PROTOCOL

The totally extraperitoneal - (TEP) versus Lichtenstein´s technique for inguinal hernia repair: a systematic review.

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INTRODUCTION

Inguinal hernia repair is one of the most frequently performed procedures in surgery and many different types of operations have been suggested. Apart from other variables 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 either open or endoscopic/laparoscopic (Table 1).

Many meta-analyses being systematically or non-systematically have been performed in the past (e.g. McKormack [1], Grant [2]). It has been shown that using a mesh prevents the occurring of a recurrent inguinal hernia (Scott [3]). Many meta-analyses compare combinations of different techniques for inguinal hernia repair in one intervention group with combinations of other techniques. However, there are problems using the evidence supporting the superiority of a group of interventions compared to another group of 'controls' as an argument to claim the superiority of one specific technique for inguinal hernia repair. [4] In nearly all previous meta-analyses the groups of interventions consist of heterogeneous techniques. [1]

Guidelines in many West European countries consider the Lichtenstein technique as the reference technique. Recent reports suggest that an endoscopic posterior ap proach using a sublay position technique for the mesh, being either TAPP or TEP, may result in reduced incidences of chronic pain and a quicker recovery. When considering the TAPP and TEP methods, we think that the TEP technique may be conceptually most logical.
We are convinced that a systematic review is needed comparing one specific technique versus one other specific technique for inguinal hernia repair. When considering the guidelines and recent promising reports we conclude that it is appropriate to compare the TEP technique with the Lichtenstein technique for inguinal hernia repair in a systematic review.

Objective

The objective is to perform a systematic review using the Cochrane methodology with meta-analyses and trial sequential analyses (TSA) of randomised clinical trials (RCT´s) comparing the benefits and harms of the Totally Extraperitoneal (TEP) technique with the Lichtenstein technique for inguinal hernia repair in primary uni - or bilateral inguinal hernias. This protocol will be online available at **http://www.ctu.dk**.

METHODS

Criteria for considering trials for this review.

Studies

We considered all randomised clinical trials irrespective of language, blinding, publication status, or sample size for inclusion. Quasi-randomised trials (where the method of allocating participants to a treatment are not strictly random, for example, date of birth, hospital record number, alternation) were not included regarding assessment of benefit, but were to be considered for inclusion regarding assessment of harms. Since complications are of the main interest here, we included quasi-randomised trials.

Patients

Only adult patients will be included. Patients with primary uni- or bilateral inguinal hernias will be considered. Hernia repair for recurrent hernia's will be excluded since chronic pain incidences may be different for primary versus recurrent hernia repair. Moreover, the TEP technique is considered the standard technique for recurrent hernia repair.

Interventions

TEP: Totally extraperitoneal technique hernia repair using any type of mesh. Trials using the TAPP technique will be excluded.

Lichtenstein: open anterior technique using any type of mesh. Any other anterior open technique will not be included in this study.

Outcomes

Primary outcomes

- Mortality
- Recurrences
- Chronic pain: measured as a dichotomous outcome
- (Serious) adverse events: a composite outcome measure will be constructed summarizing all severe complications (including chronic pain) necessitating an intervention, operation, or prolonged hospital stay.

The following complications are considered adverse events: mesh/deep infections, vascular injuries, visceral injuries, port-site hernia's, persisting pain, persisting numbness, hernia recurrence, death, severe hematoma, seroma, wound/superficial infections, or any other complications.

Secondary outcomes

- Conversions
- Time to return to usual activity
- Length of stay (days/hours)
- Duration of operation

All outcomes are graded according to the patients' perspective (GRADE work group 2004). [5]

Search methods for identification of studies:

We search the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *PubMed/MEDLINE*, and *EMBASE*. We give the search strategies in appendix 1 with the time span of the searches until January 2011. We also search the references of the identified trials to identify further relevant trials.

Data collection and analysis

Trial selection and extraction of data

Two authors (GK and FK), independently of each other, identify the trials for inclusion. We have also listed the excluded studies with the reasons for the exclusion.

Two authors (GK and FK) will independently extract the following data.

1. Year and language of publication.
2. Country in which the trial was conducted.
3. Year of conduct of trial.
4. Single-center or multicenter trial.
5. Inclusion and exclusion criteria.
6. All outcomes (as mentioned above).
7. Risk of bias according to the domains of bias in the Cochrane Handbook (Higgins 2008) as described below.

Any unclear or missing information will be sought by contacting the authors of the individual trials. If there was any doubt whether the trial reports shared the same participants - completely or partially (by identifying common authors and centers) - the authors of the trials will be contacted to clarify whether the trial report had been duplicated. We resolved any differences in opinion through discussion or arbitration of a third author (JW) and (CL).

Assessment of bias risk

Two authors assess the risk of bias of the trials independently, without masking of the trial names. We will follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions*.[4] According to empirical evidence [6-9], the following risk of bias components will be extracted from each trial.

Sequence generation

• Low risk of bias (the methods used is either adequate (eg, computer generated random numbers, table of random numbers) or unlikely to introduce confounding).
• Uncertain risk of bias (there is insufficient informati on to assess whether the method used is likely to introduce confounding).
• High risk of bias (the method used is improper and likely to introduce confounding).

Allocation concealment

• Low risk of bias (the method used (eg, central allocation) is unlikely to induce bias on the final observed effect).
• Uncertain risk of bias (there is insufficient information to assess whether the method used is likely to induce bias on the estimate of effect).
• High risk of bias (the method used (eg, open random allocation schedule) is likely to induce bias on the final observed effect).

Blinding of participants, personnel, and outcome assessors

It is difficult to blind the personnel to the groups for surgical interventions. However, it is possible to blind the patients and outcome assessors. Thus, only blinding of patients and outcomes assessors was considered for assessing the risk of bias in trials.
• Low risk of bias (blinding was performed adequately, or the outcome measurement is not likely to be influenced by lack of blinding).

• Uncertain risk of bias (there is insufficient information to assess whether the type of blinding used is likely to induce bias on the estimate of effect).
• High risk of bias (no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding).

Incomplete outcome data

• Low risk of bias (the underlying reasons for missingness are unlikely to make treatment effects departure from plausible values, or proper methods have been employed to handle missing data).
• Uncertain risk of bias (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect).
• High risk of bias (the crude estimate of effects (e.g. complete case estimate) will clearly be biased due to the underlying reasons for missingness, and the methods used to handle missing data are unsatisfactory).

Selective outcome reporting

• Low risk of bias (the trial protocol is available and all of the trial's pre-specified outcomes that are of interest in the review have been reported or similar or all of the primary outcomes in this review have been reported).
• Uncertain risk of bias (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting).
• High risk of bias (not all of the primary outcomes in this review have been reported and not all of the trial's pre-specified outcomes that are of interest in the review have been reported).

Academic bias

• Low risk of bias (the author of the trial has not conducted previous trials addressing the same interventions).
• Uncertain risk of bias (It is not clear if the author has conducted previous trials addressing the same interventions).
• High risk of bias (the author of the trial has conducted previous trials addressing the same interventions).

Source of funding bias

• Low risk of bias (the trial's source(s) of funding did not come from any parties that might have conflicting interest (e.g. drug manufacturer).
• Uncertain risk of bias (the source of funding was not clear).
• High risk of bias (the trial was funded by a drug manufacturer).

Further we will register and describe other characteristics of the trials as:
-Baseline imbalance
-Early stopping

We will consider trials classified as low risk of bias in sequence generation, allocation concealment, blinding, incomplete data, and selective outcome reporting as trials with low risk of bias.

Statistical methods

We will perform the meta-analyses according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[4] We use the software package Review Manager 5. [10]
For dichotomous variables, we calculate the risk ratio (RR) with 95% confidence interval (CI) if there are two or more trials for an outcome. For rare events we will calculate odds ratios (OR) with 95% CI. We report the proportion of patients with the outcome in each group and the *p*-value for the comparison between the groups. For continuous variables, we calculate the mean difference (MD) or the standardized mean difference (SMD) with 95% confidence interval. For both dichotomous and continuous outcomes a *p*-value of less than 0.05 will be considered statistically significant.

We use a random-effects model [11] and a fixed-effect model [12] for meta-analysis in the presence of two or more trials included under the outcomes. In case of discrepancy between the two models, we will report both the results of the random-effects model and the fixed effect model. Considering the anticipated abundant clinical heterogeneity we will emphasize the random affects model except if one or two trials dominate the available evidence.

Heterogeneity will be explored by chi-squared test with significance set at *p*-value 0.10, and the quantity of heterogeneity will be measured by I^2 set at 30%. [13,4] We will, if possible, explore reasons for heterogeneity by applying metaregression for the covariates mean age,

mean body mass index (BMI) or mean body weight and the ratio of man/female. A *p*-value of 0.10 will be taken as statistically significant in the univariate metaregression analyses.

The analysis will be performed on an intention-to-treat basis whenever possible using the good outcome and poor outcome scenarios. Otherwise, we adopt the 'available-case analysis´.[4] We do not impute any data for the post-randomisation drop-outs for any of the continuous outcomes. We also report the results of risk difference if they are different from the results of risk ratio.

Sensitivity analyses

In sensitivity analyses we impute the standard deviation from *p*-values according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* and use the median for the meta-analysis when mean was not available.[4] If it is not possible to calculate the standard deviation from the *p*-value or confidence intervals, we impute the standard deviation as the highest standard deviation noted for that group under that outcome.

Subgroup analysis

We intend to perform the following subgroup analyses:

- Trials with low risk of bias (adequate generation of allocation sequence, allocation concealment, blinding, incomplete data outcomes, and selective reporting) compared to trials with high risk of bias (one or more of the five components inadequate or unclear).
- The intervention effect in trials using general anaesthesia or neuroaxial blocks will be compared to trials using infiltration anaesthesia.
- Trials will be divided in two groups based on the time of publication. Results of an initial first group will be 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 ($p<0.05$) will provide evidence of an intervention effect pending the subgroup.

Bias exploration

We plan to use a funnel plot to explore small trial bias [14,15] and to use asymmetry in funnel plot of trial size against treatment effect to assess this bias.

Trial sequential analysis

Meta analyses may result in type-I errors due to an increased risk of random error when few data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials. [16,17] To assess the risk of type-I errors, we will use TSA.

TSA combines information size estimation for meta analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta analysis. [16-18] The latter, called trial sequential monitoring boundaries, reduce type-I errors. In TSA the addition of each 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 the cumulative Z-curve crosses the trial sequential monitoring boundary, a sufficient level of evidence has been reached and no further trials are needed. If the Z-curve doesn´t cross the boundary and the required information size has not been reached, there is insufficient evidence to reach a conclusion. [16,17,19,20] We will apply TSA since it reduces the risk of type-I error in a cumulative meta analysis and may provide important information on how many more patients need to be included in further trials. Information size will be calculated as diversity adjusted information size (DIS) [21], suggested by the relative risk reduction (RRR) of the intervention in the included trials. We will perform trial sequential analysis (TSA) on all primary outcomes and on all secondary outcomes showing statistically significant differences between the two interventions. The required information size will be calculated based on a relative risk reduction of 20-40% and appropriately adjusted for heterogeneity according to an overall type-I error of 5% and a power of 80% considering early and repetitive testing.

Table 1: Overview of limited number of techniques for inguinal hernia repair and their main characteristics.

	mesh	onlay / inlay / sublay	approach	open / endoscopic	
McVay	-		Anterior	Open	
Bassini	-		Anterior	Open	
Shouldice	-		Anterior	Open	
Lichtenstein	M	Inlay	Anterior	Open	
Ugahary	M	Sublay	Posterior	Open	
TEP	M	Sublay	Posterior	Endoscopic	
TAPP	M	Sublay	Posterior	Endoscopic	
TIPP	M	Sublay	Anterior	Open	

Lichtenstein: open/anterior approach placing a mesh between the abdominal wall layers (onlay or tranverse fascia plasty or tension free mesh repair).

TEP: totally extraperitoneal endoscopic placing of a mesh in the preperitoneal space.

TAPP: transabdominal preperitoneal laparoscopic placing of a mesh (thus: through the abdominal cavity, a transperitoneal approach).

TIPP: transinguinal preperitoneal hernia repair. An open/anterior approach placing a mesh in the preperitoneal space through the internal ring (annulus internus).

Appendix 1: search strategy

PubMed/MEDLINE:

(random* OR trial) AND (TEP OR TEPP OR (total* AND extraperiton*) OR lichten* OR liechten* OR laparosc* OR preperiton* OR (endosc* AND inguinal hernia))

CENTRAL:

Inguinal hernia or groin hernia in Title, Abstract or Keywords, from 1990 to 2011 in Cochrane Central Register of Controlled Trials

EMBASE:

1. (TEP or TEPP or (total* and extraperiton*) or lichten* or liechten* or laparosc* or preperiton* or (endosc* and inguinal hernia)).mp.

2. tep.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
3. tepp.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufactur er]
4. (total* and (extraperiton* or extra periton*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
5. (lichtenst* or liechtenst*).mp. [mp=title, abstract, subject headings, he ading word, drug trade name, original title, device manufacturer, drug manufacturer]
6. laparosc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
7. (pre periton* or preperiton*) .mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
8. (endosc* and inguinal hernia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, devi ce manufacturer, drug manufacturer]
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. (random* and trial).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

11. 9 and 10

REFERENCES

1.McCormack K, Scott N, Go PM, Ross SJ, Grant A, Collaboration the EU Hernia Trialists . Laparoscopic techniques versus open techniques for inguinal hernia repair. The Cochrane Collaboration and published in The Cochrane Library;2008,Issue 4.

2.Grant AM. Laparoscopic versus open groin hernia repair: meta-analysis of randomised trials based on individual patient data. Hernia:2002,6:2-10.

3.Scott NW, Grant AM, Ross S, Smith A, Macintyre IMC and O'Dwyer PJ, for the MRC Laparoscopic Groin Hernia Trial Group. Patient-assessed outcome up to three months in a randomised controlled trial comparing laparoscopic with open groin hernia repair. Hernia: 2000,4:73-9.

4.Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration;2008.

5.Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group:What is "quality of evidence" and why is it important to clinicians? BMJ 2008, 336:995-8.

6.Schulz KF, Chalmers I, Hayes RJ, Altman DG: Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995,273:408-12.

7.Moher D, Jadad AR, Tugwell P: Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care 1996, 12:195-208.

8.Kjaergard LL, Villumsen J, Gluud C: Reported methodologic qu ality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001, 135:982-9.

9.Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA: Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008, 336:601-5.

10.Review Manager (RevMan). Version 5.0 for Windows. (updated to 5.0.25 on 15 September 2010) The Nordic Cochrane Centre, The Cochrane Collaboration: Copenhagen, 2008.

11.DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7(3):177–88.

12.DeMets DL. Methods of combining randomized clinical trials: strengths and limitations. Statistics in Medicine 1987;6(3):341–50.

13.Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002, 21:1539-58.

14.Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–34.

15.Macaskill P,Walter SD, Irwig L. A comparison of methods to detect publication bias inmeta-analysis. Statistics inMedicine 2001;20:641–54.

16. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta -analysis. J Clin Epidemiol 2008;61:64–75.

17. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently concl usive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009;38:287–98.

18. Thorlund K, Devereaux PJ,Wetterslev J, et al.Can trial sequentialmonitoring boundaries reduce spurious inferences from meta -analyses? Int J Epidemiol 2009;38:276–86.

19. Pogue J, Yusuf S. Overcoming the limitations of current meta -analysis of randomised controlled trials. Lancet 1998;351:47–52.

20.Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta -analysis. Control Clin Trials 1997;18: 580–93 discussion 661-6.

21. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random -effects modelmeta-analyses. BMCMed Res Methodol 2009;9:86.

Website: http://www.ctu.dk