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Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery (Review)

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[Intervention Review]

Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery

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ABSTRACT

Background

Fibrin glue (FG) combines fibrinogen and thrombin, under the presence of factor XIII and calcium chloride, and produces a 'fibrin clot' as would occur through the natural clotting cascade. FG is thought to close over any small vessels including lymphatics that are too small for conventional surgical closure, thereby reducing seroma formation, seroma incidence and related comorbidities.

Objectives

To assess the evidence on the effectiveness of FG in people undergoing breast and axillary surgery and to establish whether FG is an efficient modality to prevent postoperative seroma and seroma-related outcomes.

Search methods

We searched the Cochrane Breast Cancer Group's (CBCG) Specialised Register (9 December 2011), the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1 2012), MEDLINE (9 December 2011), EMBASE (9 December 2011), LILACS (22 October 2012), SCI-E (22 October 2012), the World Health Organization's International Clinical Trial Registry (9 December 2011) and ClinicalTrials.gov (22 October 2012).

Selection criteria

Randomised controlled trials (RCTs) comparing the effectiveness of FG in terms of reducing the postoperative seroma incidence and related comorbidities in people undergoing breast and axillary surgery.

Data collection and analysis

At least two review authors independently scrutinised search results, selected eligible studies and extracted the data. The pooled analysis of the extracted data was achieved by the statistical analysis on Review Manager software. The quality of studies was assessed using The Cochrane Collaboration's 'Risk of bias' tool.

Main results

The search of four standard electronic databases yielded 119 potentially relevant studies but only 18 RCTs involving 1252 people were found suitable for statistical analysis. There was significant heterogeneity among trials and the majority of trials were of poor quality. The use of FG under skin flaps following breast and axillary surgery failed to reduce the incidence of postoperative seroma (risk ratio (RR) 1.02; 95% Confidence Interval (CI) 0.90 to 1.16, P value = 0.73), mean volume of seroma (standardised mean difference (SMD) -0.25; 95% CI -0.92

to 0.42, P value = 0.46), wound infection (RR 1.05; 95% CI 0.63 to 1.77, P value = 0.84), postoperative complications (RR 1.13; 95% CI 0.63 to 2.04, P value = 0.68) and length of hospital stay (SMD -0.2; 95% CI -0.78 to 0.39, P value = 0.51). FG reduced the total volume of drained seroma (SMD -0.75, 95% CI -1.24 to -0.26, P value = 0.003) and duration of persistent seromas requiring frequent aspirations (SMD -0.59; CI 95% -0.95 to -0.23, P value = 0.001).

Authors' conclusions

FG did not influence the incidence of postoperative seroma, the mean volume of seroma, wound infections, complications and the length of hospital stays in people undergoing breast cancer surgery. Due to significant methodological and clinical diversity among the included studies this conclusion may be considered weak and biased. Therefore, a major multicentre and high-quality RCT is required to validate these findings.

PLAIN LANGUAGE SUMMARY

Fibrin glue instillation under skin flaps to prevent seroma-related morbidity following breast and axillary surgery

A higher incidence of postoperative seroma (fluid collection under skin) in people undergoing breast and axillary (under-arm) surgery for breast cancer is responsible for longer hospital stays, frequent repeat aspiration procedures, increased cost of breast disease, delays in the provision of adjunctive treatments and consequently potentially reduced overall all-cause survival. Fibrin glue (FG) instillation under skin flaps after surgery produces a 'fibrin clot', sealing leaky lymph vessels, which leads to reduced seroma formation and related comorbidities.

We systematically analysed the published trials comparing the usefulness of FG as a small-vessel sealing agent. Eighteen randomised controlled trials on 1252 people were retrieved following bibliographic searches on standard medical databases. There were significant clinical and methodological differences among the included trials. The use of FG following breast and axillary surgery did not reduce the incidence of postoperative seroma, mean volume of seroma, wound infections, postoperative complications and the length of hospital stays. FG reduced the total volume of drained seroma and the duration of persistent seroma requiring frequent aspirations.

This review showed no overall benefit of using FG. Although this conclusion is based on the combined analysis of 18 trials, the majority of these were of poor quality due to flaws in trial methods. Therefore, this conclusion should be taken cautiously and a major, multicentre, high-quality randomised controlled trial on people undergoing breast and axillary surgery for breast cancer is required to corroborate this conclusion.

Summary of findings 1. Fibrin glue instillation under skin flaps compared to no-fibrin for breast and axillary surgery

Fibrin glue instillation under skin flaps compared to no-fibrin for breast and axillary surgery

Patient or population: people with breast and axillary surgery
Settings:
Intervention: fibrin glue instillation under skin flaps
Comparison: no-fibrin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No-fibrin	Fibrin glue instillation under skin flaps				
Incidence of postoperative**seroma** RR Follow-up: 4-16 weeks	**Study population**		**RR 1.02** (0.9 to 1.16)	1252 (18 studies)	⊕⊕⊝⊝ **low**	
	281 per 1000	**286 per 1000** (253 to 326)				
	Moderate					
	229 per 1000	**234 per 1000** (206 to 266)				
Mean volume of seroma SMD Follow-up: 4-16 weeks		The mean volume of seroma in the intervention groups was **0.25 standard deviations lower** (0.92 lower to 0.42 higher)		731 (10 studies)	⊕⊕⊝⊝ **low** [1]	SMD -0.25 (-0.92 to 0.42)
Total volume of drained seroma SMD Follow-up: 4-16 weeks		The mean total volume of drained seroma in the intervention groups was **0.75 standard deviations lower** (1.24 to 0.26 lower)		888 (13 studies)	⊕⊕⊝⊝ **low**	SMD -0.75 (-1.24 to -0.26)
Number of days for persistent drainage SMD Follow-up: 4-16 weeks		The mean number of days for persistent drainage in the intervention groups was **0.59 standard deviations lower** (0.95 to 0.23 lower)		861 (13 studies)	⊕⊕⊝⊝ **low**	SMD -0.59 (-0.95 to -0.23)
Surgical site infection RR	**Study population**		**RR 1.05** (0.63 to 1.77)	1009 (13 studies)	⊕⊕⊝⊝ **low**	

Follow-up: 4-16 weeks	**48 per 1000**	**50 per 1000** (30 to 85)				
	Moderate					
	25 per 1000	**26 per 1000** (16 to 44)				
Postoperative**complications** RR Follow-up: 4-16 weeks	**Study population**		**RR 1.13** (0.63 to 2.04)	981 (11 studies)	⊕⊕⊖⊖ **low**	
	39 per 1000	**44 per 1000** (24 to 79)				
	Moderate					
	44 per 1000	**50 per 1000** (28 to 90)				
Length of hospital stay SMD Follow-up: 4-16 weeks		The mean length of hospital stay in the intervention groups was **0.2 standard deviations lower** (0.78 lower to 0.39 higher)		364 (6 studies)	⊕⊕⊖⊖ **low**	SMD -0.2 (-0.78 to 0.39)

*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; **RR:** risk ratio; **SMD:** standardised mean difference.

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] There was inadequate randomisation technique and absence of power calculations, blinding and intention-to-treat analysis.

BACKGROUND

Description of the condition

Breast cancer remains the second most common cancer in women with a reported mortality reaching 460,000 deaths worldwide in 2008 (WHO 2011). Surgical resection of the breast cancer is the only mode of curative intervention. Surgical management consists primarily of tumour resection and is frequently associated with either axillary sentinel node biopsy or axillary sampling, or axillary dissection/clearance. The extent of surgical resection is determined by tumour type, size and stage and can involve a modified radical mastectomy (MRM) or more limited breast-conserving operations such as lumpectomy, wide local excision and quadrantectomy (de Lorenzi 2010; Denewer 2011; Krekel 2011; Loukas 2011; Sakorafas 2010).

Seroma formation is the most common postoperative complication following breast cancer surgery (Boostorm 2009; Ferreira 2008; Gong 2010; Kuroi 2005; Saratzis 2009). Although rarely serious, seroma formation can predispose to surgical site infection; skin flap dehiscence or necrosis, or both; a requirement for continued aspirations; extended recovery time; delayed start of neoadjuvant chemotherapy or radiotherapy influencing disease-free survival; and an overall longer hospital stay (Braithwaite 2010; Hoefer 1990; Moore 1996; Pinnaro 2011; Woodworth 2000).

The reported incidence of postoperative wound seroma following breast and axillary surgery ranges from 10% to 85% within the medical literature (Kuroi 2005). Two fundamental issues partly underlie why such a large range of seroma incidence was reported in the medical literature. First, there is a lack of consensus on the definition of a seroma; the majority of articles describe a seroma as a palpable fluid collection under the wound; however, some studies have stipulated that a seroma is present only when multiple aspirations are required (Burak 1997), or an aspirate over a specific volume is recorded, or both (Kumar 1995; Schultz 1997). Second, where some authors detect seromas on clinical grounds of a palpable fluid collection, other authors utilise ultrasound to quantify the presence of seroma at the wound site accurately, resulting in the detection of subclinical fluid collections. The reported seroma incidence is therefore dictated by both author definition and the detection method used. The exact cellular composition of a seroma is also in contention. Some studies postulate an excess of lymph (Tadych 1987), while others have suggested that the fluid production results from an acute inflammatory process and, as such, is an exudate in nature (McCaul 2000; Watt-Boolsen 1989). Understanding the pathophysiology of seroma development has major implications on the therapeutic targets and likely confounding factors. Factors thought to affect seroma development include the person's age, body mass index (BMI), tumour size, use of neoadjuvant chemotherapy (Woodworth 2000), type of surgery (MRM versus breast-conserving surgery), axillary lymph node status, axillary lymph nodes sampled or removed, and subsequently the extent of surgical dead space produced.

Description of the intervention

A lack of thorough understanding of seroma composition, formation and resolution is still posing a significant challenge to breast surgeons. A number of technical procedures or adjunct therapies, or both, have been tried to counteract the proposed aetiological factors involved in seroma development in an attempt to reduce wound site drainage postoperatively and subsequently seroma formation. The most commonly tested strategy to reduce the incidence of seroma following breast or axillary surgery comprises drainage at the wound site (Corion 2009). Drainage of the dead space after mastectomy or axillary dissection has been reported with the use of half versus full suction drains (Chintamani 2005), non-suction drains (Divino 2000), no drains (Puttawibul 2003), drains for five days versus eight days (Gupta 2001), single versus multiple drains (Petrek 1992), axillary versus axillary and pectoral drains (Terrell 1992), and the use of suction versus corrugated drains (Bourke 1976). A reduction in dead space by suture fixation (Dancey 2010), or external compression dressing, or both, is also reported (O'Hea 1999), with a variable success rate. Use of mastectomy flap dissection tools, ultrasound scissors, electrocautery and scalpel dissection (Galatius 2003; Kozomara 2010; Porter 1998) have been evaluated with equivocal results. Other seroma reduction interventions after mastectomy and axillary dissection include postoperative shoulder immobilisation to prevent shearing forces at the wound site (Chen 1999), use of tetracycline sclerotherapy (Rice 2000) or talc poudrage (Coons 1993) underneath skin flaps, various sealants (Taflampas 2009), ketoprofen therapy (Hidar 2007), coated collagen patches (Berger 2001), bovine thrombin instillation (Burak 1997), and fibrin glue (FG) or spray (Carless 2006; Ruggiero 2008; Ruggiero 2009).

Fibrin sealants have been used in surgery since the early 1980s. Their potential role as a haemostatic and sealing agent has expanded across a wide range of surgical disciplines, such as cardiac surgery, vascular surgery, hepatobiliary surgery, partial splenectomy, cosmetic surgery, orthopaedic surgery and gynaecological surgery (Briceno 2010; Brieler 1986; Franceschi 2006; Kram 1989; Modi 2005; Sierra 1993). Following completion of axillary and breast surgery, FG is sprayed over raw wound areas underneath the skin flaps and an adjunctive pressure dressing is applied. Suction drains, non-suction drains and upper-limb physiotherapy may also be applied depending upon the surgeon's choice. FG seals leaking lymph and other vessels and subsequently reduces the seroma formation.

How the intervention might work

Since the first reports of FG alleviating seroma production following mastectomy in animal models (Eroglu 1996; Sanders 1996; Wang 1996), it has been considered one of the most frequently scrutinised and reported modalities in humans after breast and axillary surgery. FG combines fibrinogen and thrombin and in the presence of factor XIII and calcium chloride produces a 'fibrin clot''', as would occur through the natural clotting cascade. FG is thought to act as both a haemostatic agent and as an adhesive, closing over any small vessels, including lymphatics, that are too small for conventional surgical closure (Rousou 1984).

Why it is important to do this review

We aim to review the published literature to establish whether FG is an effective modality for seroma prevention following breast and axillary surgery. It is important to establish that routine use of FG under skins flaps can prevent the consequences of seroma and related morbidities.

OBJECTIVES

1. To determine whether the application of FG following breast cancer surgery reduces the incidence of seroma formation.
2. To determine the effect of FG on the total drain volume, mean volume of seroma aspirate, frequency of wound infection or complications and the length of hospital stay.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing the effectiveness of FG in terms of reducing the incidence of seroma and its related morbidity following breast and axillary surgery for breast cancer. We considered the inclusion of trials published in all languages regardless of the number of participants, their age and gender. We excluded trials recruiting people with redo surgery, trials evaluating outcomes other than our intended primary outcome, people with recurrent disease, people having chemotherapy or radiotherapy and people with a diagnosis of renal failure, heart failure or liver failure.

Types of participants

We included trials recruiting people with breast cancer undergoing simple mastectomy, MRM, breast-conserving surgery, oncoplastic breast surgery, lumpectomy, quadrantectomy, axillary sentinel node biopsy, axillary sampling, axillary dissection of any level, and immediate partial or total breast reconstruction.

Types of interventions

We compared outcomes following the use of FG underneath skin flaps in people undergoing breast and axillary surgery. Seroma incidence and related morbidity were compared between groups of people receiving FG instillation under the skin flaps versus no use of FG. We also included trials in which other adjunctive therapies of seroma prevention were used, such as pressure dressing, single drain, multiple drains, suction drains and use of other adhesives or sealants.

Types of outcome measures

Primary outcomes

- Incidence of seroma, defined as the presence of fluid collection under the skin flap diagnosed by clinical and radiological assessment and requiring prolonged hospital stay, frequent clinic visits or aspiration(s), or a combination of these.
- Morbidity, including all adverse events such as wound infection, seroma, skin necrosis, shoulder stiffness, respiratory tract infection, urinary tract infection, deep vein thrombosis, pulmonary embolism, bleeding and haematoma.

Secondary outcomes

- Long-term morbidity up until five years after surgery.
- Long-term mortality up until five years after surgery.
- Cost analysis using various health economic decision models (William 2006).
- Health-related quality of life (HRQoL) using any measuring tool such as the European Organisation for Research and Treatment of Cancer (EORTC) breast cancer-specific quality of life questionnaire (QLQ BR-23), Functional Assessment of Cancer Therapy (FACT-B), Hopwood Body Image Scale (HBIS), Body Image After Breast Cancer Questionnaire (BIBCQ) and BREAST-Q (Chen 2010).
- Seroma volume (measured radiologically as well on aspiration, if required).
- Re-intervention rate.
- Length of hospital stay, in days.
- Any other variable that was evaluated in the RCT that authors consider to be an important outcome.

Search methods for identification of studies

See: Breast Cancer Group methods used in reviews.

Electronic searches

We searched the following electronic databases.

- The Cochrane Breast Cancer Group (CBCG) Specialised Register. Details of the search strategies used by the CBCG for the identification of studies and the procedure used to code references are outlined in the Group's module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials coded with the key words 'early breast cancer', 'locally advanced breast cancer', 'surgery', 'mammoplasty', 'axilla', 'fibrin tissue adhesive', 'lymph node excision', 'mastectomy', 'modified radical mastectomy', 'MRM', 'postoperative complications', 'seroma', 'tissue adhesives', 'fibrin glue', 'fibrin adhesive glue', 'fibrin glue instillation', 'breast surgery', 'breast conserving surgery', 'lumpectomy', 'quadrantectomy', 'oncoplastic breast surgery', axillary sampling', 'axillary sentinel node biopsy', 'breast reconstruction' and 'seroma prevention therapies' were extracted and considered for inclusion in the review.
- MEDLINE (via OvidSP) (to 9 December 2011). See Appendix 1 for the search strategy.
- EMBASE (via Embase.com) (to 9 December 2011). See Appendix 2 for the search strategy.
- LILACS via Virtual Health Library (VHL - bases.bireme.br/cgi-bin/wxislind.exe/iah/online/) (to 22 October 2012). See Appendix 3 for search strategy.
- SCI-E via Web Of Science (to 22 October 2012). See Appendix 4 for search strategy.
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/Default.aspx) (to 9 December 2011). See Appendix 5 for the search strategy.
- ClinicalTrials.gov (clinicaltrials.gov/ct2/home, to 22 October 2012) . See Appendix 6 for the search strategy.
- CENTRAL (Issue 1). See Appendix 7 for the search strategy.

A filter for identifying relevant study designs that is recommended by The Cochrane Collaboration (Higgins 2011) was used to filter out irrelevant studies in MEDLINE and EMBASE.

Searching other resources

We searched the references from the included studies to identify further trials. The 'related article' function of MEDLINE was also searched thoroughly in order to identify additional studies. We

attempted to gather information on all published, unpublished and ongoing trials from all possible data sources. In addition, breast cancer experts, breast surgeons, breast care nurses and pharmaceutical companies involved in the provision of necessary materials were contacted and asked to provide details of outstanding clinical trials or any relevant unpublished reports. The international societies of breast surgery (British Association of Surgical Oncology, European Association of Surgical Oncology, Association of Breast Surgeons, etc.) and oncoplastic breast surgery (British Association of Plastic Reconstructive and Aesthetic Surgeons) were contacted and asked to provide information on any unpublished studies.

Data collection and analysis

Selection of studies

Studies were selected according to predefined inclusion criteria. The studies identified through searching the electronic databases were independently screened by two review authors (MSS and KHH). Each title and abstract was scanned and, if this was inconclusive, the full copy of the article was retrieved and read. Any disagreements regarding study eligibility were resolved by discussion and, if necessary, with the third and fourth review authors (IFR and RB). The excluded studies were recorded in the 'Characteristics of excluded studies' table with details of the reasons for their exclusion.

Data extraction and management

Data were collected on a Microsoft Excel spread sheet by three review authors (MSS, KHH, IFR) working independently, and confirmed by the fourth review author (RB). The conflict about data and recording was resolved by mutual agreement among all authors. We conducted this systematic review according to the protocol and the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We recorded the inclusion and exclusion criteria in each trial that fulfil our criteria for inclusion. In order to check for adequacy and the quality of included trials, we scored them according to the published guidelines of Jadad et al and Chalmers et al (Chalmers 1981; Jadad 1996). For those studies with more than one publication, we extracted the data from all publications but considered the final or updated version of each study as the primary reference.

The following details on methods were extracted:

- operation technique;
- use of prophylactic antibiotics;
- type of fibrin used;
- perioperative untoward events;
- postoperative untoward events;
- measuring scales of different variables;
- information regarding the BMI status of participants and extent of axillary surgery, for example axillary sampling, axillary sentinel node biopsy and axillary dissection of level I, II and III; and
- data on participants with advanced malignancy, renal failure, heart failure, liver failure, malnutrition and conditions that may contribute to body fluid retention.

The following data on randomisation and blinding procedures were extracted:

- number of randomised participants;
- number of participants not randomised and reasons for their non-randomisation;
- exclusion after randomisation;
- drop-outs;
- blinding of participants and observers;
- intention-to-treat (ITT) analysis;
- internal validity;
- external validity; and
- power calculation.

Assessment of risk of bias in included studies

We defined the methodological quality as the confidence that we can have the design of the study as its reporting restricted the bias in the intervention comparison (Chalmers 1981; Higgins 2011; Jadad 1996; Moher 1998). We also looked for power calculations and the strength of the trial in order to score it precisely and accurately. Due to the risk of overestimating intervention effects in randomised trials with inadequate methodological quality (Chalmers 1981; Higgins 2011; Jadad 1996; Kjaergard 2001; Schulz 1995), we assessed the influence of the methodological quality on the review findings. In short, our group used the full Cochrane 'Risk of bias' tool in addition to the guidelines published by Chalmers et al and Jadad et al (Chalmers 1981; Jadad 1996).

Generation of the allocation sequence

- Low, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards or throwing dice were considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names or admittance numbers was used for the allocation of participants. These studies are known as quasi-randomised and were excluded from the present review when assessing beneficial effects of the intervention.

Allocation concealment

- Low, if the allocation of participants involved a central independent unit, an on-site locked computer or sealed envelopes.
- Unclear, if the trial was described as randomised but the method used to conceal the allocation was not described.
- High, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Double blinding or masking

- Low, if the trial was described as double blind and the method of blinding was described.
- Unclear, if the trial was described as double blind but the method of blinding was not described.
- Not performed, if there was no blinding at all.

Follow-up and intention-to-treat analysis

- Low, if the numbers and reasons for drop-outs and withdrawals in all intervention groups were described, or if it was specified that there were no drop-outs or withdrawals.
- Unclear, if the report gave the impression that there had been no drop-outs or withdrawals but this was not specifically stated.
- High, if the number or reasons for drop-outs and withdrawals were not described.

Measures of treatment effect

The risk ratio (RR) with a 95% confidence interval (CI) was calculated for binary data variables such as the incidence of seroma, mortality, morbidity and re-intervention rate. We reported the RRs of treatment effects for responses so that RRs less than 1.0 favour FG and RRs greater than 1.0 favour no-fibrin glue (NFG).The standardised mean difference (SMD) with a 95% CI was calculated for continuous data variables, such as seroma volume, hospital stay, cost analysis and measurement of HRQoL. If the mean values were not available for continuous outcomes, median values were used for the purpose of the meta-analysis. We estimated the mean from the median, range and sample size according to the method recommended by Hozo et al (Hozo 2005). If the standard deviation was not available, we calculated it according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 16.1.3) (Higgins 2011). This involved the assumption that both groups had the same variance, which may not be true.

Unit of analysis issues

RR for binary data and SMD for continuous data were used to express the combined outcome. Mean values ± standard deviations were used for the statistical analysis. If mean values were not reported, median values were used according to the formula already described in the Methods section. If the standard deviation was not reported, it was estimated either from the range value or from the P value as described in the Methods section.

Dealing with missing data

We contacted the first author of a study via personal communication in order to retrieve missing data. If further information was required from any source, we contacted all relevant people involved in the running of that published trial. If missing data could not be obtained, and the particular trial did not score according to our inclusion criteria, we excluded the trial giving reasons for its exclusion in the Characteristics of excluded studies table. We looked at the missing data on an outcome by outcome basis.

Assessment of heterogeneity

Heterogeneity was explored using the Chi^2 test, with significance set at P value < 0.05, and it was quantified using the I^2 statistic (Higgins 2002), with a maximum value of 30% identifying low heterogeneity (Higgins 2002; Higgins 2011). We also inspected the graphical representation of the data. In case of heterogeneity, we reported the results of random-effects model.

Assessment of reporting biases

We employed the recommendations on testing for funnel plot asymmetry and discussed plot asymmetry, possibly as a consequence of reporting bias, as outlined in Section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

The random-effects model (DerSimonian 1986), as well as the fixed-effect model (DeMets 1987), were used to calculate the combined outcome in cases of both binary and continuous variables. For dichotomous outcomes, the Mantel-Haenszel method was used for the calculation of RR under the fixed-effect and random-effects models (Egger 2006). In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either the treatment or control group, according to the recommended method (Deeks 2001). The estimate of the difference between groups was pooled, depending upon the effect weights in results determined by each trial estimate variance. The forest plot was used for the graphical display of the results from the meta-analyses. The square around the estimate stood for the accuracy of the estimation (sample size) and the horizontal line represented the 95% CI. The statistical analysis was performed by MSS and confirmed by KHH and IFR. The software package Review Manager 5.1.2 (RevMan 2011), provided by The Cochrane Collaboration was used for analysis.

A Summary of findings 1 was developed to assess the overall quality of the body of evidence.

Subgroup analysis and investigation of heterogeneity

Based on the duration of follow-up there were insufficient data to perform subgroup analyses. We performed the subgroup analysis on trials in breast surgery and breast plus axillary surgery to find out if there was any difference depending upon the site of surgery for breast cancer.

Sensitivity analysis

When adequate data were available, we performed sensitivity analysis to assess the robustness of our results by repeating the analysis with the following adjustments:

- repeating the analysis excluding studies with high risk of bias.

RESULTS

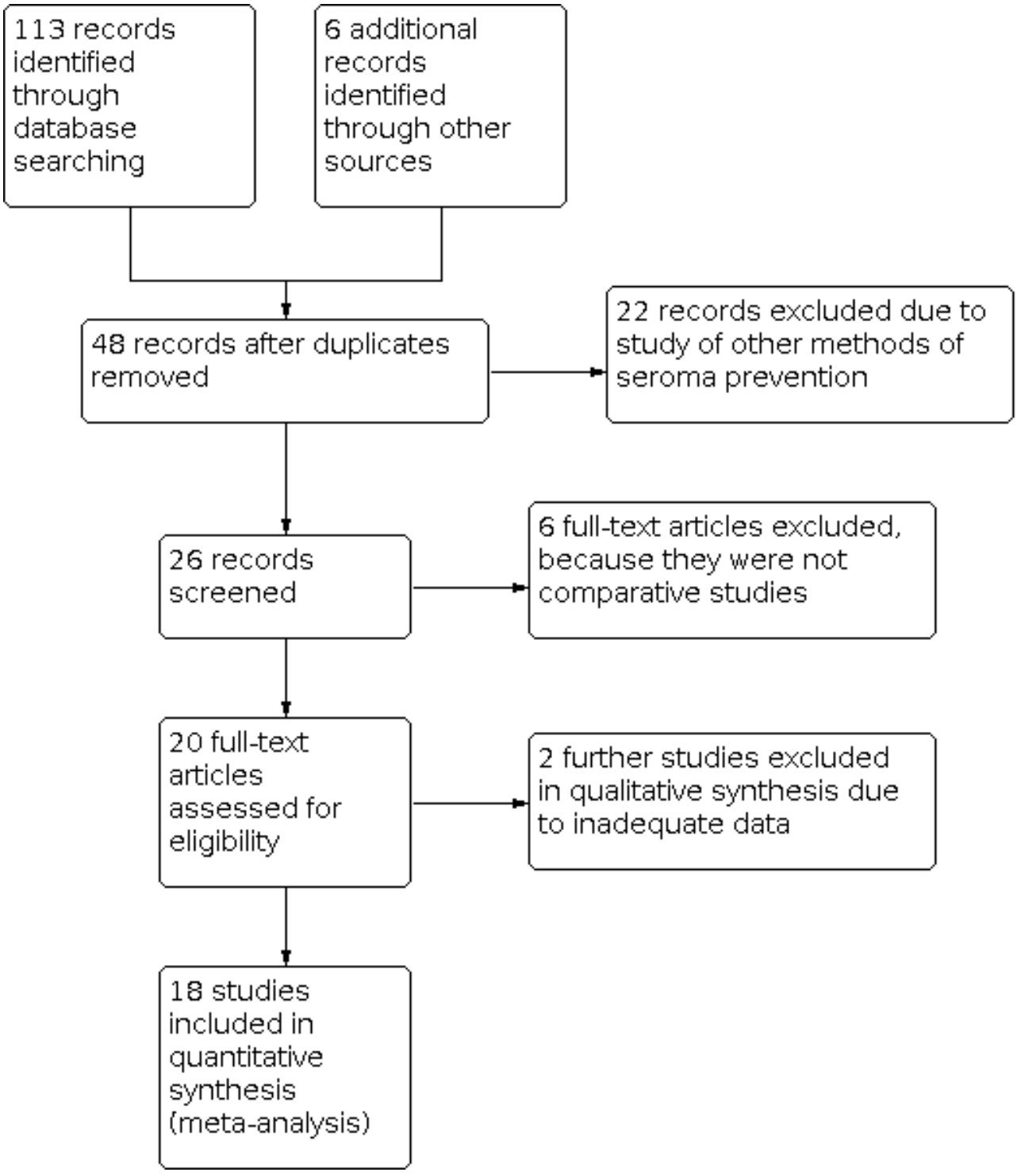
Description of studies

See: Characteristics of included studies.

Results of the search

We searched four electronic databases using MeSH headings mentioned in the Methods section and search strategies explained in Appendix 1, Appendix 2 and Appendix 3, yielding 119 potentially relevant records. The CENTRAL database search produced 23 relevant trials while MEDLINE, EMBASE and the WHO ICTRP electronic databases yielded 53, 31 and 12 relevant trials potentially suitable for inclusion, respectively. Further screening of these potentially relevant studies was performed and outlined in the PRISMA flow chart (see: Figure 1). Eighteen RCTs encompassing 1252 participants undergoing breast and axillary surgery for breast cancer were retrieved from the electronic databases (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995).

Figure 1. PRISMA flow chart showing trial selection methodology.



Included studies

We identified 18 eligible RCTs encompassing 1252 participants undergoing breast and axillary surgery for breast cancer (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995). There were 625 participants in the FG group and 627 participants in the NFG group. Recruited participants in the included trials had not had clinical, biochemical and radiological evidence of metastatic breast carcinoma. All of the included studies were small, with sample sizes ranging from 21 (Moore 1997) to 159 (Cipolla 2010) participants. All participants were considered to have early breast cancer requiring

mastectomy, sector mastectomy, MRM, wide local excision, axillary dissection and axillary procedure alone or as an adjunctive procedure. Preoperative risk stratification for poor wound healing and wound breakdown was not reported; however, the majority of trials did not recruit people with multiple comorbidities potentially contributing to the wound complications. None of the reported trials were multicentre.

Cipolla et al recruited 159 participants undergoing MRM and quadrantectomy (Cipolla 2010). Eighty people were in the FG group and 79 people were in the NFG group. There were no preoperative or postoperative confounding interventions reported in this trial apart from the allocated application of FG in the relevant arm of the trial. This trial was run in Italy. The primary outcome was mean duration of axillary drainage and the secondary outcomes included the incidence of seroma, mean total drainage volume, mean seroma aspirate volume, wound infection, complications and mean number of seroma aspirations.

Dinsmore et al recruited 27 participants undergoing MRM (Dinsmore 2000). Fourteen people were in the FG group and 13 people were in the NFG group. There were no preoperative or postoperative confounding interventions reported in this trial apart from the allocated application of FG in the relevant arm of the trial. This trial was run in the USA. The primary outcome was incidence of seroma and the secondary outcomes included total volume of seroma, duration of axillary drainage volume and wound complications.

El-Nakeeb et al recruited 50 participants undergoing MRM (El-Nakeeb 2009). Twenty-five people were in the FG group and 25 people were in the NFG group. There were no preoperative or postoperative confounding interventions reported in this trial apart from the allocated application of FG in the relevant arm of the trial. This trial was run in Egypt. The primary outcome was seroma incidence and the secondary outcomes included total volume of seroma, duration of drainage and wound complications.

Gilly et al recruited 108 participants undergoing MRM (Gilly 1998). Fifty people were in the FG group and 58 people were in the NFG group. The postoperative local pressure dressing and shoulder physiotherapy were confounding interventions reported in this trial. This trial was run in France. The primary outcome was seroma incidence and the secondary outcomes included total volume of seroma, length of hospital stay and wound complications.

Gioffre Florio et al recruited 24 participants undergoing MRM, wide local excision and axillary dissection (Gioffrè Florio 1993). Twelve people were in the FG group and 12 people were in the NFG group. The perioperative drain insertion under the skin flaps was one confounding intervention reported in this trial apart from the allocated application of FG in the relevant arm of the trial. This trial was run in Italy. The primary outcome was seroma incidence and the secondary outcome included mean volume of seroma.

Jain et al recruited 87 participants undergoing MRM, segmentectomy and axillary dissection (Jain 2004). Twenty-nine people were in the FG group and 58 people were in the NFG group. The postoperative local pressure dressing and drain insertion were confounding interventions reported in this trial apart from the allocated application of the FG in the relevant arm of the trial. This trial was run in the UK. The primary outcome was seroma incidence and the secondary outcomes included mean volume of seroma, wound infection, postoperative complications and length of hospital stay.

Johnson et al recruited 82 participants undergoing MRM, wide local excision and axillary dissection (Johnson 2005). Thirty-eight people were in the FG group and 44 people were in the NFG group. There was no confounding intervention reported in this trial. This trial was run in the USA. The primary outcome was seroma incidence and the secondary outcomes included mean volume of seroma, wound infection, postoperative complications and length of hospital stay.

Ko et al recruited 100 participants undergoing lumpectomy (Ko 2009). Fifty people were in the FG group and 50 people were in the NFG group. The postoperative local pressure dressing was a confounding intervention reported in this trial apart from the allocated application of FG in the relevant arm of the trial. This trial was run in South Korea. The primary outcome was seroma incidence and the secondary outcomes included mean volume of seroma, total volume of seroma, mean number of drainage days, wound infection and postoperative complications.

Langer et al recruited 55 participants undergoing lumpectomy (Langer 2003). Twenty-six people were in the FG group and 29 people were in the NFG group. The postoperative reduced shoulder mobilisation was a confounding intervention reported in this trial. This trial was run in the USA. The primary outcome was seroma incidence and the secondary outcomes included total volume of seroma, mean number of drainage days and wound infection.

Moore et al recruited 21 participants undergoing MRM (Moore 1997). Eleven people were in the FG group and 10 people were in the NFG group. There was no postoperative confounding intervention in this trial. This trial was run in the USA. The primary outcome was total volume of seroma and the secondary outcomes included seroma incidence and length of hospital stay.

Moore et al recruited 80 participants undergoing MRM and lumpectomy (Moore 2001). Fifty-nine people were in the FG group and 21 people were in the NFG group. There was no postoperative confounding intervention in this trial. This trial was run in the USA. The primary outcome was seroma incidence and the secondary outcomes included wound infection, length of seroma drainage in days, total seroma volume and postoperative complications.

Mustonen et al recruited 40 participants undergoing MRM (Mustonen 2004). Nineteen people were in the FG group and 21 people were in the NFG group. The postoperative compression dressing of the thoracic wall was a confounding intervention reported in this trial. This trial was run in Finland. The primary outcome was seroma incidence and the secondary outcomes included total volume of seroma, mean number of drainage days, mean volume of seroma, length of hospital stay and wound infection.

Ruggiero et al recruited 90 participants undergoing MRM and quadrantectomy (Ruggiero 2009). Forty-five people were in the FG group and 45 people were in the NFG group. The postoperative compression dressing of the thoracic wall was a confounding intervention reported in this trial. This trial was run in Italy. The primary outcome was seroma incidence and the secondary outcomes included total volume of seroma, postoperative complications and wound infection.

Segura-Castillo et al recruited 45 participants undergoing MRM and axillary dissection (Segura-Castillo 2005). Twenty-two people were in the FG group and 23 people were in the NFG group. There was no postoperative confounding intervention reported in this trial. This trial was run in Mexico. The primary outcome was seroma incidence and the secondary outcomes included mean number of drainage days, postoperative complications and wound infection.

Tasinato et al recruited 127 participants undergoing axillary dissection (Tasinato 1993). Sixty-six people were in the FG group and 61 people were in the NFG group. The postoperative compression dressing of the thoracic wall was a confounding intervention reported in this trial. This trial was run in Italy. The primary outcome was mean seroma volume and secondary outcomes included seroma incidence, drainage days, postoperative complications and wound infection.

Uden et al recruited 68 participants undergoing MRM (Uden 1993). Thirty-six people were in the FG group and 32 people were in the NFG group. The postoperative compression dressing of the thoracic wall was a confounding intervention reported in this trial. This trial was run in Sweden. The primary outcome was the incidence of seroma and secondary outcomes included mean seroma volume, total volume of seroma, drainage days, postoperative complications, length of hospital stay and wound infection.

Ulusoy et al recruited 54 participants undergoing MRM (Ulusoy 2003). Twenty-seven people were in the FG group and 27 people were in the NFG group. There was no postoperative confounding intervention reported in this trial. This trial was run in Turkey. The primary outcome was the incidence of seroma and secondary outcomes included mean seroma volume, total volume of seroma, drainage days and wound infection.

Vaxman et al recruited 40 participants undergoing MRM (Vaxman 1995). Twenty people were in the FG group and 20 people were in the NFG group. The postoperative compression dressing of the thoracic wall and shoulder physiotherapy were confounding interventions reported in this trial. This trial was run in France. The primary outcome was the incidence of seroma and secondary outcomes included mean seroma volume, total volume of seroma, drainage days, length of hospital stay and postoperative complications.

Excluded studies

See: Characteristics of excluded studies.

Risk of bias in included studies

Allocation

The random sequence generation and allocation concealment of the recruited participants in these RCTs were not reported precisely. In good-quality RCTs, the optimum sequence generation was reported in four trials only where participants were randomly distributed to the control or experimental group according to computer-generated codes, web-based sequences and lottery-based systems (Jain 2004; Ko 2009; Moore 1997; Moore 2001). We classified an additional four RCTs with low risk of bias because the technique of randomisation was random numbers based (Mustonen 2004; Segura-Castillo 2005; Tasinato 1993; Uden 1993). Ten trials were classified with high risk of bias due to the absence of reporting the randomisation technique and kind of allocation concealment (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Johnson 2005; Langer 2003; Ruggiero 2009; Ulusoy 2003; Vaxman 1995).

Blinding

Blinding of the operating surgeon was not possible due to the nature of the RCTs. However, blinding of the trial participants and outcome assessors was neither investigated nor reported adequately by the majority of the included studies. RCTs with an optimum blinding approach was adopted in only five studies (Jain 2004; Ko 2009; Moore 1997; Moore 2001; Segura-Castillo 2005). Therefore, based on the blinding technique, 13 RCTs were classified as inadequate with a high risk of bias (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Johnson 2005; Langer 2003; Mustonen 2004; Ruggiero 2009; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995).

Incomplete outcome data

In judging the risk of bias for incomplete data reporting, we evaluated the primary outcome measure, namely incidence of seroma. We also considered whether an ITT analysis was considered for the primary outcome and missing data were imputed appropriately. We judged that there was a high risk of bias due to the lack of reporting on missing participants recruited in the RCT. RCTs with optimum ITT analysis was adopted in five studies only (Jain 2004; Ko 2009; Moore 1997; Moore 2001; Segura-Castillo 2005). Therefore, based on the lack of ITT analysis, 17 RCTs were classified inadequate with high risk of bias (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Johnson 2005; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995).

Selective reporting

In judging the risk of bias for selective reporting, we were unable to assess the trial protocols and therefore assessed the studies based on the prespecified outcome measures reported in the methods section of the trial report. There were 16 studies with a low risk of bias due to adequate reporting of primary and secondary outcomes whereas two studies had a high risk of bias due to not optimally reporting secondary outcomes (Jain 2004; Vaxman 1995).

Other potential sources of bias

There have been published studies suggesting that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004; Thomas 2008). Six included trials did not report the ethics approval of the trial (El-Nakeeb 2009; Gioffrè Florio 1993; Gilly 1998; Ruggiero 2009; Ulusoy 2003; Vaxman 1995). In addition, five of these trials also failed to report any conflict of interest (El-Nakeeb 2009; Gilly 1998; Ruggiero 2009; Ulusoy 2003; Vaxman 1995). The acknowledgement section of the published RCTs was incompletely reported.

Effects of interventions

See: **Summary of findings 1** Fibrin glue instillation under skin flaps compared to no-fibrin for breast and axillary surgery

All trials analysis

See: Summary of findings 1.

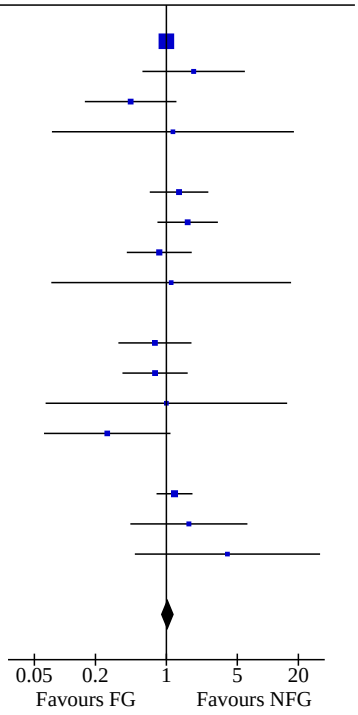
Incidence of postoperative wound site seroma

All trials contributed to the combined calculation of this variable (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995).There was no significant heterogeneity (I^2 = 15%) among studies. Therefore, in the fixed-effect model, FG was statistically ineffective in reducing the incidence of postoperative seroma in people undergoing breast and axillary surgery (RR 1.02; 95% CI 0.90 to 1.16, P value = 0.73; Analysis 1.1, refer to Figure 2).

Figure 2. Forest plot of comparison: 1 All trials analysis, outcome: 1.1 Incidence of postoperative seroma.

Study or Subgroup	FG group Events	FG group Total	NFG group Events	NFG group Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	80	80	79	79	45.9%	1.00 [0.98 , 1.02]
Dinsmore 2000	6	14	3	13	1.8%	1.86 [0.58 , 5.94]
El-Nakeeb 2009	4	25	9	25	5.2%	0.44 [0.16 , 1.26]
Gilly 1998	1	50	1	58	0.5%	1.16 [0.07 , 18.07]
Gioffrè Florio 1993	0	12	0	12		Not estimable
Jain 2004	10	29	15	58	5.7%	1.33 [0.69 , 2.59]
Johnson 2005	14	38	10	44	5.3%	1.62 [0.82 , 3.22]
Ko 2009	10	47	12	48	6.8%	0.85 [0.41 , 1.78]
Langer 2003	1	26	1	29	0.5%	1.12 [0.07 , 16.95]
Moore 1997	0	10	0	11		Not estimable
Moore 2001	13	59	6	21	5.1%	0.77 [0.34 , 1.77]
Mustonen 2004	7	19	10	21	5.5%	0.77 [0.37 , 1.62]
Ruggiero 2009	1	45	1	45	0.6%	1.00 [0.06 , 15.50]
Segura-Castillo 2005	2	22	8	23	4.5%	0.26 [0.06 , 1.10]
Tasinato 1993	0	66	0	61		Not estimable
Uden 1993	23	36	17	32	10.3%	1.20 [0.80 , 1.81]
Ulusoy 2003	5	27	3	27	1.7%	1.67 [0.44 , 6.29]
Vaxman 1995	4	20	1	20	0.6%	4.00 [0.49 , 32.72]
Total (95% CI)		**625**		**627**	**100.0%**	**1.02 [0.90 , 1.16]**
Total events:	181		176			

Heterogeneity: Chi² = 16.50, df = 14 (P = 0.28); I² = 15%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



Mean volume of seroma

There was significant heterogeneity (I^2 = 94%) among 10 studies contributing to the combined calculation of this variable (Cipolla 2010; El-Nakeeb 2009; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Mustonen 2004; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995). In the random-effects model, the mean volume of the seroma remained unchanged with and without application of FG under skin flaps following axillary and breast surgery (SMD -0.25; 95% CI -0.92 to 0.42, P value = 0.46; Analysis 1.2).

Total volume of drained fluid

There was significant heterogeneity (I^2 = 91%) among 13 studies (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Uden 1993; Ulusoy 2003; Vaxman 1995) contributing to the combined calculation of this variable. In the random-effects model, the total volume of drained seroma fluid reduced significantly with the application of FG under skin flaps following axillary and breast surgery (SMD -0.75; 95% CI -1.24 to -0.26, P value = 0.003; Analysis 1.3).

Number of days for persistent seroma drainage

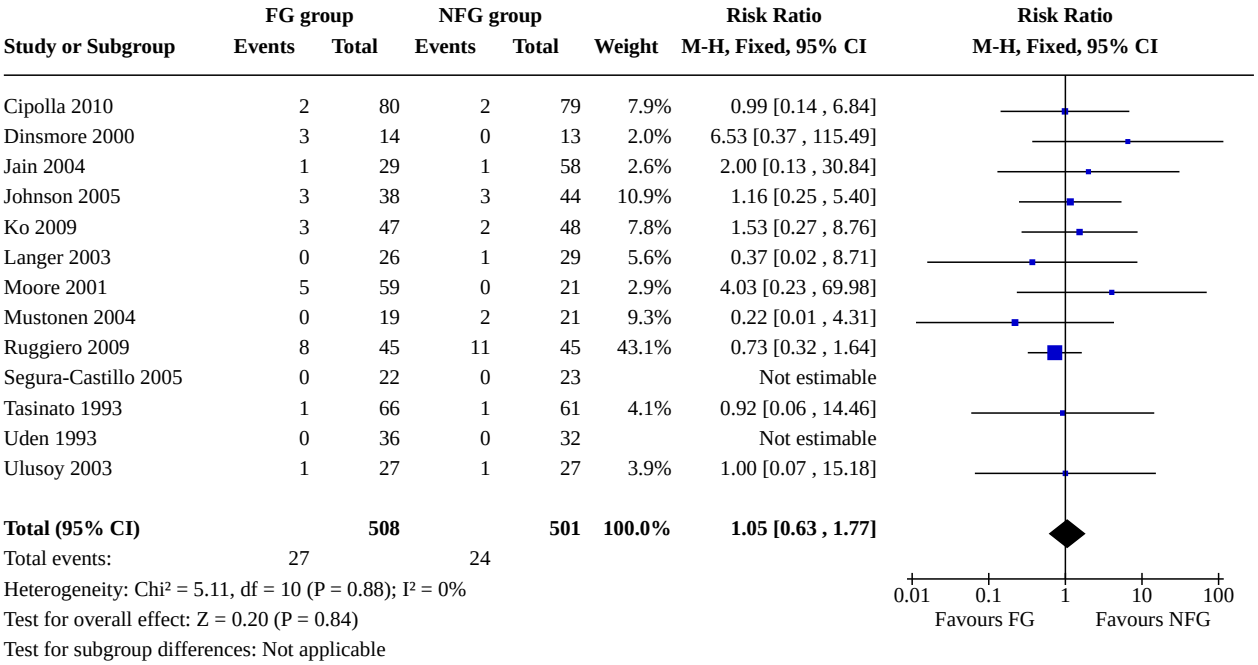
There was significant heterogeneity (I^2 = 83%) among 13 studies contributing to the combined calculation of this variable (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Ko 2009; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995). In the random-effects model, the total duration of persistent seroma drainage reduced significantly with the application of FG under skin flaps following axillary and breast surgery (SMD -0.59; 95% CI -0.95 to -0.23, P value < 0.001; Analysis 1.4).

Surgical site infection

Thirteen trials contributed to the combined calculation of the risk of surgical site infection in participants with and without the use of FG (Cipolla 2010; Dinsmore 2000; Jain 2004; Johnson 2005 ; Ko 2009; Langer 2003; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Ulusoy 2003). There was no heterogeneity (I^2 = 0%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of surgical site infection in people undergoing

breast and axillary surgery for cancer (RR 1.05; 95% CI 0.63 to 1.77, P value = 0.84; Analysis 1.5, refer to Figure 3).

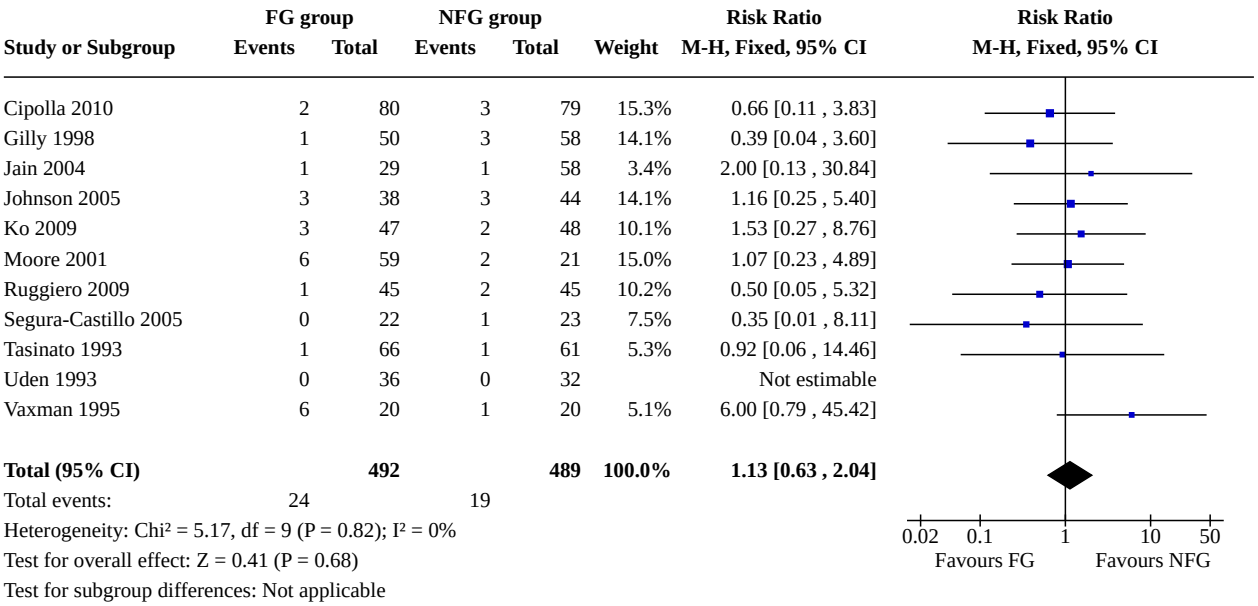
Figure 3. Forest plot of comparison: 1 All trials analysis, outcome: 1.5 Surgical site infection.



Postoperative complications

Eleven trials contributed to the combined calculation of the risk of surgical site infection in participants with and without the use of FG (Cipolla 2010; Gilly 1998; Jain 2004; Johnson 2005; Ko 2009; Moore 2001; Ruggiero 2009; Segura-Castillo 2005; Tasinato 1993; Uden 1993; Vaxman 1995). There was no heterogeneity (I^2 = 0%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of postoperative complications in people undergoing breast and axillary surgery for cancer (RR 1.13; 95% CI 0.63 to 2.04, P value = 0.68; Analysis 1.6, refer to Figure 4).

Figure 4. Forest plot of comparison: 1 All trials analysis, outcome: 1.6 Postoperative complications.



Length of hospital stay

There was significant heterogeneity (I^2 = 86%) among six studies contributing to the combined calculation of this variable (Gilly 1998; Jain 2004; Moore 1997; Mustonen 2004; Uden 1993; Vaxman 1995). In the random-effects model, the length of hospital stay between two groups was statistically the same (SMD -0.20; 95% CI -0.78 to 0.39, P value = 0.51; Analysis 1.7).

Subgroup analysis of trials on mastectomy

Ten RCTs encompassing 629 participants undergoing breast surgery for breast cancer were retrieved from the electronic databases (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Moore 1997; Moore 2001; Mustonen 2004; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995). There were 335 people in the FG group and 294 people in the NFG group.

Incidence of postoperative wound site seroma

All 10 trials contributed to the combined calculation of this variable (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Moore 1997; Moore 2001; Mustonen 2004; Tasinato 1993; Uden 1993; Ulusoy 2003; Vaxman 1995). There was no significant heterogeneity (I^2 = 10%) among studies. Therefore, in the fixed-effect model, FG was statistically ineffective in reducing the incidence of postoperative seroma in people undergoing breast and axillary surgery (RR 1.02; 95% CI 0.90 to 1.15, P value = 0.80; Analysis 2.1).

Mean volume of seroma

There was significant heterogeneity (I^2 = 72%) among six studies (Cipolla 2010; El-Nakeeb 2009; Mustonen 2004; Uden 1993; Ulusoy 2003; Vaxman 1995) contributing to the combined calculation of this variable. In the random-effects model, the mean volume of the seroma remained unchanged with and without the application of FG under skin flaps following axillary and breast surgery (SMD -0.24; 95% CI -0.63 to 0.15, P value = 0.23; Analysis 2.2).

Total volume of drained fluid

There was significant heterogeneity (I^2 = 93%) among 10 studies contributing to the combined calculation of this variable (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Uden 1993; Ulusoy 2003; Vaxman 1995). In the random-effects model, the total volume of drained seroma fluid reduced significantly with the application of FG under skin flaps following axillary and breast surgery (SMD -0.83; 95% CI -1.50 to -0.17, P value < 0.01; Analysis 2.3).

Number of days for persistent seroma drainage

There was significant heterogeneity (I^2 = 72%) among nine studies contributing to the combined calculation of this variable (Cipolla 2010; Dinsmore 2000; El-Nakeeb 2009; Moore 1997; Moore 2001; Mustonen 2004; Uden 1993; Ulusoy 2003; Vaxman 1995). In the random-effects model, the total duration of persistent seroma drainage reduced significantly with the application of FG under skin flaps following axillary and breast surgery (SMD -0.36; 95% CI -0.71 to -0.01; P value < 0.04; Analysis 2.4).

Surgical site infection

Eight trials contributed to the combined calculation of the risk of surgical site infection in people with and without the use of FG (Cipolla 2010; Dinsmore 2000; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Uden 1993; Ulusoy 2003). There was no heterogeneity (I^2 = 0%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of surgical site infection in people undergoing breast and axillary surgery for cancer (RR 1.13; 95% CI 0.60 to 2.10, P value = 0.71; Analysis 2.5).

Postoperative complications

Five trials contributed to the combined calculation of the risk of surgical site infection in people with and without the use of FG (Cipolla 2010; Moore 2001; Ruggiero 2009; Uden 1993; Vaxman 1995). There was no heterogeneity (I^2 = 14%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of postoperative complications in people undergoing breast and axillary surgery for cancer (RR 1.35; 95% CI 0.59 to 3.12, P value = 0.48; Analysis 2.6).

Length of hospital stay

There was no heterogeneity (I^2 = 0%) among four studies contributing to the combined calculation of this variable (Moore 1997; Mustonen 2004; Uden 1993; Vaxman 1995). In the random-effects model, the length of hospital stay between two groups was statistically the same (SMD 0.28; 95% CI -0.02 to 0.59, P value = 0.07; Analysis 2.7).

Subgroup analysis of trials on mastectomy plus axillary surgery

Seven RCTs encompassing 496 participants undergoing breast plus axillary surgery for breast cancer were retrieved from the electronic databases (Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Segura-Castillo 2005). There were 224 people in the FG group and 272 people in the NFG group.

Incidence of postoperative wound site seroma

Seven trials contributed to the combined calculation of this variable (Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Segura-Castillo 2005). There was no significant heterogeneity (I^2 = 16%) among studies. Therefore, in the fixed-effect model, FG was statistically ineffective in reducing the incidence of postoperative seroma in participants undergoing breast and axillary surgery (RR 1.04; 95% CI 0.72 to 1.51; P value = 0.82; Analysis 3.1).

Mean volume of seroma

There was significant heterogeneity (I^2 = 96%) among three studies contributing to the combined calculation of this variable (Gioffrè Florio 1993; Jain 2004; Johnson 2005). In the random-effects model, the mean volume of the seroma remained unchanged with and without the application of FG under skin flaps following axillary and breast surgery (SMD -1.06; 95% CI -3.23 to 1.11, P value = 0.34; Analysis 3.2).

Total volume of drained fluid

There was significant heterogeneity (I^2 = 76%) among three studies contributing to the combined calculation of this variable (Gilly 1998; Ko 2009; Langer 2003). In the random-effects model, the total volume of drained seroma fluid reduced significantly with the application of FG under skin flaps following axillary and breast

surgery (SMD -0.54; 95% CI -1.06 to -0.02, P value < 0.04; Analysis 3.3).

Number of days for persistent seroma drainage

There was significant heterogeneity (I^2 = 86%) among three studies contributing to the combined calculation of this variable (Ko 2009; Langer 2003; Segura-Castillo 2005). In the random-effects model, the total duration of persistent seroma drainage reduced significantly with the application of FG under skin flaps following axillary and breast surgery (SMD -0.68; 95% CI -0.98 to -0.39, P value < 0.001; Analysis 3.4).

Surgical site infection

Five trials contributed to the combined calculation of the risk of surgical site infection in participants with and without the use of FG (Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Segura-Castillo 2005). There was no heterogeneity (I^2 = 0%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of surgical site infection in people undergoing breast and axillary surgery for cancer (RR 1.18; 95% CI 0.44 to 3.16, P value = 0.74; Analysis 3.5).

Postoperative complications

Five trials contributed to the combined calculation of the risk of surgical site infection in participants with and without the use of FG (Gilly 1998; Jain 2004; Johnson 2005 ; Ko 2009; Segura-Castillo 2005). There was no heterogeneity (I^2 = 0%) among included studies. Therefore, in the fixed-effect model, the use of FG was not associated with an increased incidence of postoperative complications in participants undergoing breast and axillary surgery for cancer (RR 0.95; 95% CI 0.39 to 2.28, P value = 0.91; Analysis 3.6).

Length of hospital stay

There was significant heterogeneity (I^2 = 40%) among two studies contributing to the combined calculation of this variable (Gilly 1998; Jain 2004). In the random-effects model, the length of hospital stay was slightly shorter in the FG group (SMD -0.93; 95% CI -1.23 to -0.62, P value < 0.001; Analysis 3.7).

DISCUSSION

Summary of main results

Based on the results of this systematic review of 18 RCTs involving 1252 people undergoing breast and axillary surgery for breast cancer, the use of FG failed to reduce the incidence of postoperative seroma, mean volume of seroma, surgical site infection, postoperative complications and length of hospital stay. FG statistically reduced the total volume of drained seroma and duration of persistent seroma requiring frequent aspirations.

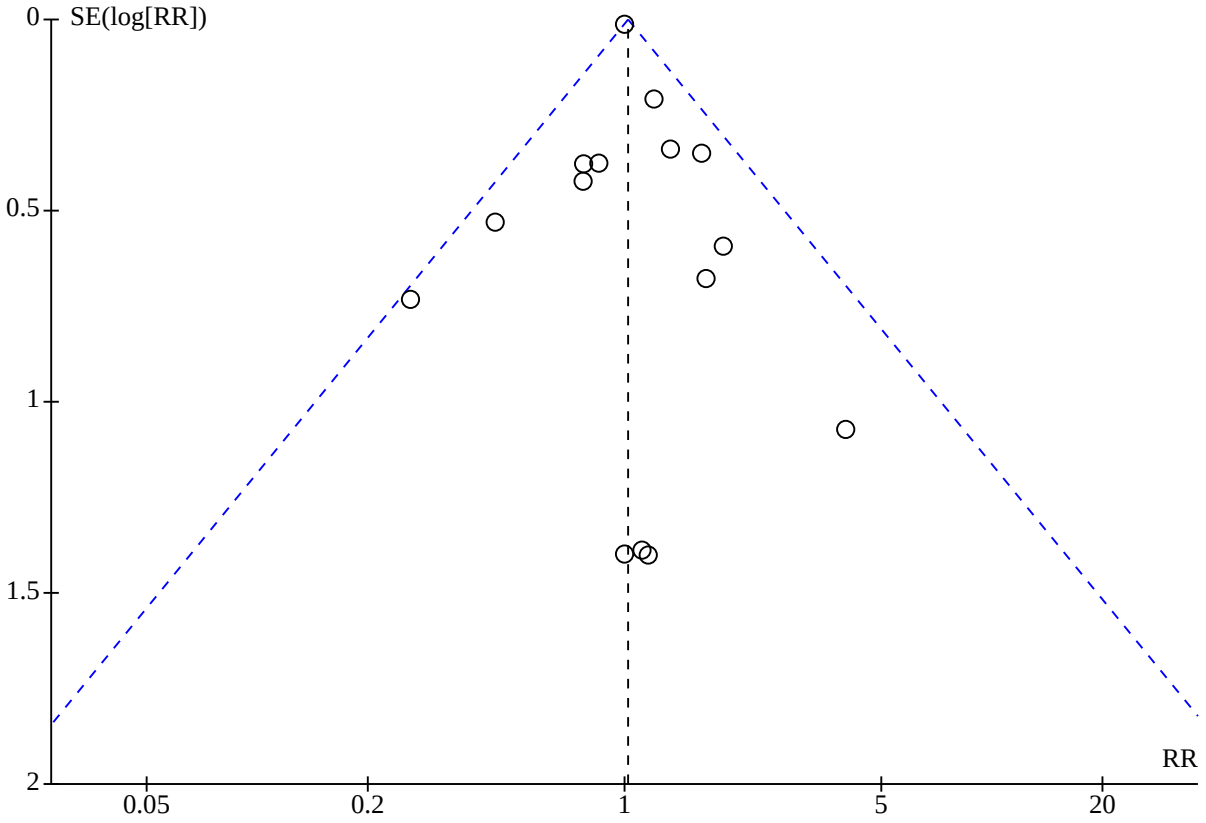
Overall completeness and applicability of evidence

The majority of the included RCTs evaluated the primary outcome of seroma incidence according to the pretrial analysis strategy (Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Uden 1993; Ulusoy 2003; Vaxman 1995). The utilisation of seroma incidence as a primary end point following breast and axillary surgery was well targeted because the presence of seroma at the surgery site is associated with frequent re-interventions, prolonged hospital stay, increased utilisation of healthcare resources, and delayed adjuvant chemotherapy or radiotherapy, or both. The primary outcome was thoroughly investigated and adequately reported in all RCTs including three trials (Cipolla 2010; Moore 1997; Tasinato 1993), which investigated the incidence of postoperative seroma as a secondary outcome. The summated outcome of the primary variable was conclusive and may be considered adequate. However, due to the inadequate quality of the majority of the included RCTs, the generalised application of this evidence is difficult to recommend. The review authors believe that a major, multicentre, high-quality RCT is mandatory to strengthen the existing evidence and validate these findings.

Quality of the evidence

There was a lack of adequate randomisation technique, allocation concealment, single or double blinding, ITT analysis, power of the study, conflict of interest declaration and ethics approval in the majority of the included trials (Dinsmore 2000; El-Nakeeb 2009; Gilly 1998; Gioffrè Florio 1993; Jain 2004; Johnson 2005; Ko 2009; Langer 2003; Moore 2001; Mustonen 2004; Ruggiero 2009; Segura-Castillo 2005; Uden 1993; Ulusoy 2003; Vaxman 1995). Therefore, the quality of this evidence may be considered inadequate and biased. The sensitivity analysis (Figure 5) performed on the combined analysis of all RCTs displayed the majority of trials away from the central bar, indicating diversity among the trials and potential outliers.

Figure 5. Funnel plot of comparison: 1 All trials analysis, outcome: 1.1 Incidence of postoperative seroma.



Potential biases in the review process

The routine use of FG under skin flaps following breast and axillary surgery may not be recommended because of inadequate evidence and several limitations in the present review. There were significant differences in the inclusion and exclusion criteria among the included trials, such as the recruitment of people undergoing simultaneous breast and axillary surgery, breast surgery alone, axillary surgery alone, radical mastectomy and breast conserving surgery. Varying degrees of differences also existed among the trials for the definitions of 'post-operative seroma', 'measurement scales' and diagnostic tools for postoperative seroma. The RCTs with fewer participants in this review may not have been sufficient to recognise small differences in the primary and secondary outcomes particularly in the absence of adequate power calculations. Therefore, the conclusion of this review should be viewed cautiously in current clinical practice.

Agreements and disagreements with other studies or reviews

Findings of this review are consistent with the previously reported nine RCTs (Cipolla 2010; Dinsmore 2000; Jain 2004; Johnson 2005; Ruggiero 2009; Uden 1993; Ulusoy 2003; Vaxman 1995) and a meta-analysis (Carless 2006) conferring that the application of FG under skin flaps following axillary and breast surgery for breast cancer failed to reduce the incidence of seroma formation, volume of seroma, length of hospital stay and postoperative complications. However, a few RCTs concluded that the use of FG leads to a significant reduction in postoperative drainage, earlier removal of drains and a decrease in the amount of aspirated fluid without a reduction in the incidence of postoperative seroma in people undergoing breast and axillary surgery for breast cancer (El-Nakeeb 2009; Gioffrè Florio 1993; Langer 2003; Moore 1997; Moore 2001; Mustonen 2004; Ruggiero 2009; Tasinato 1993).

AUTHORS' CONCLUSIONS

Implications for practice

At present, there is no high-quality evidence available to suggest that FG is either effective or ineffective in reducing the incidence of postoperative seroma and related morbidities in people undergoing breast and axillary surgery for breast cancer. There is significant clinical and methodological diversity among the published RCTs investigating the role of FG and with variable outcomes and conclusions. Despite having several limitations in this review, we still believe that the meta-analysis presented in this review provides the current, best available evidence in making the clinical decision about the role of FG in breast and axillary surgery.

Implications for research

The conclusion of this review opens the channels for further research on this very important area of breast and oncoplastic surgery. A major, multicentre, RCT of high quality is required in order to strengthen the current evidence. Trials on participants with various types of surgery such as simple mastectomy, MRM, breast-conserving surgery, axillary dissection, axillary sampling and sentinel node biopsy should be conducted separately to

find which group may benefit more from the application of FG. Studies on the use of FG in people undergoing simultaneous oncoplastic procedures should also be performed to define actual effectiveness. Trials should be conducted in such a manner that the effect of confounding and adjunctive procedures can be excluded. Methodologically sound and robust RCTs are needed in order to investigate the role of various commercial brands of FG. RCTs evaluating the economic impact of FG, long-term effectiveness of FG and HRQoL should be conducted. When conducting and reporting RCTs, the investigators should follow the CONSORT statement for reporting controlled trials (CONSORT 2010) so that the RCTs can be precisely and accurately evaluated by readers and reviewers.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cipolla 2010

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: not reported Allocation concealment: inadequately reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not mentioned Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Italy Number of participants: FG: 80 and NFG: 79 Mean age (years): FG 59.1 ± 13.93; NFG 58.8 ± 10.8
Interventions	FG: Tissucol® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • quadrantectomy Confounding interventions: none
Outcomes	Primary:

Cipolla 2010 *(Continued)*

- mean duration of axillary drainage

Secondary:

- mean total drainage volume
- mean seroma aspirate volume
- mean number of seroma aspirations
- wound infection
- postoperative complications
- incidence of seroma
- complications

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Dinsmore 2000

Study characteristics

Methods	Study design: prospective randomised controlled trial Randomisation technique: not reported Allocation concealment: inadequately reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not mentioned Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported

Dinsmore 2000 *(Continued)*

	Sample size calculations (power of the study): not reported
Participants	Country: USA Number of participants: FG: 14 and NFG: 13 Mean age (years): FG 62.3 ± 2.1; NFG 64.5 ± 2.8
Interventions	FG: Tissucol® was applied under skin flaps following breast and axillary surgery Types of surgical intervention • modified radical mastectomy Confounding interventions: none
Outcomes	Primary: • incidence of seroma Secondary: • total drainage volume • postoperative complications • mean duration of axillary drainage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

El-Nakeeb 2009

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: inadequately reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not mentioned Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Egypt Number of participants: FG: 25 and NFG: 25 Mean age: not reported
Interventions	FG: make of fibrin was not reported Types of surgical intervention: • modified radical mastectomy Confounding interventions: none
Outcomes	Primary: • incidence of seroma Secondary: • total drainage volume • mean duration of drainage • complications
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported

El-Nakeeb 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	No
Other bias	High risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration were not reported

Gilly 1998

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: not reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not mentioned Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: France Number of participants: FG: 50 and NFG: 58 Mean age (years): FG 60.6 ± 10.8; NFG 62.5 ± 11.5
Interventions	FG: Tissucol® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • sector mastectomy Confounding interventions: • pressure dressing • shoulder physiotherapy
Outcomes	Primary: • incidence of seroma Secondary: • length of hospital stay • postoperative complications • total seroma volume
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported

Gilly 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	High risk	No declaration of ethics approval and conflict of interest

Gioffrè Florio 1993

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: not reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not mentioned Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Italy Number of participants: FG: 12 and NFG: 12 Mean age: not reported
Interventions	FG: Tissucol® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • wide local excision • axillary dissection Confounding interventions: • drain insertion
Outcomes	Primary: • incidence of seroma Secondary: • mean seroma volume
Notes	

Gioffrè Florio 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	High risk	No reporting of conflict of interest

Jain 2004

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: computer-generated random numbers Allocation concealment: reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: reported Sample size calculations (power of the study): reported
Participants	Country: UK Number of participants: FG: 29 and NFG: 58 Mean age (years): FG 62.3 ± 12.3; NFG 61.9 ± 13.2
Interventions	FG: Tisseel® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • segmentectomy • axillary dissection Confounding interventions: • pressure dressing

Jain 2004 *(Continued)*

	• drain insertion
Outcomes	Primary: • incidence of seroma Secondary: • length of hospital stay • postoperative complications • mean seroma volume • wound infection
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation technique
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate reporting
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reporting
Selective reporting (reporting bias)	High risk	Missing data of secondary variables
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Johnson 2005

Study characteristics

Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: inadequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported

Johnson 2005 *(Continued)*

	Sample size calculations (power of the study): not reported
Participants	Country: USA Number of participants: FG: 38 and NFG: 44 Mean age (years): FG 58.6 ± 11.3 NFG; 59.5 ± 12.8
Interventions	FG: Hemaseel® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • wide local excision • axillary dissection Confounding interventions: • none
Outcomes	Primary: • incidence of seroma Secondary: • length of hospital stay • postoperative complications • mean seroma volume • wound infection
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Ko 2009

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: web-based Allocation concealment: adequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: adequate Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: reported Sample size calculations (power of the study): reported
Participants	Country: South Korea Number of participants: FG: 50 and NFG: 50 Mean age (years): FG 48.5 ± 8.7; NFG 47.9 ± 7.7
Interventions	FG: Greemplast Kit® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • lumpectomy Confounding interventions: • compression for 5 days
Outcomes	Primary: • incidence of seroma Secondary: • mean volume of seroma • postoperative complications • wound infection • total volume of seroma • mean number of drainage days
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Web based
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate
Blinding of outcome assessment (detection bias)	Low risk	Adequate

Ko 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Langer 2003

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: inadequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: USA Number of participants: FG: 26 and NFG: 29 Mean age (years): FG 60.8 ± 7.3; NFG 56.3 ± 11.8
Interventions	FG: Tisseel® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • sector mastectomy • axillary dissection Confounding interventions: • reduced shoulder mobilisation
Outcomes	Primary: • incidence of seroma Secondary: • drainage days • total seroma volume • wound infection
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement

Langer 2003 *(Continued)*

Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported.

Moore 1997

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: lottery based Allocation concealment: adequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: adequate Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: USA Number of participants: FG: 11 and NFG: 10 Mean age (years): FG 56.5 ± 13.5; NFG 62.9 ± 14.9
Interventions	FG: autologous fibrinogen + thrombin was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy Confounding interventions: • none
Outcomes	Primary: • total seroma volume Secondary:

Moore 1997 *(Continued)*

- length of hospital stay
- seroma incidence

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Lottery based
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Inadequate
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Moore 2001

Study characteristics

Methods	Study design: prospective randomised controlled trial Randomisation technique: computer generated Allocation concealment: adequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: adequate Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: USA Number of participants: FG: 59 and NFG: 21 Mean age (years): FG 59 ± 16 NFG 56 ± 14
Interventions	FG: fibrinogen + thrombin was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy

Moore 2001 *(Continued)*

	• lumpectomy Confounding interventions: • none
Outcomes	Primary: • seroma incidence Secondary: • wound infection • length of seroma drainage in days • total seroma volume • postoperative complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Adequately adopted
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequately reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequately reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Mustonen 2004

Study characteristics

Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: adequate Inclusion criteria: well explained Exclusion criteria: well explained

Mustonen 2004 *(Continued)*

	Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): reported
Participants	Country: Finland Number of participants: FG: 19 and NFG: 21 Mean age (years): FG 67.5 ± 13.6 NFG 66.1 ± 12
Interventions	FG: Tisseel® was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy Confounding interventions: • compression bandage of the chest wall
Outcomes	Primary: • seroma incidence Secondary: • wound infection • length of seroma drainage in days • total seroma volume • mean seroma volume • length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation
Allocation concealment (selection bias)	High risk	Inadequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No

Mustonen 2004 *(Continued)*

Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Ruggiero 2009

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: not reported Allocation concealment: inadequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Italy Number of participants: FG: 45 and NFG: 45 Mean age: not reported
Interventions	FG: not reported Types of surgical intervention: • modified radical mastectomy • quadrantectomy Confounding interventions: • compression dressing for 24-72 hours
Outcomes	Primary: • incidence of seroma Secondary: • postoperative complications • total seroma volume • wound infection
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Not reported

Ruggiero 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	High risk	No declaration of conflict of interest and ethics approval

Segura-Castillo 2005

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: adequate Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Mexico Number of participants: FG: 22 and NFG: 23 Mean age (years): FG 48.36 ± 8.9; NFG 52.87 ± 9.74
Interventions	FG: Quixil ™ was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • axillary dissection Confounding interventions: • none
Outcomes	Primary: • seroma incidence Secondary: • wound infection • length of seroma drainage in days • postoperative complications
Notes	
Risk of bias	

Segura-Castillo 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers
Allocation concealment (selection bias)	Low risk	Reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Tasinato 1993

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: not reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Italy Number of participants: FG: 66 and NFG: 61 Mean age (years): FG 49 ± 22; NFG 47 ± 19
Interventions	FG: Tissucol®was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • axillary dissection Confounding interventions: • pressure dressing
Outcomes	Primary:

Tasinato 1993 *(Continued)*

- mean seroma volume

Secondary:

- wound infection
- length of seroma drainage in days
- seroma incidence
- postoperative complications

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation
Allocation concealment (selection bias)	High risk	Inadequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported.

Uden 1993

Study characteristics

Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): reported
Participants	Country: Sweden Number of participants: FG: 36 and NFG: 32

Uden 1993 *(Continued)*

	Age (years): FG 73 (42-89); NFG 70 (40-84)
Interventions	FG: Tisseel®was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy Confounding interventions: • none
Outcomes	Primary: • incidence of seroma Secondary: • wound infection • length of seroma drainage in days • mean volume of seroma • total volume of seroma • complications • length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation
Allocation concealment (selection bias)	High risk	No clear reporting
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	Inclusion, exclusion criteria, ethics approval and conflict of interest declaration was adequately reported

Ulusoy 2003

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: not reported Allocation concealment: not reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: Turkey Number of participants: FG: 27 and NFG: 27 Age (years): FG 51.4 ± 12.2; NFG 50.9 ± 10.9
Interventions	FG: Tisseel®was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy Confounding interventions: • none
Outcomes	Primary: • incidence of seroma Secondary: • wound infection • length of seroma drainage in days • mean volume of seroma • total volume of seroma
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported

Ulusoy 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	No
Other bias	High risk	No declaration of conflict of interest and ethics approval

Vaxman 1995

Study characteristics	
Methods	Study design: prospective randomised controlled trial Randomisation technique: random allocation Allocation concealment: not reported Inclusion criteria: well explained Exclusion criteria: well explained Lost to follow-up: not reported Baseline variables: matching between both limbs of the trial Intention-to-treat analysis: not reported Sample size calculations (power of the study): not reported
Participants	Country: France Number of participants: FG: 20 and NFG: 20 Age (years): FG 55.6 ± 12; NFG 56.2 ± 10
Interventions	FG: Tisseel®was applied under skin flaps following breast and axillary surgery Types of surgical intervention: • modified radical mastectomy • lumpectomy Confounding interventions: • pressure dressing • shoulder physiotherapy
Outcomes	Primary: • incidence of seroma Secondary: • postoperative complications • length of seroma drainage in days • mean volume of seroma • total volume of seroma • length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Vaxman 1995 *(Continued)*

Random sequence generation (selection bias)	High risk	Participants were allocated randomly to both arms of the trial
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	High risk	Missing data on secondary variables
Other bias	High risk	No declaration of conflict of interest and ethics approval

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berger 2001	Use of fibrin glue-coated collagen patch to reduce seroma following axillary dissection
Medl 1995	Non-randomised study
Neuss 2008	Use of fibrin glue to reduce the duration of suction drainage in people undergoing axillary dissection for melanoma

FG: fibrin glue; NFG: no-fibrin glue.

DATA AND ANALYSES

Comparison 1. All trials analysis

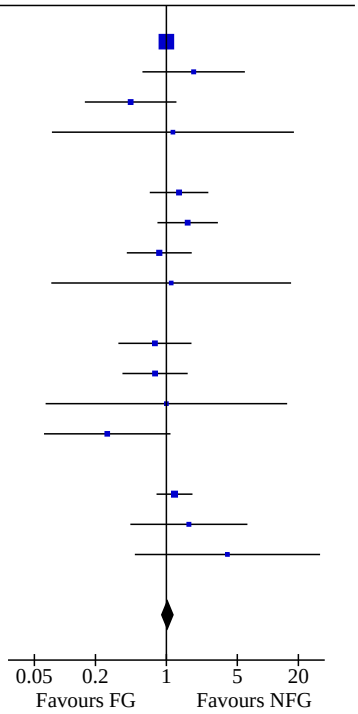
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of postoperative seroma	18	1252	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.16]
1.2 Mean volume of seroma	10	731	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.92, 0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Total volume of drained seroma	13	888	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.24, -0.26]
1.4 Number of days for persistent drainage	13	861	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.95, -0.23]
1.5 Surgical site infection	13	1009	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.63, 1.77]
1.6 Postoperative complications	11	981	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.04]
1.7 Length of hospital stay	6	364	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.78, 0.39]

Analysis 1.1. Comparison 1: All trials analysis, Outcome 1: Incidence of postoperative seroma

Study or Subgroup	FG group Events	FG group Total	NFG group Events	NFG group Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	80	80	79	79	45.9%	1.00 [0.98 , 1.02]
Dinsmore 2000	6	14	3	13	1.8%	1.86 [0.58 , 5.94]
El-Nakeeb 2009	4	25	9	25	5.2%	0.44 [0.16 , 1.26]
Gilly 1998	1	50	1	58	0.5%	1.16 [0.07 , 18.07]
Gioffrè Florio 1993	0	12	0	12		Not estimable
Jain 2004	10	29	15	58	5.7%	1.33 [0.69 , 2.59]
Johnson 2005	14	38	10	44	5.3%	1.62 [0.82 , 3.22]
Ko 2009	10	47	12	48	6.8%	0.85 [0.41 , 1.78]
Langer 2003	1	26	1	29	0.5%	1.12 [0.07 , 16.95]
Moore 1997	0	10	0	11		Not estimable
Moore 2001	13	59	6	21	5.1%	0.77 [0.34 , 1.77]
Mustonen 2004	7	19	10	21	5.5%	0.77 [0.37 , 1.62]
Ruggiero 2009	1	45	1	45	0.6%	1.00 [0.06 , 15.50]
Segura-Castillo 2005	2	22	8	23	4.5%	0.26 [0.06 , 1.10]
Tasinato 1993	0	66	0	61		Not estimable
Uden 1993	23	36	17	32	10.3%	1.20 [0.80 , 1.81]
Ulusoy 2003	5	27	3	27	1.7%	1.67 [0.44 , 6.29]
Vaxman 1995	4	20	1	20	0.6%	4.00 [0.49 , 32.72]
Total (95% CI)		**625**		**627**	**100.0%**	**1.02 [0.90 , 1.16]**
Total events:	181		176			

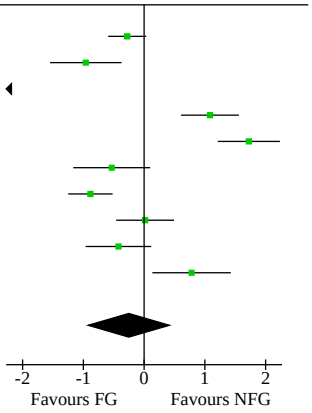
Heterogeneity: Chi² = 16.50, df = 14 (P = 0.28); I² = 15%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: All trials analysis, Outcome 2: Mean volume of seroma

Study or Subgroup	FG group Mean	FG group SD	FG group Total	NFG group Mean	NFG group SD	NFG group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	432.6	192.7	80	489.2	212.5	79	11.2%	-0.28 [-0.59 , 0.03]
El-Nakeeb 2009	150	75.9	25	253.51	129.5	25	10.6%	-0.96 [-1.55 , -0.37]
Gioffrè Florio 1993	244.5	5.8	12	319	7.45	12	2.9%	-10.77 [-14.20 , -7.35]
Jain 2004	165	27.75	29	140	20	58	10.9%	1.08 [0.61 , 1.56]
Johnson 2005	438.9	260.9	38	120.9	59.6	44	10.8%	1.72 [1.21 , 2.24]
Mustonen 2004	112.9	230.6	19	285.6	379.5	21	10.4%	-0.53 [-1.17 , 0.10]
Tasinato 1993	187.3	219.75	66	379.6	212.5	61	11.1%	-0.88 [-1.25 , -0.52]
Uden 1993	90	687.5	36	80	451.25	32	10.9%	0.02 [-0.46 , 0.49]
Ulusoy 2003	62	21.59	27	70	15.27	27	10.7%	-0.42 [-0.96 , 0.12]
Vaxman 1995	410.4	169.2	20	275.5	169.2	20	10.4%	0.78 [0.14 , 1.43]
Total (95% CI)			**352**			**379**	**100.0%**	**-0.25 [-0.92 , 0.42]**

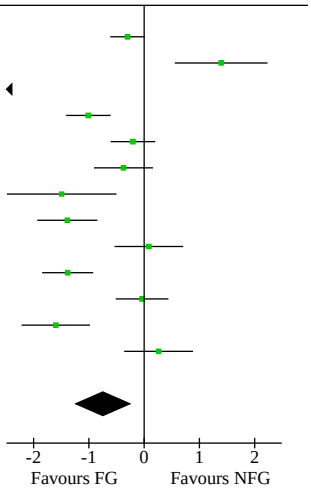
Heterogeneity: Tau² = 1.01; Chi² = 147.44, df = 9 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: All trials analysis, Outcome 3: Total volume of drained seroma

Study or Subgroup	FG group Mean	FG group SD	FG group Total	NFG group Mean	NFG group SD	NFG group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	326.5	112.3	80	361.6	120.3	79	8.5%	-0.30 [-0.61 , 0.01]
Dinsmore 2000	1308	386.1	14	754	386.1	14	7.0%	1.39 [0.55 , 2.23]
El-Nakeeb 2009	770.48	70.81	25	1089.51	75	25	6.3%	-4.31 [-5.34 , -3.27]
Gilly 1998	214.4	105.9	50	407.8	240.1	58	8.3%	-1.01 [-1.41 , -0.61]
Ko 2009	174	87	47	197	132	48	8.3%	-0.20 [-0.61 , 0.20]
Langer 2003	411	280	26	504	209.5	29	8.0%	-0.37 [-0.91 , 0.16]
Moore 1997	346.1	245.3	10	745.7	267.3	11	6.4%	-1.49 [-2.48 , -0.50]
Moore 2001	473	255.9	59	893.8	400.9	21	7.9%	-1.39 [-1.93 , -0.85]
Mustonen 2004	181.25	141.01	19	168.95	140.95	21	7.7%	0.09 [-0.54 , 0.71]
Ruggiero 2009	120	72.5	45	250	110	45	8.1%	-1.38 [-1.85 , -0.92]
Uden 1993	520	745	36	546	618.75	32	8.1%	-0.04 [-0.51 , 0.44]
Ulusoy 2003	738.48	90.65	27	886.44	91.75	27	7.7%	-1.60 [-2.22 , -0.98]
Vaxman 1995	479.8	190.3	20	425.9	212.6	20	7.7%	0.26 [-0.36 , 0.88]
Total (95% CI)			**458**			**430**	**100.0%**	**-0.75 [-1.24 , -0.26]**

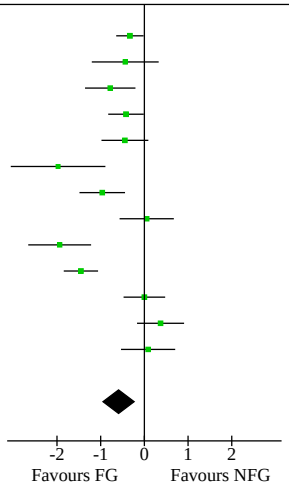
Heterogeneity: Tau² = 0.71; Chi² = 132.06, df = 12 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: All trials analysis, Outcome 4: Number of days for persistent drainage

Study or Subgroup	FG group Mean	FG group SD	FG group Total	NFG group Mean	NFG group SD	NFG group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	4.5	1.7	80	5.1	1.9	79	9.0%	-0.33 [-0.64 , -0.02]
Dinsmore 2000	12.3	9.3	14	16.5	9.3	13	6.7%	-0.44 [-1.20 , 0.33]
El-Nakeeb 2009	9.88	1.56	25	11.62	2.68	25	7.7%	-0.78 [-1.36 , -0.20]
Ko 2009	3.3	0.9	47	3.8	1.4	48	8.6%	-0.42 [-0.83 , -0.01]
Langer 2003	7	3.25	26	8.3	2.5	29	8.0%	-0.45 [-0.98 , 0.09]
Moore 1997	3.9	1.7	10	6.9	1.2	11	5.1%	-1.97 [-3.06 , -0.89]
Moore 2001	5.38	2.4	59	8	3.4	21	8.0%	-0.96 [-1.48 , -0.44]
Mustonen 2004	2.75	1.02	19	2.7	0.81	21	7.5%	0.05 [-0.57 , 0.67]
Segura-Castillo 2005	5.09	1.48	22	8.96	2.33	23	6.9%	-1.94 [-2.66 , -1.22]
Tasinato 1993	9.4	6.5	66	20.2	8.25	61	8.7%	-1.45 [-1.84 , -1.06]
Uden 1993	3	1	36	3	1	32	8.3%	0.00 [-0.48 , 0.48]
Ulusoy 2003	9.88	0.59	27	9.66	0.58	27	7.9%	0.37 [-0.17 , 0.91]
Vaxman 1995	4.08	2.04	20	3.92	1.59	20	7.5%	0.09 [-0.53 , 0.71]
Total (95% CI)			**451**			**410**	**100.0%**	**-0.59 [-0.95 , -0.23]**

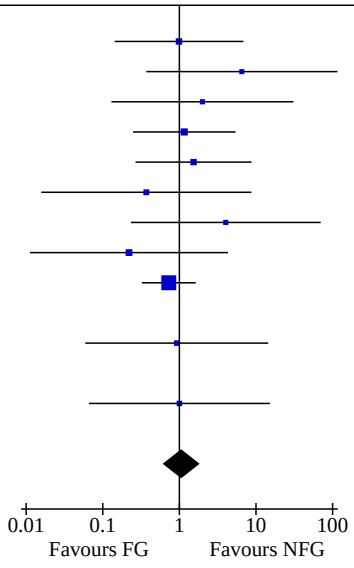
Heterogeneity: Tau² = 0.34; Chi² = 70.80, df = 12 (P < 0.00001); I² = 83%
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: All trials analysis, Outcome 5: Surgical site infection

Study or Subgroup	FG group Events	FG group Total	NFG group Events	NFG group Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	2	80	2	79	7.9%	0.99 [0.14 , 6.84]
Dinsmore 2000	3	14	0	13	2.0%	6.53 [0.37 , 115.49]
Jain 2004	1	29	1	58	2.6%	2.00 [0.13 , 30.84]
Johnson 2005	3	38	3	44	10.9%	1.16 [0.25 , 5.40]
Ko 2009	3	47	2	48	7.8%	1.53 [0.27 , 8.76]
Langer 2003	0	26	1	29	5.6%	0.37 [0.02 , 8.71]
Moore 2001	5	59	0	21	2.9%	4.03 [0.23 , 69.98]
Mustonen 2004	0	19	2	21	9.3%	0.22 [0.01 , 4.31]
Ruggiero 2009	8	45	11	45	43.1%	0.73 [0.32 , 1.64]
Segura-Castillo 2005	0	22	0	23		Not estimable
Tasinato 1993	1	66	1	61	4.1%	0.92 [0.06 , 14.46]
Uden 1993	0	36	0	32		Not estimable
Ulusoy 2003	1	27	1	27	3.9%	1.00 [0.07 , 15.18]
Total (95% CI)		**508**		**501**	**100.0%**	**1.05 [0.63 , 1.77]**
Total events:	27		24			

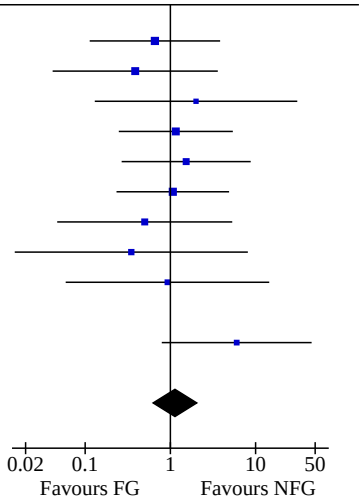
Heterogeneity: Chi² = 5.11, df = 10 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: All trials analysis, Outcome 6: Postoperative complications

Study or Subgroup	FG group Events	FG group Total	NFG group Events	NFG group Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	2	80	3	79	15.3%	0.66 [0.11 , 3.83]
Gilly 1998	1	50	3	58	14.1%	0.39 [0.04 , 3.60]
Jain 2004	1	29	1	58	3.4%	2.00 [0.13 , 30.84]
Johnson 2005	3	38	3	44	14.1%	1.16 [0.25 , 5.40]
Ko 2009	3	47	2	48	10.1%	1.53 [0.27 , 8.76]
Moore 2001	6	59	2	21	15.0%	1.07 [0.23 , 4.89]
Ruggiero 2009	1	45	2	45	10.2%	0.50 [0.05 , 5.32]
Segura-Castillo 2005	0	22	1	23	7.5%	0.35 [0.01 , 8.11]
Tasinato 1993	1	66	1	61	5.3%	0.92 [0.06 , 14.46]
Uden 1993	0	36	0	32		Not estimable
Vaxman 1995	6	20	1	20	5.1%	6.00 [0.79 , 45.42]
Total (95% CI)		**492**		**489**	**100.0%**	**1.13 [0.63 , 2.04]**
Total events:	24		19			

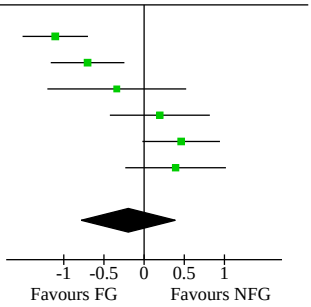
Heterogeneity: Chi² = 5.17, df = 9 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: All trials analysis, Outcome 7: Length of hospital stay

Study or Subgroup	FG group Mean	FG group SD	FG group Total	NFG group Mean	NFG group SD	NFG group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gilly 1998	8	1.6	50	10.1	2.1	58	18.2%	-1.11 [-1.51 , -0.70]
Jain 2004	1.9	0.9	29	2.9	1.6	58	17.8%	-0.70 [-1.16 , -0.25]
Moore 1997	1.18	0.6	10	1.41	0.69	11	13.9%	-0.34 [-1.20 , 0.52]
Mustonen 2004	3.9	1	19	3.7	1	21	16.3%	0.20 [-0.43 , 0.82]
Uden 1993	5.7	3	36	4.3	3	32	17.6%	0.46 [-0.02 , 0.94]
Vaxman 1995	10.8	3.5	20	9.4	3.5	20	16.2%	0.39 [-0.23 , 1.02]
Total (95% CI)			**164**			**200**	**100.0%**	**-0.20 [-0.78 , 0.39]**

Heterogeneity: Tau² = 0.45; Chi² = 34.68, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Comparison 2. Trials on mastectomy

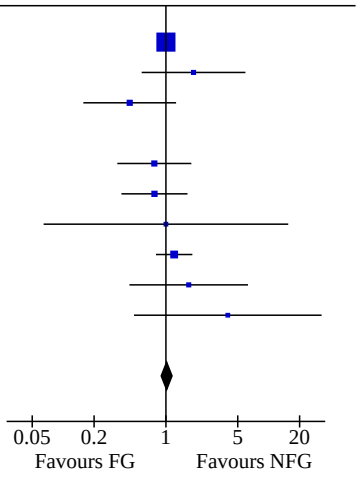
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of postoperative seroma	10	629	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
2.2 Mean volume of seroma	6	411	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.63, 0.15]
2.3 Total volume of drained seroma	10	629	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.17]
2.4 Number of days for persistent drainage	9	539	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.71, -0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Surgical site infection	8	522	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.60, 2.10]
2.6 Postoperative complications	5	437	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.59, 3.12]
2.7 Length of hospital stay	4	169	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.02, 0.59]

Analysis 2.1. Comparison 2: Trials on mastectomy, Outcome 1: Incidence of postoperative seroma

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	80	80	79	79	59.9%	1.00 [0.98 , 1.02]
Dinsmore 2000	6	14	3	13	2.3%	1.86 [0.58 , 5.94]
El-Nakeeb 2009	4	25	9	25	6.7%	0.44 [0.16 , 1.26]
Moore 1997	0	10	0	11		Not estimable
Moore 2001	13	59	6	21	6.6%	0.77 [0.34 , 1.77]
Mustonen 2004	7	19	10	21	7.1%	0.77 [0.37 , 1.62]
Ruggiero 2009	1	45	1	45	0.7%	1.00 [0.06 , 15.50]
Uden 1993	23	36	17	32	13.5%	1.20 [0.80 , 1.81]
Ulusoy 2003	5	27	3	27	2.2%	1.67 [0.44 , 6.29]
Vaxman 1995	4	20	1	20	0.7%	4.00 [0.49 , 32.72]
Total (95% CI)		**335**		**294**	**100.0%**	**1.02 [0.90 , 1.15]**
Total events:	143		129			

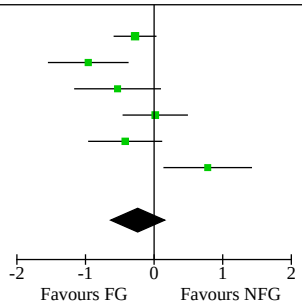
Heterogeneity: Chi² = 8.86, df = 8 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Trials on mastectomy, Outcome 2: Mean volume of seroma

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	432.6	192.7	80	489.2	212.5	79	20.8%	-0.28 [-0.59 , 0.03]
El-Nakeeb 2009	150	75.9	25	253.51	129.5	25	15.6%	-0.96 [-1.55 , -0.37]
Mustonen 2004	112.9	230.6	19	285.6	379.5	21	14.8%	-0.53 [-1.17 , 0.10]
Uden 1993	90	687.5	36	80	451.25	32	17.7%	0.02 [-0.46 , 0.49]
Ulusoy 2003	62	21.59	27	70	15.27	27	16.5%	-0.42 [-0.96 , 0.12]
Vaxman 1995	410.4	169.2	20	275.5	169.2	20	14.6%	0.78 [0.14 , 1.43]
Total (95% CI)			**207**			**204**	**100.0%**	**-0.24 [-0.63 , 0.15]**

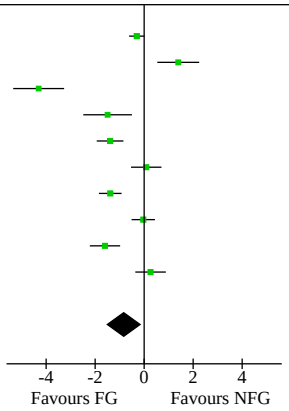
Heterogeneity: Tau² = 0.17; Chi² = 17.80, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Trials on mastectomy, Outcome 3: Total volume of drained seroma

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	326.5	112.3	80	361.6	120.3	79	10.9%	-0.30 [-0.61 , 0.01]
Dinsmore 2000	1308	386.1	14	754	386.1	13	9.4%	1.39 [0.54 , 2.25]
El-Nakeeb 2009	770.48	70.81	25	1089.51	75	25	8.8%	-4.31 [-5.34 , -3.27]
Moore 1997	346.1	245.3	10	745.7	267.3	11	8.9%	-1.49 [-2.48 , -0.50]
Moore 2001	473	255.9	59	893.8	400.9	21	10.4%	-1.39 [-1.93 , -0.85]
Mustonen 2004	181.25	141.01	19	168.95	140.95	21	10.2%	0.09 [-0.54 , 0.71]
Ruggiero 2009	120	72.5	45	250	110	45	10.6%	-1.38 [-1.85 , -0.92]
Uden 1993	520	745	36	545	618.75	32	10.5%	-0.04 [-0.51 , 0.44]
Ulusoy 2003	738.48	90.65	27	886.44	91.75	27	10.2%	-1.60 [-2.22 , -0.98]
Vaxman 1995	479.8	190.3	20	425.9	212.6	20	10.2%	0.26 [-0.36 , 0.88]
Total (95% CI)			**335**			**294**	**100.0%**	**-0.83 [-1.50 , -0.17]**

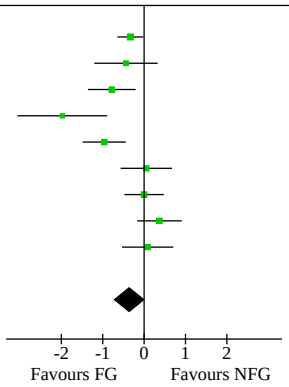
Heterogeneity: Tau² = 1.04; Chi² = 122.75, df = 9 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Trials on mastectomy, Outcome 4: Number of days for persistent drainage

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cipolla 2010	4.5	1.7	80	5.1	1.9	79	14.5%	-0.33 [-0.64 , -0.02]
Dinsmore 2000	12.3	9.3	14	16.5	9.3	13	9.3%	-0.44 [-1.20 , 0.33]
El-Nakeeb 2009	9.88	1.56	25	11.62	2.68	25	11.4%	-0.78 [-1.36 , -0.20]
Moore 1997	3.9	1.7	10	6.9	1.2	11	6.4%	-1.97 [-3.06 , -0.89]
Moore 2001	5.38	2.4	59	8	3.4	21	12.1%	-0.96 [-1.48 , -0.44]
Mustonen 2004	2.75	1.02	19	2.7	0.81	21	10.9%	0.05 [-0.57 , 0.67]
Uden 1993	3	1	36	3	1	32	12.6%	0.00 [-0.48 , 0.48]
Ulusoy 2003	9.88	0.59	27	9.66	0.58	27	11.9%	0.37 [-0.17 , 0.91]
Vaxman 1995	4.08	2.04	20	3.92	1.59	20	10.9%	0.09 [-0.53 , 0.71]
Total (95% CI)			**290**			**249**	**100.0%**	**-0.36 [-0.71 , -0.01]**

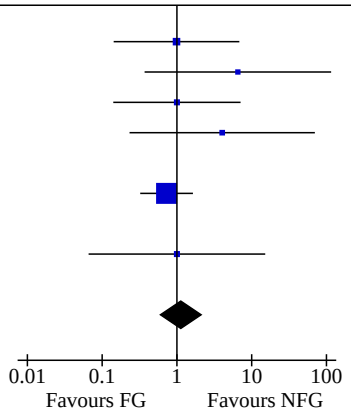
Heterogeneity: Tau² = 0.20; Chi² = 28.47, df = 8 (P = 0.0004); I² = 72%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Trials on mastectomy, Outcome 5: Surgical site infection

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	2	80	2	79	12.4%	0.99 [0.14 , 6.84]
Dinsmore 2000	3	14	0	13	3.2%	6.53 [0.37 , 115.49]
Moore 1997	1	2	1	2	6.1%	1.00 [0.14 , 7.10]
Moore 2001	5	59	0	21	4.5%	4.03 [0.23 , 69.98]
Mustonen 2004	0	19	0	21		Not estimable
Ruggiero 2009	8	45	11	45	67.6%	0.73 [0.32 , 1.64]
Uden 1993	0	36	0	32		Not estimable
Ulusoy 2003	1	27	1	27	6.1%	1.00 [0.07 , 15.18]
Total (95% CI)		**282**		**240**	**100.0%**	**1.13 [0.60 , 2.10]**
Total events:	20		15			

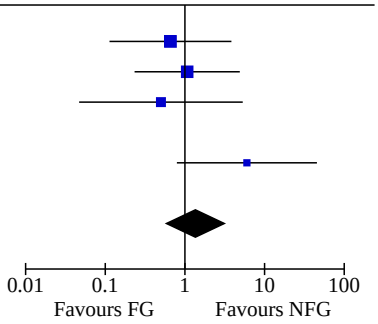
Heterogeneity: Chi² = 3.36, df = 5 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Trials on mastectomy, Outcome 6: Postoperative complications

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cipolla 2010	2	80	3	79	33.7%	0.66 [0.11 , 3.83]
Moore 2001	6	59	2	21	32.9%	1.07 [0.23 , 4.89]
Ruggiero 2009	1	45	2	45	22.3%	0.50 [0.05 , 5.32]
Uden 1993	0	36	0	32		Not estimable
Vaxman 1995	6	20	1	20	11.1%	6.00 [0.79 , 45.42]
Total (95% CI)		**240**		**197**	**100.0%**	**1.35 [0.59 , 3.12]**
Total events:	15		8			

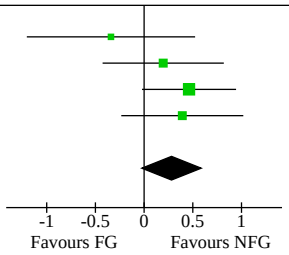
Heterogeneity: Chi² = 3.50, df = 3 (P = 0.32); I² = 14%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Trials on mastectomy, Outcome 7: Length of hospital stay

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Moore 1997	1.18	0.6	10	1.41	0.69	11	12.5%	-0.34 [-1.20 , 0.52]
Mustonen 2004	3.9	1	19	3.7	1	21	24.0%	0.20 [-0.43 , 0.82]
Uden 1993	5.7	3	36	4.3	3	32	39.9%	0.46 [-0.02 , 0.94]
Vaxman 1995	10.8	3.5	20	9.4	3.5	20	23.7%	0.39 [-0.23 , 1.02]
Total (95% CI)			**85**			**84**	**100.0%**	**0.28 [-0.02 , 0.59]**

Heterogeneity: Chi² = 2.71, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



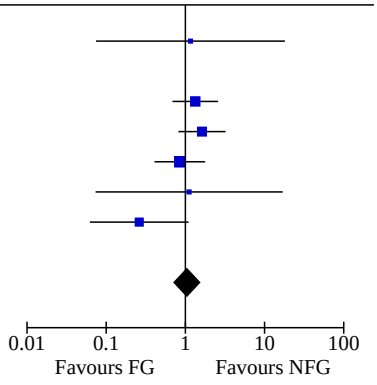
Comparison 3. Trials on mastectomy and axillary surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Incidence of postoperative seroma	7	496	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.72, 1.51]
3.2 Mean volume of seroma	3	193	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-3.23, 1.11]
3.3 Total volume of drained seroma	3	258	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.06, -0.02]
3.4 Number of days for persistent drainage	3	195	Std. Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.98, -0.39]
3.5 Surgical site infection	5	364	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.44, 3.16]
3.6 Postoperative complications	5	417	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.39, 2.28]
3.7 Length of hospital stay	2	195	Std. Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.23, -0.62]

Analysis 3.1. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 1: Incidence of postoperative seroma

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gilly 1998	1	50	1	58	2.3%	1.16 [0.07 , 18.07]
Gioffrè Florio 1993	0	12	0	12		Not estimable
Jain 2004	10	29	15	58	24.5%	1.33 [0.69 , 2.59]
Johnson 2005	14	38	10	44	22.7%	1.62 [0.82 , 3.22]
Ko 2009	10	47	12	48	29.1%	0.85 [0.41 , 1.78]
Langer 2003	1	26	1	29	2.3%	1.12 [0.07 , 16.95]
Segura-Castillo 2005	2	22	8	23	19.2%	0.26 [0.06 , 1.10]
Total (95% CI)		**224**		**272**	**100.0%**	**1.04 [0.72 , 1.51]**
Total events:	38		47			

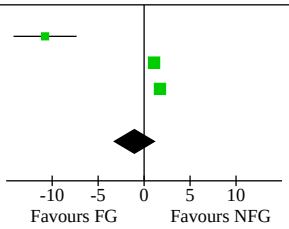
Heterogeneity: Chi² = 5.98, df = 5 (P = 0.31); I² = 16%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 2: Mean volume of seroma

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gioffrè Florio 1993	244.5	5.8	12	319	7.45	12	20.2%	-10.77 [-14.20 , -7.35]
Jain 2004	165	27.75	29	140	20	58	40.0%	1.08 [0.61 , 1.56]
Johnson 2005	438.9	260.9	38	120.9	59.6	44	39.8%	1.72 [1.21 , 2.24]
Total (95% CI)			**79**			**114**	**100.0%**	**-1.06 [-3.23 , 1.11]**

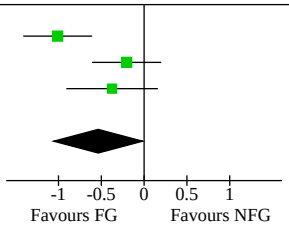
Heterogeneity: Tau² = 3.02; Chi² = 51.01, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 3: Total volume of drained seroma

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gilly 1998	214.4	105.9	50	407.8	240.1	58	35.0%	-1.01 [-1.41 , -0.61]
Ko 2009	174	87	47	197	132	48	34.9%	-0.20 [-0.61 , 0.20]
Langer 2003	411	280	26	504	209	29	30.1%	-0.37 [-0.91 , 0.16]
Total (95% CI)			**123**			**135**	**100.0%**	**-0.54 [-1.06 , -0.02]**

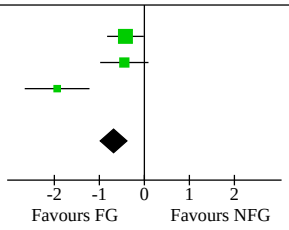
Heterogeneity: Tau² = 0.16; Chi² = 8.26, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 4: Number of days for persistent drainage

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ko 2009	3.3	0.9	47	3.8	1.4	48	52.8%	-0.42 [-0.83 , -0.01]
Langer 2003	7	3.25	26	8.3	2.5	29	30.4%	-0.45 [-0.98 , 0.09]
Segura-Castillo 2005	5.09	1.48	22	8.96	2.33	23	16.9%	-1.94 [-2.66 , -1.22]
Total (95% CI)			**95**			**100**	**100.0%**	**-0.68 [-0.98 , -0.39]**

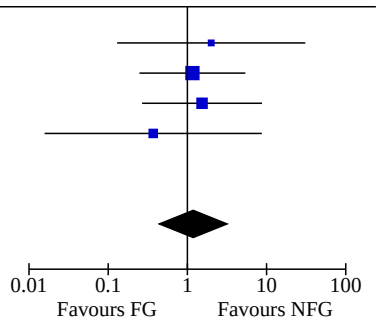
Heterogeneity: Chi² = 14.06, df = 2 (P = 0.0009); I² = 86%
Test for overall effect: Z = 4.54 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 5: Surgical site infection

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jain 2004	1	29	1	58	9.7%	2.00 [0.13 , 30.84]
Johnson 2005	3	38	3	44	40.6%	1.16 [0.25 , 5.40]
Ko 2009	3	47	2	48	28.9%	1.53 [0.27 , 8.76]
Langer 2003	0	26	1	29	20.8%	0.37 [0.02 , 8.71]
Segura-Castillo 2005	0	22	0	23		Not estimable
Total (95% CI)		**162**		**202**	**100.0%**	**1.18 [0.44 , 3.16]**
Total events:	7		7			

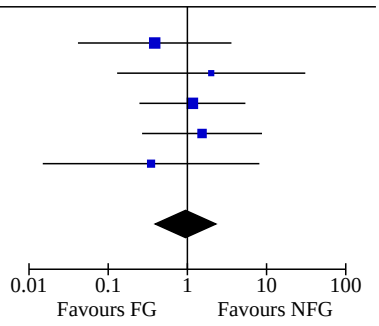
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 6: Postoperative complications

Study or Subgroup	FG Events	FG Total	NFG Events	NFG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gilly 1998	1	50	3	58	28.7%	0.39 [0.04 , 3.60]
Jain 2004	1	29	1	58	6.9%	2.00 [0.13 , 30.84]
Johnson 2005	3	38	3	44	28.7%	1.16 [0.25 , 5.40]
Ko 2009	3	47	2	48	20.5%	1.53 [0.27 , 8.76]
Segura-Castillo 2005	0	22	1	23	15.2%	0.35 [0.01 , 8.11]
Total (95% CI)		**186**		**231**	**100.0%**	**0.95 [0.39 , 2.28]**
Total events:	8		10			

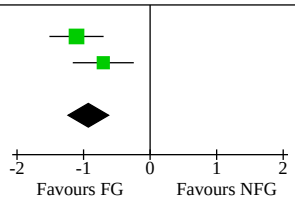
Heterogeneity: Chi² = 1.65, df = 4 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Trials on mastectomy and axillary surgery, Outcome 7: Length of hospital stay

Study or Subgroup	FG Mean	FG SD	FG Total	NFG Mean	NFG SD	NFG Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Gilly 1998	8	1.6	50	10.1	2.1	58	55.9%	-1.11 [-1.51 , -0.70]
Jain 2004	1.9	0.9	29	2.9	1.6	58	44.1%	-0.70 [-1.16 , -0.25]
Total (95% CI)			**79**			**116**	**100.0%**	**-0.93 [-1.23 , -0.62]**

Heterogeneity: Chi² = 1.65, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 5.98 (P < 0.00001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE via OvidSP (to 22 October 2012)

1	randomised controlled trial.pt.

(Continued)

2	randomized controlled trial.pt.
3	controlled clinical trial.pt.
4	randomized.ab.
5	randomised.ab.
6	placebo.ab.
7	randomly.ab.
8	trial.ab.
9	groups.ab.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp Breast Neoplasms/
12	exp Mastectomy/
13	mastectomy.mp.
14	exp Mastectomy, Modified Radical/
15	MRM.mp.
16	breast surgery.mp.
17	breast conserving surgery.mp.
18	oncoplastic breast surgery.mp.
19	exp Mastectomy, Segmental/
20	lumpectomy.mp.
21	quadrantectomy.mp.
22	axillary sentinel node biopsy.mp.
23	axillary sampling.mp.
24	axillary dissection.mp.
25	immediate total breast reconstruction.mp.
26	immediate partial breast reconstruction.mp.
27	exp Mammaplasty/
28	mammoplasty.mp.
29	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

(Continued)

30	11 and 29
31	exp Fibrin Tissue Adhesive/
32	exp Tissue Adhesives/
33	fibrin adhesive glue.mp.
34	fibrin glue.mp.
35	fibrin glue instillation.mp.
36	exp post-operative Complications/
37	exp Seroma/pc [Prevention & Control]
38	seroma prevention therapy.mp.
39	seroma prevention therapies.mp.
40	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	30 and 40
42	10 and 41
43	limit 42 to humans

Appendix 2. EMBASE via Embase.com (to 22 October 2012)

#45 #43 AND [humans]/lim AND [embase]/lim
#44 #8 AND #43
#43 #30 AND #42
#42 #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #39 OR #40 OR #41
#41 'seroma prevention therapies'
#40 'seroma prevention therapy'
#39

(Continued)

#37 AND #38
#38
'seroma'/exp OR seroma
#37
'prevention and control'/exp
#36
'postoperative complications'/exp OR 'postoperative complications'
#35
'fibrin glue instillation'
#34
'fibrin glue'/exp OR 'fibrin glue'
#33
'fibrin adhesive glue'
#32
'tissue adhesives'
#31
'fibrin glue adhesive'/exp OR 'fibrin glue adhesive'
#30
#14 AND #29
#29
#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#28
'mammaplasty'/exp OR mammaplasty
#27
'immediate partial breast reconstruction'
#26
'immediate total breast reconstruction'
#25
'axillary dissection'
#24
'acillary sampling'

(Continued)

#23
'axillary sentinel ndoe biopsy'
#22
'quadrantectomy'/exp OR quadrantectomy
#21
'lumpectomy'/exp OR lumpectomy
#20
'oncoplastic breast surgery'
#19
'breast conserving surgery'/exp OR 'breast conserving surgery'
#18
'breast surgery'/exp OR 'breast surgery'
#17
mrm
#16
'modified radical mastectomy'
#15
'mastectomy'/exp OR mastectomy
#14
#9 OR #10 OR #11 OR #12 OR #13
#13
'breast tumor'/exp OR 'breast tumor'
#12
'breast tumour'
#11
'breast carcinoma'/exp OR 'breast carcinoma'
#10
'breast cancer'/exp OR 'breast cancer'
#9
'breast neoplasm'
#8

(Continued) #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7 groups:ab
#6 trial:ab
#5 randomly:ab
#4 placebo:ab
#3 randomi*ed:ab
#2 controlled AND clinical AND trial
#1 randomised AND controlled AND trial

Appendix 3. LILACS via VHL (to 22 October 2012)

(((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple $ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))) [Words] and (Tw fibrin glue OR Tw fibrin tissue adhesive OR Tw fibrin adhesive glue OR Tw postoperative complications OR Tw seroma prevention therap$) [Words] and (Tw breast cancer OR Tw breast neoplasm OR Tw mastectomy OR Tw MRM OR TW breast surgery OR Tw breast conserving surgery OR Tw oncoplastic breast surgery OR Tw lumpectomy OR Tw quadrantectomy OR Tw axillary sentinel node biopsy OR Tw acillary sampling OR Tw axillary dissection OR Tw breast reconstruction OR Tw mammoplasty) [Words]

Appendix 4. SCI-E via Web Of Science (to 22 OCtober 2012)

#8	#7 AND #6 AND #5 *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
#7	Topic=(Postoperative Complications) OR Topic=(seroma prevention therap*) OR Topic=(seroma related morbidity prevention) OR Topic=(prevent* seroma related morbidity) *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*

(Continued)

#6	Topic=(Fibrin Tissue Adhesive) OR Topic =(Tissue Adhesives) OR Topic=(fibrin adhesive glue) OR Topic=(fibrin glue) OR Topic=(fibrin glue instillation) *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
#5	#4 AND #3 *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
#4	Topic=(randomised controlled trial) OR Topic=(randomized controlled trial) OR Topic=(controlled clinical trial) OR Topic=(randomized) OR Topic=(randomised) OR Topic=(randomly) OR Topic=(trial) *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
#3	#2 OR #1 *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
# 2	Topic=(mastectomy) OR Topic=(MRM) OR Topic=(breast surgery) OR Topic=(breast conserving surgery) OR Topic=(oncoplastic breast surgery) OR Topic=(lumpectomy) OR Topic=(quadrantectomy) OR Topic=(axillary sentinel node biopsy) OR Topic=(axillary sampling) OR Topic=(axillary dissection) OR Topic=(immediate total breast reconstruction) OR Topic=(immediate partial breast reconstruction) OR Topic=(Mammaplasty) *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*
#1	Topic=(breast cancer) OR Topic=(breast neoplas*) *Databases=SCI-EXPANDED Timespan=All Years* *Lemmatization=On*

Appendix 5. World Health Organization (WHO) ICTRP search portal

Basic search:

1. Fibrin glue instillation under skin flaps following breast and axillary surgery for preventing seroma related morbidity

2. breast neoplasm AND fibrin glue instillation

3. breast neoplasm AND fibrin glue

4. breast neoplasm AND seroma prevention AND fibrin glue

Advanced search:

1. Title: fibrin glue instillation under skin flaps following breast and axillary surgery for preventing seroma related morbidity

Recruitment status: ALL

2. Condition: breast neoplasm AND (mastectom% OR MRM OR breast surgery OR breast conserving surgery OR lumpectomy OR quandrantectomy OR axillary sentinel node biopsy OR axillary sampling OR axillary dissection OR mammoplasty)

Intervention: fibrin tissue adhesive% OR fibrin adhesive glue OR fibrin glue OR fibrin glue instillation tissue adhesive%

Recruitment status: ALL

3. Condition: breast neoplasm AND (mastectom% OR MRM OR breast surgery OR breast conserving surgery OR lumpectomy OR quandrantectomy OR axillary sentinel node biopsy OR axillary sampling OR axillary dissection OR mammoplasty)

Intervention: seroma prevention therap% OR seroma prevention

Recruitment status: ALL

Appendix 6. ClinicalTrials.gov

Basic search:

1. Fibrin glue instillation under skin flaps following breast and axillary surgery for preventing seroma related morbidity

2. breast neoplasm AND fibrin glue instillation

3. breast neoplasm AND fibrin glue

4. breast neoplasm AND seroma prevention AND fibrin glue

Advanced search:

1. Title: Fibrin glue instillation under skin flaps following breast and axillary surgery for preventing seroma related morbidity

Recruitment:ALL

Study Results:ALL

Study Type:ALL

Gender:ALL

2. Condition: breast neoplasm AND (mastectom* OR MRM OR breast surgery OR breast conserving surgery OR lumpectomy OR quandrantectomy OR axillary sentinel node biopsy OR axillary sampling OR axillary dissection OR mammoplasty)

Intervention: fibrin tissue adhesive* OR fibrin adhesive glue OR fibrin glue OR fibrin glue instillation tissue adhesive*

Recruitment:ALL

Study Results:ALL

Study Type:ALL

Gender:ALL

3. Condition: breast neoplasm AND (mastectom* OR MRM OR breast surgery OR breast conserving surgery OR lumpectomy OR quandrantectomy OR axillary sentinel node biopsy OR axillary sampling OR axillary dissection OR mammoplasty)

Intervention: seroma prevention therap* OR seroma prevention

Recruitment:ALL

Study Results:ALL

Study Type:ALL

Gender:ALL

Appendix 7. CENTRAL

#1 (mastectomy OR radical mastectomy OR wide local excision OR lumpectomy OR axillary dissection OR axillary sampling OR axillary sentinel node biopsy
#2 MeSH descriptor axillary surgery explode all trees

#3 MeSH descriptor breast surgery explode all trees
#4 MeSH descriptor seroma drainage explode all trees
#5 (#1 OR #2 OR #3 OR #4)
#6 (breast conserving surgery* OR conservative breast surgery* OR breast saving surgery*
#7 MeSH descriptor fibrin glue explode all trees
#8 (#6 OR #7)
#9 MeSH descriptor seroma explode all trees
#10 MeSH descriptor seroma prevention explode all trees
#11 fibrin glue OR seroma OR seroma prevention OR wound complications OR axillary complications
#12 #9 OR #10 OR #11
#13 (#5 AND #8 AND #12)

WHAT'S NEW

Date	Event	Description
31 October 2018	Review declared as stable	After a search of the evidence in 2018, it appears that three relatively small studies have been conducted since review publication and the results are unlikely to change the overall findings (specifically the primary outcomes) of this review. Therefore we do not expect to update this review.

HISTORY

Protocol first published: Issue 1, 2012
Review first published: Issue 5, 2013

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities: authors of this review have agreed to perform the following tasks during the course of writing and publication according to the rules of authorship	
TASK	WHO HAS AGREED TO UNDERTAKE THE TASK
Draft the protocol	MSS, KHH, IFR
Develop a search strategy	MSS, KHH, IFR
Search for trials	MSS, KHH, IFR
Select which trials to include	MSS, KHH, IFR, RB
Extract data from trials	MSS, KHH, IFR, RB
Enter data into RevMan	MSS, KHH, IFR
Carry out the analysis	MSS, KHH, IFR, RB
Interpret the analysis	MSS, KHH, RB
Draft the final review	MSS, KHH, IFR, RB

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None to declare, Other

External sources

- None to declare, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Based on the duration of follow-up, there was insufficient data to perform subgroup analysis. In addition, there were no unpublished studies. Therefore, authors were unable to perform subgroup analyses on both groups. Data on cost analysis, HRQoL and long-term morbidity were not reported and therefore could not be analysed and reported.

INDEX TERMS

Medical Subject Headings (MeSH)

Axilla; Breast Neoplasms [*surgery]; Fibrin Tissue Adhesive [*administration & dosage]; Hemostatics [*administration & dosage]; Lymph Node Excision [*adverse effects]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Seroma [*prevention & control]; *Surgical Flaps; Treatment Failure

MeSH check words

Female; Humans