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Mesh fixation with glue versus suture for chronic pain and recurrence in Lichtenstein inguinal hernioplasty (Review)

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TABLE OF CONTENTS

[Intervention Review]

Mesh fixation with glue versus suture for chronic pain and recurrence in Lichtenstein inguinal hernioplasty

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ABSTRACT

Background

Chronic pain following mesh-based inguinal hernia repair is frequently reported, and has a significant impact on quality of life. Whether mesh fixation with glue can reduce chronic pain without increasing the recurrence rate is still controversial.

Objectives

To determine whether tissue adhesives can reduce postoperative complications, especially chronic pain, with no increase in recurrence rate, compared with sutures for mesh fixation in Lichtenstein hernia repair.

Search methods

We searched the following electronic databases with no language restrictions: the Cochrane Central Register of Controlled Trials (CENTRAL; issue 4, 2016) in the Cochrane Library (searched 11 May 2016), MEDLINE Ovid (1986 to 11 May 2016), Embase Ovid (1986 to 11 May 2016), Science Citation Index (Web of Science) (1986 to 11 May 2016), CBM (Chinese Biomedical Database), CNKI (China National Knowledge Infrastructure), VIP (a full-text database in China), Wanfang databases. We also checked reference lists of identified papers (included studies and relevant reviews).

Selection criteria

We included all randomised and quasi-randomised controlled trials comparing glue versus sutures for mesh fixation in Lichtenstein hernia repair. Cluster-RCTs were also eligible.

Data collection and analysis

Two review authors extracted data and assessed the risk of bias independently. Dichotomous outcomes were expressed as odds ratio (OR) with 95% confidence intervals (CI). Continuous outcomes were expressed as mean differences (MD) with 95% CIs.

Main results

Twelve trials with a total of 1932 participants were included in this review. The overall postoperative chronic pain in the glue group was reduced by 37% (OR 0.63, 95% CI 0.44 to 0.91; 10 studies, 1418 participants, low-quality evidence) compared with the suture group. However, the results changed when we conducted subgroup analysis with regard to the type of mesh. Subgroup analysis of included

studies using lightweight mesh showed the reduction of chronic pain was less profound and insignificant (OR 0.77, 95% CI 0.50 to 1.17). Subgroup analysis of included studies using heavyweight mesh resulted in a significant benefit from the fixation with glue (OR 0.38, 95% CI 0.17 to 0.82).

Hernia recurrence was similar between the two groups (OR 1.44, 95% CI 0.63 to 3.28; 12 studies, 1932 participants, low-quality evidence). Fixation with glue was superior to suture regarding duration of the operation (MD −3.13, 95% CI −4.48 to −1.78; 9 studies, 1790 participants, low-quality evidence); haematoma (OR 0.52, 95% CI 0.31 to 0.86; 10 studies, 1384 participants, moderate-quality evidence); and recovery time to daily activities (MD −1.26, 95% CI −1.89 to −0.63; 3 studies, 403 participants, low-quality evidence).

We also investigated adverse events. There were no significant differences between the two groups. For superficial wound infection pooled analyses showed OR 1.23, 95% CI 0.37 to 4.11; 7 studies, 763 participants (low-quality evidence); for mesh/deep infection OR 0.67, 95% CI 0.16 to 2.83; 8 studies, 1393 participants (low-quality evidence). Furthermore, we investigated seroma (a postoperative swelling caused by fluid) (OR 0.83, 95% CI 0.51 to 1.33); and persisting numbness (OR 0.81, 95% CI 0.57 to 1.14).

Finally, six trials involving 1009 participants reported postoperative length of stay, resulting in non-significant difference between the two groups (MD −0.12, 95% CI: −0.35 to 0.10)

Due to the lack of data, it was impossible to draw any distinction between synthetic glue and biological glue.

Eight out of 12 trials showed high risk of bias in at least one of the investigated domains. Two studies were quasi-randomised controlled trials and the allocation sequence of one trial was not concealed. Nearly half of the included trials either did not provide adequate information or had high risk of bias regarding blinding processes. The risk of bias for incomplete outcome data of all the included studies varied from low to high risk of bias. Two trials did not report on some important outcomes. One study was funded by the manufacturer producing the fibrin sealant. Therefore, according to the 'Summary of findings' tables, the quality of the evidence (GRADE) for the outcomes is moderate to low.

Authors' conclusions

Based on the short-term results, glue may reduce postoperative chronic pain and not simultaneously increase the recurrence rate, compared with sutures for mesh fixation in Lichtenstein hernia repair. Glue may therefore be a sensible alternative to suture for mesh fixation in Lichtenstein repair. Larger trials with longer follow-up and high quality are warranted. The difference between synthetic glue and biological glue should also be assessed in the future.

PLAIN LANGUAGE SUMMARY

Glue may be a sensible alternative to suture for mesh fixation in Lichtenstein inguinal hernioplasty

Review question

We reviewed whether glue can reduce chronic pain after surgery, without increasing the postoperative recurrence rate, compared with sutures for mesh fixation in Lichtenstein inguinal hernia repair.

Background

A hernia is a weakness of the abdominal wall and allows escape of soft tissue or internal organs. It usually appears as a reducible lump and might cause discomfort and pain, limit daily activities, and affect quality of life. It can be life threatening if the bowel is ischemic or necrotic. Lichtenstein inguinal hernioplasty, which employs a synthetic mesh prosthesis to bridge the defect, is the standard open tension-free repair of inguinal hernia. The recurrence rate of the Lichtenstein technique is acceptable. However, postoperative chronic pain is common and difficult to deal with. Suture is the traditional method for fixation of the mesh, but it may cause irritation or nerve compression which in turn leads to postoperative neuropathic pain. Therefore glue, as a non-traumatic method for mesh fixation, is thought to reduce chronic pain. However, glue fixation might have an effect on the postoperative hernia recurrence rate.

Investigation

The Lichtenstein technique was first described in 1986, thus we searched the literature from 1986 to May 2016 for randomised controlled trials comparing glue versus sutures for mesh fixation in Lichtenstein hernia repair. We also considered studies including both primary and recurrent inguinal hernia when the report allowed us to separate the extraction of data on the primary repair.

Study characteristics

We identified 12 relevant randomised controlled trials comparing glue versus suture for fixation of the mesh, with a total of 1932 participants.

Main results

Glue fixation is superior to suture for the outcomes of chronic pain, duration of operation, haematoma and recovery time to daily activities.

Glue fixation is not associated with an increased risk of infection, hernia recurrence, seroma (a collection of fluid that builds up under the surface of the skin after surgery), persisting numbness (loss of sensation or feeling), quality of life, and postoperative length of stay.

We do not know the role of glue fixation in people with recurrent hernia, femoral hernia or complicated hernia. Meanwhile no conclusions could be drawn on which type of glue should be used because of lack of trials.

Quality of the evidence

Eight out of 12 trials showed high risk of bias in at least one of the investigated domains. Two studies were quasi-randomised controlled trials. Nearly half of the included trials either did not provide adequate information or had high risk of bias regarding blinding processes. The risk of bias for incomplete outcome data of all the included studies is low to high. Two trials did not report on some important outcomes. One study was funded by the manufacturer producing the fibrin sealant. As the quality of the evidence (GRADE) for the outcomes is moderate to low and the results of chronic pain is not robust, the findings should be interpreted with caution.

However, the evidence is still sufficient to conclude that glue fixation of mesh for the Lichtenstein procedure is comparable, if not superior, to fixation with suture. Glue may be a sensible alternative to suture for mesh fixation in Lichtenstein repair.

Summary of findings for the main comparison. Glue versus suture for recurrence and pain in Lichtenstein inguinal hernioplasty

Glue versus suture for recurrence and pain in Lichtenstein inguinal hernioplasty

Patient or population: patients with recurrence and pain in Lichtenstein inguinal hernioplasty
Settings:
Intervention: Fixation with glue

Comparison: Fixation with suture

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk Glue versus suture	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Chronic pain Follow-up: 3 to 60 months	**Study population** **71 per 1000** (51 to 99) **Moderate** **74 per 1000** (53 to 103)	**OR 0.63** (0.44 to 0.91)	1473 (10 studies)	⊕⊕⊝⊝ **low** [1,2]	
Hernia recurrence Follow-up: 3 to 60 months	**Study population** **13 per 1000** (6 to 28) **Moderate** **0 per 1000** (0 to 0)	**OR 1.44** (0.63 to 3.28)	1987 (12 studies)	⊕⊕⊝⊝ **low** [1,2,4]	
Duration of operation (mins) Follow-up: 4.7 to 60 months	The mean duration of operation (mins) in the intervention groups was **0.37 standard deviations lower** (0.52 to 0.23 lower)		1790 (9 studies)	⊕⊕⊝⊝ **low** [1,5]	

Wound/superficial infection Follow-up: 3 to 15 months	**Study population** **12 per 1000** (4 to 39) **Moderate** **0 per 1000** (0 to 0)	**OR 1.23** (0.37 to 4.11)	818 (7 studies)	⊕⊕⊖⊖ **low** [1,2,4]
Mesh/deep infection Follow-up: 3 to 60 months	**Study population** **5 per 1000** (1 to 19) **Moderate** **0 per 1000** (0 to 0)	**OR 0.67** (0.16 to 2.83)	1448 (8 studies)	⊕⊕⊖⊖ **low** [1,2,4]
Haematoma Follow-up: 3 to 60 months	**Study population** **34 per 1000** (21 to 55) **Moderate** **35 per 1000** (21 to 56)	**OR 0.52** (0.31 to 0.86)	1439 (10 studies)	⊕⊕⊕⊖ **moderate** [1]
Recovery time to daily activities (days) Follow-up: 4.7 to 16.7 months	The mean recovery time to daily activities (days) in the intervention groups was **0.81 standard deviations lower** (1.05 to 0.58 lower)		403 (3 studies)	⊕⊕⊖⊖ **low** [1,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] The risk of bias of most included studies is moderate or high.
[2] Total number of events is less than 300.
[3] The number of trials was too few to assess inconsistency.
[4] Imprecision of results (wide confidence intervals).
[5] Unexplained heterogeneity or inconsistency of results.

BACKGROUND

Description of the condition

Inguinal (groin) hernia repair is one of the most frequent operations in general surgery. Rutkow 2003 reports 800,000 groin hernia repairs in the US in 2003. The Lichtenstein technique, first described in 1986 (Lichtenstein 1986), is the standard open tension-free method of inguinal hernia repair and is used worldwide. In this method, a synthetic mesh is placed over the defect so that the hernia is repaired without the need to pull the tissues together under tension. The advantages of this procedure are that it is technically easy, associated with lower recurrence rates, has shorter recovery times compared with tension repair (Grant 2002; Nordin 2002), and can be performed using local anaesthesia as a day procedure. However, postoperative chronic pain is frequently reported following mesh-based inguinal hernia repair, from 11.0% to as high as 40.5% (Eklund 2010; MRC Group 1999; Nienhuijs 2007; Nikkolo 2012; Paajanen 2002; Willaert 2012), and has a significant impact on quality of life (van Hanswijck de Jonge 2008). It is difficult to overcome this problem, as surgery and the use of additional local analgesics have not shown a clear benefit to those treated (Nienhuijs 2007).

Description of the intervention

Sutures are generally used to secure the prosthetic mesh but may contribute to chronic pain or other problems, such as numbness or groin discomfort, presumably through irritation or nerve compression (Heise 1998). This has prompted the development of less traumatic means of mesh fixation. The original technique for fixation of mesh in Lichtenstein hernioplasty used non-absorbable sutures. Since then, other surgeons have described using absorbable sutures (Paajanen 2002), various tissue adhesives (Canonico 2005), or novel self-fixing meshes (Kapischke 2010). Fibrin glue and N-butyl-2-cyanoacrylate are two of the most commonly used products for mesh fixation. Fibrin glue is a bio-degradable adhesive that combines human-derived fibrinogen and thrombin. In addition to its haemostatic action, the fibrinogen component gives the product tensile strength and adhesive properties (Katkhouda 2001), as well as promoting fibroblast proliferation (Zieren 1999). N-butyl-2-cyanoacrylate is a new generation of cyanoacrylate that has been used as a surgical tissue adhesive since the 1960s, polymerizing at room temperature, and resulting in lower toxicity and fewer inflammatory reactions compared to cyanoacrylate (Levrier 2003; Montanaro 2001).

How the intervention might work

Tissue adhesives aim to reduce chronic neuropathic pain and simultaneously speed up the surgical procedure. Because the possibility of trapping nerves with suturing is eliminated, direct nerve irritation is reduced. Therefore, mesh fixation with glue (tissue adhesive) seems to be an optimal choice to reduce postoperative chronic pain. However, there may be increased recurrence associated with glue fixation.

Why it is important to do this review

As inguinal hernia repair is performed so frequently and is often associated with postoperative chronic pain, even relatively modest improvements in clinical outcomes would have a significant medical and economic impact. If a reduction of postoperative chronic pain without affecting the recurrence rate can be demonstrated by fixation with tissue adhesives (glue), compared to mesh fixation with sutures, this may support change in current surgical practice. However, there is concern of increased recurrence associated with glue fixation because the fibrin glue is fully absorbed within two weeks of application (Petersen 2004). Several randomised trials and observational studies have compared the two methods (Campanelli 2012; Helbling 2003; Paajanen 2011), but consensus regarding which method is better has not been reached. Thus, a thorough and systematic evaluation of the use of mesh fixation with glue would be welcomed to support the ongoing discussions.

OBJECTIVES

To determine whether tissue adhesives can reduce postoperative complications, especially chronic pain, with no increase in recurrence rate, compared with sutures for mesh fixation in Lichtenstein hernia repair.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion randomised and quasi-randomised controlled trials (RCTs) comparing glue versus sutures for mesh fixation in Lichtenstein hernia repair. Cluster-RCTs were also eligible. We also considered studies including both primary and recurrent inguinal hernia if data on primary repair were reported separately. We included trials in any language.

Types of participants

Adults (at least 18 years of age) undergoing Lichtenstein hernia repair for primary inguinal hernia (direct and indirect), unilateral as well as bilateral. We excluded participants with femoral hernias.

Types of interventions

Lichtenstein hernia repair with mesh fixation by:

1. glue (tissue adhesive); or
2. sutures.

Types of outcome measures

Primary outcomes

1. Chronic pain: pain persisting beyond three months postoperatively.
2. Hernia recurrence: clinically or radiologically diagnosed. We will use any time point reported by the authors, as there is no standard and widely accepted method to differentiate between recurrence and a new hernia that can be prespecified.

Secondary outcomes

1. Duration of operation (minutes).
2. Wound/mesh infection.
3. Haematoma/seroma.
4. Persistent numbness: numbness in the groin or testicle persisting beyond three months postoperatively.
5. Postoperative length of stay (days).

6. Recovery time to daily activities (walking, driving, manual work) (days)
7. Quality of life

Search methods for identification of studies

Electronic searches

The Lichtenstein technique was first described in 1986, thus searches were limited to publications from 1986 to 11 May 2016. The following electronic databases were searched with no language or publication restrictions.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) in the Cochrane Library (searched 11 May 2016) (Appendix 1).
2. MEDLINE Ovid (January 1986 to 11 May 2016) (Appendix 2).
3. EMBASE Ovid (January 1986 to 11 May 2016) (Appendix 3).
4. Science Citation Index (Web of Science) (January 1986 to 11 May 2016) (Appendix 4).
5. CBM (Chinese Biomedical Database) (Appendix 5).
6. CNKI (China National Knowledge Infrastructure) (Appendix 6).
7. VIP (a full-text database from China) (Appendix 7).
8. Wanfang databases (Appendix 8).

Searching other resources

We contacted experts in the field for information about any further completed and ongoing trials. Relevant websites were searched and reference lists of all the included studies were checked for additional studies suitable for inclusion.

We searched the following trial registers.

1. ClinicalTrials.gov (clinicaltrials.gov).
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/).

Data collection and analysis

Selection of studies

Two review authors (SP and CX) independently assessed all abstracts identified by the search strategies and excluded studies that were clearly not relevant. We obtained the full-text publications of all possibly relevant abstracts and formally assessed them for inclusion. Eligible studies were included irrespective of whether measured outcome data were reported. Review authors were not blinded to the names of the authors, their institutions, the journal of publication or the results. We resolved any disagreements by discussion or a third review author (SY) acted as arbiter. We also listed the excluded trials and the reasons for their exclusion.

Data extraction and management

A data extraction form was developed and two review authors (SP and DS) independently extracted data and completed these forms. Data on the following were extracted.

1. Study Information: study identification, first author, country, year of publication.
2. Methods of the study: study design, method of randomisation, allocation concealment, blinding.
3. Participants: setting, country, enrolment dates, inclusion criteria, exclusion criteria, age, sex, body mass index (where documented), activities (i.e. job, sport, hobbies), health status (i.e. chronic obstructive pulmonary disease, constipation, prostatism), details of hernia (type and size, unilateral/bilateral), total number of participants originally assigned to each intervention group.
4. Intervention: material for fixation.
5. Duration of follow-up.
6. Outcomes: chronic pain, recurrence, length of operation (minutes), haematoma/seroma, wound infection, mesh infection, persistent numbness, postoperative hospital length of stay (days), recovery time (days) to achieving normal daily activities (walking, driving, manual work), quality of life.
7. Routine prophylactic use of perioperative antibiotics.
8. Economic aspects.
9. Other technical details: type of mesh, overlap to the pubic tubercle, fixation locations, handling of nerves.

Where a difference of opinion arose between authors, it was resolved through discussion with a third review author (HQ). We contacted study authors to request missing or updated information.

Assessment of risk of bias in included studies

We assessed all studies that met the inclusion criteria for methodological quality, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (SP and CX) independently assessed the risk of bias of included studies and a third review author (SY) resolved disagreements where necessary.

We assessed the following risk of bias domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting. and
- Other bias (sample size calculation, differences at baseline between allocation groups, registered in trial database and funds from industry).

We judged each domain as low, high or unclear risk of bias according to criteria stated in the Cochrane 'Risk of bias' tool (see Appendix 9) (Chapter 8.5.d, Higgins 2011).

We classified trials as low risk of bias if none of the domains were associated with unclear or high risk of bias. Otherwise, the trials were classified as moderate or high risk of bias (one of the domains has unclear risk of bias or one of the domains has high risk of bias, respectively).

We searched for the protocols of studies included in the review using electronic databases, or by contacting the authors of the respective studies. If we suspected selective reporting, we contacted the study authors for clarification.

Measures of treatment effect

We analysed the data using Cochrane's Review Manager 5 (RevMan) computer program (RevMan 2012), following recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Dichotomous outcomes were expressed as odds ratio (OR) with 95% confidence intervals (CI). Continuous outcomes were expressed as mean differences (MD) with 95% CI.

Unit of analysis issues

If people randomised had bilateral hernias and each hernia received the same intervention, the number of participants was used as the denominator in the analysis.
One trial treated each hernia in people with bilateral hernias with a different method of fixation, therefore the number of hernias was used as the denominator in the analysis. All included studies were parallel in design, and we did not identify any cluster-RCTs, hence the unit of analysis was the participant or the hernia.

Dealing with missing data

Where essential data were missing, insufficient or unclear, we attempted to contact study authors for further information. The current update reported data from original studies regardless of whether intention-to-treat (ITT) analysis was employed by the authors of the included studies. If data were missing due to participants dropping out of the studies, and being unable to receive any information on reasons from the primary authors, we conducted an intention-to-treat analysis and treated dropouts as successful rehabilitation when they occurred. For those data derived from completers only, we conducted best/worst case scenario sensitivity analyses to assess the impact of missing data on the estimates of effect (Analysis 2.1; Analysis 2.2).

Assessment of heterogeneity

First, we assessed the clinical diversity among the included studies, focusing on the participants, interventions, and measurement of outcomes.

Second, we judged methodological diversity in terms of variability in study design and risk of bias. We assessed statistical heterogeneity using the Chi^2 test (significance set at $P < 0.1$) and I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2002; Higgins 2011).

Data synthesis

Where appropriate, for dichotomous outcomes we pooled data in meta-analyses using the Mantel-Haenszel approach (fixed-effect model); and for continuous outcomes we used the inverse variance method (fixed-effect model). If homogeneity between studies was deemed invalid (with substantial or considerable heterogeneity), a random-effects model was adopted instead after exploring the causes of heterogeneity. We used the RevMan software (RevMan 2012) to analyse the data.

Subgroup analysis and investigation of heterogeneity

We intended to perform the following subgroup analyses.

1. Synthetic glue versus sutures.
2. Biological glue versus sutures.
3. Synthetic glue versus biological glue.
4. Lightweight mesh versus heavyweight mesh.

Due to lack of data, we were not able to perform the synthetic glue versus biological glue subgroup analysis.

Sensitivity analysis

We planned sensitivity analyses to explore the influence of the following factors on effect size.

1. Repeating the analysis taking into account risk of bias of the studies, i.e. removing those that at least one criterion classified as high or unclear risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Only Paajanen 2011 was considered to be at an overall low risk of bias.
2. Repeating the analysis removing the hernia level trial, Hidalgo 2005, in order to get the patient level result.

Summary of findings

We assessed the quality of the evidence for recurrence and chronic pain for glue versus suture following Lichtenstein inguinal hernioplasty using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann 2011) in the 'Summary of findings' table.

The GRADE system classifies the quality of evidence in one of four grades:

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Factors that influence the quality of evidence:

Downgrades the evidence	Upgrades the evidence for non-randomised trials
Study limitation	Large magnitude of effect
Inconsistency of results	All plausible confounding would reduce the demonstrated effect
Indirectness of evidence	Dose-response gradient
Imprecision	
Publication bias	

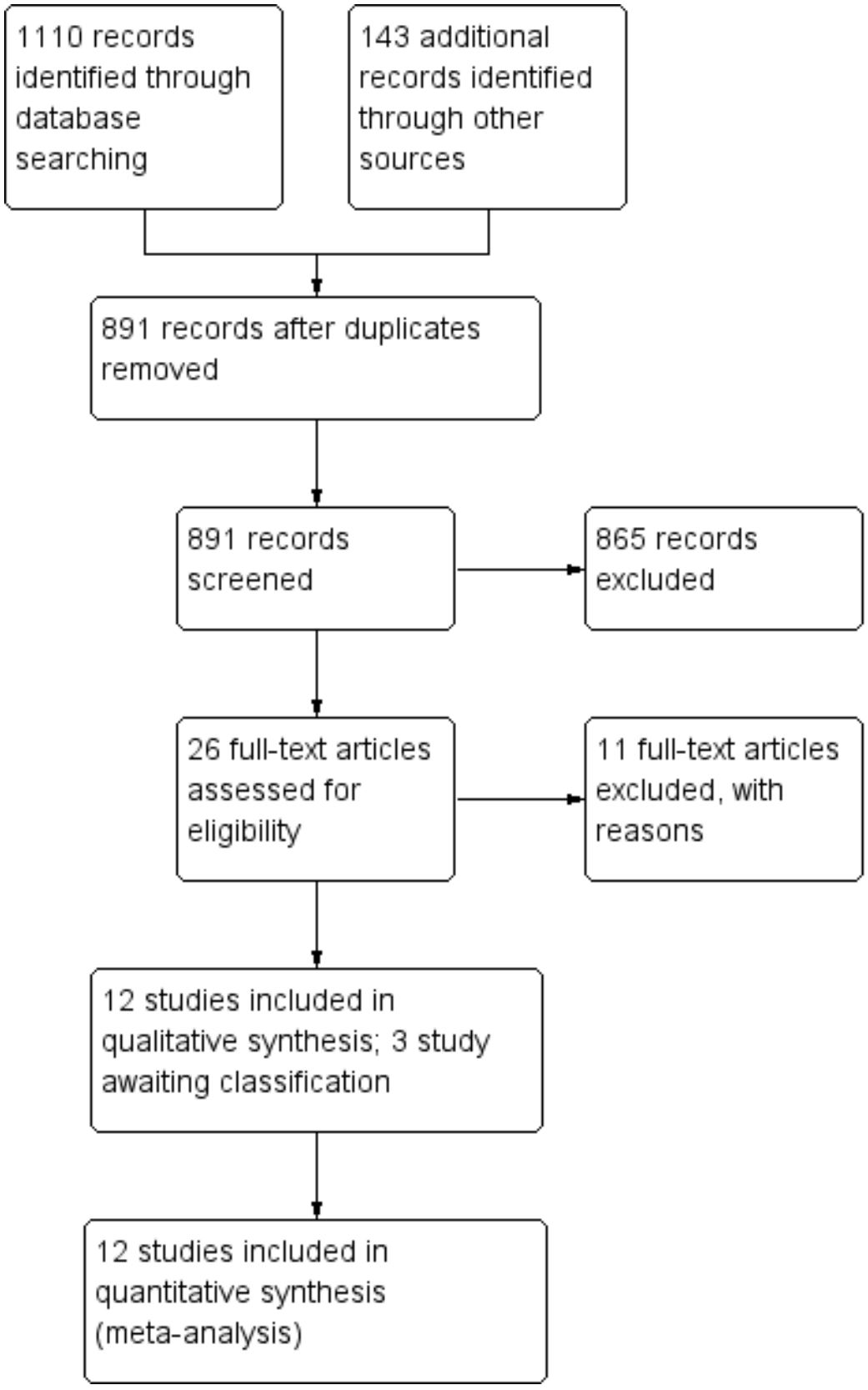
RESULTS

Description of studies

Results of the search

The study screening process is shown in Figure 1. For duplicated publications, only the most recent or the most complete report was included. There were 1253 publications, including 1110 records identified through database searching and 143 additional records identified through other sources. From these, 362 duplicates were removed. From the remaining 891 publications, 865 records were excluded due to non-randomised designs or lack of relevance to our topic. We assessed the full-text versions of the remaining 26 publications. Two publications were excluded because they were found to be duplicated publications and nine did not meet our inclusion criteria (see Excluded studies section, below). Finally, from the remaining 15 publications, 12 trials were included in the quantitative synthesis (meta-analysis) and 3 studies are awaiting classification.

Figure 1. Study flow diagram.



Included studies

Ten RCTs and two quasi-RCTs — Hidalgo 2005 and Jain 2009 — were included in this systematic review; one of the quasi-RCTs used within-patient allocation in people with bilateral hernia. No cluster-RCTs were identified. The detailed information of the included trials is presented in the Characteristics of included studies table. All the included trials were published in English.

Eight studies applied synthetic glue for mesh fixation, while the other four — Hidalgo 2005, Bracale 2012, Campanelli 2012 and Damiano 2014 — used biological glue. A total of 1932 participants were included in this systematic review, among which 970 were in glue groups and 1017 in suture groups. Most of the participants were male, with six studies including only males (Campanelli 2012; Dabrowiecki 2012; Hidalgo 2005; Jain 2009; Kim-Fuchs 2012; Nowobilski 2004).

The average follow-up period in nine of the 12 included studies was similar, at 12 to 17 months; follow-up was less than five months in two studies (Helbling 2003; Nowobilski 2004), and about five years in another (Kim-Fuchs 2012). Eight of the included studies tried their best to identify and preserve the nerves in the inguinal region; Helbling 2003 resected the nerves of most of the participants and in three studies this information was not clear (Damiano 2014; Hidalgo 2005; Jain 2009).

Excluded studies

See: Characteristics of excluded studies table.

Three studies did not have randomised allocations of glue and suture (Negro 2011; Shen 2011; Sözen 2012), two trials reported data already included in Campanelli 2012 (Campanelli 2008; Campanelli 2014), three trials were not controlled studies and included people who underwent plug and mesh procedures other than Lichtenstein (Eldabe Mikhail 2012; Lionetti 2012; Testini 2010), and in three studies the intervention and control groups received different kinds of mesh (Arslani 2010; Stabilini 2010; Torcivia 2011).

Risk of bias in included studies

The results of the 'Risk of bias' assessments are summarised graphically (Figure 2, Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

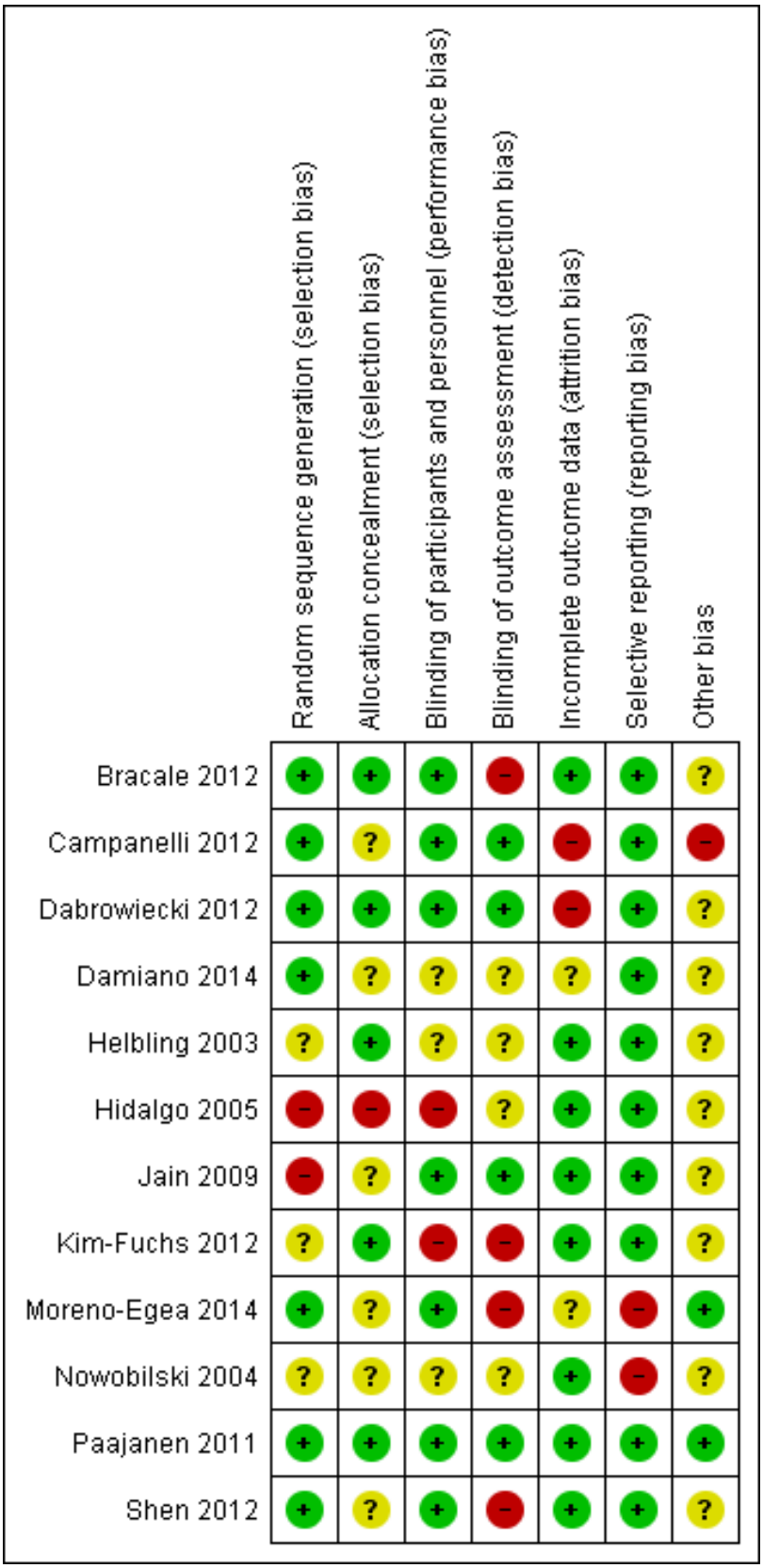
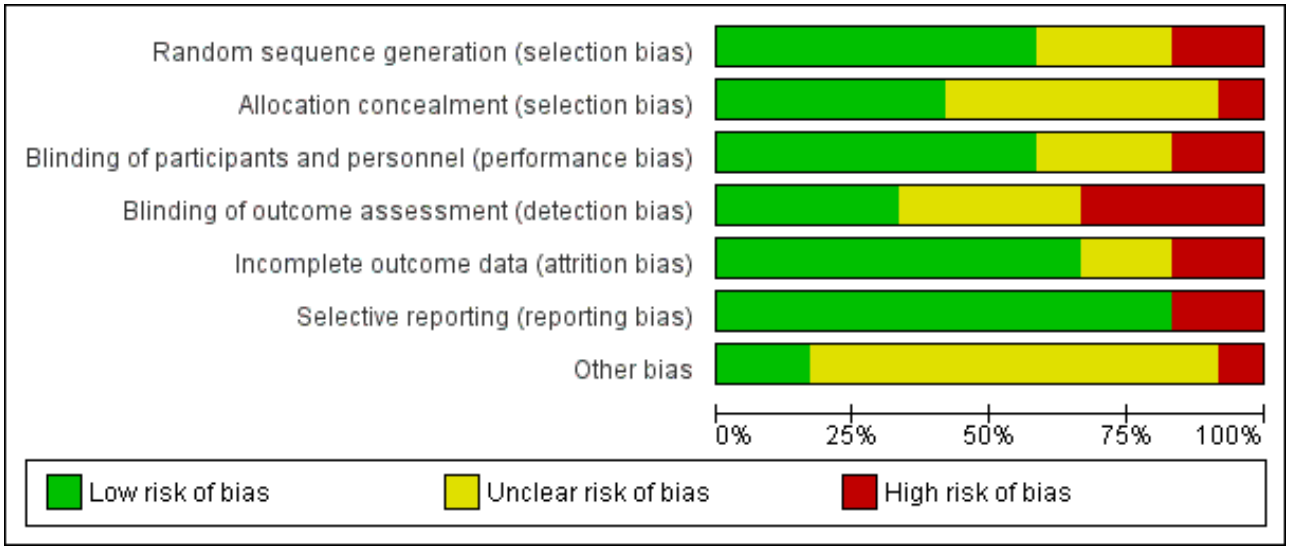


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Two included studies are quasi-randomised trials. In Hidalgo 2005, on the right side polypropylene sutures were used, while on the left, attachment was done using glue. In Jain 2009, participants were alternately assigned to one of two groups. For the 10 randomised trials, six reported specific method of randomisation (Bracale 2012; Campanelli 2012; Dabrowiecki 2012; Damiano 2014; Moreno-Egea 2014; Shen 2012); but only five studies reported the method of allocation concealment (by sealed envelope) (Bracale 2012; Dabrowiecki 2012; Helbling 2003; Kim-Fuchs 2012; Paajanen 2011).

Blinding

Both the participants and outcome assessment were blinded in four studies (Campanelli 2012; Dabrowiecki 2012; Jain 2009; Paajanen 2011). In Shen 2012, Bracale 2012 and Moreno-Egea 2014, only the participants were blinded. In Helbling 2003, Damiano 2014 and Nowobilski 2004, the blinding was not clear. In Hidalgo 2005, the participants were not blinded and the blinding of outcome assessors was not clear. For Kim-Fuchs 2012, neither the participants nor the outcome assessors were blinded.

Incomplete outcome data

Attrition bias was not clear in two trials (Damiano 2014; Moreno-Egea 2014). In Helbling 2003, Nowobilski 2004, Hidalgo 2005, Jain 2009 and Shen 2012, the outcome data were complete. The proportion of missing outcomes was comparable between two groups, or was not big enough to have a clinically relevant impact on the intervention effect estimate, in Paajanen 2011, Kim-Fuchs 2012 and Bracale 2012. Attrition bias was high in two trials (Campanelli 2012; Dabrowiecki 2012).

Selective reporting

Nowobilski 2004 reported pain within seven days, which did not meet our definition of chronic pain. Moreno-Egea 2014 did not report the result of time required to return to normal activities (days) as they planned in the study protocol. The remaining 10 studies reported both primary outcomes of this review. For most of the studies there was no protocol.

Other potential sources of bias

The potential conflict of interest and source of funding was described in three trials (Campanelli 2012; Moreno-Egea 2014; Paajanen 2011). For Paajanen 2011 the source of funding was a hospital research grant, free from financial or material support from any commercial company, thus judged to be free from risk of 'source of funding' bias. The study by Campanelli 2012 was funded by Baxter Healthcare, which is a manufacturer producing fibrin sealant; thus we consider this trial to be at high risk of 'source of funding' bias. In the Moreno-Egea 2014 study, the authors declared no potential conflicts of interest and no financial support. The remaining included trials did not declare any source of funding.

Effects of interventions

See: **Summary of findings for the main comparison** Glue versus suture for recurrence and pain in Lichtenstein inguinal hernioplasty

See: Data and analyses.

All 12 studies available for classification were included in quantitative synthesis (meta-analysis).

1. Primary outcomes

1.1 Chronic postoperative pain

Ten trials, with a total of 1418 participants reported the number of people with chronic pain (at least 3 months postoperatively; follow-up 3 to 60 months). There was an overall reduction of chronic pain by 37% (OR 0.63, 95% CI 0.44 to 0.91, low-quality evidence; Analysis 1.1) with fibrin glue. There was no significant heterogeneity (I^2 = 37%, P = 0.12).

For subgroup analyses based on the type of glue used, there was no statistically significant difference between the synthetic glue group and the suture group (OR 0.69, 95% CI 0.46 to 1.04; Analysis 1.1.1) with moderate heterogeneity (I^2 = 48%, P = 0.07). The biological

glue group also had less chronic pain (OR 0.46, 95% CI 0.20 to 1.03; Analysis 1.1.2) with no statistical heterogeneity (I^2 = 0, P = 0.83), but the difference was not statistically significant.

After we only included studies that used lightweight mesh (Bracale 2012; Helbling 2003; Kim-Fuchs 2012; Moreno-Egea 2014; Paajanen 2011; Shen 2012), the result of chronic pain became less profound and statistically insignificant (OR 0.77, 95% CI 0.50 to 1.17). However, when we only included studies using heavyweight mesh (Campanelli 2012 and Jain 2009), a significant and more profound benefit from the fixation with glue regarding the outcome chronic pain was observed (OR 0.38, 95% CI 0.17 to 0.82).

When trials with at least one risk of bias criterion classified as unclear or high were removed from the analysis, this left only Paajanen 2011, which showed no statistically significant difference between the two groups (OR 1.39, 95% CI 0.76 to 2.56). When the hernia level trial was removed (Hidalgo 2005), none of the results changed.

Three studies did not present specific information of dropouts (Dabrowiecki 2012; Damiano 2014; Moreno-Egea 2014). We conducted a worst case scenario analysis with the data of the four studies reporting dropouts (Bracale 2012; Campanelli 2012; Kim-Fuchs 2012; Paajanen 2011), and found that none of the results changed (OR 0.69, 95% CI 0.47 to 1.02 for synthetic glue versus suture; OR 0.53, 95% CI 0.27 to 1.05 for biological glue versus suture; and OR 0.65, 95% CI 0.46 to 0.91 for glue versus suture; Analysis 2.1).

1.2 Postoperative hernia recurrence

All twelve included trials, with a total of 1932 participants, reported the primary outcome 'hernia recurrence' (follow-up 3 to 60 months), with a median length of follow-up just less than 17 months. One could argue whether a hernia is new or whether it is a recurrent one, but so far there is no standard and widely accepted method to differentiate between recurrence and a new hernia. Seven of the trials reported no recurrence events in either group. There was no statistically significant difference between the two groups (OR 1.44, 95% CI 0.63 to 3.28, low-quality evidence; Analysis 1.2) with no statistical heterogeneity (I^2 = 0, P = 0.84). Subgroup analyses also showed no statistically significant difference between the suture group and the synthetic glue (OR 1.58, 95% CI 0.62 to 4.05, P = 0.34; Analysis 1.2.1; five of the eight trials reported no recurrence in either group) or biological glue (OR 1.02, 95% CI 0.17 to 5.90, P = 0.99; Analysis 1.2.2; two of the four trials reported no recurrence in either group).

When we only included studies that used lightweight mesh (Bracale 2012; Helbling 2003; Kim-Fuchs 2012; Moreno-Egea 2014; Paajanen 2011; Shen 2012), the result of recurrence remained unchanged (OR 1.58, 95% CI 0.62 to 4.04). When we only included studies using heavyweight mesh (Campanelli 2012 and Jain 2009), there was also no statistically significant difference between the two groups (OR 0.50, 95% CI 0.04 to 5.54). When the hernia level trial was removed (Hidalgo 2005), none of the results changed.

As for the previous outcome 'postoperative chronic pain', we conducted a worst case scenario analysis which confirmed the robustness of the results (OR 1.31, 95% CI 0.84 to 2.04 for synthetic glue versus suture; OR 0.67, 95% CI 0.19 to 2.40 for biological glue versus suture; and OR 1.22, 95% CI 0.80 to 1.85 for glue versus suture; Analysis 2.2).

2. Secondary outcomes

2.1 Duration of operation

Nine trials, with a total of 1790 participants, reported duration of operation in minutes. The glue group had a shorter duration of operation (MD −3.13, 95% CI −4.48 to −1.78, low-quality evidence; Analysis 1.3). Test for heterogeneity was significant (I^2 = 60%, P = 0.01). Subgroup analyses showed that both the synthetic glue group and the biological glue group had shorter durations of operation than the suture group (MD −3.67, 95% CI −6.10 to −1.24 and MD −2.72, 95% CI −3.67 to −1.77, respectively; Analyses 1.3.1 and 1.3.2).

2.2 Wound/superficial infection

Seven trials, with a total of 763 participants, reported this outcome (follow-up 3 to 15 months). There was no statistically significant difference between the two groups (OR 1.23, 95% CI 0.37 to 4.11, low-quality evidence; Analysis 1.4) with no statistical heterogeneity (I^2 = 0, P = 0.38). As the only trials that reported any events were those comparing synthetic glue with sutures, the pooled result was the same for this subgroup (Analysis 1.4.1).

2.3 Mesh/deep infection

Eight trials, with a total of 1393 participants, reported this outcome (follow-up 3 to 60 months). There was no statistically significant difference between the two groups (OR 0.67, 95% CI 0.16 to 2.83, low-quality evidence; Analysis 1.5). Subgroup analyses also showed no statistically significant differences between the synthetic or biological glue group and the suture group (OR 1.00, 95% CI 0.06 to 16.14 and OR 0.58, 95% CI 0.11 to 3.19, respectively; Analyses 1.5.1 and 1.5.2).

2.4 Haematoma

Ten trials, with a total of 1384 participants, reported on the incidence of haematoma (follow-up 3 to 60 months). The glue group had fewer haematomas than the suture group (OR 0.52, 95% CI 0.31 to 0.86, moderate-quality evidence; Analysis 1.6) with no statistical heterogeneity (I^2 = 0, P = 0.78). Subgroup analyses showed that the synthetic glue group also had fewer haematomas than the suture group (OR 0.54, 95% CI 0.32 to 0.91; Analysis 1.6.1). However, there was no statistically significant difference between the biological glue group and the suture group (OR 0.33, 95% CI 0.05 to 2.13; Analysis 1.6.2).

2.5 Seroma

Seroma is a swelling caused by fluid that builds up under the surface of the skin, and may develop after a surgical procedure. Eight trials involving 1184 participants reported this outcome (follow-up 3 to 16.7 months). There was no statistically significant difference between the two groups (OR 0.83, 95% CI 0.51 to 1.33; Analysis 1.7) with no statistical heterogeneity (I^2 = 0, P = 0.89). Subgroup analyses also showed no statistically significant differences between the synthetic or biological glue group and the suture group (OR 0.74, 95% CI 0.14 to 4.02 and OR 0.83, 95% CI 0.51 to 1.37, respectively; Analyses 1.7.1 and 1.7.2).

2.6 Persisting numbness

Only four trials, with a total of 728 participants, reported this outcome (follow-up 3 to 60 months). There was no statistically significant difference between the two groups (OR 0.81, 95% CI 0.57

to 1.14; Analysis 1.8) with no statistical heterogeneity (I^2 = 0, P = 0.49). Subgroup analyses also showed no statistically significant differences between the synthetic or biological glue group and the suture group (OR 0.78, 95% CI 0.46 to 1.32 and OR 0.82, 95% CI 0.52 to 1.31, respectively; Analyses 1.8.1 and 1.8.2).

2.7 Postoperative length of hospital stay

Six trials, with a total of 1009 participants, reported this outcome. There was no statistically significant difference between the two groups (MD −0.12, 95% CI −0.35 to 0.10; Analysis 1.9) with moderate heterogeneity (I^2 = 51%, P = 0.10). In Nowobilski 2004, the glue group had shorter postoperative length of hospital stay (MD −0.50, 95% CI −0.85 to −0.15). But the cause of heterogeneity was unknown.

Subgroup analyses showed no statistical difference between the synthetic or biological glue group and the suture group (MD −0.21, 95% CI −0.54 to 0.12 and MD 0.00, 95% CI −0.00 to 0.00, respectively; Analyses 1.9.1 and 1.9.2).

2.8 Recovery time to daily activities

Only three trials involving 403 people reported the outcome. The glue group had shorter recovery time to daily activities (MD −1.26, 95% CI −1.89 to −0.63, low-quality evidence; Analysis 1.10) without statistically significant heterogeneity (I^2 = 33%, P = 0.23). Subgroup analyses showed that both the synthetic and biological glue group had shorter recovery times to daily activities than the suture group (MD −1.87, 95% CI −2.86 to −0.88 and MD −1.00, 95% CI −1.26 to −0.74, respectively; Analyses 1.10.1 and 1.10.2).

2.9 Quality of life

Only Campanelli 2012 reported the quality of life evaluations (SF-12v2 questionnaire) and participant satisfaction. Numerical improvements from baseline seen in the fibrin sealant group relative to sutures in terms of general health at 1, 6, and 12 months were not significant. Physical and mental component summary scores were similar between groups at each time point, as were scores on individual SF-12v2 domains. Regarding participant satisfaction with the overall procedure, more people in the fibrin sealant group than in the sutures group answered positively when asked if they would have the same procedure again (98.7% vs 92.2%; P = 0.0035).

DISCUSSION

Summary of main results

Compared to fixation with suture, our review shows that people undergoing Lichtenstein's procedure may benefit more from fixation with glue in terms of chronic pain, duration of operation, haematoma, and recovery time to daily activities. Meanwhile, there are no statistically significant differences between the two groups in other aspects such as hernia recurrence, wound/superficial infection, mesh/deep infection, seroma, persisting numbness, quality of life and postoperative length of stay. Given the low event rates for outcomes such as recurrence and infection, a lack of statistical significance cannot be interpreted as there being no difference — it may be that the analyses were just unable to detect it due to the relatively small number of participants (lack of statistical power).

As for subgroup analysis: fixation with synthetic glue and with biological glue showed similar results to fixation with suture, with the exception of haematoma, where there was no statistically significant difference between the biological glue and suture group in terms of the number of people experiencing haematoma.

The overall estimate of postoperative chronic pain was altered in subgroup analyses of lightweight versus heavyweight mesh. Analysis of included studies using lightweight mesh — Bracale 2012, Helbling 2003, Kim-Fuchs 2012, Moreno-Egea 2014, Paajanen 2011 and Shen 2012 — showed a less profound and insignificant reduction of chronic pain in the glue group (OR 0.77, 95% CI 0.50 to 1.17) compared to the suture group. Interestingly, when we only included studies using heavyweight mesh — (Campanelli 2012 and Jain 2009) — a significant benefit from the fixation with glue was still evident and even more profound (OR 0.38, 95% CI 0.17 to 0.82) than in the overall analyses (OR 0.63, 95% CI 0.44 to 0.91). Thus, participants in a subgroup of heavyweight mesh might therefore benefit more from fixation with glue compared to those in a subgroup of lightweight mesh. In a recent publication by Miserez 2014, results showed that lightweight mesh can cause less chronic pain compared to heavyweight mesh, which has been recommended in a guideline from the European Hernia Society on the treatment of inguinal hernia in adults (Miserez 2014) (Grade B). However in this study, we find that fewer people suffered from chronic pain when heavyweight mesh was applied compared to lightweight mesh (9/158, 5.7% vs 43/459, 9.4% in the glue group; 18/158, 11.4% vs 55/467, 11.8% in the suture group). It was hard to explain as these were not controlled trials studying the difference between heavyweight mesh and lightweight mesh. Maybe it was because of the heterogeneity between studies or the relatively small number of people in the subgroup analysis. But our result shows that a smaller proportion of people in the glue group suffered from chronic pain in both subgroups of heavyweight mesh and lightweight mesh compared to the suture group. Whether patients treated with lightweight mesh can benefit from fixation with glue needs to be further studied, as more and more lightweight mesh is applied worldwide.

Only one study was judged to be at overall low risk of bias (Paajanen 2011). In this study chronic pain did not differ significantly between the two groups (OR 1.39, 95% CI 0.76 to 2.56), but with only 302 participants the power of the analysis was greatly reduced.

Overall completeness and applicability of evidence

Much dissimilarity with regard to inclusion criteria, outcome definitions, experience of surgeons, mesh type, nerve identification and protection, details of fixation and period of follow-up may raise doubts as to whether pooling of data was appropriate in the present meta-analysis. One critical issue is the definition of chronic pain: the duration and intensity of chronic pain is not uniform, making the incidence of chronic pain quite different between studies. Most authors define chronic pain as a pain lasting for more than three months according to the International Association for the Study of Pain (IASP) (Aasvang 1986). However, this definition is based on non-surgical chronic pain. A clinical diagnosis of neuropathic pain is still not well defined. A second issue is the handling of the three nerves at the groin region. As damaged or trapped nerves are the main cause of neuropathic pain after hernioplasty, identification and protection of all three nerves during open inguinal hernia repair is recommended to reduce the risk of chronic incapacitating pain, according to the

international guidelines for prevention and management of post-operative chronic pain following inguinal hernia surgery (Alfieri 2011). However, the majority of the included studies did not provide sufficient information on this issue. Only the study by Helbling 2003 covered resection of nerves, but the average rate of nerve resection was less than 41% (18/48 versus 18/44). Furthermore the iliohypogastric nerve, one of the three nerves in this region, was not mentioned throughout the full text. Most importantly, in their Discussion section the authors mentioned that they meant to preserve these nerves. The nerves were resected because neuralgias were feared caused by intraoperatively damaged nerve fibres.

To control clinical heterogeneity, only studies applying Lichtenstein hernioplasty were included. Accordingly, our review cannot tell whether glue fixation is superior or inferior to fixation with suture during the Milligan procedure or hernioplasty with other kinds of mesh like PHS (Prolene Hernia System), UHS (Ultrapro Hernia System) and Modified Kugel Patch. Compared with Lichtenstein hernioplasty, these procedures differ materially, and the demand for stitching is much less.

As all the included trials only included people with primary inguinal hernia without complication, the role of glue fixation in people with recurrent hernia, femoral hernia or complicated hernia is still unknown. We also cannot answer the role of glue in TAPP (Transabdominal Pre-Peritoneal) or TEP (Totally Extraperitoneal) repair. Two systematic reviews evaluating the role of glue in hernioplasty have been published (Fortelny 2012; Morales-Conde 2011). Both of them found benefit in glue fixation during laparoscopic hernioplasty. An associated Cochrane Systematic Review is in preparation. According to the guidelines for laparoscopic (TAPP) and endoscopic (TEP) treatment of inguinal hernia published in 2011 (Bittner 2011), available evidence shows that fibrin glue is associated with low recurrence rates (Level 1B) and less acute and chronic pain than stapling. And the update with level 1 studies of the European Hernia Society guidelines on the treatment of inguinal hernia in adults concludes that there is possibly a short-term benefit (postoperative pain) of atraumatic mesh fixation in endoscopic procedures (TAPP) (Miserez 2014).

Quality of the evidence

We identified no unpublished studies in this review.

Although we developed strict inclusion and exclusion criteria, the clinical heterogeneity noted above in terms of outcome definitions, experience of surgeon, mesh type, nerve identification and protection, details of fixation and period of follow-up still translated into statistical heterogeneity. It is difficult to eliminate between-study heterogeneity completely so we applied the random-effects model instead if substantial statistical heterogeneity existed.

The potential influence of publication bias on the results of this systematic review can be considered small. Due to the extensive literature search using electronic databases without language restriction and our checking of reference lists of identified papers, it is unlikely that we failed to identify important studies.

Three out of 12 trials were assessed as having moderate risk of bias; eight trials showed high risk of bias in at least one of the investigated domains. Selection bias may have played a role in some of the included trials as two studies were quasi-randomised controlled trials and the allocation sequence of one trial was not concealed. Nearly half of the included trials either did not provide adequate information or had high risk of bias regarding blinding processes, which raises the possibility of performance bias. With regard to blinding of outcome assessment, only four of 12 trials had low risk of bias, which raises the possibility of detection bias. The risk of bias for incomplete outcome data of all the included studies is moderate to low. Therefore, no obvious attrition bias existed. Ten of the 12 trials reported on all primary and secondary outcomes, but two trials did not report on some important outcomes: reporting bias may play a role here. Most trials did not provide details of funding sources and any declarations of interest; however one study was funded by Baxter Healthcare, which is a manufacturer of fibrin sealant, so an additional risk of bias may exist. For quite a number of outcomes, the total number of events was small and the confidence intervals were wide, which indicates that the estimates of effects obtained are imprecise. Meanwhile, the number of trials was too few to assess inconsistency for recovery time to daily activities. Taking into account all of these negative factors, the quality of evidence across the comparisons in this review is low to moderate and needs to be carefully considered (Summary of findings for the main comparison).

Potential biases in the review process

We tried many ways, including asking for help from the authors and from the staff of the Cochrane Colorectal Cancer Group, to get the full text of Bar 2009 but failed. The trial is therefore listed as a study awaiting classification. This might have produced some publication bias.

Agreements and disagreements with other studies or reviews

Several other meta-analyses have been published in this field. Colvin 2013 included not only the Lichtenstein procedure, but also other open repair techniques of inguinal hernia using plug and mesh, or PHS or Modified Kugel patch. They included 10 RCTs and reported similar results to ours. Ladwa 2013 also included all kinds of open repair procedure. They conclude that glue fixation is comparable to suture fixation in terms of postoperative complications including chronic pain and recurrence, and can reduce operative time. They included only seven trials. Goede 2013 only included the Lichtenstein procedure. Although they reported similar results to ours, they included only seven trials, two of which (Arslani 2010 and Torcivia 2011) were excluded from this review (See Characteristics of excluded studies).

Our review included more trials (12) focusing on the Lichtenstein procedure. This allowed us to produce more precise estimates. We also performed GRADE assessments to highlight the quality of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Glue fixation of mesh for the Lichtenstein procedure is comparable to, and seemingly superior to, fixation with suture in terms of chronic pain. People having repairs with heavyweight mesh may benefit more from fixation with glue compared to those having repair with lightweight mesh with regard to chronic pain. Glue fixation appears superior in outcomes like duration of operation, haematoma and recovery time to daily activities. Glue fixation

is not apparently associated with an increased risk of infection, hernia recurrence, seroma, persisting numbness, quality of life or postoperative length of stay. Based on these results, glue may be a sensible alternative to suture for mesh fixation in Lichtenstein repair. However, these results should be interpreted with caution, as the quality of the evidence for most of the outcomes is low to moderate, meaning that we are not confident that further research would not alter the pooled results and therefore the conclusions drawn from the analyses. The only trial with well presented methodology showed no statistically significant difference between groups, but it is not clear if that means there is no difference or rather that the trial was too underpowered to detect one. We do not know the role of glue fixation in people with recurrent hernia, femoral hernia or complicated hernia. Whether synthetic glue is superior to biological glue, or vice versa, is also still unknown.

Implications for research

Hernia recurrence is considered a primary concern, despite being a relatively rare complication. Currently, available evidence is limited by the short duration of follow-up, the relatively small number of participants included and the overall quality of the primary trials. It is generally agreed that follow-up of three to five years is necessary to detect the majority of recurrences, so larger high-quality trials reporting longer follow-up are warranted. Postoperative chronic pain is also considered a primary concern, and has been reported before and after three months postoperatively in the included trials in this review. As most experts in this field currently recommend reporting chronic pain for more than three months, this should be considered and adopted in future study protocols. Potential benefits of using either synthetic glue or biological glue, as well as the role of nerve identification and protection, should also be assessed in future trials.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

Helbling 2003

Methods	Randomised controlled trial Unilateral hernia. Country: Switzerland. Setting: not reported. Enrolment dates: From January 2001 until December 2001.
Participants	Inclusion criteria: • Age > 25 years; elective setting; primary hernia; inguinal hernia; size of defect (L III, M II, M III, ML). Exclusion criteria: • Age < 25 years; urgent setting; recurrent hernia; femoral hernia; size of defect (L I, L II, M I); hydrocele or varicocele on hernia side; infected operation field; immunodeficiency. Glue group: • 22 participants • Male: 95.5% • Age: not reported. • Direct:indirect: not reported. • Right:left: not reported. • Risk factors: diabetes: 13.6%; obesity:18.2%; COPD: 9.1%; constipation: 9.1%; hyperplasia of prostate: 9.1% • Hernia type: L III: 31.8%; M II: 13.6%; M III: 22.7%; ML III: 13.6% Suture group: • 24 participants • Male: 95.8% • Age: not reported. • Direct:indirect: not reported. • Right:left: not reported. • Risk factors: diabetes: 8.3%; obesity:8.3%; COPD: 4.2%; constipation: 8.3%; hyperplasia of prostate: 12.5% • Hernia type: L III: 33.3%; M II: 4.2%; M III: 29.2%; ML II: 4.2%; ML III: 29.2%
Interventions	Lichtenstein inguinal hernioplasty with Vipro II-mesh (14 cm × 8 cm) (pliable lightweight multi-filament mesh). Glue group: • n-butyl-cyanoacrylate (Histoacryl B. Braun Melsungen, Germany) Suture group: • PDS 2/0
Outcomes	Recurrences, chronic pain, infection, hematoma, recovery time to normal activity
Notes	Handling of nerves:

Helbling 2003 *(Continued)*

- Nerves are preserved if possible. But the nerves of some people were resected because neuralgias were feared caused by intraoperatively damaged nerve fibers. The ilioinguinal nerve was resected in 7 participants (32%) of group 2 and in 4 participants (16.5%) of group 1. The genital branch of the genitofemoral nerve was resected in 11 people (50% of group 2) and in 14 peiople (58% of group 1). The proximal ends of the nerves were coagulated with bipolar coagulation at a distance of 7 to 10 mm and not intra-musculary implanted.

Length of follow-up: 3 months.

Time points of the analysis: 3 months.

Intention-to-treat analysis: yes.

The number of participants randomized: 22 in Glue group; 24 in Suture group

The number of participants evaluated: 22 in Glue group; 24 in Suture group

Information from publication only.

No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear.
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 months after the operation, all but 1 person resumed normal physical activity, so we can believe that all the participants completed follow-up.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Nowobilski 2004

Methods	Randomized controlled trial. Unilateral hernia. Country: Poland. Setting: Department of General & Gastroenterological Surgery, St. Vincent a'Paulo Hospital of Gdynia, Poland.

Nowobilski 2004 *(Continued)*

	Enrolment dates: between May and November 2003.
Participants	Inclusion criteria: • Unilateral inguinal hernias that underwent elective surgical treatment. • Male: 100% Glue group: • 22 participants • Median (range) age: 60.5 (30 to 76) • Right:left: 12:10 • Direct:indirect: 9:13 • Hernia type: not reported Suture group: • 24 participants • Median (range) age: 52.6 (20 to 78) • Right: left: 14:10 • Direct: indirect: 8:16 • Hernia type: not reported
Interventions	Lichtenstein inguinal hernioplasty with polypropylene mesh. Glue group: • Butyl-2-cyanoacrylate adhesive (Indermil; Loctite, Dublin, Ireland) Suture group: • 3/0 Dexon, Tyco
Outcomes	Recurrences, infection, seroma, length of operation, time to discharge, recovery time to normal activity
Notes	Handling of nerves: • The genitofemoral nerve was lifted in order to avoid any direct contact until the glue was dried. Length of follow-up: median of 4.7 (range 3 to 9) months. Time points of the analysis: last day of the follow-up. Intention-to-treat analysis：yes. The number of people randomized: 22 in Glue group; 24 in Suture group The number of people evaluated: 22 in Glue group; 24 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear.

Nowobilski 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had been followed up for at least 3 months.
Selective reporting (reporting bias)	High risk	Without the result of chronic pain.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Hidalgo 2005

Methods	Quasi-randomised controlled trials. Bilateral hernia; by hernia. Country: Spain. Setting: not reported. Enrollment dates: January 2001 to July 2003.
Participants	Inclusion criteria: • bilateral inguinal hernia Male: 100% Age: between the ages of 49 and 71 years Complications: obesity (56.3%); hypertension (32.7%); and obstructive pulmonary disease (20%) Hernia type: not reported. Direct:indirect: not reported.
Interventions	Lichtenstein inguinal hernioplasty with polypropylene mesh for both sides in 1 operation. 55 participants Glue group (left side): • Fibrin sealant (Tissucol Duo) (2 cc) Suture group (right side): • Polypropylene 2/0

Hidalgo 2005 *(Continued)*

Outcomes	Recurrences, infection, seroma, hematoma, chronic pain, recovery time to normal activity
Notes	Handling of nerves: • Not clear. Length of follow-up: 1 year. Time points of the analysis: 1 year. Intention-to-treat analysis: yes. The number of people randomized: 55 in Glue group; 55 in Suture group The number of people evaluated: 55 in Glue group; 55 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	On the right side polypropylene sutures were used (prolene 2/0); while on the left, attachment was done using glue (Tissucol).
Allocation concealment (selection bias)	High risk	No.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had been followed for at least 1 year.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Jain 2009

Methods	Quasi-randomised controlled trials. Alternately assigned to 1 of 2 groups. Unilateral hernia. Country: India. Setting: the surgery outpatient department of Lok Nayak Hospital, New Delhi.

Jain 2009 *(Continued)*

	Enrolment dates: not reported.
Participants	Inclusion criteria: • Presence of an uncomplicated primary inguinal hernia; subjects eligible for elective inguinal hernia repair using Lichtenstein technique. Exclusion criteria: • Recurrent, complicated (irreducible/incarcerated), or femoral hernias; bilateral hernias; concomitant abdominal surgery; ongoing long-term analgesic or steroid treatment; people receiving antiplatelet agents or anticoagulants; known history of alcohol or drug abuse; any chronic disease affecting outcome of the surgery directly (COPD, cirrhosis, diabetes); severely compromised physical or psychological health. Glue group: • 40 participants • Mean age (years): 45.65 • Male: 100% • Type of hernia: right, 70%; left, 30%; indirect, 75%; direct, 25% Suture group: • 40 participants • Mean age (years): 51.98 • Male: 100% • Type of hernia: right, 65%; left, 35%; indirect, 70%; direct, 30%
Interventions	Lichtenstein inguinal hernioplasty with 15 cm × 10 cm heavyweight polypropylene mesh. Glue group: • gelatin–resorcin–formalin (GRF) glue Suture group: • 3-0 polypropylene interrupted sutures
Outcomes	Recurrences, chronic pain, length of operation, time to discharge, recovery time to normal activity
Notes	Handling of nerves: • Not clear. Length of follow-up: 1 year. Time points of the analysis: 6 months for chronic pain and 1 year for recurrence. Intention-to-treat analysis：yes. The number of people randomized: 40 in Glue group; 40 in Suture group The number of people evaluated: 40 in Glue group; 40 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jain 2009 *(Continued)*

Random sequence generation (selection bias)	High risk	Alternately assigned to 1 of 2 groups.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were blinded for the type of procedure to be performed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The follow-up was performed by a surgery registrar who was blinded for the method of hernia repair employed in the participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 80 participants had been followed for at least 1 year.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Paajanen 2011

Methods	Randomized multi-centre trial conducted in the ambulatory surgery unit of 3 hospitals in Finland. Unilateral hernia. Country: Finland. Setting: 3 hospitals in Finland (100 in hospital A, 80 in hospital B and 122 in hospital C). Enrolment dates: between June 2007 and May 2009.
Participants	Inclusion criteria: • The study subjects were all over 18 years old with unilateral or bilateral inguinal hernia. People who fulfilled the criteria for day-case surgery received written and oral information about the aims and conduct of the study. Every included participant gave informed consent. Exclusion criteria: • Known femoral hernia, large scrotal hernia, emergency operation for strangulated hernia, recurrent hernia, allergy to polypropylene and participant refusal. Glue group: • 151 participants • Age (years), Mean (SD): 53 (15) • Sex ratio (M:F): 131:20 • Body mass index (kg/m2), Mean (SD): 25(3) • Side of hernia: left, 39.1%; right, 60.9% • Hernia type: direct, 27.2%; indirect, 68.8%; combined, 4.0% • Size of defect (cm): < 1.5, 36.4%; 1.5 to 3.0, 54.3%; > 3.0, 9.3% • Preoperative use of analgesia: 25.8%

Paajanen 2011 *(Continued)*

- Preoperative pain score (VAS), Mean (SD): 4.0 (2.4)
- Duration of symptoms (months), mean (SD): 18 (28)

Suture group:

- 151 participants
- Age (years), Mean (SD): 53 (15)
- Sex ratio (M:F): 135:16
- Body mass index (kg/m2), mean (SD): 25(3)
- Side of hernia: left, 52.3%; right, 47.7%
- Hernia type: direct, 36.4%; indirect, 59.6%; combined, 4.0%
- Size of defect (cm): < 1.5, 33.1%; 1.5–3.0, 60.3%; > 3.0, 6.6%
- Preoperative use of analgesia: 23·2%
- Preoperative pain score (VAS), mean (SD): 4.0(2.5)
- Duration of symptoms (months), mean (SD): 28 (58)

Interventions	Lichtenstein inguinal hernioplasty with 9 × 13 cm trimmed lightweight polypropylene mesh (Optilene® 60 gr/m^2; B. Braun, Melsungen, Germany). Glue group: • Butyl-2-cyanoacrylate tissue glue (Glubran®; GEM, Viareggio, Italy). Suture group: • Absorbable polyglycolic acid 3/0 sutures (Dexon®).
Outcomes	Recurrences, chronic pain, postoperative complications (e.g. haematoma, infection), length of operation, time to discharge, recovery time to normal activity
Notes	Handling of nerves: • The ilioinguinal, genitofemoral and iliohypogastric nerves were identified and preserved, if possible. Care was taken not to include the nerves within the sutures. Length of follow-up: 1 year. Time points of the analysis: 3 months for chronic pain and 1 year for recurrence. Intention-to-treat analysis:no. The number of participants randomized: 151 in Glue group; 151 in Suture group The number of participants evaluated: 144 in Glue group; 142 in Suture group In people with bilateral hernia, each one was treated individually; the second operation began when the first had finished in order to time each operation precisely. NCT00659542 (http://www.clinicaltrials.gov). The costs of research nurses and other technical assistants were covered by the hospitals' research funds. No financial or material support was received from any commercial company. The authors declare no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done separately in each participating center."; "Treatment allocation was by means of sealed, numbered envelopes opened in sequence."

Paajanen 2011 *(Continued)*

		Comment: probably done, since report from the same investigators in the same period was published on JAMA (APPAC trial, NCT01022567), and this study has also been registered. The registration number is NCT00659542 (http://www.clinicaltrials.gov).
Allocation concealment (selection bias)	Low risk	Treatment allocation was by means of sealed, numbered envelopes opened in sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The staff who conducted the postoperative assessment and the participants themselves were blinded to the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The staff who conducted the postoperative assessment and the participants themselves were blinded to the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of missing outcomes was comparable between 2 groups (144/151 in the cyanoacrylate glue group and 142/151 in the suture group completed 1-year follow-up).
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Low risk	The source of funding was a hospitals' research funds. No financial or material support was received from any commercial company. The source of funding was a medical foundation and we consider this trial to be free from risk of 'source of funding' bias.

Dabrowiecki 2012

Methods	A randomized, double-blind single-centre study. Randomization was prepared with the use of software available at www.randomization.com (1st generator was employed). Both participants and evaluators were blinded. Unilateral hernia. Country: Poland. Setting: Department of General and Endocrine Surgery, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz. Enrolment dates: from July 2008 to November 2010.
Participants	Inclusion criteria: • Men, age ≥ 21 years, with primary inguinal hernia (in case of contralateral hernia, one side was selected for the study). Exclusion criteria: • Men aged below 21 years, with a recurrent or incarcerated hernia, after attempted reduction of a hernia (with hospital stay), with a postoperative scar in the area of the planned procedure, cryptorchism, varices of the spermatic cord (clinical trial – no such cases were observed), degenerative spine diseases or other pathologies causing pain radiating to the abdomen and groin were excluded from the study. Men who did not fully understand the nature of the study or did not give their consent to participate were also excluded.

Dabrowiecki 2012 *(Continued)*

	100% unilateral; Glue group: • 20 participants • 47.4 ±13.4 years • 60% direct • 40% indirect • Right:left: 10:10 • Width of hernia ring 1/2/3 fingers: 8/8/4 Suture group: • 21 participants • 45.4 ±14.8 years • 71.4% indirect • 23.8% direct • 4.8% both • Right:left: 11:10 • Width of hernia ring 1/2/3 fingers: 11/8/2
Interventions	Lichtenstein inguinal hernioplasty with Prolene (Ethicon) polypropylene mesh sized 15 cm × 7 to 10 cm was employed (its transverse size adapted to participant's anatomy). Glue group: • Glubran sealant (N-butyl-2-cyanoacrylate; GEM S.r.l., Viareggio, Italy). Suture group: • The mesh was fixed to the inguinal ligament with the continuous 2-0 polypropylene suture, and to the aponeurosis of the internal oblique muscle with single 2-0 PDS sutures.
Outcomes	Length of hospital stay, recovery time to normal activity, chronic pain, hernia recurrence
Notes	Handling of nerves: • Ilioinguinal nerve, hypogastric nerve and genital branch of genitofemoral nerve were always identified. Length of follow-up: 16.7 months. Time points of the analysis: 80 days for chronic pain and the last day of follow-up for recurrence. Intention-to-treat analysis: yes. The number of participants randomized: 20 in Glue group; 21 in Suture group The number of participants evaluated: 20 in Glue group; 21 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was prepared with the use of software available at www.randomization.com (1st generator was employed).

Dabrowiecki 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Probably done. During mesh fixation stage, randomly chosen envelope was opened.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	During mesh fixation stage, randomly chosen envelope was opened and the information was discreetly passed to the surgeon so that the conscious participant would not be aware of the surgeon's proceedings. Data concerning mesh fixation were gathered in a separate database, but were excluded from the surgical protocol, participant's history and release form.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were evaluated during follow-up appointments by a surgeon who did not know the method used and had no access to documentation.
Incomplete outcome data (attrition bias) All outcomes	High risk	A large proportion of participants (10/41) were lost to follow-up and the authors did not give the numbers in each group.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Bracale 2012

Methods	Prospective multicentric parallel randomized controlled trial. A randomization was achieved by computer-generated random numbers. The participants were blinded to group assignment. Unilateral hernia. Country: Italy. Setting: 3 hospitals in 3 different Italian towns: University Hospital "Federico II" in Naples, "San Camillo" Hospital in Trento and Cairo Montenotte Hospital. Enrollment dates: from January 2009 to June 2010.
Participants	Inclusion criteria: • Adult subjects (≥ 18 years) of both genders with primary uncomplicated inguinal hernia (classified by Rutkow and Robbins classification) suitable for LT were included in this study. Exclusion criteria: • Immunological or coagulation disorders, steroid therapy and psychiatric disorders, and refusal to give informed consent. Glue group: • 50 participants • Median age: 59 yrs. • Male: 96% • ASA: I (52%); II (36%); III (12%) • Median BMI: 25.97 • Hernia location: Right (58%); Left (42%) • Direct:indirect: not reported. • Hernia classification: I (38%); II (32%); IV (30%)

Bracale 2012 *(Continued)*

	Suture group: • 52 participants • Median age: 56 yrs. • Male: 94% • ASA: I (56%); II (38%); III (6%) • Median BMI: 25.86 • Hernia location: Right (53.9%); Left (46.1%) • Direct:indirect: not reported. • Hernia classification: I (28.8%); II (28.8%); IV (36.5%); V (5.8%)
Interventions	Lichtenstein inguinal hernioplasty with ULTRAPRO® (Ethicon Products, Sommerville NJ, USA A semi-absorbable lightweight mesh), 11 cm × 6 cm. Glue group: • Fibrin sealant (QUIXIL®, Omrix Biopharmaceuticals S.A., Belgium); Suture group: • Prolene N° 3–0
Outcomes	Recurrences, chronic pain, numbness, overall postoperative complications (e.g. haematoma, ecchymosis, seroma, infection), length of operation, time to discharge, cost analysis
Notes	Handling of nerves: • Nerves are preserved if possible. Length of follow-up: 15 month (range 12 to 18). Time points of the analysis: 6 months for chronic pain and the last day of follow-up for recurrence. Intention-to-treat analysis: yes. The number of participants randomized: 50 in Glue group; 52 in Suture group The number of patients evaluated: 50 in Glue group; 52 in Suture group Information from publication only. The authors declare that they have no conflict of interest. No details of funding sources provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomization was achieved by computer-generated random numbers with block sizes and an allocation ratio of 1:1 that allowed balance recruitment within each centre.
Allocation concealment (selection bias)	Low risk	The random allocations were placed into shuffled, numbered, sealed, opaque envelopes at the beginning of the study before the inclusion of the first subject. The envelopes were opened during the operation just before mesh fixation.
Blinding of participants and personnel (performance bias)	Low risk	The participants were blinded to group assignment.

Bracale 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was a single-blinded study as the evaluators were not completely blinded to treatment. Evaluators for post discharge and follow-up outcomes were blinded, but some surgeons participated in the evaluation process.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of missing outcomes compared with observed event was not big enough to have a clinically relevant impact on the intervention effect estimate (Only 2 participants were lost to follow-up at the twelfth month)
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources.

Campanelli 2012

Methods	Randomized, controlled, participant- and evaluator-blinded study enrolled people from 7 centres in 7 European countries. Unilateral hernia. Country: 7 European countries — Italy, France, Spain, Germany, UK, Belgium, Denmark. Setting: 7 centres in 7 European countries — Department of Surgical Sciences, University of Insubria-Varese, Multimedica Santa Maria Hospital, Castellanza, Varese, Italy; Hospital Universitario 12 de Octubre, Madrid, Spain; Hernienpraxis-Mainz, Mainz, Germany; Department of Surgery, Herlev Hospital, University of Copenhagen, Herlev, Denmark; CH Jean Verdier, Bondy, France; Peninsula Medical School, Derriford Hospital, Plymouth, UK; and Department of Abdominal Surgery, Gasthuisberg University Hospital, Leuven, Belgium. Enrolment dates: started in January 2006 and ended in April 2007, with last study visit on 25 May 2008.
Participants	Inclusion criteria: • Men aged between 18 and 80 years who were active (normal daily activities); diagnosed with an uncomplicated unilateral primary inguinal hernia or an uncomplicated bilateral hernia (L1–L2 or M1–M2 according to the EHS Groin Hernia Classification), provided that only 1 hernia was operated upon during the 12 months of study follow-up; eligible for elective inguinal hernia repair using the Lichtenstein technique. Exclusion criteria: • Recurrent, scrotal, incarcerated, or femoral hernia; large hernia (L3 or M3 EHS Groin Hernia Classification); body mass index (BMI) ≥ 35 kg/m2; concomitant abdominal surgery; ongoing long-term analgesic or steroid treatment; previous treatment or hypersensitivity to bovine aprotinin; people receiving clopidogrel or warfarin therapy (unless therapy is interrupted and changed to low-molecular-weight heparin); known abuse of alcohol or drugs; Child-Pugh class C hepatic cirrhosis; known immunodeficiency; severely compromised health which, in the opinion of the investigator, was likely to affect participant compliance; and having received another investigational drug or device within the previous 30 days. 158 participants in each group. Median age: 59.0 yrs. BMI, Mean (SD): 25.5 (2.7) General health: ASA I/II 95.6%

Campanelli 2012 *(Continued)*

	Level of activity: • Sportive—professional or leisure 50.6% • Non-sportive 49.4% Employed (full/part time): 63.5% Smoker: 23.1% Hypertension: 44.5% Hypercholesterolemia: 9.1% Based on the EHS classifications: 23% were L1, 13% M1, 33% L2,and 30% M2 Direct:indirect: not reported. Right:left: not reported.
Interventions	Lichtenstein inguinal hernioplasty with 8 cm × 15 cm macro-porous, heavyweight polypropylene flat mesh. Glue group: • Tissucol/Tisseel: 2 mL of Tissucol/Tisseel was prepared according to the manufacturer's instructions (Baxter Healthcare, Deerfield, IL, United States; 1 mL of fibrinogen and 1 mL of thrombin solution). Before the mesh was positioned, 0.5 mL of fibrin sealant was applied drop-wise using the Duploject device provided by the manufacturer (no spraying) on the pubic tubercle and the mesh pressed on it for 2 minutes. The remainder (1.5 mL) was sprayed over the entire surface of the mesh in a thin layer. Suture group: • The mesh was fixed with sutures as described for the classical Lichtenstein technique, that is, with running suture fixation to the inguinal ligament with polypropylene 2/0 and resorbable interrupted sutures on internal oblique muscle aponeurosis.
Outcomes	Chronic pain and/or numbness and/or groin discomfort, hernia recurrence, intraoperative complications, postoperative complications, duration of surgery, hospital stay, time to return to normal activities, quality of life
Notes	Handling of nerves: • Nerves were preserved if possible. Handling of ilioinguinal, iliohypogastric, and genitofemoral nerves was comparable: recognition (98.1 vs 97.5%) and preservation (80.3 vs 76.6%), in the fibrin sealant and suture group respectively. Length of follow-up: 1 year. Time points of the analysis: 6 months for chronic pain and 1 year for recurrence. Intention-to-treat analysis:yes. The number of participants randomized: 158 in Glue group; 158 in Suture group The number of participants evaluated: 158 in Glue group; 158 in Suture group Italy, France, Spain, Germany, UK, Belgium, Denmark NCT00306839 (http://www.clinicaltrials.gov). The fibrin sealant group had slightly more smokers than the sutures group (27.8% vs 18.4%, P = 0.045 [Chi^2 test]). Information from publication only.

Campanelli 2012 *(Continued)*

	This study was funded by Baxter Healthcare. No declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by means of computerized randomization, in block sizes of 2, 4, or 6. The randomization procedure was stratified on the basis of the study site to ensure balance between study groups at each site.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and evaluators were blinded to the method of surgical fixation. Surgical staff members were not permitted to divulge this information to participants or other staff.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All VAS scores were ascertained by a blinded evaluator, who explained the scale to participants verbally.
Incomplete outcome data (attrition bias) All outcomes	High risk	Though the proportion of missing outcomes was comparable and not big enough to have a clinically relevant impact on the intervention effect estimate between 2 groups (2/151 in the fibrin sealant group and 2/157 in the sutures group), 7 participants in the fibrin sealant group and 1 in the sutures group were excluded due to major protocol violations after randomization.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	High risk	This study was funded by Baxter Healthcare, which is a manufacturer producing the fibrin sealant. So we consider this trial with high risk of 'source of funding' bias.

Kim-Fuchs 2012

Methods	Two-armed randomized trial. Randomized by numbered sealed envelopes. The trial was unblinded. Unilateral hernia. Country: Switzerland. Setting: Kantonspital Aarau, Switzerland. Enrolment dates: between January 2001 and December 2004.
Participants	Inclusion criteria: • Male, age over 25 years, primary unilateral hernia, elective surgery, and hernias classified as LIII, MII, MIII and ML. Exclusion criteria: • Age < 25 years, emergency, recurrent hernia, femoral hernia, size of defect (LI, LII, MI), hydrocele or varicocele on hernia side, infected operation field, immune deficiency.

Kim-Fuchs 2012 *(Continued)*

	131 participants with mean age of 55.1 (28 to 85) years in Glue group 133 participants with mean age of 56.8 (25 to 83) years in Suture group. Sex: not reported. Direct:indirect: not reported. Right:left: not reported.
Interventions	Lichtenstein inguinal hernioplasty with VIPRO II (lightweight, Ethicon, Johnson & Johnson Medical Products, Vienna, Austria). Glue group: • Histoacryl® (Braun Medical, Sempach, Switzerland); Suture group: • PDS 2.0 (polydioxanone; Ethicon);
Outcomes	Haematoma, hospital stay, hypersthesia, chronic pain, hernia recurrence, hospital length of stay, length of operation, mesh infection.
Notes	Handling of nerves: • For most of the participants, the nerves were identified and preserved during surgery. Length of follow-up: 5 years. Time points of the analysis: 3 months for chronic pain and 5 year for recurrence. Intention-to-treat analysis: no. The number of participants randomized: 131 in Glue group; 133 in Suture group The number of participants evaluated: 129 in Glue group; 131 in Suture group Registered with the Swiss Federal Office of Public Health (SFOPH-99-0021). Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear.
Allocation concealment (selection bias)	Low risk	Randomized by numbered sealed envelopes. The envelope was opened intraoperatively after the hernia was classified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was unblinded.

Kim-Fuchs 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	After 3 months, 2 participants in each group were lost to follow-up, after 12 months 13 in group I and 17 in group II. After 5 years, 33 participants were lost in group I and 41 in group II. But the proportion of missing outcomes is comparable between the 2 groups.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Shen 2012

Methods	Randomized, single-blind study. Randomized using a computerized randomization process. All participants were blinded to the allocation. Unilateral hernia. Country: China. Setting: Hernia and Abdominal Wall Surgery department of Beijing Chao-Yang Hospital, Capital Medical University. Enrolment dates: between January 2010 and April 2010.
Participants	Inclusion criteria: • (1) clinical diagnosis of primary unilateral inguinal hernia; (2) age > 18 years; and (3) no significant cardiopulmonary, hepatic, or renal impairment, and no contraindications for surgery. Exclusion criteria: • (1) bilateral inguinal hernia, recurrent hernia, and incarcerated hernia; (2) allergy to multiple classes of drugs, recent allergic disease, or use of drugs that are known harmful to vital organs during the 4 weeks before surgery; (3) participation in other clinical studies in the 3 months before surgery; (4) atopic allergy history; (5) mental illness history; (6) disease that may significantly increase IAP (Intra-abdominal pressure) and cannot be effectively controlled, such as severe ascites, severe asthma caused by bronchitis, pulmonary emphysema, or urine retention caused by significant benign prostatic hyperplasia (BPH); and (7) infection located at the surgical site or bacteremia. Body mass index: 25 ± 2 Glue group: • 55 participants • 63 ± 10 years old • 81.8% Male • Cerebral or cardiovascular disease: 18.2% • Diabetes: 16.4% • Other diseases related to increased IAP: 36.4% • 85.5% indirect • 14.5% direct • Right:left: not reported • Size: 2 cm ± 1 cm Suture group: • 55 participants • 60 ± 12 years old

Shen 2012 *(Continued)*

- 85.5% Male
- Cerebral or cardiovascular disease: 14.5%
- Diabetes: 21.8%
- Other diseases related to increased IAP: 32.7%
- 89.1% indirect
- 10.9% direct
- Right:left: not reported
- Size: 3 cm ± 1cm

Interventions	Lichtenstein inguinal hernioplasty with lightweight polypropylene mesh (ProLite-Ultra Mesh Sheets, 7.5 cm × 15 cm, weight 52 gr/m^2, lightweight; Atrium Medical Co., Hudson, NH). Glue group: • n-butyl-2-cyanoacrylate (NBCA) medical adhesive gel (Compont Medical Adhesive, 0.5 mL/tube; Beijing Compont Medical Devices Co., Ltd., Beijing, China) Suture group: • 2-0 Prolene suture (Ethicon; Johnson & Johnson, New Brunswick, NJ)
Outcomes	chronic pain, hernia recurrence, haematoma, operative duration, length of stay, wound infection.
Notes	Handling of nerves: • The major nerves dominating the inguinal area, such as the iliohypogastric and ilioinguinal nerve, were identified and selectively anesthetized and protected. Length of follow-up: mean of 13 ± 1 months. Time points of the analysis: 3 months for chronic pain and the last day of follow-up for recurrence. Intention-to-treat analysis: yes. The number of participants randomized: 55 in Glue group; 55 in Suture group The number of patients evaluated: 55 in Glue group; 55 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using a computerized randomization process.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to the allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind study.

Shen 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and any declarations of interest.

Moreno-Egea 2014

Methods	Randomized, single-blind trial. Unilateral hernia. Country: Spain. Setting: Ambulatory Abdominal Wall Unit of Morales Meseguer University Hospital in Murcia, Spain. Enrolment dates: between January 2008 and January 2011.
Participants	Inclusion criteria: • Age > 18 years old; clinical diagnosis of primary inguinal hernia, and no comorbidity (no significant cardiopulmonary, hepatic, or renal impairment). The unilateral inguinal hernias were selected for open repair (Open study). Exclusion criteria: • People with incarcerated or strangulated hernia; known femoral hernia; scrotal hernia; those receiving corticosteroid therapy, radiotherapy, or chemotherapy; concurrent neoplasms; proven mental illness or other circumstances that might compromise the participant's cooperation; and those who refused to give informed consent. Glue group: • 50 participants • Mean age: 57 yrs • Male: 68% • Mean BMI: 29.3 • Type of hernia: Indirect: 80%; Direct: 20% • Right:left: not reported Suture group: • 52 participants • Mean age: 55 yrs • Male: 71.2% • Mean BMI: 29.8 • Type of hernia: Indirect: 82.7%; Direct: 17.3% • Right:left: not reported
Interventions	Under local anaesthetic, a standard Lichtenstein technique was performed with a lightweight polypropylene-coated titanium mesh, 35 gr/m2 (Pfm, Cologne, Germany). Glue group:

Moreno-Egea 2014 *(Continued)*

- The surgical management of the site, hernia, sac, and the position of the mesh were the same, but this was fixed to the pubis, inguinal ligament, and internal oblique muscle with 8 well-spaced drops of glue (Ifabond, Fimed, France). The rest of the planes (aponeurosis of the external oblique, Scarpa, and skin) were also closed with adhesive.
- The cyanoacrylate monomer, n-hexyl-α-cyanoacrylate (Ifabond, Fimed, France) was used.

Suture group:

- The mesh was fixed with two interrupted 2/0 prolene sutures (Ethicon; Johnson & Johnson, New Brunswick, NJ), the aponeurosis of the external oblique muscle with 0 prolene sutures, and the skin with staples.

Outcomes	The primary endpoints were pain and recurrence. Secondary endpoints were morbidity, operating time (minutes), need for oral analgesia (days), and the time required to return to normal activities (days).
Notes	Handling of nerves: • The iliohypogastric, genitofemoral, and ilioinguinal nerves were identified and protected. Length of follow-up: 15 months. Time points of the analysis: 3 months for chronic pain and the last day of follow-up for recurrence. Intention-to-treat analysis: yes. The number of participants randomized: 50 in Glue group; 52 in Suture group The number of participants evaluated: 50 in Glue group; 52 in Suture group Information from publication only. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The author(s) received no financial support for the research, authorship, and/or publication of this article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was achieved by a computer program.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to the allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Detailed information about the participants lost during monitoring was not presented.
Selective reporting (reporting bias)	High risk	In Method section, it is recorded that secondary endpoints were morbidity, operating time (minutes), need for oral analgesia (days), and the time required

Moreno-Egea 2014 *(Continued)*

		to return to normal activities (days). But the Result section did not include the time required to return to normal activities (days).
Other bias	Low risk	The author declared no potential conflicts of interest and no financial support.

Damiano 2014

Methods	Prospective, observational, randomized study. Unilateral hernia. Country: Italy. Setting: not reported. Enrollment dates: between January 2004 and February 2010.
Participants	Inclusion criteria: • Primary unilateral inguinal hernia repair. Exclusion criteria: • Recurrent and femoral hernia, urgent cases, metabolic diseases (diabetes and obesity), people in oral anticoagulant treatment and no more than 2 years of symptomatic hernias. Glue group: • 216 participants • Mean age: 52.94 yrs • Sex: not reported • Right:left: not reported • Type of hernia: indirect: 74%; direct: 15%; combined: 11% Suture group: • 252 participants • Mean age: 55.1 yrs • Sexual: not reported • Right:left: not reported • Type of hernia: indirect: 74%; direct: 20%; combined: 6%
Interventions	The suture group hernia repair was performed as described by Lichtenstein. Glue group: • The mesh was fixed to the posterior wall of the inguinal canal and to the inguinal ligament by applying the HFG (Human Fibrin Glue – Tissucol®, Baxter Healthcare, Deerfield, IL, USA) over the mesh surface. Successively the edges of external aponeurosis were approximated and the HFG was applied to allow the complete closure. Suture group: • The mesh was secured by running 3/0 polypropylene and interrupted 3/0 Dexon® (Davis-Geck, Wayne, NJ, USA) to the inguinal ligament and to the internal oblique and transverse muscles, respectively.
Outcomes	For all the participants the following parameters were recorded: operative time, intra-operative and post-operative complications, first and seventh postoperative-day pain according to a 0 to 10 numeric rate scale (NRS) (14 to 20), persistent pain and recurrences.

Damiano 2014 *(Continued)*

Notes	Handling of nerves: • Not clear. Length of follow-up: 12 months. Time points of the analysis: 12 months. Intention-to-treat analysis: yes. The number of participants randomized: 216 in Glue group; 252 in Suture group The number of patients evaluated: 216 in Glue group; 252 in Suture group Information from publication only. No details of funding sources and any declarations of interest provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was achieved by a blind draw.
Allocation concealment (selection bias)	Unclear risk	Not clear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear.
Selective reporting (reporting bias)	Low risk	It is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Not clear. Without details of funding sources and conflicts of interest.

Characteristics of excluded studies [ordered by year of study]

Study	Reason for exclusion
Campanelli 2008	Data reprised in Campanelli 2012.
Stabilini 2010	Not a controlled study. Besides the method of fixation, 2 groups applied different kinds of meshes.
Testini 2010	It did not meet inclusion criteria. All the participants underwent the plug and mesh procedure rather than Lichtenstein's.

Study	Reason for exclusion
Arslani 2010	Not a controlled study. Besides the method of fixation, 2 groups applied different kinds of meshes.
Torcivia 2011	It did not meet inclusion criteria. Two groups applied different kinds of meshes with a natural beta-D-glucan coating.
Negro 2011	Not a randomized study.
Shen 2011	Not a randomized study.
Lionetti 2012	It did not meet inclusion criteria. All the participants underwent the plug and mesh procedure rather than Lichtenstein's.
Eldabe Mikhail 2012	It did not meet inclusion criteria. All the participants underwent the plug and mesh procedure rather than Lichtenstein's.
Sözen 2012	Not a randomized study.
Campanelli 2014	Data reprised in Campanelli 2012.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bar 2009

Methods	Not stated in the available abstract.
Participants	60 participants with unilateral inguinal hernia.
Interventions	BioGlue™ versus conventional suture for mesh fixation.
Outcomes	Postoperative pain intensity, relapse, mesh infection, wound infection.
Notes	Awaiting full text.

Ronka 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	It included participants with recurrent hernia; we could not extract the data of participants with primary inguinal hernia. Contact with the authors was also failed. We are still trying to receive additional information from the authors.

Wajid 2015

Methods	It is a descriptive case series. 300 participants were selected by non-probability, consecutive sampling and were divided into 2 groups randomly by using lottery method.
Participants	Clinically reducible inguinal hernia.
Interventions	Lichtenstein repair vs sutureless repair.
Outcomes	Hematoma and postoperative pain within 7 days.
Notes	The method of this study is not specific and comprehensive enough: the full text did not tell us whether the sutureless repair group had some kind of glue applied. We have tried to contact the authors but without any answer. We are not sure whether this study fulfilled the inclusion criteria.

DATA AND ANALYSES

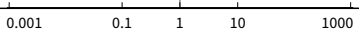
Comparison 1. Glue versus suture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chronic pain	10	1473	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.91]
1.1 Synthetic glue versus suture	7	945	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.46, 1.04]
1.2 Biological glue versus suture	3	528	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.03]
2 Hernia recurrence	12	1987	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.63, 3.28]
2.1 Synthetic glue versus suture	8	991	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.62, 4.05]
2.2 Biological glue versus suture	4	996	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.17, 5.90]
3 Duration of operation (mins)	9	1790	Mean Difference (IV, Random, 95% CI)	-3.13 [-4.48, -1.78]
3.1 Synthetic glue versus suture	6	904	Mean Difference (IV, Random, 95% CI)	-3.67 [-6.10, -1.24]
3.2 Biological glue versus suture	3	886	Mean Difference (IV, Random, 95% CI)	-2.72 [-3.67, -1.77]
4 Wound/superficial infection	7	818	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.37, 4.11]
4.1 Synthetic glue versus suture	5	606	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.37, 4.11]
4.2 Biological glue versus suture	2	212	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Mesh/deep infection	8	1448	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.16, 2.83]
5.1 Synthetic glue versus suture	5	768	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.14]
5.2 Biological glue versus suture	3	680	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.11, 3.19]
6 Haematoma	10	1439	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.31, 0.86]
6.1 Synthetic glue versus suture	7	911	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.32, 0.91]
6.2 Biological glue versus suture	3	528	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.13]
7 Seroma	8	1239	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.51, 1.33]
7.1 Synthetic glue versus suture	4	243	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.14, 4.02]
7.2 Biological glue versus suture	4	996	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.51, 1.37]
8 Persisting numbness	4	728	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.14]
8.1 Synthetic glue versus suture	2	310	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.46, 1.32]
8.2 Biological glue versus suture	2	418	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.31]
9 Postoperative length of hospital stay (days)	6	1009	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.35, 0.10]
9.1 Synthetic glue versus suture	5	541	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.54, 0.12]
9.2 Biological glue versus suture	1	468	Mean Difference (IV, Random, 95% CI)	0.0 [-0.00, 0.00]
10 Recovery time to daily activities (days)	3	403	Mean Difference (IV, Random, 95% CI)	-1.26 [-1.89, -0.63]
10.1 Synthetic glue versus suture	2	87	Mean Difference (IV, Random, 95% CI)	-1.87 [-2.86, -0.88]
10.2 Biological glue versus suture	1	316	Mean Difference (IV, Random, 95% CI)	-1.0 [-1.26, -0.74]

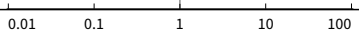
Analysis 1.1. Comparison 1 Glue versus suture, Outcome 1 Chronic pain.

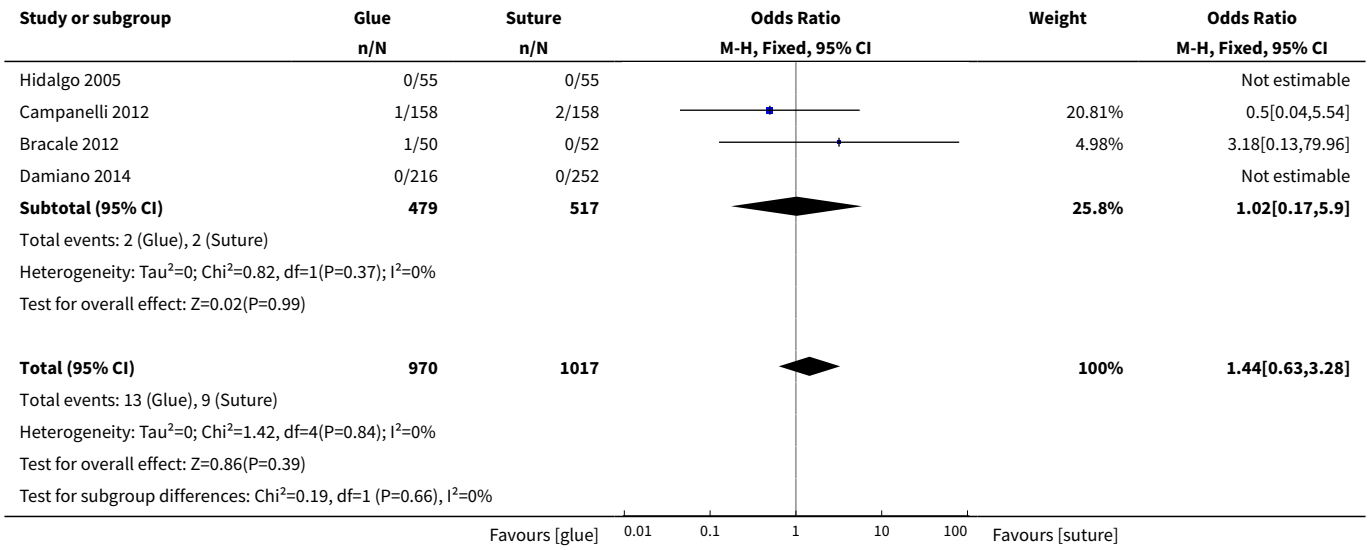
Study or subgroup	Glue n/N	Suture n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Synthetic glue versus suture					
Helbling 2003	1/22	3/24		3.68%	0.33[0.03,3.47]
Jain 2009	0/40	5/40		7.3%	0.08[0,1.49]
Paajanen 2011	29/151	22/151		23.87%	1.39[0.76,2.56]
Shen 2012	0/55	6/55		8.65%	0.07[0,1.25]
Kim-Fuchs 2012	13/131	21/133		25.21%	0.59[0.28,1.23]
Dabrowiecki 2012	0/20	1/21		1.92%	0.33[0.01,8.67]
Moreno-Egea 2014	0/50	3/52		4.57%	0.14[0.01,2.78]
Subtotal (95% CI)	**469**	**476**		**75.2%**	**0.69[0.46,1.04]**
Total events: 43 (Glue), 61 (Suture)					
Heterogeneity: Tau^2=0; Chi^2=11.52, df=6(P=0.07); I^2=47.92%					
Test for overall effect: Z=1.79(P=0.07)					
1.1.2 Biological glue versus suture					
Hidalgo 2005	0/55	1/55		2%	0.33[0.01,8.21]
Bracale 2012	0/50	0/52			Not estimable
Campanelli 2012	9/158	18/158		22.8%	0.47[0.2,1.08]
Subtotal (95% CI)	**263**	**265**		**24.8%**	**0.46[0.2,1.03]**
Total events: 9 (Glue), 19 (Suture)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=1.9(P=0.06)					
Total (95% CI)	**732**	**741**		**100%**	**0.63[0.44,0.91]**
Total events: 52 (Glue), 80 (Suture)					
Heterogeneity: Tau^2=0; Chi^2=12.79, df=8(P=0.12); I^2=37.47%					
Test for overall effect: Z=2.47(P=0.01)					
Test for subgroup differences: Chi^2=0.78, df=1 (P=0.38), I^2=0%					



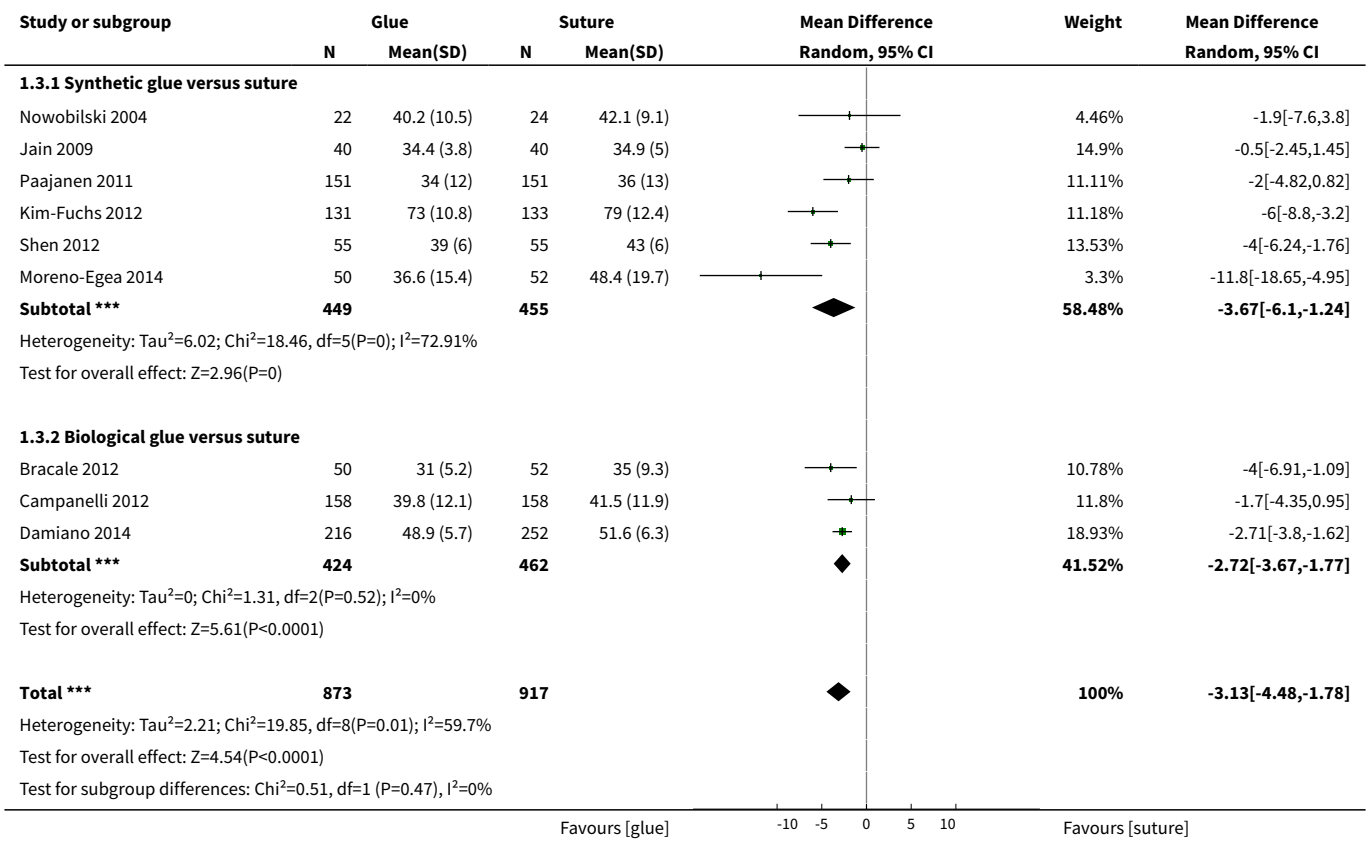
Analysis 1.2. Comparison 1 Glue versus suture, Outcome 2 Hernia recurrence.

Study or subgroup	Glue n/N	Suture n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Synthetic glue versus suture					
Helbling 2003	0/22	0/24			Not estimable
Nowobilski 2004	0/22	0/24			Not estimable
Jain 2009	0/40	0/40			Not estimable
Paajanen 2011	2/151	2/151		20.67%	1[0.14,7.19]
Shen 2012	0/55	0/55			Not estimable
Dabrowiecki 2012	1/20	0/21		4.75%	3.31[0.13,86.06]
Kim-Fuchs 2012	8/131	5/133		48.79%	1.67[0.53,5.23]
Moreno-Egea 2014	0/50	0/52			Not estimable
Subtotal (95% CI)	**491**	**500**		**74.2%**	**1.58[0.62,4.05]**
Total events: 11 (Glue), 7 (Suture)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					
1.2.2 Biological glue versus suture					



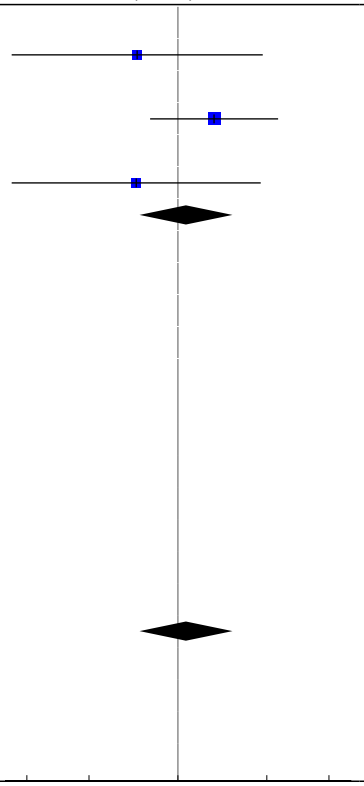


Analysis 1.3. Comparison 1 Glue versus suture, Outcome 3 Duration of operation (mins).



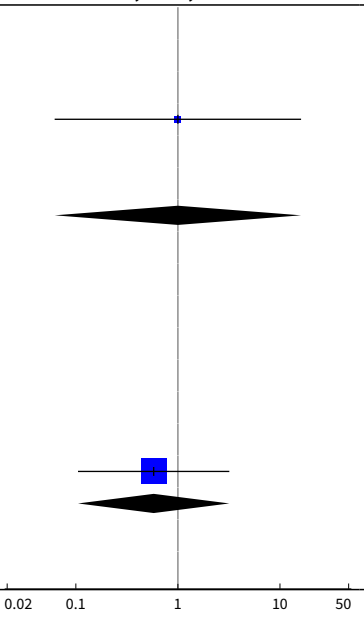
Analysis 1.4. Comparison 1 Glue versus suture, Outcome 4 Wound/superficial infection.

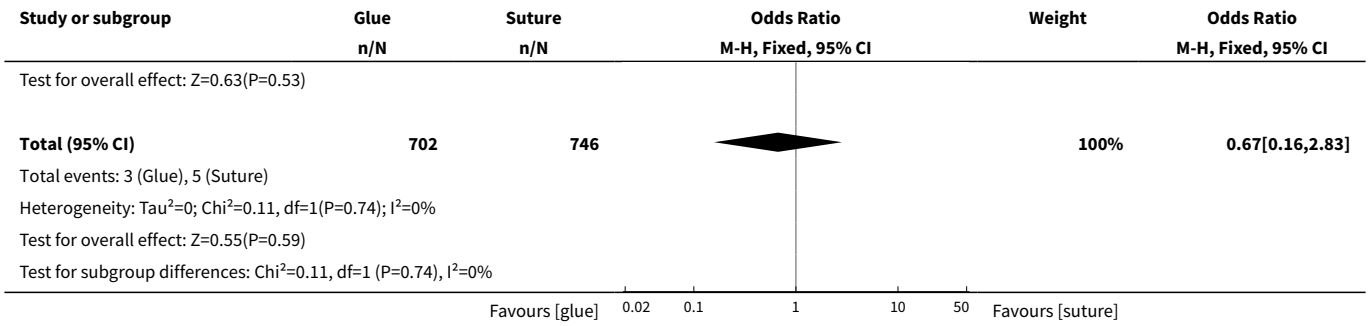
Study or subgroup	Glue n/N	Suture n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Synthetic glue versus suture					
Helbling 2003	0/22	1/24		29.32%	0.35[0.01,9]
Nowobilski 2004	0/22	0/24			Not estimable
Paajanen 2011	5/151	2/151		40.31%	2.55[0.49,13.36]
Shen 2012	0/55	0/55			Not estimable
Moreno-Egea 2014	0/50	1/52		30.37%	0.34[0.01,8.54]
Subtotal (95% CI)	**300**	**306**		**100%**	**1.23[0.37,4.11]**
Total events: 5 (Glue), 4 (Suture)					
Heterogeneity: Tau²=0; Chi²=1.94, df=2(P=0.38); I²=0%					
Test for overall effect: Z=0.34(P=0.73)					
1.4.2 Biological glue versus suture					
Hidalgo 2005	0/55	0/55			Not estimable
Bracale 2012	0/50	0/52			Not estimable
Subtotal (95% CI)	**105**	**107**			**Not estimable**
Total events: 0 (Glue), 0 (Suture)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**405**	**413**		**100%**	**1.23[0.37,4.11]**
Total events: 5 (Glue), 4 (Suture)					
Heterogeneity: Tau²=0; Chi²=1.94, df=2(P=0.38); I²=0%					
Test for overall effect: Z=0.34(P=0.73)					
Test for subgroup differences: Not applicable					



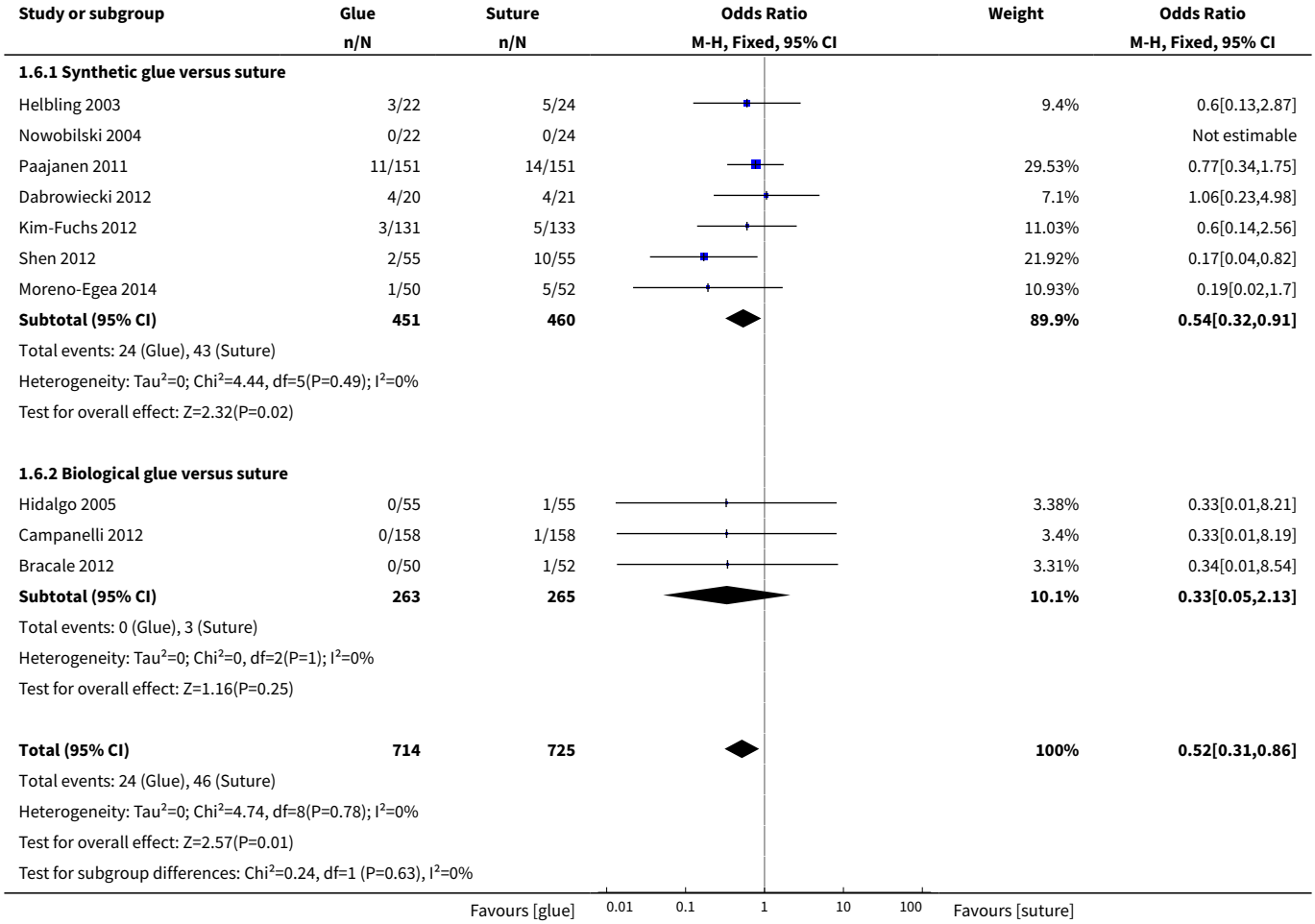
Analysis 1.5. Comparison 1 Glue versus suture, Outcome 5 Mesh/deep infection.

Study or subgroup	Glue n/N	Suture n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Synthetic glue versus suture					
Helbling 2003	0/22	0/24			Not estimable
Nowobilski 2004	0/22	0/24			Not estimable
Paajanen 2011	1/151	1/151		21.36%	1[0.06,16.14]
Shen 2012	0/55	0/55			Not estimable
Kim-Fuchs 2012	0/131	0/133			Not estimable
Subtotal (95% CI)	**381**	**387**		**21.36%**	**1[0.06,16.14]**
Total events: 1 (Glue), 1 (Suture)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.5.2 Biological glue versus suture					
Hidalgo 2005	0/55	0/55			Not estimable
Bracale 2012	0/50	0/52			Not estimable
Damiano 2014	2/216	4/252		78.64%	0.58[0.11,3.19]
Subtotal (95% CI)	**321**	**359**		**78.64%**	**0.58[0.11,3.19]**
Total events: 2 (Glue), 4 (Suture)					
Heterogeneity: Not applicable					

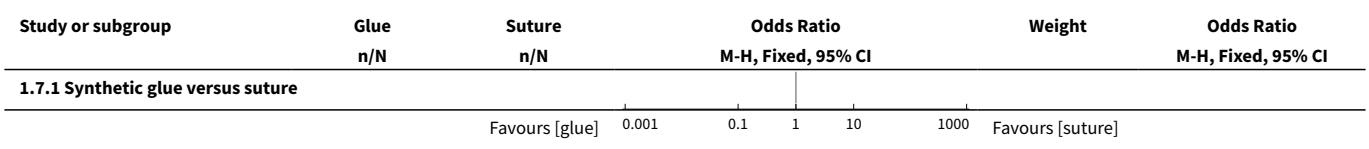


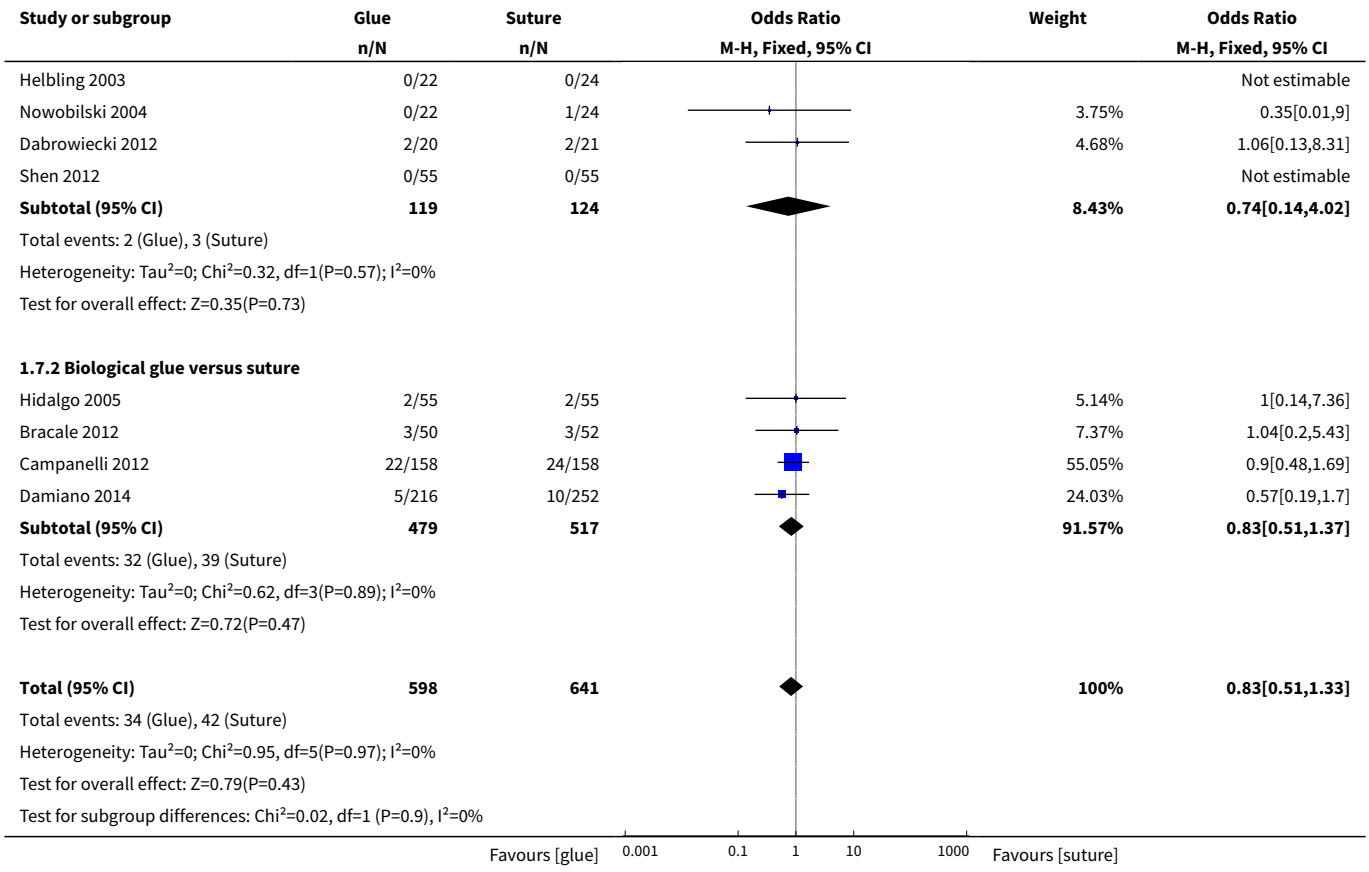


Analysis 1.6. Comparison 1 Glue versus suture, Outcome 6 Haematoma.

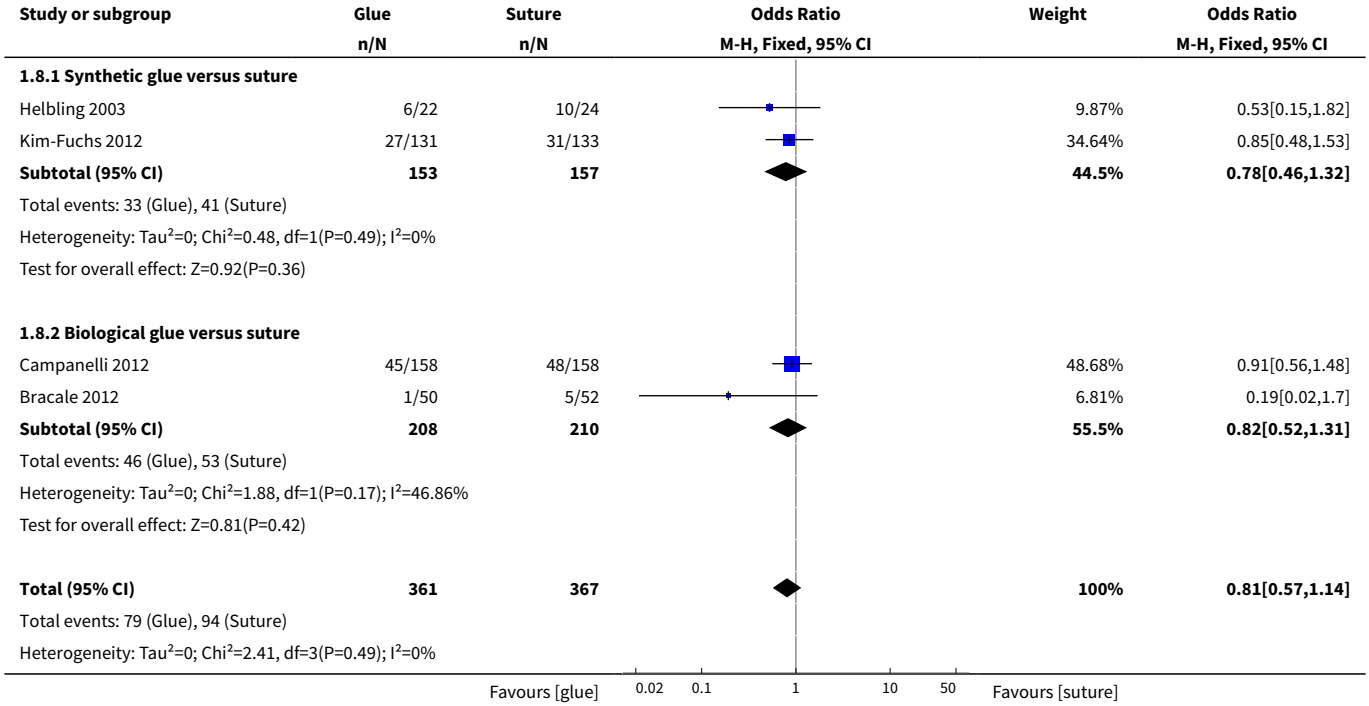


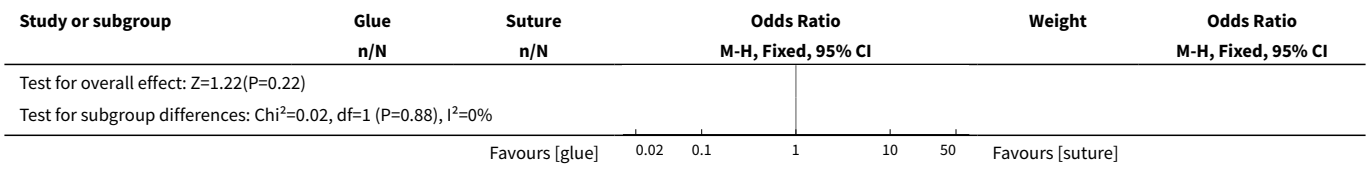
Analysis 1.7. Comparison 1 Glue versus suture, Outcome 7 Seroma.



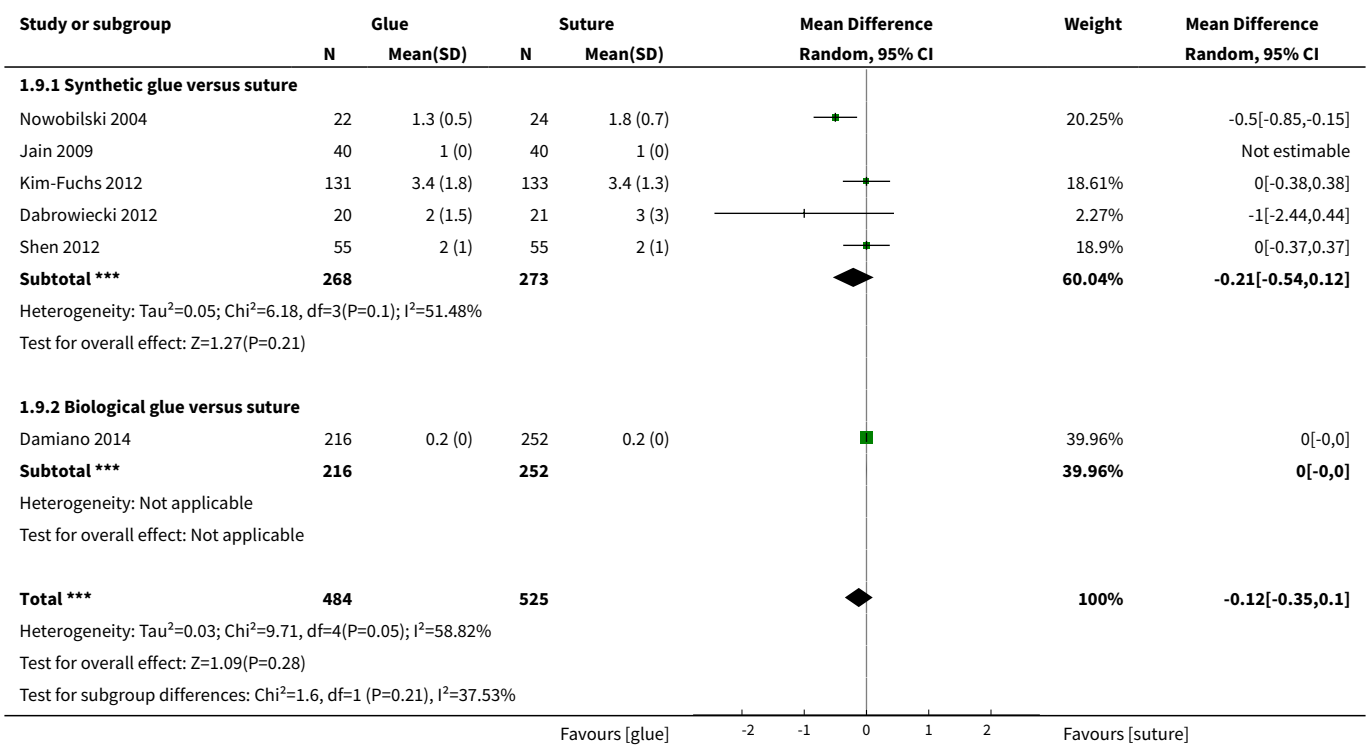


Analysis 1.8. Comparison 1 Glue versus suture, Outcome 8 Persisting numbness.

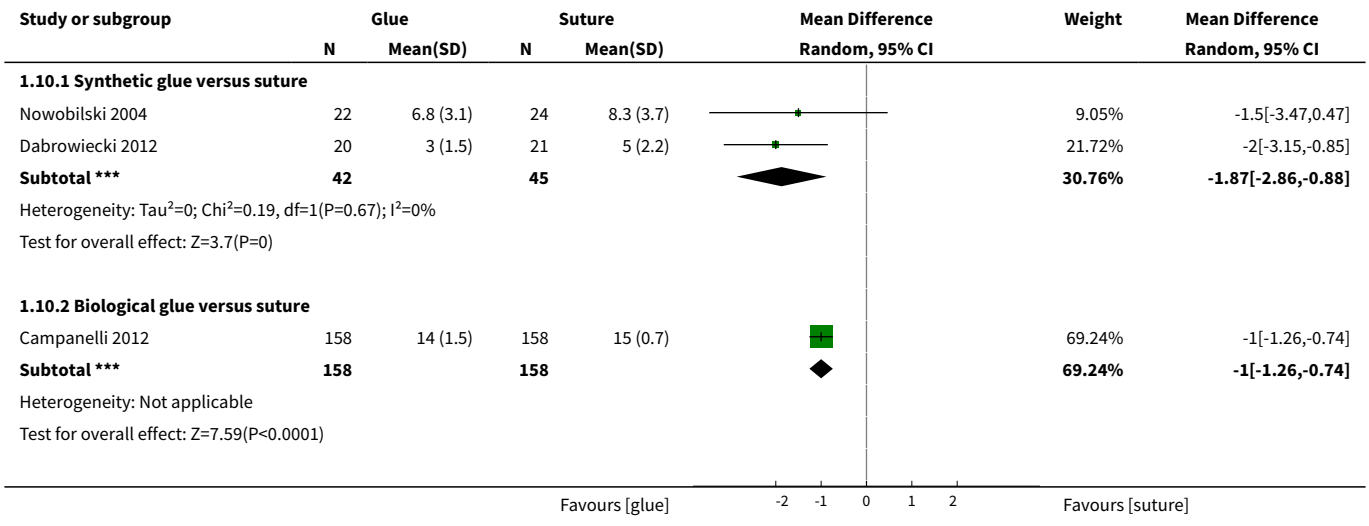




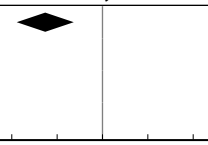
Analysis 1.9. Comparison 1 Glue versus suture, Outcome 9 Postoperative length of hospital stay (days).



Analysis 1.10. Comparison 1 Glue versus suture, Outcome 10 Recovery time to daily activities (days).



Study or subgroup	Glue N	Glue Mean(SD)	Suture N	Suture Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**200**		**203**			**100%**	**-1.26[-1.89,-0.63]**
Heterogeneity: Tau²=0.13; Chi²=2.97, df=2(P=0.23); I²=32.77%							
Test for overall effect: Z=3.93(P<0.0001)							
Test for subgroup differences: Chi²=2.79, df=1 (P=0.09), I²=64.15%							

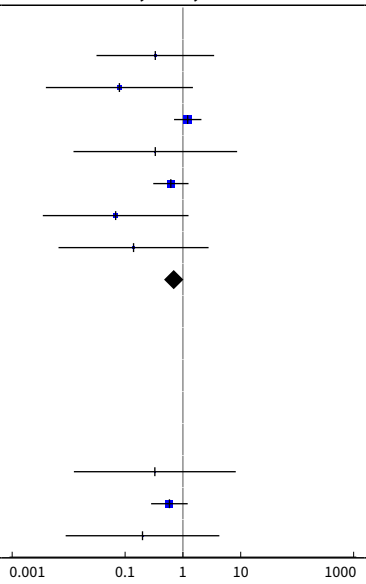


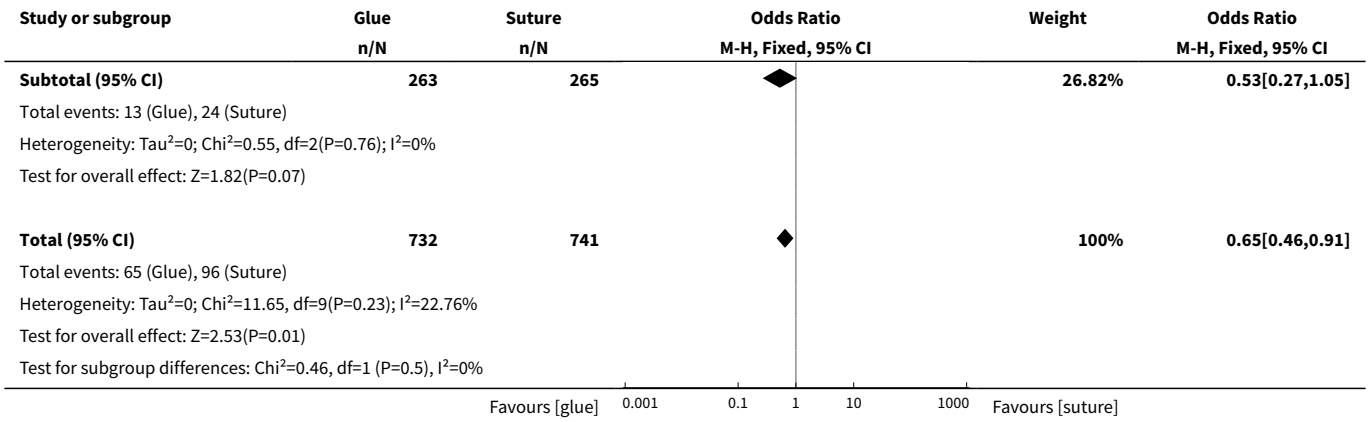
Comparison 2. Glue versus suture: *worst case scenarios*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chronic pain	10	1473	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.46, 0.91]
1.1 Synthetic glue versus suture	7	945	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.47, 1.02]
1.2 Biological glue versus suture	3	528	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.27, 1.05]
2 Hernia recurrence	12	1987	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.80, 1.85]
2.1 Synthetic glue versus suture	8	991	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.84, 2.04]
2.2 Biological glue versus suture	4	996	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.40]

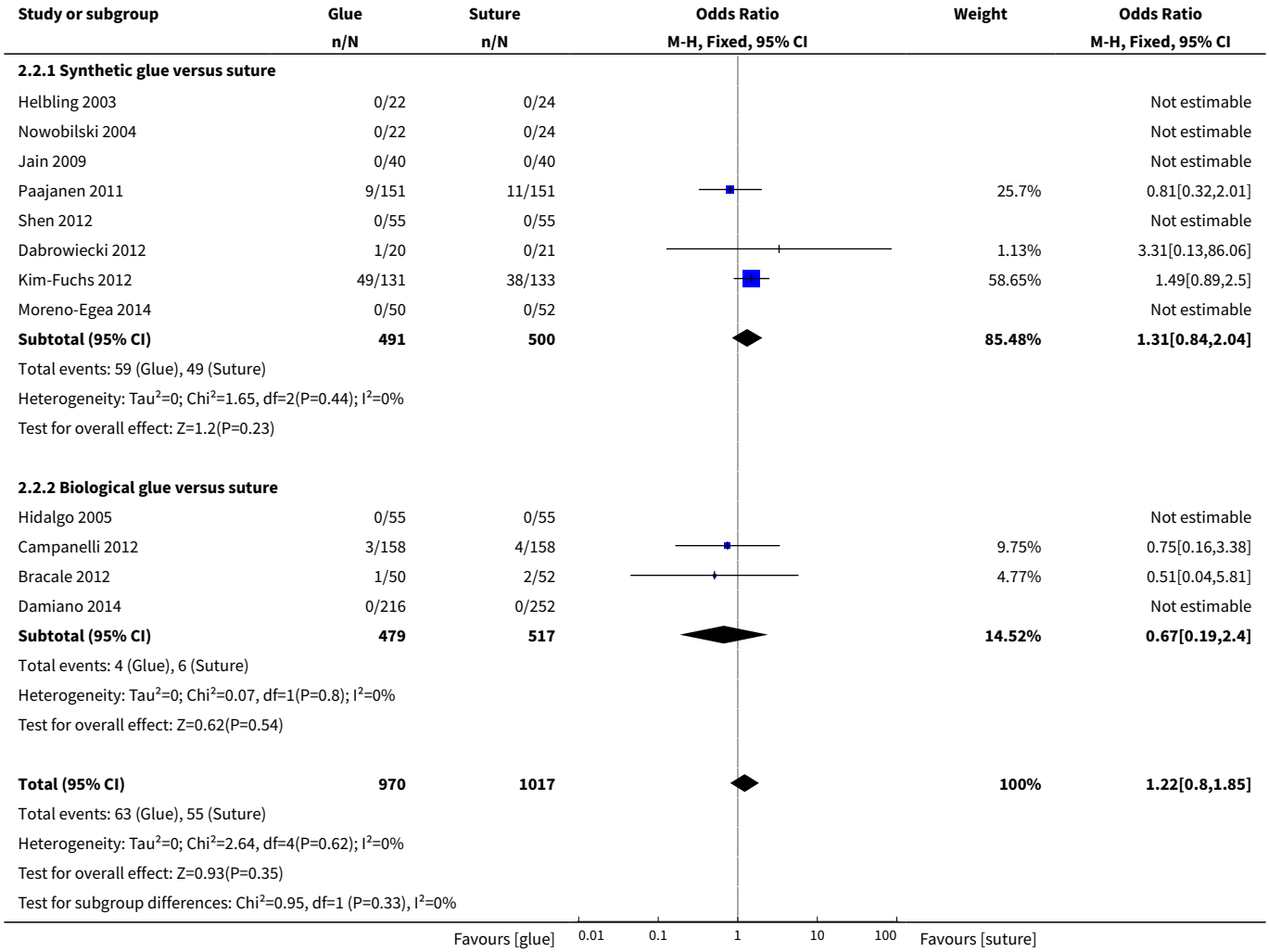
Analysis 2.1. Comparison 2 Glue versus suture: *worst case scenarios*, Outcome 1 Chronic pain.

Study or subgroup	Glue n/N	Suture n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Synthetic glue versus suture					
Helbling 2003	1/22	3/24		3.17%	0.33[0.03,3.47]
Jain 2009	0/40	5/40		6.28%	0.08[0,1.49]
Paajanen 2011	36/151	31/151		27.31%	1.21[0.7,2.09]
Dabrowiecki 2012	0/20	1/21		1.65%	0.33[0.01,8.67]
Kim-Fuchs 2012	15/131	23/133		23.38%	0.62[0.31,1.25]
Shen 2012	0/55	6/55		7.45%	0.07[0,1.25]
Moreno-Egea 2014	0/50	3/52		3.93%	0.14[0.01,2.78]
Subtotal (95% CI)	**469**	**476**		**73.18%**	**0.69[0.47,1.02]**
Total events: 52 (Glue), 72 (Suture)					
Heterogeneity: Tau²=0; Chi²=10.35, df=6(P=0.11); I²=42.05%					
Test for overall effect: Z=1.87(P=0.06)					
2.1.2 Biological glue versus suture					
Hidalgo 2005	0/55	1/55		1.72%	0.33[0.01,8.21]
Campanelli 2012	13/158	21/158		22.29%	0.58[0.28,1.21]
Bracale 2012	0/50	2/52		2.81%	0.2[0.01,4.27]





Analysis 2.2. Comparison 2 Glue versus suture: *worst case scenarios*, Outcome 2 Hernia recurrence.



APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Library (CENTRAL) - Issue 5, 2016

#1 MeSH descriptor: [Sutures] explode all trees
#2 MeSH descriptor: [Adhesives] explode all trees
#3 MeSH descriptor: [Fibrin Tissue Adhesive] explode all trees
#4 MeSH descriptor: [Tissue Adhesives] explode all trees
#5 MeSH descriptor: [Suture Techniques] explode all trees
#6 MeSH descriptor: [Cyanoacrylates] explode all trees
#7 MeSH descriptor: [Polyglycolic Acid] explode all trees
#8 glue or suture* or tissue adhesiv* or fibrin or N-butyl-2-cyanoacrylate or Tisseel or Tissucol or cyanoacrylate* or polyglycolic* acid* or adhesiv*:ti,ab,kw
#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10 MeSH descriptor: [Surgical Mesh] explode all trees
#11 mesh:ti,ab,kw
#12 (#10 or #11)
#13 MeSH descriptor: [Herniorrhaphy] explode all trees
#14 lichtenstein or open or repair or tension-free or hernio*:ti,ab,kw
#15 (#13 or #14)
#16 MeSH descriptor: [Hernia, Inguinal] explode all trees
#17 ((inguina* or groin*) near/3 hernia*):ti,ab,kw
#18 (#16 or #17)
#19 (#9 and #12 and #15 and #18) Publication year from 1986

Appendix 2. MEDLINE search strategy

MEDLINE (OVID) - 1986 to May 2016

1. exp Sutures/
2. exp Adhesives/
3. exp Fibrin Tissue Adhesive/
4. exp Tissue Adhesives/
5. exp Suture Techniques/
6. exp Cyanoacrylates/
7. exp Polyglycolic Acid/
8. (glue or suture* or tissue adhesiv* or fibrin or N-butyl-2-cyanoacrylate or Tisseel or Tissucol or cyanoacrylate* or polyglycolic* acid* or adhesiv*).mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Surgical Mesh/
11. mesh.mp.
12. 10 or 11
13. exp Herniorrhaphy/
14. (lichtenstein or open or repair or tension-free or hernio*).mp.
15. 13 or 14
16. exp Hernia, Inguinal/
17. ((inguina* or groin*) adj3 hernia*).mp.
18. 16 or 17
19. 9 and 12 and 15 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. clinical trials as topic.sh.
25. randomly.ab.
26. trial.ti.
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. exp animals/ not humans.sh.
29. 27 not 28
30. 19 and 29
31. limit 30 to yr="1986 -Current"

Appendix 3. Embase search strategy

Embase (OVID) - 1986 to May 2016

1. exp suture/
2. exp adhesive agent/
3. exp suturing method/
4. exp cyanoacrylate derivative/
5. exp polyglycolic acid/
6. (glue or suture* or tissue adhesiv* or fibrin or N-butyl-2-cyanoacrylate or Tisseel or Tissucol or cyanoacrylate* or polyglycolic* acid* or adhesiv*).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp surgical mesh/
9. exp mesh sling/
10. mesh.mp.
11. 8 or 9 or 10
12. exp hernioplasty/
13. exp herniorrhaphy/
14. exp herniotomy/
15. (lichtenstein or open or repair or tension-free or hernio*).mp.
16. 12 or 13 or 14 or 15
17. exp inguinal hernia/
18. ((inguina* or groin*) adj3 hernia*).mp.
19. 17 or 18
20. 7 and 11 and 16 and 19
21. CROSSOVER PROCEDURE.sh.
22. DOUBLE-BLIND PROCEDURE.sh.
23. SINGLE-BLIND PROCEDURE.sh.
24. (crossover* or cross over*).ti,ab.
25. placebo*.ti,ab.
26. (doubl* adj blind*).ti,ab.
27. allocat*.ti,ab.
28. trial.ti.
29. RANDOMIZED CONTROLLED TRIAL.sh.
30. random*.ti,ab.
31. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
33. 31 not 32
34. 20 and 33
35. limit 34 to yr="1986 -Current"

Appendix 4. Science Citation Index search strategy

Science Citation Index - 1986 to May 2016

#1 Topic=(glue or suture* or tissue adhesiv* or fibrin or N-butyl-2-cyanoacrylate or Tisseel or Tissucol or cyanoacrylate* or polyglycolic* acid* or adhesiv*)
#2 Topic=(mesh)
#3 Topic=(lichtenstein or open or repair or tension-free or hernio*)
#4 Topic=(((inguina* or groin*) near/3 hernia*))
#5 Topic=(multicenter or phase 3 or phase 4 or singl* or doubl* or trebl* or tripl* or blind* or mask* or random* or control* or trial or RCT or group or cross* over* or factorial* or placebo* or volunteer*)
#6 (#1 AND #2 AND #3 AND #4 AND #5)

Appendix 5. CBM (Chinese Biomedical Database) search strategy

全部字段:疝 and 全部字段:缝 and 全部字段:补片 and 全部字段:胶 or 粘 or 氰基丙烯酸酯

English translation: (All fields: hernia) and (All fields: suture) and (All fields: mesh) and All fields: (glue or stick or cyanoacrylate)

Appendix 6. CNKI (China National Knowledge Infrastructure) search strategy

FT="补片" AND FT="缝" AND FT=("胶" + "氰基丙烯酸酯" + "粘") and FT="疝"

English translation: (FT="hernia") and (FT="suture") and (FT="mesh") and (FT=("glue" or "stick" or "cyanoacrylate"))

(Note: FT means full text)

Appendix 7. VIP (a full-text database of China) search strategy

U=补片*(U=缝)*(U=(胶+氰基丙烯酸酯+粘))*(U=疝)

English translation: U=mesh*(U=suture)*(U=(glue + cyanoacrylate + stick))*(U=hernia)

(Note: U means any field)

Appendix 8. Wanfang databases search strategy

补片*缝*（胶+氰基丙烯酸酯+粘）*疝

English translation: mesh*suture*(glue + cyanoacrylate + stick)*hernia

Appendix 9. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

RANDOM SEQUENCE GENERATION

Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • referring to a random number table; • using a computer random number generator; • coin tossing; • shuffling cards or envelopes; • throwing dice; • drawing of lots;
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. • Sequence generated by odd or even date of birth. • Sequence generated by some rule based on date (or day) of admission. • Sequence generated by some rule based on hospital or clinic record number. • Allocation by judgement of the clinician. • Allocation by preference of the participant. • Allocation based on the results of a laboratory test or a series of tests. • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT

Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation. • Central allocation (including telephone, web-based and pharmacy-controlled randomization). • Sequentially numbered drug containers of identical appearance. • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

(Continued)

	• using an open random allocation schedule; • assignment envelopes were used without appropriate safeguards; • alternation or rotation; • date of birth; • case record number; • any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

BLINDING OF PARTICIPANTS AND PERSONNEL

Criteria for a judgement of 'Low risk' of bias.	Any one of the following. • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following. • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following. • Insufficient information to permit judgement of 'Low risk' or 'High risk'. • The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT

Criteria for a judgement of 'Low risk' of bias.	Any one of the following. • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following. • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following. • Insufficient information to permit judgement of 'Low risk' or 'High risk'. • The study did not address this outcome.

INCOMPLETE OUTCOME DATA

Criteria for a judgement of 'Low risk' of bias.	Any one of the following. • No missing outcome data. • Reasons for missing outcome data unlikely to be related to true outcome. • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following. • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size. • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization. • Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following. • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided). • The study did not address this outcome.

SELECTIVE REPORTING

Criteria for a judgement of 'Low risk' of bias.	Any of the following. • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following. • Not all of the study's pre-specified primary outcomes have been reported. • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified. • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).

(Continued)

	• One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criterion for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

OTHER BIAS

Criterion for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • had a potential source of bias related to the specific study design used; or • has been claimed to have been fraudulent; or • had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • insufficient information to assess whether an important risk of bias exists; or • insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Draft the protocol	Sun P with advice from Hu Q/Sun Y
Develop a search strategy	Sun P with advice from Sun Y/the Cochrane Colorectal Cancer Group
Search for trials	Sun P with advice from the Cochrane Colorectal Cancer Group
Select which trials to include	Sun P/Cheng X with advice from Sun Y
Extract data from trials	Sun P/Deng S with advice from Hu Q
Assess risk of bias	Sun P/Cheng X with advice from Sun Y
Enter data into RevMan	Sun P/Deng S
Carry out the analysis	Sun P with advice from Sun Y
Interpret the analysis	Sun P with advice from Zheng Q
Draft the final review	Sun P with advice from Hu Q/Sun Y/Zheng Q/Cheng X/Deng S

DECLARATIONS OF INTEREST

The authors of this review declare that there are no conflicts of interests.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We applied the random-effects model if substantial statistical heterogeneity existed, instead of the fixed-effect model as planned in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fibrin Tissue Adhesive; *Surgical Mesh; *Sutures; Chronic Pain [*prevention & control]; Herniorrhaphy [*methods]; Pain, Postoperative [*prevention & control]; Primary Prevention [methods]; Randomized Controlled Trials as Topic; Recurrence; Surgical Wound Infection [epidemiology]

MeSH check words

Humans