inguinal nerves at risk (nerve entrapment, damaging or stretching) causing postoperative chronic pain.

Presently it is unknown (in trials with low risk of bias) if the favourable TIPP outcomes are comparable with the self-fixating mesh method, a variation on the classical Lichtenstein technique. The preperitoneal positioned mesh with memory ring, in combination with the safe open approach of TIPP is an explanation for better postoperative health status for inguinal hernia patients concerning 'physical function' and 'physical pain'. Based on available evidence (recent systematic review [12, 13]) and the advantageous TIPP results of this study, the ongoing evolution of inguinal hernia repair concepts may lead to an open direct preperitoneal approach in combination with a preperitoneal mesh position. This concept will most likely lead to better health status outcomes in the dimensions of 'physical pain' and 'physical function' for inguinal hernia patients postoperatively.

In conclusion, the SF-36 'physical function' and 'physical pain' dimensions after TIPP show significant better patient outcomes at 1 year compared to the Lichtenstein patients in this study. These findings are in line with reported differences in less patients with postoperative chronic pain after TIPP compared to Lichtenstein at 1 year.

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Chapter 7

TIPP and Lichtenstein modalities for inguinal hernia repair: a cost minimisation analysis alongside a randomised trial

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Abstract

Introduction

Recently the transinguinal preperitoneal (TIPP) technique using a soft mesh with memory ring was developed for inguinal hernia repair. To compare TIPP with Lichtenstein, a randomised trial was conducted (ISRCTN93798494). The aim of this study is to perform an economic evaluation of the TIPP modality compared to the Lichtenstein modality from both a hospital and societal perspective alongside the clinical trial.

Methods

The TULIP study was a double-blind randomised clinical trial comparing two techniques for inguinal hernia repair (TIPP and Lichtenstein). Correct generation of the allocation sequence, allocation concealment, blinding, and follow-up were used/applied according to the recommendations of the Cochrane Handbook. Next to the cost drivers, the short-form-36 health survey (SF-36) data from the TULIP trial were used to determine the utilities. The SF-36 data from the TULIP trial were revised by using the SF-6D algorithm according to Brazier. Two scenario's, a hospital and a societal perspective, were presented. If the analyses showed no difference in effects (on the SF-6D) the cost effectiveness decision rule to cost minimisation was altered.

Results

No significant difference in SF-6D utility between both modalities was found (mean difference: 0.888, 95%CI: -1.02 to 1.23) consequently the economic decision rule became cost minimisation. For the hospital perspective no significant differences in costs were found (mean difference: €-13, 95%CI: €-130 to €104). However, including productivity gains in the analysis, significant differences (p= 0.037) in costs favouring the TIPP modality (mean saving: €1472, 95%CI: €463 to €2714) were found.

Conclusion

The results show that TIPP is a cost-saving inguinal hernia repair technique compared to the Lichtenstein modality against equal effectiveness expressed in QALW at one year given a societal perspective. TIPP patients show on average a quicker recovery of 6.5 days compared to Lichtenstein patients in the trial.

Introduction

Annually, about 30.000 inguinal hernia repairs are performed in the Netherlands, and about 750.000 in the US [1-5]. The life time risk for developing an inguinal hernia is estimated at approximately 30% for men and 3% for women. Inguinal hernia repair, however, is not mandatory in all patients, especially not in asymptomatic patients [4,5].

Total costs in national health care are high and expanding, and many efforts have been attempted to control increasing costs. One of these efforts is the performance of an economic evaluation of innovative technologies pending for reimbursement. For such an analysis a societal perspective is recommended [6-8].

From clinical and patients perspectives costs may be considered as a less important outcome measure, and may be not qualified as a "critical factor" in decision making of alternative interventions [9]. However, at the societal level taking into account today's increasing health care costs warrant careful evaluation of the cost aspects of alternative therapies. This paper aims to present an economic evaluation about the comparison of two hernia repair modalities, the transinguinal preperitoneal method (TIPP) and the Lichtenstein technique.

Lichtenstein's tension-free inguinal hernia repair is the present global reference technique, as it is in the Netherlands [10-11]. The Lichtenstein technique reduced recurrences drastically. However, postoperative chronic pain after Lichtenstein varies from 15-40% [12]. According to the Dutch Inguinal Hernia Guideline, techniques such as the totally extraperitoneal (TEP) or transabdominal preperitoneal (TAPP) method can be considered when expertise is present [11]. Studies suggest that these procedures with an endoscope may be associated with less postoperative chronic pain. However, this is not unequivocally proven [13,14]. Furthermore, endoscopic techniques require general anesthesia and costly disposable tools.

Pélissier developed the TIPP technique for inguinal hernia repair by using a soft mesh with memory ring [15,16]. Initial studies suggest that the TIPP technique may be associated with less patients with postoperative chronic pain [17]. Additionally, this technique may be quicker to perform and no scopic equipment nor mesh fixation is needed. The TIPP technique may very well be advantageous compared to Lichtenstein considering a shorter operative time and lower costs. TIPP was compared with Lichtenstein in a double blind randomised controlled clinical trial (ISRCTN93798494). The results from the trial and the health status data have been published [17,18]. This study focuses on the economic evaluation of both modalities alongside the trial.

Trial status: *completed*. Funding: *none*.

Methods

Prior to the start of the trial, the protocol was published [12] (available online *www.ncbi.nlm.nih.gov/pmc/articles/PMC2761380).* The TULIP trial was registered (*http://www.controlled-trials.com/ISRCTN93798494)*. This study was approved by the Medical Ethical Committee, and was conducted in concordance with the principles of the Declaration of Helsinki. Details have been described in the protocol [12].

Procedure

Study Design

TULIP was a double-blind randomised multi-centre trial. Two techniques for inguinal hernia repair (TIPP and Lichtenstein) were compared. Patients were included by surgeons and (supervised) residents at the outpatient departments of the participating hospitals (St. Elisabeth Hospital and the TweeSteden Hospital, Tilburg/Waalwijk, the Netherlands).

Both centers are teaching hospitals for surgical residents. The *Hernia Center Brabant* was established in 2006 to teach and train residents, and to concentrate the care for inguinal hernia surgery.

Prior to the start of the TULIP trial, group sessions were organized in the operating theatre (and by discussion) for complete standardization and uniformity of the both hernia repair techniques with all surgeons involved. Randomised patients were operated on according to this protocol [12]. Dedicated hernia surgeons performed the operations, or directly supervised the resident. All skin incisions (TIPP and Lichtenstein) were made two centimeters above the Poupart ligament (identical approach). Nerves were identified and spared in both techniques. Wound closure occurred by closing the inguinal canal using vicryl 3.0. Scarpa's fascia was closed using (1 stitch) vicryl 3.0. The skin was intracutaneously closed with vicryl rapide 3.0 in both techniques.

Patients

Patients with a unilateral primary inguinal hernia, visiting the outpatient departments were invited to participate and written informed consent was obtained [12].

Inclusion criteria were: primary unilateral inguinal hernia, age >18 <80 years, American Society of Anesthesiologists (ASA) Classification 1-3, signed informed consent letter.

Exclusion criteria were: recurrent hernia, scrotal hernia, acute incarcerated inguinal hernia, psychiatric disease or other reasons making follow up or questionnaires unreliable, previous preperitoneal surgery (e.g. radical prostatectomy).

Intervention

The TIPP technique has been extensively described in the protocol [12]. Briefly: the transinguinal approach was used. The sac was reduced into the preperitoneal space. The preperitoneal space was developed, by digitally dissection. A soft mesh with memory ring (Polysoft™ 16x9.5cm, Bard®

Company Benelux, Belgium) was positioned in the preperitoneal space (TIPP) [15,16,19]. TIPP requires no mesh fixation (no sutures or tackers).

Control intervention

The Lichtenstein technique was performed as described by Amid [20], and was adapted to present-day insights with a soft mesh [21] (Soft Mesh 6x13.7cm, Bard® Company Benelux, Belgium). For fixation of the mesh a Prolene® suture 3.0 (Ethicon, Johnson and Johnson) was used.

Perspective economic evaluation

The aim of this study was to evaluate the economic aspects of the TIPP modality compared to the Lichtenstein modality in the relevant time frame of the first postoperative year. This economic evaluation was evaluated from both a hospital and a societal perspective.

Anesthesia and analgesia

Preoperatively, all patients visited the anesthesiology outpatient department. One anesthesia protocol was used in combination with a standardised post-operative regimen on patients demand, based on VAS score for pain, and nausea [12]. These regimes were based on current and acceptable practice and the standardization serves to avoid unnecessary bias. First choice of anesthesia technique was spinal anesthesia. When the patient refused, general anesthesia was given to fulfill the preference of the patient. Inguinal block (5cc) and wound infiltration (5cc Bupivacaine® 0.1%) was used at the end of both techniques. Escape medication for pain, was standardized as well [12].

Randomisation and blinding

Adequate generation of the allocation sequence, allocation concealment, blinding, and follow-up were used according to recommendations of the Cochrane Handbook [22]. The allocation sequence was computer-generated. Allocation concealment was achieved using sealed envelopes. Randomisation occurred in the operating room. Prior to incision the trial office was contacted by telephone. At the trial office, a sealed blinded envelope, impermeable for intense light, was opened. The nurse in the operating room did not mention but noted the technique to be applied. The patient was unaware of the technique. Operation reports were blinded in the electronic patient files, and no access was allowed for the blinded outcome assessors.

Only after completion of one year follow-up patients were informed on demand about the technique used (*after* completing forms, questionnaires and physical examination). No earlier un-blinding occurred.

Data collection

Follow-up was scheduled at 14 days, 3 months, and at one year. Each follow-up included physical examination and completion of questionnaires.

A complete case analysis was considered with regard to cost data. The prices for several sources of health care consumption were estimated based on the Dutch Manual for Cost Research in Health Care [23]. Costs prior to hospital admission were considered similar for both modalities, TIPP and Lichtenstein.

Cost and utility analysis

General cost drivers, such as work up for operation (anesthesiological screening, visiting outpatient clinics, etcetera) were considered equal in both groups. Specific cost drivers were: exact operative time (skin-to-skin), and total stay in the operation room. Admission time was recorded in hours. Costs of day-care were defined as the price per 12 hours. If a patient stayed overnight the day-care price was counted twice. All complications were recorded. Inguinal hernia recurrence associated costs were estimated by calculating an extra outpatients clinic visit of 15 minutes for a physical examination to diagnose a recurrence hernia, the re-use of the operation room with associated costs, an additional hospital admission and a postoperative outpatients´ visit (15 minutes). The severities of all complications were assumed as being financially similar.

Costs for analgesics (paracetamol, diclofenac, and combination tramadol/paracetamol) were calculated based on available prices [24]. Sick-leave was recorded in days. It was assumed that patients did not resume their work or daily-life activities (gardening, sports etcetera) on the day of operation. Only the different material costs were used (price of the different soft meshes and Prolene 3.0 suture). Costs drivers such as salary for the surgeon, resident, nurse, assisting nurse, anesthetist and anesthesia-assistant were assessed according to available target prices as described in the Dutch Manual for Cost Research in Health Care [23]. The cost drivers which were not described in this tutorial were estimated based on average institutional full cost prices.

Utilities were determined from the short form 36 (SF-36, version 1) health survey questionnaire data. The SF-36 data from the TULIP trial were transformed to utilities by using the SF-6D algorithm as described by Brazier et al. (2002) [25-27].

Analysis

Cost and utility parameters will be presented as means with 95% confidence intervals (CI). The utilities were determined as the area under the curve from 14 days postoperatively up to one year. Differences in costs and utility between both groups were tested using the t-test for independent samples. Analyses of costs and utilities were based on original sample data as well as bootstrapped data (case resampling). Type of bootstrapping was case resampling with replacement of the original dataset and was undertaken taking account of both a hospital - and societal perspective. The economic evaluation was set up as a cost-effectiveness analysis applying the decision rule that incremental cost-effectiveness ratio should be less than some threshold value for a quality adjusted life week (QALW) gained.

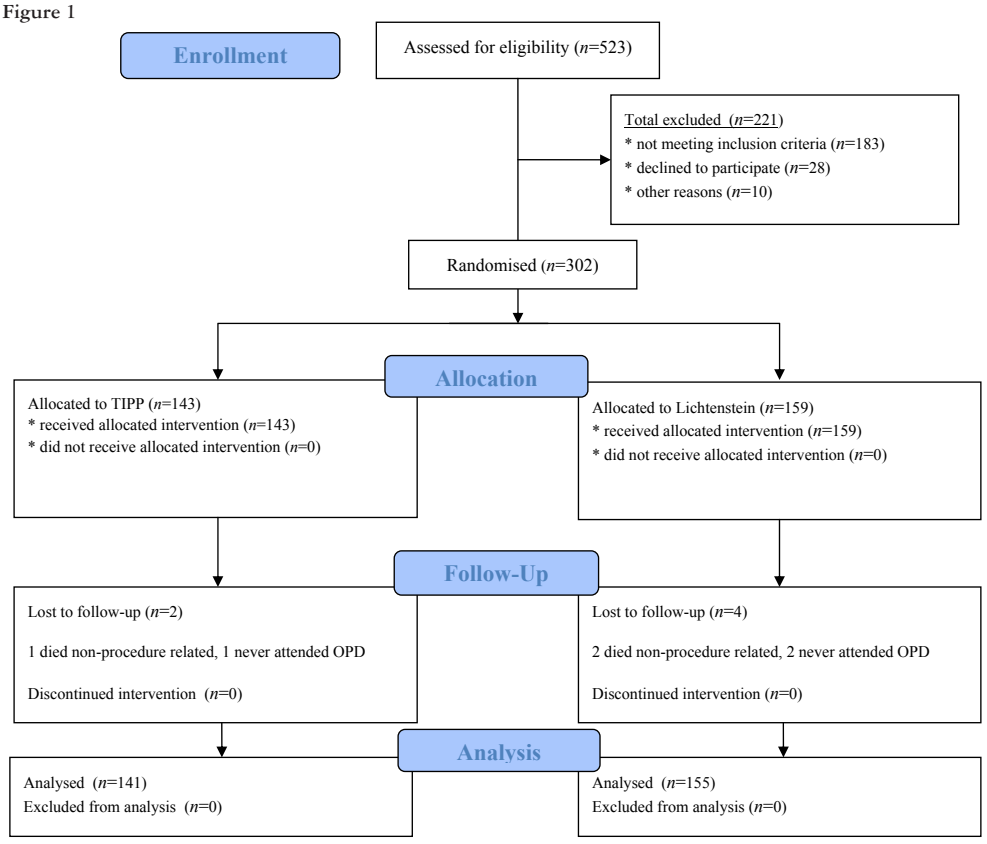
However, if results on effects as measured on the SF-6D showed no difference between the two inguinal hernia repair modalities than a cost minimisation decision rule will be applied. The societal perspective scenario differs from the hospital perspective scenario in that it includes productivity gains or productivity losses related to the TIPP modality.

Calculations were made with SPSS® Statistics (version 19.0, 2010).

Results

In the trial, a total of 302 patients were randomised to TIPP or Lichtenstein. Overall 6 patients were lost to follow up (Figure 1). Baseline characteristics of TIPP and Lichtenstein patients are presented (Table 1). At the 3 months follow-up it seemed that there were less patients attending the outpatient clinics compared to 14 days and at one year. Therefore some of the effect data (SF-36 data) was missing after three months in the trial due to various patient related reasons such as: not motivated to come to the outpatients´, forgot to come, no complaints, moved to another area, unknown reasons. The missing parts of the SF-36 data of the follow-up visits after 3 months were equally divided among the TIPP and Lichtenstein groups.

Figure 1



Revised CONSORT [30] diagram showing the flow of participants through each stage of the TULIP trial.

Table 1

	TIPP *n*=143	Lichtenstein *n*=159
Male	135 (94.4%)	153 (96.2%)
Female	8 (5.6%)	6 (3.8%)
Age (mean +/- SD)	57.0 years (12.1)	56.5 years (13.2)
Side of hernia		
Left	62	68
Right	81	91
ASA classification		
1	81 (56.6%)	99 (62.3%)
2	52 (36.4%)	50 (31.5%)
3	10 (7.0%)	10 (6.3%)
Body Mass Index (mean +/- SD)	25.1 (2.8)	25.4 (2.9)
EHS Hernia Classification		
Primary	142 (100%)	158 (100%)
Lateral size 1	24 (16.9%)	38 (24.1%)
size 2	57 (40.1%)	51 (32.3%)
size 3	15 (10.6%)	15 (9.5%)
Medial size 1	12 (8.4%)	12 (7.6.%)
size 2	14 (9.9%)	17 (10.8%)
size 3	12 (8.4%)	13 (8.2%)
Combination **L** and **M** (pantaloon)	8 (5.6%)	12 (7.6%)
Inguinal hernias without classification	*n*=1	*n*=1

Baseline characteristics of patients randomized to TIPP or Lichtenstein inguinal hernia repair.
Abbreviations: ASA: American Society of Anesthesiologists. Body mass index: calculated as weight in kilograms divided by height in meters squared. EHS: European Hernia Society. *n*: number of patients. SD: standard deviation.

Cost and utility analysis

Empirical results are presented in table 2. No difference in utility between both modalities was found (mean difference: 0.888, 95%CI: -1.02 to 1.23). in the first postoperative year. The cost drivers are presented in table 3. Cost inferences depend on the perspective: hospital or societal. From a hospital perspective no significant differences were found in costs (mean difference: €-13, 95%CI: €-130 to €104). From a societal perspective, however, including productivity gains in the analysis, significant differences in costs favouring the TIPP modality (mean saving: €1472, 95%CI: €463 to €2714) were found. Mean TIPP sick-leave was 6.5 days shorter compared to Lichtenstein´s modality (p=0.0014) (Table 3). According to these calculations an average saving of €1472 in each TIPP modality can be inferred.

Table 2

	n	Mean	Mean difference	t-test for Equality of Means	
				95% CI of difference	
				Lower	Upper
Total costs *hospital* perspective					
TIPP	122	1404 (€)	-13 (€)	-128 (€)	101 (€)
Lichtenstein	121	1420 (€)			
Total costs *societal* perspective					
TIPP	112	3825 (€)	-1472 (€)	-2620 (€)	-325 (€)
Lichtenstein	114	5298 (€)			
Utility Area 14 days to 1 year (duration of 50 weeks)	141	42,94 (QALW)	0.00983 (QALW)	-1.01250 (QALW)	1.03217 (QALW)
	152	42,93 (QALW)			

Empirical results of trial data. Costs in series mean. Complete cases based on series mean.
Abbreviations: *n*: number of complete cases for particular economic outcomes, TIPP: transinguinal preperitoneal hernia repair, QALW: quality adjusted life week.

Table 3

Main Cost Drivers	**TIPP**	**Lichtenstein**
Patients with one recurrence	2	4 ^
Mean operation time in minutes (SD)	34.1 (9.9)	39.9 (12.0)[§1]
Engaging operation room in minutes (SD)	51.7 (14.9)	58.4 (17.2) [§0]
Mean hospital stay in hours (SD)	8.1 (6.5)	9.0 (5.1) [§0]
Mean work* absence in days (SD)	9.9 (11.4)	16.4 (20.5)[§2]
Mean number of total complications (SD)	0.1 (0.5)	0.2 (0.6) [§0]
Mean use of pills first postoperative year[$]	21.0 (24.0)	19.4 (18.3) [§0]
Estimated soft mesh price in euro's	220	120
Prolene wire for mesh fixation in euro's	-	4

Main cost drivers for economic evaluation of TIPP and Lichtenstein. Cost drivers were encountered only when they showed a difference, or contributed to differences. Other costs were considered to be equal in both techniques such as outpatient department visit, work-up for operation, spinal anesthesia etc.).
Abbreviations: SD: standard deviation
*: this is work (job) and/or return to normal activity if retired
[$]: analgesics were paracetamol, diclofenac, and tramadol/paracetamol combination
^: The sample size of the trial is unable to detect a possible difference in recurrences between the 2 groups.
[§0]: not significant
[§1]: *p*-value <0.0001
[§2]: *p*-value = 0.0014

Incremental costs are displayed in table 4. Bootstrapped costs of the TIPP modality and the Lichtenstein modality as well as their difference are presented as histograms (Figure 2a,b,c). From the societal perspective it becomes clear that the efficiency increase results from including productivity gains. Here, in the societal perspective the TIPP modality is more efficient than the Lichtenstein modality as on average it saves money at equal effectiveness.

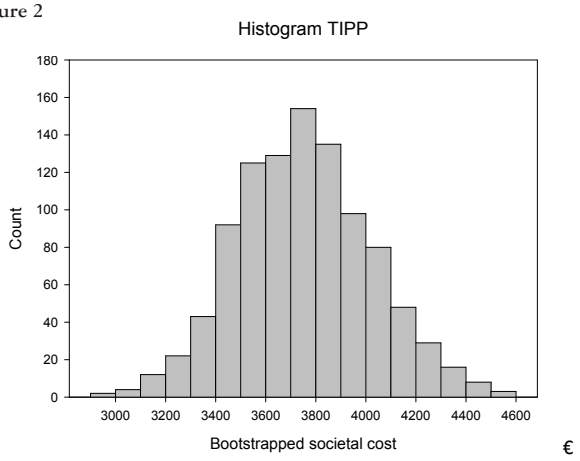
Table 4

Unit cost parameter (causing difference between TIPP & Lichtenstein)	**Unit Cost** (€)	**Source**
Hospital admittance (per 12 hours)	332	Mean of Participating Hospitals and Guideline price (CvZ)[23]
Operating room per hour (personnel included)	810	Guideline Price (CvZ) www.Loonwijzer.nl
Prolene suture (per piece)	4	Purchasing Department Hospital
Productivity gain per hour	32	Guideline Price (CvZ)
Extra costs recurrence (besides those stated above) are: 2 extra outpatients´ visits of 15 minutes	68	Guideline Price (CvZ)

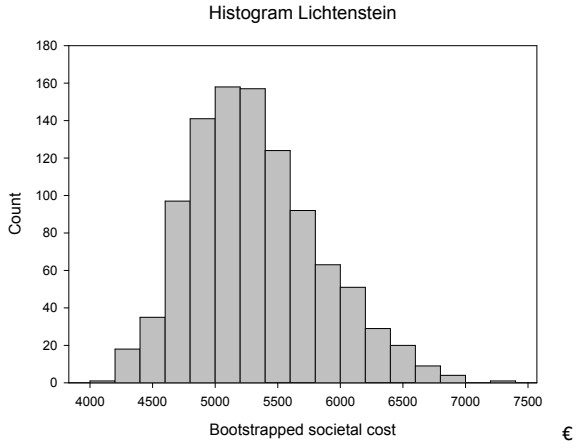
Indicating the unit costs causing differences between TIPP and Lichtenstein modalities.
Abbreviations: TIPP: trainsinguinal preperitoneal technique, OPD: outpatient department, OR: operating room, CvZ: College voor Zorgverzekeraars (Health Care Insurance Guidelines)

Figure 2

a



b



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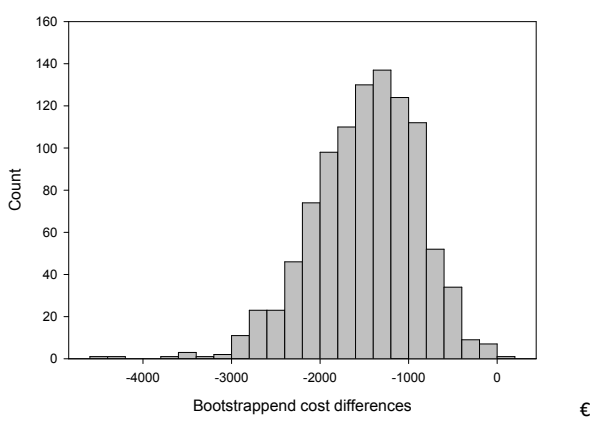

Histograms of the bootstrapped cost analyses from societal perspective for TIPP (2a), Lichtenstein (2b) and the cost differences favouring TIPP (2c), all in Euro´s (€).

Discussion

From a hospital perspective no differences in costs were found between the TIPP- and Lichtenstein modality using the data of the trial including 302 patients. The work-up for operation and hospital admission showed similar resource consumption.

From a societal perspective, including productivity gain in the analyses, the TIPP modality is cost saving compared to the Lichtenstein modality. The difference is completely based on a quicker average return to work of 6.5 days of TIPP patients compared to Lichtenstein patients. This leads to an average saving of €1472 on the total costs per TIPP modality compared to Lichtenstein's. With approximately 750.000 hernia repairs in the USA, and about 30.000 inguinal hernia operations in the Netherlands each year, considerable costs may be saved. From an employer's perspective this finding may be of interest. Applying a third-party-payer perspective would not alter the results as found in the hospital perspective as the insurance price (in Dutch: diagnose behandel combinatie (DOT)) is exactly the same for TIPP as for Lichtenstein currently.

This is the first paper describing an economic evaluation of the TIPP technique versus the Lichtenstein method for inguinal hernia repair alongside a randomised clinical trial. The TIPP patients showed quicker return to work, and/or quicker resume of their usual activities when retired, compared to the Lichtenstein group (Table 3). These findings are in line with the reported results of the TULIP trial [17,18]. The TIPP patients showed significantly less chronic pain compared to the Lichtenstein patients at one year [17]. The utilities, however, did not differ between the two modalities, despite the significant finding that less TIPP-patients suffered from postoperative chronic pain. Because other domains (e.g. `social´, `self-care´, etcetera) are figured into the utility measure, the difference in patients with postoperative chronic pain is attenuated in the utility measure. In the dimensions of the SF-36, two dimensions (`physical pain´ and `physical function´) showed relevant effects, favouring the TIPP modality in the trial [18]. The findings in this economic evaluation, revising SF-36 data to SF-6D, do not show this effect of a difference. An explanation may be that the other indifferent SF-36 dimensions compensate for this effect in the total SF-6D outcome measure. The question could raise whether the QALW-method is sensitive enough to assess a difference in the separate dimension-effects. However, it is reasonable to assume that the fact that fewer TIPP patients experiencing postoperative chronic pain is expressed by their earlier work resumption (productivity gains). QALW from a societal economic perspective makes clear that productivity gain (or loss) may be an important factor in this economic analysis.

Productivity gains (or losses) in relation to TIPP have, to the authors best knowledge, not been reported before. The Lichtenstein modality, being the global reference technique with low recurrence rates, has been postulated as cost effective. Compared with the endoscopic totally extraperitoneal procedure (TEP), the Lichtenstein has fewer expenses for hospitals [4,28]. Productivity gains (or losses) seems to be an important factor in evaluating inguinal hernia repair techniques.

The fact that many inguinal hernia patients are retired when they are operated on decreases the potential productivity gain. However, some patients are involved in voluntary work and according to the Dutch Manual for Costing Research such gains should be included as well [8]. These societal benefits may contribute to the evolution of an open approach with preperitoneal soft mesh position.

The trial was designed with special attention on reducing risks of systematic error (bias), random error, and design error (the chosen outcome measures). According to Cochrane criteria the trial methodology can be summarized as a trial with low risk of bias [22]. All the domains of generation of the allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and prevention of other bias mechanisms were warranted [12,22]. It is therefore likely that no systematic underestimation of harmful effects nor overestimation of benefits of TIPP is present compared to the Lichtenstein technique. Minimizing bias will produce more reliable data [29]. Next to primary outcomes of trials which are critical for decision making from the patient's perspective, future randomised clinical trials on inguinal hernia repair should also take into account the productivity gains or productivity losses derived from the interventional modality compared to the control intervention. In this way a total overview can be provided per modality for inguinal hernia repair.

In summary, the results show that TIPP is a cost-saving inguinal hernia repair technique compared to the Lichtenstein modality against equal effectiveness expressed in QALW at one year given a societal perspective. TIPP patients show an average quicker recovery of 6.5 days compared to Lichtenstein patients in the trial.

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Chapter 8

The transrectus sheath preperitoneal mesh repair for inguinal hernia: technique, rationale and results of the first 50 cases

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Abstract

Introduction

Laparoscopic and endoscopic hernia repair popularized the preperitoneal mesh position due to promising results concerning less chronic pain. However, considerable proportions of severe adverse events, learning curves, or added costs have to be taken into account. Therefore, open preperitoneal mesh techniques may have more advantages. The open approach to the preperitoneal space (PPS) according to transrectus sheath preperitoneal (TREPP) mesh repair is through the sheath of the rectus abdominis muscle. This technique provides an excellent view of the PPS and facilitates elective or acute hernia reduction and mesh positioning under direct vision. In concordance with the promising transinguinal preperitoneal inguinal hernia repair experiences in the literature, the feasibility of TREPP was investigated.

Methods

A rationale description of the surgical technique, available level of evidence for thoughts behind technical considerations. Furthermore, a descriptive report of the clinical outcomes of our pilot case series including 50 patients undergoing the TREPP mesh repair.

Results

A consecutive group of the first 50 patients were operated with the TREPP technique. No technical problems were experienced during the development of this technique. No conversions to Lichtenstein repair were necessary. No recurrences and no chronic pain after a mean follow-up of 2 years were notable findings.

Conclusion

This description of the technique shows that the TREPP mesh repair might be a promising method because of the complete preperitoneal view, the short learning curve, and the stay-away-from-the-nerves principle. The rationale of the TREPP repair is discussed in detail.

Introduction

After recurrences have been reduced in inguinal hernia repair since the use of mesh, chronic pain is considered to be the most important clinical evaluation after inguinal hernia surgery. Surgery-related factors which may be associated with chronic pain mainly involve nerve injury (or stretching) possibly caused by the surgical approach or the use of mesh fixation devices [1]. Therefore, it may be logical to develop a technique that minimizes or completely avoids nerve contact and does not need mesh fixation. Recently, Reinpold et al. published recommendations for nerve management during surgery [2]. We developed and investigated an easy open preperitoneal technique that may fulfill these recommendations. This open transrectus sheath preperitoneal approach (TREPP) differs essentially from other open preperitoneal techniques, such as the transinguinal preperitoneal (TIPP) technique [3–5]. The TIPP technique is possibly associated with less chronic pain because of its preperitoneal mesh position and may be associated with less adverse events compared to Lichtenstein repair [5]. However, this technique uses the inguinal canal for entry to the preperitoneal space (PPS). Easy and long-term successful alternatives in inguinal hernia correction are needed because of the considerable proportions of chronic pain (15–40%) after Lichtenstein's technique [6].

The TREPP technique was developed by Akkersdijk and is summarised in five principles:

1. Use a simple, easy-to-learn, and open technique, avoiding the scopic approaches with their considerable learning curves, severe adverse events, and lower cost effectiveness.
2. Stay away from the nerves and the inguinal canal during dissection.
3. Mesh positioning in the PPS, out of reach of the nerves.
4. No need for mesh fixation (because of the PPS mesh "up-stream" position).
5. No dissection nor reconstruction of the inguinal canal is necessary.

The aim of this report is to describe this new technique and its rationale by discussing the theoretical (dis-)advantages and the results of a pilot case series of 50 cases. This technique has already been performed in many patients in elective settings. The preperitoneal mesh technique in combination with the transrectus sheath approach has not been described before.

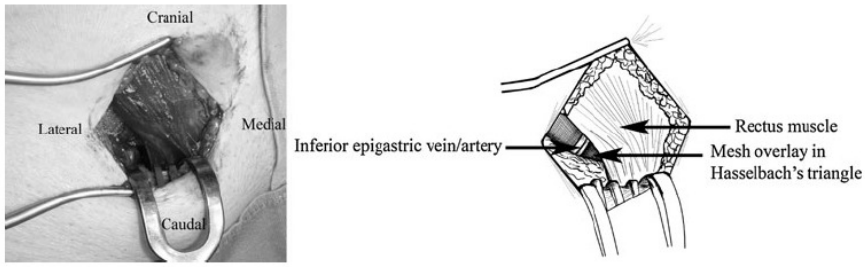
Methods

First, the patients were investigated at the outpatient department and an inguinal hernia was clinically assessed. Second, a standard preoperative screening by an anesthesiologist was undertaken.

Surgical technique

The TREPP technique can be performed under spinal anesthesia. To reach the PPS, a 5-cm straight incision is made about 1 cm above the pubic bone. The anterior rectus sheath is opened, as is the underlying fascia transversalis (Fig. 1). After retraction of the muscle fibers medially, the inferior epigastric vein and artery are identified and retracted medially as well. With a gentle movement of the dissecting finger, the PPS is created and a direct hernia can be immediately reduced. Using the iliac vessels as a landmark, the funiculus is identified with the spermatic cord, the testicular vessels, and a possible indirect hernia. The latter (if present) is now reduced. Using three long and thin retractors, a perfect PPS overview can be achieved and all possible hernia orifices (direct, indirect, and/or femoral) can be visualized. In the PPS, a self-expandable mesh is placed (Polysoft™ 'Large', BARD Benelux, Belgium) that covers the complete myopectineum of Fruchaud. After deployment, the abdominal pressure keeps the mesh positioned without necessitating fixation. The anterior rectus sheath and the fascia of Scarpa are then closed with vicryl. The skin is closed intracutaneously with monocryl.

Figure 1



The intra-operative anterior view of the repaired groin hernia using the transrectus sheath preperitoneal (TREPP) technique.

Pilot study

A prospective evaluation was carried out in 2006/2007 to assess the TREPP procedure's feasibility. Baseline characteristics and main outcome measures were evaluated directly and 2 years postoperatively. The European Hernia Society (EHS) Hernia Classification was not yet included in the operation reports at the time of the operations in 2006/2007. A more descriptive classification was used at that time. All 50 patients were evaluated after at least 2 years postoperatively. Patients

were interviewed by telephone concerning chronic pain complaints and/or limitations in daily life. Follow-up of at least 2 years was needed in order to confirm the theoretical benefits and feasibility.

Results

Fifty consecutive patients with a primary unilateral groin hernia underwent TREPP for inguinal hernia repair. The mean American Society of Anesthesiologists (ASA) classification was 1.2 (range 1–3). In a period of 5 months, 50 patients with primary unilateral groin hernias were operated. All patients were male, with a mean age of 54 years (range 24–81 years). The average skin-to-skin time was 20 min, and the mean total theater time was 46 min. Blood loss never exceeded 100 cc. There were 38 patients with a left-sided hernia (76%), 49 patients with a lateral hernia (98%), and one patient with a scrotal hernia (2%). Technical problems with TREPP did not occur. No conversions to other techniques (e.g., Lichtenstein, nor other open-mesh repairs) were necessary. Ninety-three percent of the patients were treated in the daycare setting. The mean postoperative pain did not exceed a visual analog scale (VAS) score of 4 (1–10 scale) in the first 14 days. Postoperative pain was controlled easily with paracetamol. Hematomas were observed in 18 patients (36%), but never required secondary intervention. No wound infections occurred. No patients complained of any form of (chronic) pain nor the recurrence of symptoms 2 years postoperatively.

Discussion

The present (n = 50) pilot study shows that the TREPP technique is easy to learn in our experience and facilitates good primary outcome measures. Unfortunately, at the time of operation (2006/2007), the European Hernia Society (EHS) Hernia Classification was not yet included in the operation reports at the time of the operations in 2006/2007. A more descriptive classification was used at that time. Presently, the standard operation form includes the EHS Hernia Classification, which is simple and easy to remember. Further studies are needed in order to confirm the outcomes from this TREPP pilot study. Future outcomes, together with the rationale behind this technique, may influence the future perspective on inguinal hernia repair. The rationale will be discussed according to five principle questions and their best available level of evidence [7] (LoE) in inguinal hernia repair.

Mesh rather than autologous inguinal hernia repair

During the last two decades, the use of mesh in inguinal hernia repair has become common practice since it was clearly demonstrated (LoE 1a) that, by using a mesh, the incidence of recurrences was diminished [8]. The open non-mesh techniques lost most of their popularity.

Before the standard use of a mesh (e.g., Bassini's technique), recurrence was the most important outcome measure in inguinal surgery. A recent study shows recurrence rates of at least 8% after non-mesh repair using Bassini's technique [9]. The introduction of the mesh techniques such as Lichtenstein reduced recurrences (LoE 1a) [1]. The reinforcement of the inguinal canal can be positioned on top of the transversalis fascia (inlay), as is done in Lichtenstein's repair [6]. Despite reports about 'mesh shrinking' (or may that be 'wound contraction'?), the risk for recurrence after using the Lichtenstein technique is reported as being low (2%) [10]. For placement of the mesh between the transversalis fascia and the peritoneum in the PPS ('upstream principle'), a laparoscopic (TAPP) or endoscopic (TEP) technique is most often used (Table 1).

Table 1

Name	Mesh	Position	Approach	Technique
McVay	No	-	Anterior	Open
Bassini	No	-	Anterior	Open
Shouldice	No	-	Anterior	Open
Lichtenstein	Yes	Inlay	Anterior	Open
Ugahary	Yes	Sublay	Posterior	Open
TIPP	Yes	Sublay	Anterior	Open
TREPP	Yes	Sublay	Posterior	Open
TEP	Yes	Sublay	Posterior	Endoscopic
TAPP	Yes	Sublay	Posterior	Laparoscopic

Overview of most often used mesh and non-mesh techniques for inguinal hernia repair.
Sublay: in the preperitoneal space. Inlay: dorsal position in the inguinal canal. Mesh: prosthesis used in inguinal hernia repair.

Short summary of all techniques in table 1:
McVay: transition stitch incorporating the conjoined tendon, Cooper's ligament, the femoral sheath at the medial aspect of the femoral vein and the inguinal ligament [16].
Bassini: the weakened inguinal floor is strengthened by approximating the conjoined tendon to the inguinal ligament from the pubic tubercle medially to the area of the internal ring laterally [16].
Shouldice: reconstruction in a four layer overlap utilizing continuous fine wire sutures. The defect is closed with multiple layers, none of which are placed with inordinate tension and completely obliterates the defect in the canal [16].
Lichtenstein: open/anterior approach tension-free mesh repair [17], global reference technique.
Ugahary: a 4cm skin incision 3cm craniolaterally to the internal inguinal ring through which a gridiron abdominal wall approach is used [16].
TIPP: open/anterior approach placing a mesh in the preperitoneal space through the annulus internus [3,4].
TREPP: described in this article.
TEP: endoscopic totally extraperitoneal placing of a mesh in the preperitoneal space [16].
TAPP: laparoscopic approach, through the abdominal cavity (transperitoneal/transabdominal) placing of a mesh in the preperitoneal space [16].

Preperitoneal mesh position rather than onlay

Optimizing surgical techniques to improve outcomes and reduce the rate of recurrence is of great value to healthcare [11]. Biomechanically, the position of the mesh between the peritoneum and the abdominal wall muscles, the PPS should have advantages, especially when the mesh overlaps the abdominal wall defect widely. The intra-abdominal pressure causes the mesh to be pressed against the abdominal wall, keeping it positioned, rather than pushing it away. We call this the 'upstream principle'. In contrast, the inlay (or onlay) positioned mesh, as is done in the Lichtenstein technique, does not benefit from this physiological principle and needs fixation. Therefore, based on biomechanical principles, the preperitoneal placement may be preferable (LoE 2b).

Avoidance of inguinal nerve damaging caused by dissection or nerve entrapment

The risk of nerve damage through dissection of the inguinal canal, risk of nerve entrapment due to nerve suturing, or nerve fixation on the mesh is reduced to an absolute minimum in the TREPP technique. This is mainly because of the transrectus sheath approach, avoiding contact with the nerves and providing a total overview of the PPS (LoE 4). For example, the TIPP technique uses the inguinal canal for the entrance and creation of the PPS [3, 4]. The TIPP approach (by Pélissier) may be associated with less chronic pain and may have similar results concerning recurrence rates as the Lichtenstein technique [3–5].

Evolution of the TREPP technique involved combining several described techniques, such as Ugahary and the TIPP technique. It is important to realize that the rectus sheath has no posterior layer below the linea semilunaris—half way between the umbilicus and the pubic bone. Furthermore, in the most caudal part of the rectus abdominis muscle, the fibers run relatively parallel to the inguinal ligament. The chance of collateral damage to nerve tissue is, in our opinion, reduced to an absolute minimum secondary to avoiding the inguinal canal itself during dissection. The TREPP procedure may, therefore, theoretically reduce the risk for developing postoperative nerve-related chronic pain (LoE 5).

Open rather than endoscopic approach

Several techniques have been described to achieve the preperitoneal placement of a mesh in using an open approach [3–5]. Historically, most of the techniques carry the name of the surgeon who first described it (e.g., Stoppa). More recently, Kugel and Ugahary described techniques which involved splitting the oblique abdominal muscles in order to enter the PPS [12, 13]. Recently, Pélissier described an open transinguinal preperitoneal hernia repair (TIPP). The TIPP technique uses the abdominal wall defect itself as the entrance point to the PPS, through which a preshaped self expandable hernia patch is introduced [3–5]. Since the endoscopic technique is possibly employed mostly for preperitoneal mesh placement, one could argue its superiority over the open techniques. Despite the published favourable results of both scopic approaches (TEP and

TAPP), a number of reasons can be enumerated. In general, scopic procedures are considered to be technically demanding, may have long learning curves, and the use of the required disposable instruments may not be cost-effective (LoE 2b) [11, 14]. Furthermore, patients must be operated on under general anesthesia and, although complications are described as 'rare', visceral and major vascular injuries occur, as well as port-side hernias urging surgical correction.
A considerable proportion of the TEP procedures result in adverse events [11, 15]. These adverse events, which should be graded from the patient's perspective, have to be taken into account in decision-making and the development of new techniques have to be evaluated in studies with a low risk of bias [15].

Direct rather than indirect approach

The TREPP technique provides a complete overview of the PPS in our experience. Furthermore, the digital and tactile manipulation for creating the PPS has advantages compared to other techniques, such as Ugahary's. In our experience, the Ugahary technique leads to less preperitoneal visualization due to the indirect manipulation through speculae, retractors, and the lateral approach of the PPS (LoE 4). Another TREPP advantage using the rectus sheath as the entrance point to the PPS is the direct vision of all possible hernia orifices, including the femoral hernia (LoE 4). The risk for an incisional hernia at this level is, theoretically, low because the entrance point is covered by a double layer consisting of muscle tissue and anterior rectus sheath. Moreover, the overlapping mesh may protect the abdominal wall from incisional hernia formation by covering the location of the rectus muscle in the PPS.

Future perspectives and conclusions

The evolution of all inguinal hernia repair techniques may conceptually lead to an open direct preperitoneal approach using a preperitoneal mesh position, such as TREPP. Despite the small number of patients, this pilot study shows that the TREPP technique may be a feasible method for hernia repair and seems to be promising. Based on the available evidence of systematic reviews supporting this evolution, and based on the favourable results of the first small series of TREPP patients, a randomised controlled trial is necessary to support the postulations derived from this pilot TREPP experience. Therefore, the TREPP technique will be evaluated in a randomised controlled trial in the near future.

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Chapter 9

Summary, conclusions and future perspective

G.G. Koning

General summary

Inguinal hernia repair is one of the most frequently performed surgical procedures. Low percentages of recurrence have been reported after Lichtenstein's technique.[1] The Lichtenstein technique is advocated in many guidelines globally.[2-5] The main postoperative complication presently is chronic pain after Lichtenstein's tension-free mesh repair. Chronic pain has been reported in unselected studies varying from 15 to 40 percent.[6-9] Various new techniques with preperitoneal mesh positioning are associated with a reduction of postoperative chronic pain. The aim of this thesis was to evaluate preperitoneal techniques for inguinal hernia repair compared to Lichtenstein's technique. Various techniques like the totally extraperitoneal (TEP) technique and, more recently, the transinguinal preperitoneal technique (TIPP) are available as surgical techniques that use a preperitoneal mesh to reinforce the inguinal wall.

In **chapter 2** a systematic review with trial sequential analyses (TSA) was conducted to compare the most widely used preperitoneal technique (TEP) to Lichtenstein´s technique. Recent trials suggest that the totally extraperitoneal (TEP) technique may lead to reduced proportions of chronic pain.[10] However, a considerable proportion of severe adverse events (10%) seems to be present with TEP.[10] In the systematic review, patients with primary uni- or bilateral inguinal hernias were included. [10,11] Thirteen clinical trials randomised 5404 patients. There was no significant effect of the TEP compared to Lichtenstein on the number of patients with chronic pain in a random-effects model risk ratio (RR 0.80; 95% confidence interval (CI) 0.61 to 1.04; p=0.09). There was also no significant effect on number of patients with recurrences in a random-effects model (RR 1.41; 95% CI 0.72 to 2.78; p=0.32) and the TEP technique may or may not be associated with less severe adverse events (random-effects model RR 0.91; 95% CI 0.73 to 1.12; p<0.37). TSA showed that the required information size was far from being reached for patient important outcomes.

The aim of the retrospective unmatched cohort study in **chapter 3** was to evaluate 3 years of TIPP and Lichtenstein experience since the start of `Hernia Center Brabant´ in January 2006. Patient records of unilateral primary inguinal anterior hernia corrections (TIPP and Lichtenstein) since the opening of the center (2006–2008) were evaluated in a retrospective study. The follow up period was 6 months. Chronic pain was defined in both groups as any pain sensation lasting longer than 3 months postoperatively, or when local injection of analgesia was necessary. Patients who did not come back because of chronic pain after regular follow up were regarded as free of pain. A total of 496 patients were included in this study; 225 TIPP and 271 Lichtenstein anterior inguinal hernia operations were analyzed. Ten TIPP patients (4.4%) experienced chronic pain. Eleven Lichtenstein patients (4.1%) experienced chronic pain. Limitations of this study were incomplete follow up (31.3% had only one post operative visit 14 days after surgery).

Having encouraging results from this study, and realizing the biases including in this unmatched retrospective cohort study, a randomised controlled trial with a low risk of bias was needed to truly evaluate and compare outcomes of this new anterior preperitoneal mesh technique (TIPP) to the golden standard: the Lichtenstein procedure.

Therefore, in **chapter 4** the TULIP trial protocol – published before the launch of the trial - is described. The TULIP study was a double-blind randomised controlled trial in which 300 patients had to be randomly allocated to anterior inguinal hernia repair according to TIPP or Lichtenstein. All unilateral primary inguinal hernia patients eligible for operation who met inclusion criteria were invited to participate in this trial. The primary endpoint was the amount of patients with postoperative chronic pain. Secondary endpoints were health status and cost effectiveness of the two modalities (TIPP and Lichtenstein), measured by: operation time, postoperative complications, hospital stay, costs / cost drivers, return to daily activities (e.g. work) and recurrence of inguinal hernia. To demonstrate the hypothesis that inguinal hernia repair according to the transinguinal preperitoneal (TIPP) technique may reduce the amount of patients with postoperative chronic pain to <10%, with an α of 0.05 and a power of 80%, a total sample size of 300 patients was calculated.

Patients with a primary unilateral inguinal hernia were randomised to either TIPP or the Lichtenstein technique in the TULIP trial. The primary outcome measure was patients with postoperative chronic pain (**chapter 5**). Patients and the outcome assessors were blinded. Postoperative follow up was scheduled after 14 days, 3 months, and one year. The trial design focused on reducing risks of errors in the dimensions of bias, random error, and chosen outcome measures. A total of 302 patients were randomised to TIPP (n=143) or Lichtenstein (n=159). The TIPP technique showed in this study significantly less patients with postoperative chronic pain: 5 patients (3.6%) in the TIPP group versus 20 patients (12.9%) in the Lichtenstein group (p=0.0038). An *additional* 12 TIPP patients (8.5%) and 60 Lichtenstein patients (38.7%) experienced postoperative pain sensations during activity (p<0.001).

The health status in the first postoperative year of TIPP and Lichtenstein patients was investigated in the study presented in **chapter 6**. Data of the TULIP trial were used for this purpose. It was hypothesized that the health status of inguinal hernia patients would be better after the TIPP repair compared to the Lichtenstein technique. The size of this study was based on the power calculation used for the primary outcome measure of postoperative chronic pain (the study of chapter 6). Three hundred-and-two patients were randomised. The three dimensions of possible errors were warranted. With regard to health status of all randomised patients, significant differences were found in the dimensions 'physical pain' (difference: 6.1 (95% CI: 2.3 to 9.9, p=0.002)) and 'physical functioning' (difference: 3.5 (95% CI: 0.5 to 6.7, p=0.02)), favouring the TIPP patients after the first postoperative year.

Evaluating a relatively new technique for inguinal hernia repair such as TIPP, requires a complete overview of advantages and disadvantages in a physiological, medical, scientific and economical way. Financial factors such as cost-effectiveness of the used modality is important for stakeholders, from healthcare and societal perspectives, when a new technique (such as TIPP) is evaluated. In **chapter 7** an economic study comparing TIPP and Lichtenstein modalities alongside a clinical trial is described. Next to the cost drivers, the short form 36 health survey (SF-36) questionnaire data from the TULIP trial were used to determine the utilities. The SF-36 data from the TULIP trial were revised by using the SF-6D algorithm according to Brazier. The incremental cost-effectiveness ratio (ICER) was expressed as cost per quality adjusted life week gained (QALW). Two scenario's, a hospital and a societal perspective, are presented.

No significant difference in SF-6D utility between both modalities was found (mean difference: 0.888, 95%CI: -1.02 to 1.23) and consequently the economic decision rule became cost minimisation. For the hospital perspective no significant differences in costs were found (mean difference: €-13, 95%CI: €-130 to €104). However, including productivity gains in the analysis, significant differences (p= 0.037) in costs favouring the TIPP modality (mean saving: €1472, 95%CI: €463 to €2714) were found. The results show that TIPP is a cost-saving inguinal hernia repair technique compared to the Lichtenstein modality against equal effectiveness expressed in QALW at one year given a societal perspective. TIPP patients show on average a quicker recovery of 6.5 days compared to Lichtenstein patients in the trial.

The open approach to the preperitoneal space (PPS) according to the transrectus sheath preperitoneal (TREPP) mesh repair is through the sheath of the rectus abdominis muscle. This technique provides an excellent view of the PPS, and facilitates hernia reduction and mesh positioning under direct vision. In concordance with the transinguinal preperitoneal (TIPP) inguinal hernia repair experiences of the TULIP trial and in literature, the feasibility of this new technique (TREPP) was investigated in **chapter 8**. First, a rational description of the surgical technique, accompanied with available level of evidence for thoughts behind the technical considerations are presented. Furthermore, a descriptive report of clinical outcomes of the pilot case series of the first 50 TREPP patients is presented. It was concluded that no technical problems were experienced during the development of this technique. No conversions to Lichtenstein or other techniques had been necessary. No recurrences nor postoperative chronic pain in the patients after a mean follow up of 2 years were notable findings. The TREPP mesh repair for inguinal hernia repair may be promising. Therefore a new randomised controlled clinical trial is under construction to evaluate TREPP. This trial aims to assess which open preperitoneal technique for inguinal hernia repair (TREPP or TIPP) shows most advantages or disadvantages from patients´ perspective.[12] The trial protocol has been registered, approved by the medical ethical committee (ENTREPPMENT trial, ISRCTN18591339)[12].

Conclusions of this thesis

1. TEP versus Lichtenstein for inguinal hernia repair has been evaluated by 13 trials with a high risk of bias. The review with meta-analyses, TSA and error matrix approach shows no conclusive evidence of a difference between TEP and Lichtenstein on the primary outcomes chronic pain, recurrences, and severe adverse events. High quality randomised trials between TEP and Lichtenstein would be needed to assess any superiority.

2. The TIPP technique shows in a randomised controlled trial, with low risk of bias, significantly less patients with postoperative chronic pain compared to the Lichtenstein patients in the first year.

3. The SF-36 'physical function' and 'physical pain' dimensions show significant better outcomes for the TIPP patients in the first postoperative year compared to the Lichtenstein patients in this trial.

4. The TIPP modality is a cost-saving inguinal hernia repair from a societal perspective compared to the Lichtenstein modality in the first postoperative year, against equal effectiveness expressed in quality adjusted life weeks.

5. The pilot study shows that the TREPP technique may be a feasible method for inguinal hernia repair and seems to be promising. Based on the favourable results of the first small series of TREPP patients, a randomised controlled trial is necessary to support - or to reject - the postulations derived from this pilot TREPP experience.

Future perspective on primary inguinal hernia repair

According to the author´s opinion, the anterior mesh repair of inguinal hernias according to the present gold standard (Lichtenstein) will fade out and will be replaced by the anterior preperitoneal mesh repair as the new guideline for primary inguinal hernia repair. The totally extraperitoneal (TEP) technique is too difficult, time consuming, costly, and is faced with severe adverse events. Therefore TEP will finally be abandoned in the future as well. Based on a solid rationale, and randomised controlled trials with low risk of bias (high quality trials): anterior preperitoneal mesh repairs will dominate future inguinal hernia repair. The evolution of all primary unilateral inguinal hernia repair techniques may conceptually lead to an open direct preperitoneal approach using a preperitoneal mesh position, such as the transinguinal preperitoneal technique (TIPP) or, probably, to the transrectus sheath preperitoneal repair (TREPP) to prevent postoperative chronic pain in patients. The approved TIPP technique in the TULIP trial and the promising TREPP experience will contribute to a new era of inguinal hernia repair via a safe open/anterior approach and a preperitoneal soft mesh position and, probably, with much more steep learning curves and less costs. Furthermore, the treatment of chronic pain after surgery was not the subject of interest in this thesis. However, the treatment of chronic pain is complex and may require attention in future trials as well. The combination of preventing postoperative chronic pain and, if the case should rise for a patient, an evidence based multi disciplinary treatment of postoperative chronic pain may very well contribute in solving this problem.

Describing clinical problems or complications as patient reported outcomes measures (PROM´s) are, logically, gaining popularity presently. The importance of patients reporting their experience in a structured scientific way by using validated questionnaires is becoming more important. The PROM may very well be the guide to the most important outcome at the end of the day and, also, will be important for critical decision making. Grading the PROM´s, as described by the GRADE working group, may be way of interpretation of (future) trial results. Patients will decide what is (most) important as outcome after interventions.

Future randomised controlled trials will maintain their importance to patients and their surgeons, providing evidence for surgical treatment. Future trials and studies should be well argued before they are launched. However, even though databases may provide large numbers of patients, and, given they inform on consecutive cohorts of patients and may provide some answers of the actual status on benefits and harms, they will always be prone to the huge risk of bias introduced by the choice of intervention by indication.[11] Therefore, future studies should plan to check their position along the 3 dimensions of possible errors: bias, `the play of chance´ and the choice of outcomes.[11]

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Chapter 10

Samenvatting, conclusies & toekomstperspectief

G.G. Koning

Algemene samenvatting

De chirurgische correctie van een hernia inguïnalis ('liesbreuk') is een van de meest uitgevoerde operaties in de wereld alsook in Nederland.[1] Het probleem van recidief liesbreuken is enorm teruggedrongen tot ongeveer 2% sinds de introductie van de liesbreukcorrectie met een matje (mesh), zoals de Lichtenstein techniek.[1] Deze techniek maakt gebruik van een matje welk ter versteviging wordt gehecht op de achterwand van het lieskanaal. De Lichtenstein techniek is de referentie techniek in internationale richtlijnen en is derhalve ook de eerste keus, als besloten wordt tot operatie, bij liesbreukherstel in Nederland.[2-5] Het 'nieuwe' probleem in de liesbreukchirurgie is de complicatie van postoperatieve chronische pijn die juist na deze Lichtenstein wordt aangegeven door patiënten. Chronische pijn is in verschillende studies gerapporteerd variërende van 15 – 40% postoperatief.[6-9]

Verschillende nieuwe technieken met een preperitoneaal gepositioneerd matje, dat dient om de achterwand van het lieskanaal te verstevigen en te voorkomen dat de breukzak door de buikwand `uitpuilt´, zoals de totaal extraperitoneale (TEP) techniek en recent ook de transinguïnale preperitoneale (TIPP) techniek, worden geassocieerd met een afname van postoperatieve chronische pijn.[10,11]

Deze preperitoneale mesh positie wordt geassocieerd met een reductie in postoperatieve chronische pijn bij patiënten. Recente trials suggereren dat de endoscopische totaal extraperitoneale techniek (TEP) tot een afname van chronische pijn zou leiden. Echter na analyse van data van een gepubliceerd Cochrane review blijkt dat bij een TEP een niet onaanzienlijk deel (10%) matig tot ernstige complicaties ontstaan.[10,11]

In **hoofdstuk 2** wordt een systematische review met meta-analyse en trial sequential analyses (TSA) beschreven welke werd verricht teneinde de wereldwijd meest gebruikte technieken met elkaar te vergelijken: de totaal extraperitoneale (TEP) techniek werd vergeleken met de referentie techniek volgens Lichtenstein. Gerandomiseerde trials met patiënten met een primaire enkel- of dubbelzijdige hernia inguïnalis werden geïncludeerd. Bias-evaluatie en TSA werden verricht. Dertien trials randomiseerden tezamen 5404 patiënten. Er was geen significant effect van de TEP ten opzichte van de Lichtenstein in het aantal patiënten met chronische pijn in een random-effects model (RR 0.80; 95% betrouwbaarheidsinterval (BI) 0.61 tot 1.04; p=0.09). Er was tevens geen significant effect in het aantal patiënten met recidief herniae in een random-effects model (RR 1.41; 95% BI 0.72 tot 2.78; p=0.32). Er waren geen verschillen in minder ernstige complicaties (random-effects model RR 0.91; 95% BI 0.73 tot 1.12; p<0.37). De TSA liet zien dat de vereiste 'information size´ (= totaal benodigde aantallen patiënten) ver buiten bereik was voor de belangrijke uitkomsten geordend vanuit het perspectief van de liesbreukpatiënt. Er dienen

nog meer patiënten te worden gerandomiseerd tussen TEP en Lichtenstein in 1 of in meerdere gerandomiseerde trials van goede kwaliteit (met een lage kans op bias) alvorens conclusief bewijs wordt verkregen ten voordele - of ten nadele van TEP of Lichtenstein op de uitkomstmaten `patiënten met postoperatieve chronische pijn´, `het recidief´ of een `ernstige complicatie´.

Het doel van de beschreven retrospectieve en niet gerandomiseerde studie in **hoofdstuk 3** was om drie jaar ervaring met de TIPP techniek te evalueren en te vergelijken met de Lichtenstein techniek (2 cohorten) sinds de oprichting van Liesbreukcentrum Brabant in januari 2006. Patiëntgegevens van primaire unilaterale herniae inguïnalis correcties (TIPP en Lichtenstein) die verricht waren sinds de start van het liesbreukcentrum (2006-2008) werden geëvalueerd in een retrospectieve, niet gerandomiseerde en ongeblindeerde studie. Follow-up werd nagezocht in de elektronische patiëntdossiers (EPD) tot een half jaar na de operatie als dit te achterhalen was. Chronische pijn werd gedefinieerd als postoperatieve pijn langer dan 3 maanden bestaand. Patiënten die niet terugkwamen volgens de gegevens in het EPD werden als 'vrij' van chronische pijn beschouwd. Potentieel was er een aanzienlijke kans op onderrapportage van complicaties, onder andere chronische pijn. In totaal werden 496 patiënten geïncludeerd (225 TIPP en 271 Lichtenstein). TIPP patiënten (n=10; 4.4%) en Lichtenstein patiënten (n=11; 4.1%) ervoeren chronische pijn volgens de gegevens uit het EPD. Beperkingen van deze studie waren de incomplete follow-up, 31.3% van de patiënten had 1 postoperatief polibezoek na 14 dagen.

De verkregen bemoedigende resultaten uit deze studie, daarbij de beschreven vormen van bias van deze retrospectieve studie in acht nemende, gaf de aanleiding tot een kwaliteitstrial (met een laag bias risico) om een degelijke evaluatie uit te voeren en uitkomsten van deze open preperitoneale TIPP techniek te kunnen vergelijken met de huidige referentietechniek volgens Lichtenstein. Naar aanleiding van deze step-up resultaten werd de TULIP trial vervolgens opgezet.

In **hoofdstuk 4** werd het trialprotocol beschreven. De TULIP trial was een prospectief gerandomiseerde dubbel geblindeerde trial waarin 300 patienten gerandomiseerd moesten worden voor behandeling volgens TIPP of Lichtenstein. Alle patiënten met een unilaterale primaire hernia inguïnalis werden uitgenodigd om te participeren in de trial. De primaire uitkomstmaat was het aantal patiënten met postoperatieve chronische pijnklachten. Secundaire uitkomstmaten waren de gezondheidsstatus en de kosteneffectiviteit van beide modaliteiten TIPP en Lichtenstein gemeten als: recidief hernia inguïnalis, operatietijd, postoperatieve complicaties, opnameduur, kosten, tijdstip van hervatten van activiteiten in het dagelijks leven (ADL) zoals werken of vrijwilligerswerk. Om te demonstreren dat de TIPP techniek eventueel minder dan 10% postoperatieve chronische pijn geeft, met een alfa van 0.05 en een power van 80%, een totale sample size van 300 patiënten werd berekend. De hypothese was dat de TIPP techniek het aantal patiënten met postoperatieve chronische pijn zou kunnen verminderen in vergelijking tot de Lichtenstein techniek.

In **hoofdstuk 5** werd de TULIP trial gepresenteerd. Patiënten met een primaire unilaterale hernia inguïnalis werden gerandomiseerd voor TIPP of Lichtenstein in deze trial. De primaire uitkomstmaat was het aantal patiënten met postoperatieve chronische pijn. Patiënten en onderzoekers waren beiden 'geblindeerd' (onwetend) over de uitgevoerde techniek. Follow-up werd verricht op de poli heelkunde, 14 dagen, 3 maanden en een jaar postoperatief. Bij de trialopzet werd reeds gelet op de preventie van risico's op systematische fouten in de dimensies van bias, random error en de gekozen uitkomstmaten. Er werden in totaal 302 patiënten gerandomiseerd voor TIPP (n=143) en Lichtenstein (n=159). De TIPP techniek toonde 5 patiënten (3.6%) en 20 Lichtenstein patiënten (12.9%) met postoperatieve chronische pijn na een jaar (p=0.0038). Additioneel waren er 12 TIPP patiënten (8.5%) en 60 Lichtenstein patiënten (38.7%) met pijnsensaties tijdens activiteiten zoals traplopen, hurken, sporten, tillen en bukken (p<0.001). Deze pijnsensaties verdwenen als de activiteit werd gestaakt.

De gezondheidsstatus na TIPP en Lichtenstein operaties, als functionele uitkomstmaat, werd onderzocht met data uit de trial. In **hoofdstuk 6** worden de resultaten van deze gezondheidsstatus beschreven. De hypothese was dat TIPP patiënten een betere uitkomst zouden kunnen hebben dan de Lichtenstein patiënten. Deze studie werd gebaseerd op de methodologie van de TULIP trial. Er werden significante verschillen gevonden ten voordele van de TIPP patiënten betreffende de gezondheidsstatus. Van de acht dimensies van de SF-36 vragenlijst waren de dimensies 'physical pain' (verschil: 6.1 (95% BI: 2.3 tot 9.9, p=0.002)) en 'physical function' (verschil: 3.5 (95% BI: 0.5 tot 6.7, p=0.02)) significant beter bij de TIPP patiënten na 1 jaar ten opzichte van de Lichtenstein patiënten.

Kosteneffectiviteit vanuit ziekenhuis - en maatschappelijk perspectief is belangrijk in de huidige gezondheidszorg. In **hoofdstuk 7** werd een studie gepresenteerd naar kosteneffectiviteit van de TIPP modaliteit in vergelijking met de Lichtenstein modaliteit vanuit ziekenhuis - en maatschappelijk perspectief. De 'cost drivers' werden uitgezocht en de kosten daarvan werden berekend in euro's op basis van de '*Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg*'. Daarbij werden utiliteiten gereviseerd uit de SF-36 data van de TULIP trial. Deze revisie naar SF-6D werd gedaan volgens de methodologie van Brazier. De twee dimensies 'physical pain' en 'physical function' zijn significant verschillend in de studie van hoofdstuk 7. Dit verschil verdwijnt in het economische model door de 'ruis' van de andere dimensies omdat het om het totaalbeeld in euro's gaat.

De incrementele kosteneffectiviteitsratio werd uitgedrukt als besparing per 'quality adjusted life week' (QALW). Twee relevante scenario's werden gepresenteerd. Er werd geen verschil in SF-6D utiliteiten vastgesteld tussen de TIPP en Lichtenstein modaliteit (mean difference: 0.888, 95%BI: -1.02 tot 1.23). Voor de kosten was dit afhankelijk van de verkozen basis voor

analyse; ziekenhuis- of maatschappelijk perspectief. Er werd geen verschil in kosten gevonden vanuit ziekenhuis perspectief (mean difference: €-13, 95%BI: €-130 tot €104). Echter, wanneer productiviteitswinst in de analyse werd opgenomen, werd een significant verschil in kosten (p= 0.037) tussen de TIPP en Lichtenstein modaliteit vastgesteld (mean besparing: €1472, 95%BI: €463 tot €2714). Vanuit maatschappelijk perspectief is de TIPP modaliteit een kostenbesparende techniek vergeleken met de Lichtenstein modaliteit tegenover een gelijke effectiviteit uitgedrukt in QALW. De TIPP techniek laat een gemiddeld sneller herstel zien ("return-to-work") van 6.5 dagen.

Naast de gerandomiseerde trial waarbij TIPP en Lichtenstein dubbelblind werden vergeleken, is ook een 'feasibility' studie verricht naar de recent ontwikkelde transrectusschede preperitoneale techniek (TREPP). Deze studie is beschreven in **hoofdstuk 8**. De TREPP techniek verschilt qua chirurgische benadering significant van de TIPP methode. Dit verschil is met name gelegen in de toegang tot de preperitoneale ruimte. In de TREPP methode heeft het matje dezelfde (preperitoneale) positie als bij de TIPP techniek. Er werd bij de ontwikkeling van de TREPP uitgegaan van vijf principes (danwel aanbevelingen):

- gebruik een open techniek die gemakkelijk aan te leren is, zodat de scopische procedures met hun lange leercurve, ernstige complicaties en lage kosteneffectiviteit vermeden kunnen worden.

- blijf weg van de inguïnale zenuwen en uit het inguïnale kanaal tijdens dissectie.

- positioneer de mesh in de preperitoneale ruimte.

- er is geen meshfixatie nodig door de abdominale druk tegen de buikwand ("up-stream principe").

- er is geen dissectie noch reconstructie van het lieskanaal nodig.

Een gedetailleerde chirurgische beschrijving van de TREPP techniek werd gegeven. Tevens werd een pilot studie verricht van de TREPP techniek bij 50 patiënten. Deze werden postoperatief 2 jaar lang gevolgd en telefonisch geënquêteerd. Postoperatieve chronische pijn noch recidieven traden op vanuit patiëntenperspectief, er waren geen majeure complicaties, noch secundaire interventies, noch conversies nodig naar een andere techniek. Echter, gezien de onderzoeksopzet met een retrospectief karakter dient er rekening gehouden te worden met bias en onderrapportage van complicaties. Desondanks, op zoek naar de 'ultieme liesbreuktechniek', lijkt de TREPP op meer fronten dan ooit (veiligheid, preperitoneaal overzicht, leercurve, complicaties en kosten), veelbelovend. Gebaseerd op systematische reviews welke de evolutie naar een open preperitoneale techniek met soft mesh positie in de preperitoneale ruimte, zoals TIPP (of TREPP), onderschrijven,

is nader onderzoek nodig. De ENTREPPMENT trial, welke wordt opgezet, zal op zoek gaan naar de beste open preperitoneale techniek vanuit patiëntenperspectief. Het protocol van deze trial waarin TREPP en TIPP zullen worden vergeleken (ENTREPPMENT trial, ISRCTN18591339) is inmiddels geregistreerd, goedgekeurd door de Medisch Ethische Toetsingscommissie (METC) en geaccepteerd voor publicatie.[12]

Conclusies van dit proefschrift

1.De endoscopische totaal extraperitoneale techniek (TEP) versus de Lichtenstein techniek voor correctie van een hernia inguïnalis is geëvalueerd in 13 trials met 'high risk of bias'. Deze review met meta-analyse, trial sequential analyses en 'error matrix approach' laat geen conclusief bewijs zien van een verschil tussen TEP en Lichtenstein in de primaire uitkomsten chronische pijn, recidief hernia inguïnalis en ernstige complicaties.

2.De transinguïnale preperitoneale (TIPP) techniek met een mesh voorzien van geheugenring laat in een prospectief gerandomiseerde klinische trial met een 'low risk of bias' significant minder patiënten met postoperatieve chronische pijn zien vergeleken met de Lichtenstein patiënten na een jaar.

3.De TIPP patiënten laten in de uitkomsten van de SF-36 vragenlijst van de TULIP trial in de dimensies 'fysieke pijn' en 'fysieke functie' een significant betere status zien dan de Lichtenstein patiënten na een jaar.

4.De TIPP modaliteit is vanuit maatschappelijk perspectief een kostenbesparende hernia inguïnalis correctie vergeleken met de Lichtenstein modaliteit.

5.De pilot studie naar de transrectusschede preperitoneale (TREPP) techniek, met een mesh voorzien van een geheugenring, zou een geschikte methode kunnen zijn en lijkt veelbelovend. Gebaseerd op de veelbelovende resultaten van de eerste (kleine) serie van TREPP patiënten is een hoogwaardige prospectief gerandomiseerde trial nodig om de resultaten te bevestigen danwel te ontkrachtigen.

Toekomstperspectief

De liesbreukcorrectie volgens Lichtenstein (de huidige referentietechniek) zal op termijn verdwijnen en in de nieuwe richtlijnen vervangen worden door open (anterieure) liesbreuk technieken met een preperitoneale mat positie. De totaal extraperitoneale (TEP) techniek is te moeilijk, kost teveel tijd, heeft kans op ernstige complicaties, vergt algehele anesthesie en kost teveel. De TEP zal naar onze verwachting op termijn dan ook verdwijnen. Gebaseerd op een gedegen rationale en gerandomiseerde trials van hoge kwaliteit zullen anterieure preperitoneale correcties met een matje (dat preperitoneaal gepositioneerd is) de toekomst van de liesbreukchirurgie domineren. De evolutie van alle primaire unilaterale hernia inguïnalis correcties zal conceptueel uiteindelijk leiden naar een (variant) open directe preperitoneale benadering met gebruik van een preperitoneale mat zoals de transinguïnale preperitoneale (TIPP) techniek, of mogelijk de veelbelovende trans-rectusschede preperitoneale (TREPP) techniek, teneinde postoperatieve chronische pijn te voorkomen bij liesbreukpatiënten. De bewezen TIPP techniek en, na de eerste positieve ervaringen, mogelijk ook de TREPP zullen hun bijdrage leveren aan een nieuw tijdperk van liesbreukcorrecties via een veilige open (anterieure) benadering en een preperitoneale mesh positie. Naar aanleiding van de eerste voorzichtige resultaten en ervaringen van liesbreukexperts met deze nieuwe technieken lijkt de leercurve stijl te zijn en de kosten kunnen mogelijk zelfs gereduceerd worden.

De behandeling van chronische pijn was niet het onderwerp van onderzoek in dit proefschrift. Echter, de preventie en/of behandeling van chronische pijn is complex en vereist tevens aandacht in de toekomst met nader onderzoek zodat, mocht dit voor een patiënt toch aan de orde komen na een liesbreukcorrectie, er volgens het principe van `evidence-based-medicine´ multidisciplinair behandeld kan worden.

Het beschrijven van klinische problemen of complicaties als patiënt gerapporteerde uitkomstmaten (patient reported outcome measures (PROM´s)) zien we, logischerwijs, steeds belangrijker worden. Het is noodzakelijk dat patiënten hun ervaringen rondom een operatie en tijdens de follow-up op een gestructureerde en wetenschappelijk gevalideerde wijze kenbaar kunnen maken zodat de zoektocht naar betere technieken zeer zeker ook klinisch relevant blijft. Het is dan ook de verwachting dat de PROM´s uiteindelijk de belangrijkste uitkomstmaten en daarmee een kritische `gids´ zullen zijn voor de toekomstige chirurgische behandeling van de liesbreuk, welke steeds in prospectief gerandomiseerde trials geëvalueerd zullen worden. Het gestructureerd kwalificeren van deze PROM´s volgens de termen van de GRADE werkgroep zal de wijze zijn om toekomstige trial resultaten te kunnen interpreteren. Patiënten `bepalen´ uiteindelijk mede wat daadwerkelijk belangrijke en klinisch relevante uitkomsten zijn. Toekomstige klinische trials zoals TULIP zullen daarom waarde houden voor patiënten en hun chirurgen ter `bewijsvoering´

voor een overeengekomen chirurgische interventie zoals de correctie van een hernia inguïnalis. Dergelijke trials zullen adequaat opgezet moeten worden alvorens deze van start gaan, daarbij rekening houdend met de drie dimensies van mogelijke fouten: bias, toeval en de gekozen uitkomsten.[11]

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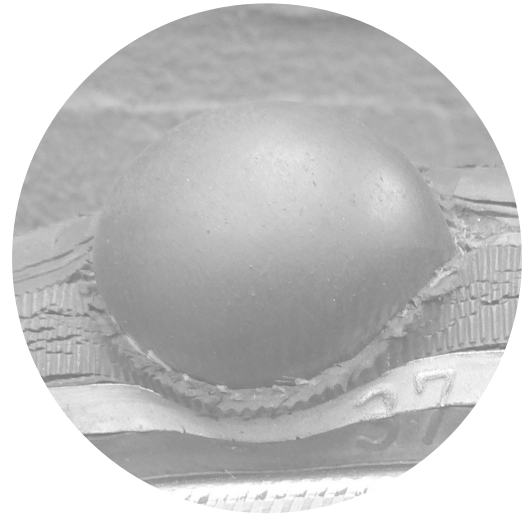

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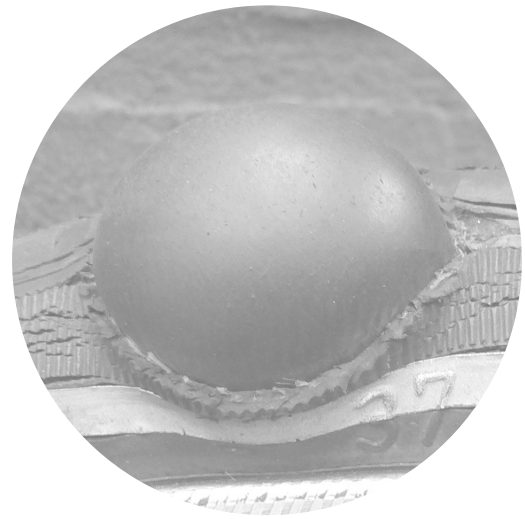

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Dankwoord

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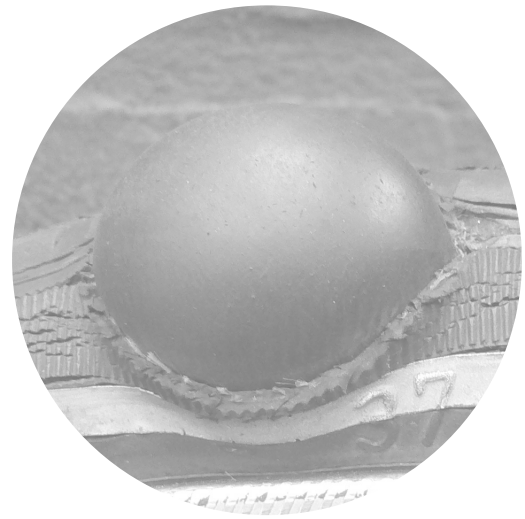


Curriculum Vitae

Curriculum Vitae

The author was born on the 10th of November in 1975 in the city of Arnhem, the Netherlands. He lived with his parents and two younger sisters in Rozendaal, a small but independent village close to Arnhem. He graduated from high school at the Christelijk Lyceum Arnhem (CLA) and at Thomas à Kempis College in Arnhem.

He had to wait some time because of the *numerus fixus* for medical school. He started with medical school at the Radboud University Nijmegen in 1999.

He completed his essay in vascular surgery in 2004 (dr. R.J.F. Laheij, prof. dr. J.D. Blankensteijn and dr. J.A. van der Vliet) at the department of Vascular- and Transplant Surgery, Radboud University Nijmegen Medical Centre.

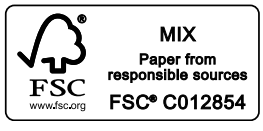
In 2005 he went to Africa for surgical rotations at the Holy Family Hospital, Techiman in Ghana (H.H.J. Wegdam).

In 2006 he was selected to participate in the Surgery Programme at the University of Oxford, John Radcliffe Hospital, Oxford, UK (Mr. R. Mihai and Mr. G. Sadler).

He graduated from medical school in 2006. He started to work as a surgical resident at the Emergency Department of VieCuri Hospital in Venlo (dr. H.M.J. Janzing). In 2007 he started with his surgical training in the St. Elisabeth Hospital in Tilburg (at that time: dr. C.J.H.M. van Laarhoven, later on: prof. dr. J.A. Roukema).

In 2008 he prepared the start of the TULIP trial in Tilburg, finally resulting in this doctoral thesis. His 4th and 5th year of surgical training were performed at the department of Surgery, Radboud University Nijmegen Medical Centre (prof. dr. C.J.H.M. van Laarhoven). He completed his surgical training in 2012 in the Canisius Wilhelmina Hospital Nijmegen (dr. C. Rosman). In this hospital he differentiated in vascular surgery (dr. A.P.M. Boll and dr. W.B. Barendregt).

In December 2012 he started with his two years of advanced surgical training in vascular surgery (*CHIV0*) at the department of Vascular- and Transplant Surgery, Radboud University Nijmegen Medical Centre (dr. J.A. van der Vliet).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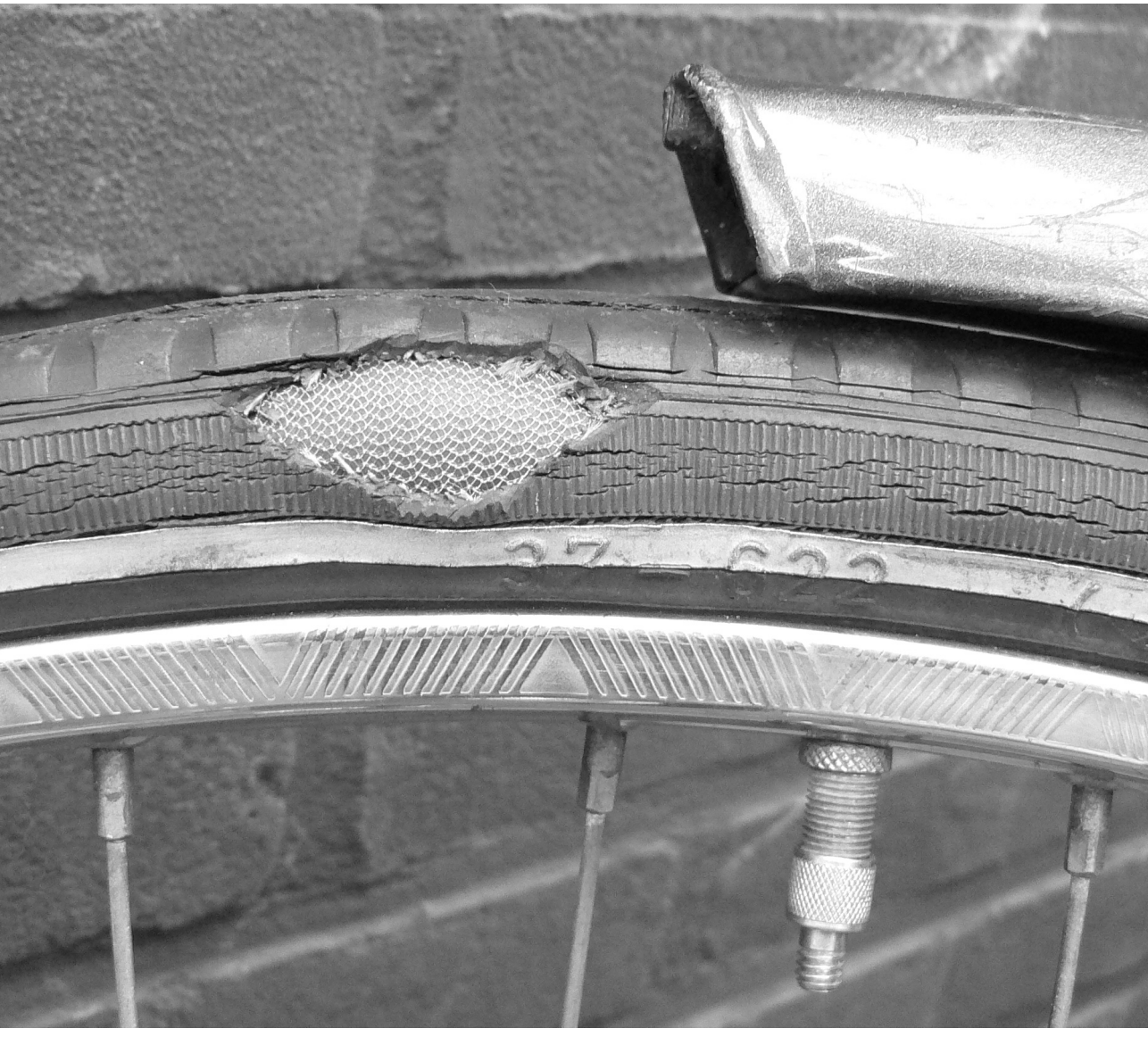
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