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Mesh fixation methods in open inguinal hernia repair: a protocol for network meta-analysis and trial sequential analysis of randomised controlled trials

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ABSTRACT

Introduction: Randomised clinical trials (RCTs) have been used to compare and evaluate different types of mesh fixation usually employed to repair open inguinal hernia. However, there is no consensus among surgeons on the best type of mesh fixation method to obtain optimal results. The choice often depends on surgeons' personal preference. This study aims to compare different types of mesh fixation methods to repair open inguinal hernias and their role in the incidences of chronic groin pain, risk of hernia recurrence, complications, operative time, length of hospital stay and postoperative pain, using Bayesian network meta-analysis and trial sequential analysis of RCTs.

Methods and analysis: A systematic search will be performed using PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM) and Chinese Journal Full-text Database, to include RCTs of different mesh fixation methods (or fixation vs no fixation) during open inguinal hernia repair. The risk of bias in included RCTs will be evaluated according to the Cochrane Handbook V.5.1.0. Standard pairwise meta-analysis, trial sequential analysis and Bayesian network meta-analysis will be performed to compare the efficacy of different mesh fixation methods.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies. The results of this network meta-analysis and trial sequential analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: PROSPERO CRD42015023758.

Strengths and limitations of this study

- To the best of our knowledge, this is the first network meta-analysis and trial sequential analysis protocol comparing different types of mesh fixation methods to repair open inguinal hernias.
- The results of this systematic review will help clinicians and patients to select appropriate mesh fixation methods.
- Our results will be limited by both the quantity and quality of the trials available for review.

INTRODUCTION

The inguinal hernia, a common health issue, is a protrusion of abdominal contents into the inguinal canal through an abdominal wall defect, and its repair represents one of the most common surgical procedures. The lifetime rate of inguinal hernia is 2% in females and 25% in males.[1 2] However, the risk of inguinal hernia increases with age, from 0.25% at 18 years of age to 4.2% at 75–80 years of age.[3] Surgical repair of inguinal hernias is the most common general surgical procedure in the world.[4] It is already well known that the surgical procedure of inguinal hernia repair is generally represented by one of the following three procedures: open repair with a mesh, open repair without the use of a mesh implant (ie, sutured) and laparoscopic repair with a mesh.[5] One of the main problems associated with open mesh repair is chronic groin pain,[6] which can be reduced using laparoscopic inguinal hernia repair.[7] However, open mesh repair still plays an important role in the repair of inguinal hernias because it is generally less expensive and easy to perform, can be performed under local anaesthesia, and it is the method chosen when laparoscopic repair has failed.[8]

The current surgical options for mesh fixation include, but are not limited to, sutures, tacks or staples, self-fixing meshes and fibrin or other glues.[9] However, there is no consensus among doctors on the best surgical technique. The choice of options often depends on surgeons' personal preference.[9] Two meta-analyses compared glue fixation to suture fixation, and concluded that glue

fixation was superior to suture fixation, especially regarding the reduction of chronic groin pain and its short operative time.[6 10] Five meta-analyses comparing self-gripping mesh with sutured mesh suggested that self-gripping mesh was associated with shorter operative time compared to sutured mesh.[11–15] All of these meta-analyses conducted only pairwise meta-analysis to compare efficacy of different types of mesh fixation methods. Moreover, they lack information required for size sample calculation (sample size included in pooling outcomes). To evaluate the effects of different types of mesh fixation methods in open inguinal hernia repair, highly compelling and persuasive evidence is required to draw a firm conclusion.

Network meta-analysis has become increasingly popular to evaluate healthcare interventions, since it allows for estimation of the relative effectiveness among all interventions and rank ordering of the interventions even if head-to-head comparisons are lacking.[16] Trial sequential analysis (TSA) is a tool for quantifying the statistical reliability of the data in a cumulative meta-analysis,[17 18] controlling α and β values for sparse data and repetitive testing on accumulation data.[19 20]

This study is a comprehensive network meta-analysis and TSA on different types of mesh fixation available for open inguinal hernia repair.

OBJECTIVE

The objectives of this study are to compare the role of different types of mesh fixation in the incidences of chronic groin pain, risk of hernia recurrence, complications, operative time, length of hospital stay and postoperative pain for open inguinal hernia repair using Bayesian network meta-analysis and TSA of randomised clinical trials (RCTs).

METHODS AND ANALYSIS

Design

Bayesian network meta-analysis and TSA will be carried out in this study.

Registration

We registered on the international prospective register of systematic reviews (PROSPERO) to publish our study protocol. The protocol of network meta-analysis is performed according to the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) recommendation, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions.[21 22]

Information source

A systematic search will be performed using PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM) and Chinese Journal Full-text Database. The search strategy will be developed by LG and JHT, who have over 10 years of experience as information specialists. The references of included articles and reviews will be tracked to identify other relevant studies. We will not contact authors for detailed information of primary studies.

Search strategy

Search terms will be: inguinal hernia, groin hernia, inguinal hernioplasty, mesh, random* and others. Full details of the search strategy regarding PubMed, EMBASE and CENTRAL are:

PubMed: ((‘Inguinal hernia[Title/Abstract] OR ‘groin hernia[Title/Abstract] OR ‘inguinal hernioplasty[Title/Abstract] OR ‘Hernia, Inguinal[Mesh]) AND (mesh [Title/Abstract])) AND (Random*[All Fields] OR ‘randomized controlled trial*[All Fields] OR ‘randomized trial*[All Fields] OR Randomized Controlled Trial[ptyp] OR ‘Randomized Controlled Trials as Topic[Mesh])

EMBASE: (‘inguinal hernia’/exp/mj OR ‘inguinal hernia’ OR ‘groin hernia’/exp/mj OR ‘groin hernia’ OR ‘inguinal hernioplasty’) AND (mesh) AND (random* OR[controlled clinical trial]/lim OR(randomized controlled trial]/lim) NOT [MEDLINE]/lim

CENTRAL: #1 ‘Inguinal hernia’ or ‘groin hernia’ or ‘inguinal hernioplasty’:ti, ab, kw (Word variations have been searched)
#2 MeSH descriptor:[Hernia, Inguinal] explode all trees
#3 #1 OR #2
#4 mesh:ti, ab, kw (Word variations have been searched)
#5 random*
#6 #3 AND #4 AND #5.

Eligibility criteria

Type of patients: adults (aged 18 years or older) with inguinal hernia, who scheduled for open inguinal hernia repair. The open mesh repair includes all kinds of techniques, such as Stoppa, Lichtenstein and mesh plug. Patients will be excluded if the hernia is inoperable with open inguinal hernia repair, or if the hernia repair technique changed to another one (eg, laparoscopic access methods).

Type of designs: truly random or quasi-random controlled trials; systematic reviews or meta-analyses will also be included to track their references.

Type of interventions: different mesh fixation methods (or fixation vs no fixation) in open inguinal hernia repair, including, but not limited to, sutures, tacks or staples, self-fixing meshes and fibrin or other glues.

Type of outcomes: the primary outcomes are incidence of chronic groin pain and risk of hernia recurrence. The secondary outcomes include complications, operative time, length of hospital stay and postoperative pain. The end points are defined in table 1.

Other criteria: we will include RCTs reported in the English and Chinese languages. There will be no limitations on year of publication, publication status, duration of study follow-up or period of study conduct.

Table 1 Data extraction items

Category	Description
Patient characteristics	
Median age	Median age and range of included patients
Type of inguinal hernia	Unilateral or bilateral inguinal hernia; medial, lateral, femoral (and combinations); size of hernia defect/opening
Details of intervention	Details on different mesh fixation methods
Size of mesh	Size of mesh used
Type of mesh	Material, pore size, weight
Number of tacks	Details on number and types of tacks
Mesh fixation methods	Details on other types of fixation
Follow-up	Period of follow-up and lost to follow-up
Study characteristics	
First authors	Name of the first author
Year of publication	PubTime of included trials
Study arms	Details on the intervention and control group
Sample size	Sample size of included trials
Type of design	Type of design of included trials
Outcomes	
Chronic groin pain	Groin pain persisting at least 3 months after the index operation Visual analogue scale (VAS) ≥40 mm if scoring system was utilised
Recurrence	Clinical or radiologic recurrence of inguinal hernia
Postoperative pain	VAS immediately after and during 1 week of the operation
Complications	Any complications requiring further procedures in the theatre during the same surgical admission
Operative time	Time from skin incision to skin closure
Length of hospital stay	Time from the index operation to discharge

Study records

Literature search records will be imported into ENDNOTE X6 literature management software, while a standard data abstraction form will be created using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, http://www.microsoft.com) to collect data of interest. A pilot test will be performed for literature selection and data extraction, and a 'cheat sheet' with detailed definitions and examples will be developed to ensure high inter-rater reliability among the reviewers.

Two independent reviewers will examine the title and abstract of studies found in the search, to identify related studies according to eligibility criteria. Thus, full-text versions of all potentially relevant studies will be obtained. Excluded trials and the reasons for their exclusion will be listed and examined by a third reviewer.

To extract the data, a rigorous process will be used. First, a draft data extraction form will be conducted. Subsequently, a random sample of five included RCTs will be pilot tested, and the k statistic will be calculated. The form will be revised, as necessary, to confirm the final data extraction form. Finally, two reviewers will independently extract the data of interest, and conflicts will be resolved by a third reviewer.

Data items

We will extract all data of interest from each included RCT, including patient characteristics, study characteristics and outcomes. Data extraction item details can be found in table 1. We will consider the following factors as effect modifiers: median age, intervention, size and type of mesh, number and type of fixation, follow-up, and sample size.

Risk of bias of individual studies

The risk of bias of included RCTs will be evaluated according to the Cochrane Handbook V.5.1.0,[23] including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias) and other bias. We will evaluate methodological quality as low, high or unclear risk of bias. The risk of bias assessment will be completed by two independent reviewers, and conflicts will be resolved by a third reviewer.

Dealing with missing data

We will not contact authors to obtain missing information of primary studies. If binary outcomes are missing, we will perform an available-case analysis, but we will assess the impact of 'best-best', 'best-worst', 'worst-best' and 'worst-worst' scenario analyses.[24] Regarding the continuous outcomes, we will impute the mean from median and SD for SE, interquartile range, or p values, according to the Cochrane Handbook for Systematic Reviews of Interventions. If such studies are included, we will perform a sensitivity analysis to assess their impact.

Standard pairwise meta-analysis

We will perform pairwise meta-analysis, using STATA V.12.0 software (Stata Corporation, College Station, Texas, USA). Pooled ORs with 95% CI will be calculated for dichotomous outcomes, mean differences (MDs) with 95% CI for continue outcomes. Heterogeneity of treatment effects across trials will be assessed by c^2 and I^2 statistics. If the p value ≥0.1 and I^2 is ≤50%, it suggests that there is no statistical heterogeneity, and the Mantel-Haenszel fixed effects model will be used for meta-analysis. If the p value <0.1 and I^2 is >50%, we will explore sources of heterogeneity by subgroup analysis and meta-regression. If there is no clinical heterogeneity, the Mantel-Haenszel random effects model will be used to perform meta-analysis.[23] Reporting bias will be examined using the Begg's and Egger's funnel plot method.[25 26] In addition, the contour-enhanced funnel plot will be used as an aid to distinguish asymmetry due to publication bias from that due to other factors.[27]

Trial sequential analysis

TSA[18] will be performed to reduce the risk of random errors. We will add trials according to the year of publication, and if more than one trial is published in a year, the trials will be alphabetically added according to the last name of the first author.[28] TSA will be performed for dichotomous outcomes as well as for continuous outcomes, to control the risks of random errors due to sparse data and multiplicity.[29 30] We will also adapt a relative risk reduction of 20%, an α (type I error) of 5%, a β (type II error) of 20% and the diversity of the meta-analysis.[19 30]

Geometry of the network

A network plot will be drawn to describe and present the geometry of the treatment network of comparisons across trials to ensure if a network meta-analysis is feasible. Trials will be excluded if the trials are not connected by treatments. Network geometry will use nodes to represent different interventions and edges to represent the head-to-head comparisons between interventions. The size of nodes and thickness of edges are associated with sample sizes of intervention and numbers of included trials, respectively.

Network meta-analysis

A Bayesian network meta-analysis will be performed using WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK). The random and fixed effect models with vague priors for multiarm trials developed by Ade *et al*[31] will be used. The pooled estimation and the probability of which treatment is the best will be obtained using the Markov Chains Monte Carlo method. Three Markov Chains will be run simultaneously with different arbitrarily chosen initial values. We will first generate 50 000 simulations for each chain, and these simulations will then be discarded as the 'burn-in' period. Then posterior summaries will be based on 100 000 subsequent simulations. The model convergence will be assessed by trace plots and Brooks-Gelman-Rubin plots.[32] The statistical heterogeneity in the entire network will be assessed on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from the network meta-analysis models using R-3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria). The results of dichotomous outcomes will be reported as posterior medians of OR with 95% credible intervals (CrIs), and medians of MD with 95% CrI for continue outcomes. If a loop connecting three arms exists, inconsistency between direct and indirect comparisons will be evaluated using a node splitting method.[33] The choices between fixed and random effect models, consistency and inconsistency models, will be made by comparing the deviance information criteria (DIC) for each model.[34 35] The model with the lowest DIC will be preferred (differences >3 are considered significant).

Clinical decisions about the choice of treatments can be recommended based on the probability results of ranking when the differences in effect size of different treatments are small.[36] The surface under the cumulative ranking area (SUCRA) will be calculated to summarise and report the probability values. SUCRA values are expressed as percentages—SUCRA value will be 100% for the best treatment, while SUCRA value will be 0% for the worst treatment.[37]

In order to explore the sources of heterogeneity or inconsistency in the entire network, we will perform network meta-regression or subgroup analysis. Network meta-regression will be conducted using random effects network meta-regression models to examine potential effect moderators such as size of mesh, number of tack, follow-up and sample size.

If we include enough trials per comparison, a sensitivity analysis will be conducted. We will conduct a sensitivity analysis excluding trials that are missing relative data, and we will conduct another sensitivity analysis excluding trials with a total sample size of <50 randomised patients.

The quality of evidence will be classified by the GRADE group into four levels—high quality, moderate quality, low quality and very low quality.[38] This process will be performed using GRADE pro 3.6 software (http://www.gradeworkinggroup.org/).

Furthermore, a comparison-adjusted funnel plot will be conducted to identify whether there will be a small sample effect among intervention networks, using STATA V.12.0 software (Stata Corporation, College Station, Texas, USA).

ETHICS AND DISSEMINATION

Ethical issues

Ethical approval and patient consent are not required since this is a meta-analysis based on published studies.

Publication plan

This protocol has been registered on the international prospective register of systematic reviews

(PROSPERO).[39] The procedures of network meta-analysis will be conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions. The results of this network meta-analysis and TSA will be submitted to a peer-reviewed journal for publication.

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