Fibrin Sealants Do Not Reduce the Rate of Seroma Formation in Postmastectomy Breast Reconstruction: A Systematic Review and Meta-analysis

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► breast reconstruction
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► DIEP flap
► latissimus dorsi flap
► LD flap
► donor site

Abstract

Background Breast reconstruction using deep inferior epigastric perforator (DIEP) and latissimus dorsi (LD) flaps following mastectomy are associated with seroma formation, most commonly at the donor site. We sought to perform an updated systematic review and meta-analysis on the effects of fibrin sealant on donor-site complications following DIEP and LD flap breast reconstruction.

Methods A comprehensive literature search was conducted (March 2021) in PubMed, OVID, and Cochrane databases. Articles analyzing the efficacy of fibrin glue in reducing donor-site morbidity in DIEP and LD breast reconstruction were included. The outcomes assessed were seroma formation and duration of drainage.

Results A total of 17,265 articles were screened, and 9 articles were selected for analysis, which comprised 632 surgical sites in 611 patients. Comparing fibrin glue and quilting to quilting alone showed no significant difference in seroma formation (pooled risk ratio [RR]: 0.51; 95% confidence interval [CI]: 0.12, 2.25). Similarly, comparing fibrin glue alone to no fibrin glue showed no significant difference in seroma formation (pooled RR: 1.03; 95% CI: 0.66, 1.61) or duration of drain (pooled RR: −0.85; 95% CI: −4.09, 2.40); there was however a difference in duration of drain in those who received fibrin glue and quilting versus quilting alone (pooled RR: −2.13; 95% CI: −3.27, −0.99).

Conclusion The existing literature supports that the use of fibrin glue is not associated with a decrease in seroma formation in DIEP and LD flaps and is weakly associated with a reduction in the drainage duration only if used in conjunction with quilting.
For patients undergoing mastectomy, breast reconstruction can provide psychosocial, emotional, and functional improvement. Options for breast reconstruction are numerous but broadly include the use of implants, autologous flaps, or a hybrid of both. In 2018, at least 101,657 breast reconstructions were performed in the United States as reported by American Society of Plastic Surgeons, of which 89.9% were implant-based reconstruction and 18.1% were autologous-based reconstruction. Autologous-based reconstruction is typically thought to be more natural in appearance and feeling. This technique uses the patient’s native tissue harvested from typical sites of the abdomen and back to reconstruct breast shape, appearance, and size. Because of the dual-incision nature of this flap-based method of reconstruction, complications can occur at both the donor and recipient sites.

One of the most common local surgical complications of breast reconstruction is seroma formation at the donor site. Seromas can form at varying rates, at different stages of the reconstruction process, and in multiple locations depending on the type of flap utilized. Latissimus dorsi (LD) flaps have a rate of seroma formation from 12 to 21% at the donor site, while deep inferior epigastric perforator (DIEP) flaps have a rate of 5% at the donor-site postreconstruction.

Seroma formation is known to be caused by dead space that remains after tissue rearrangement. Complications associated with seroma formation are numerous and include infection, tissue necrosis, prolonged wound healing time, and repeated office visits for aspiration. Several methods have been used thus far to prevent seroma formation including surgical drain placement, quilting sutures, and fibrin sealants in an attempt to obliterate dead space and prevent seroma formation.

Closed suction surgical drains are used in many procedures to remove unwanted fluid accumulation after surgery. Drains are strategically placed where dependent fluid would accumulate if the patient were in the upright position. These drains are usually left in place until the rate of drainage decreases to approximately 25 to 30 mL per day for 2 consecutive days. However, the criteria for removal can vary depending on surgeon preference or on the clinical scenario. If the drains are removed too soon, the risk for seroma formation increases. Since seromas may require percutaneous aspiration or reinsertion of a drain, seroma prevention is key to successful breast reconstruction outcomes. Quilting sutures, on the other hand, are placed between the subcutaneous skin flap and the underlying fascia to "tack down" flaps and eliminate dead space. This method has shown a decreased incidence of high-grade seroma formation postmastectomy.

Interest in fibrin sealants within the scientific community has stemmed from its triple property nature as a coagulant, sealant, and adhesive. As a coagulant, fibrin allows hemostasis in the surgical field by promoting the formation of blood clots. Fibrin also polymerizes into a sealing structure that secures opposing tissues together. Fibrin sealant used in operative fields is a combination of thrombin, fibrinogen, factor XIII, occasionally antifibrinolytic agents, and bovine aprotinin. Commercially available fibrin glue is usually derived from a pool of plasma from donors of blood products and packaged as two components—fibrinogen and coagulation factor XIII. Thrombin dissolved in calcium chloride, fibrinogen, and factor XIII are mixed at the time of usage to create a solution that triggers the coagulation cascade in which thrombin converts fibrinogen into fibrin. The use of fibrin glue has been reported in multiple surgical specialties, specifically in breast surgeries after mastectomies, in the axilla after lymph node dissection, and at donor and recipient sites during reconstruction for the prevention of seroma formation.

In a systematic review and meta-analysis conducted in 2017, Lee et al concluded that the use of quilting sutures and fibrin glue synergistically reduces the rate of seroma formation in LD flap donor sites; however, fibrin glue alone was not beneficial. Seroma formation can also ensue in breast reconstruction using DIEP flaps, yet there have not been any consensus studies on the use of fibrin glue with DIEP flap breast reconstruction. We sought, therefore, to perform an updated systematic review and meta-analysis on the effect of fibrin sealant on the rate of seroma formation and duration of drainage following either LD or DIEP flap breast reconstruction.

Methods

Study Selection

A detailed review of the literature was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The research question, search strategy, inclusion and exclusion criteria, outcome measures, and data extraction protocols were determined prior to completing the analysis. A comprehensive literature search was conducted using articles published since the inception of the following databases until March 2021: PubMed, OVID, and Cochrane. The search resulted in 17,265 studies (Cochrane: 9,320 articles, OVID: 7,886 articles, and PubMed: 43 articles). Studies were screened by title and abstract by two blinded and independent reviewers. Only human studies were included for full-text articles screening. Articles were excluded if they had insufficient primary data (primarily descriptive articles, biomechanical studies, and case reports) or no English translation. Selected articles compared patients who underwent LD or DIEP flap breast reconstruction who received fibrin glue with or without quilting sutures with patients who did not receive fibrin glue for the same procedure and additionally reported the following outcomes: seroma formation rate and drainage duration.

Data Extraction and Statistical Analysis

Data extraction was performed independently by two reviewers for studies that included at least five patients, a follow-up period of at least 12 months, and reported at least one of the following outcomes for each study group: number of patients with seroma formation or duration of surgical closed suction drainage. The data for the primary
outcomes of interest of seroma rate formation and drainage duration were summed into forest plots so that the risk ratio (RR) could be assessed for each study individually and overall. Pooled estimates and relative risks were determined using a random effects model and the Review Manager 5.4 software. Study heterogeneity was defined using $I^2$ with $p$-value less than 0.10 indicating significant heterogeneity.

**Results**

**Study Characteristics and Quality Assessment**

Three databases were screened from their inception up to March 2021, which returned 17,265 articles. Upon review by title and abstract, 17,246 articles were excluded. Nineteen articles were then screened by full-text analysis, with 10 being excluded for lacking the primary outcomes of interest, and 9 articles were ultimately chosen for quantitative analysis (► Fig. 1). Study characteristics for the nine selected articles are listed in ► Table 1. In total, 623 surgical sites in 611 patients were analyzed. The nine articles were separated by intervention into two groups: (1) fibrin glue with quilting versus fibrin glue alone, which included three studies, and (2) fibrin glue alone versus no fibrin glue, which included six studies. Of these studies, seven involved LD or extended latissimus dorsi (ELD) flaps and two involved DIEP flaps. All nine studies contained data on seroma rate formation, while four of the six studies in the fibrin glue alone versus no fibrin glue group had information on drainage duration, and two of the three studies in the fibrin glue versus no fibrin glue had reported information on drainage duration.

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### Table 1  Characteristics of the final articles selected for analysis in this systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Flap</th>
<th>Fibrin glue type</th>
<th>Fibrin glue location</th>
<th>Fibrin glue Cohort: n</th>
<th>Control cohort: n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cha et al</td>
<td>2012</td>
<td>Retrospective cohort</td>
<td>LD</td>
<td>Tisseel</td>
<td>Over donor site and two skin flaps</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Fang et al</td>
<td>2020</td>
<td>Retrospective cohort</td>
<td>DIEP</td>
<td>ARTISS</td>
<td>Between abdominal skin flap and anterior rectus sheath</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Hart et al</td>
<td>2017</td>
<td>Randomized clinical trial</td>
<td>Tisseel</td>
<td>ARTISS</td>
<td>Chest wall and undersurface of skin</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Hivelin et al</td>
<td>2011</td>
<td>Randomized clinical trial</td>
<td>Tissucol</td>
<td>Tisseel</td>
<td>Flap, thoracic, and axillary areas</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Hivelin et al</td>
<td>2012</td>
<td>Randomized clinical trial</td>
<td>Tissucol</td>
<td>Tisseel</td>
<td>Upper and lower back</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Llewellyn-Bennett et al</td>
<td>2012</td>
<td>Retrospective cohort</td>
<td>Tissucol</td>
<td>Tisseel</td>
<td>Donor site</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Weinreich et al</td>
<td>2010</td>
<td>Retrospective cohort</td>
<td>Tissucol</td>
<td>Tisseel</td>
<td>Between quilting spaces</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Bailey et al a</td>
<td>2010</td>
<td>Randomized clinical trial</td>
<td>Quixil</td>
<td>Evicel</td>
<td>Donor site</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Dacres et al a</td>
<td>2010</td>
<td>Randomized clinical trial</td>
<td>ELD</td>
<td>Evicel</td>
<td>Between quilting spaces</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

**Abbreviations:** DIEP, deep inferior epigastric perforator; ELD, extended latissimus dorsi; LD, latissimus dorsi.

**Notes:** Trademark drugs: ARTISS (Baxter International Inc.; Deerfield, IL); Tisseel/Tissucol (Baxter International Inc); Evicel/Quixil (Omira Biopharmaceuticals Ltd, Manufacturer in Kiryat, Israel; Distributed by: Ethicon, Inc., Somerville, NJ).
Clinical Outcomes

Significant heterogeneity was defined as p-value less than 0.10 for all outcomes. Patients who received fibrin glue in addition to quilting sutures did not experience a significant difference in the rate of seroma formation compared with those who received quilting sutures alone (pooled RR: 0.51, 95% confidence interval [CI]: 0.12, 2.25). There was no significant heterogeneity among studies as p = 0.86 and I² = 0% (►Fig. 2).

Patients who received fibrin glue alone also did not experience a significant difference in the rate of seroma formation compared with those who did not receive fibrin glue (pooled RR: 1.03, 95% CI: 0.66, 1.61). There was no significant heterogeneity among studies as p = 0.35 and I² = 8% (►Fig. 3).

The duration of drainage (in days) was also not significantly impacted by the use of fibrin glue in patients who received the intervention versus those who did not (pooled RR: −0.85, 95% CI: −4.09, 2.40). There was however a significant heterogeneity among studies as p = 0.0001 and I² = 89% (►Fig. 4).

When comparing the fibrin glue and quilting versus quilting only groups, however, the differences in the duration of drainage (in days) were significant (pooled RR: −2.13, 95% CI: −3.27, −0.99). There was heterogeneity though among the studies as p = 0.15 and I² = 52% (►Fig. 5).

Discussion

Initially, there were several clinical studies that showed evidence of fibrin sealants reducing seroma formation. Fibrin sealants were assumed to be effective in achieving hemostasis and sealing tissues in surgical settings due to their components of fibrinogen and thrombin leading to activation of the coagulation cascade. This both reduces the dead space between tissues through adhesion as well as reduces hematoma and seroma fluid from the involved surfaces by aiding hemostasis and blocking lymphatic channels that lead to drainage into the operative site. Although seroma formation and prolonged drainage are not life threatening, they are substantial medical expenses to the patient and can also
result in pain, infection, delayed healing, decreased mobility, and reoperation. The use of suction drains has been routine, but they are associated with significant patient dissatisfaction including pain, restriction of activity, and causing a delay in return to normal daily functioning. Suction drains can also be associated with infection while also frequently leading to seroma formation after removal.

Although initial evidence would suggest that fibrin sealants have potential as being a good option for reducing seroma formation, it appears based on further investigation that fibrin sealants may only be beneficial when used in smaller surgical sites, whereas in surgeries with larger sites such as breast reconstruction, it may be of limited value. Based on conflicting evidence supporting the use of fibrin sealants, we aimed to perform an updated systematic review and meta-analysis to demonstrate the possible efficacy of fibrin sealants on donor-site complications, namely seroma formation and drainage duration, following both LD and DIEP flaps breast reconstruction.

Overall, the results of our study do not support the use of fibrin glue to reduce the rate of seroma formation; the results however slightly favor the use of fibrin glue and quilting versus quilting alone to reduce the duration of drainage following LD or DIEP flap breast reconstruction. While previous studies had mostly focused on the use of fibrin glue with LD flaps, we sought to expand the understanding of fibrin glue and seroma formation to DIEP flaps as well. In our pooled analysis, seven of the nine studies examined LD or ELD flaps and two examined DIEP flaps. Overall, the use of fibrin glue was not beneficial for decreasing seroma formation rate or drainage duration when compared with the no fibrin glue cohort, and only mildly favored the quilting sutures cohort.

Additionally, while all nine studies selected for analysis reported data on the rates of seroma formation, only six of the studies provided information on the duration of drainage following the initial operation; four of these studies were in the fibrin glue only intervention and two studies were in the fibrin glue with quilting sutures intervention. The two studies in the fibrin glue with quilting intervention group that reported data on drainage duration revealed a forest plot that is 97.7% weighted toward the Dancey et al’s study. The data reported on this plot therefore are significantly biased toward the larger study. This comparison was going to be excluded initially, but the authors of this article deemed it important to add for completeness of the data presented. The association between the reduced duration of drain when comparing the fibrin glue with quilting to the quilting alone is therefore weak and further research is needed to elucidate whether fibrin glue truly reduces the duration of drain placement, especially since the fibrin glue versus no fiber glue cohort did not yield any significance.

These results do align with previously published work on the lack of efficacy of fibrin glue in the reduction of seroma formation or drainage duration. As Oliver et al concluded from a randomized controlled trial, fibrin sealant may be beneficial only in the setting of small surgical areas as opposed to cases of breast reconstruction. Tsim et al and Soumian et al had similar results as they found no reduction in the rate of seroma formation on the back following LD breast reconstruction. Similarly, Lee et al conducted a retrospective cohort study demonstrating that fibrin sealant was neither effective as a hemostatic agent nor as a seroma reductant.

Among the individual cohorts analyzed in our study, Weinrach et al demonstrated a significant reduction in seroma formation following fibrin glue application. Similarly, Ali et al and Hivelin et al found that fibrin glue led to a significant reduction in the duration of drainage and earlier drain removal following reconstruction. Dancy et al and Fang et al found a significant reduction in both drainage duration and seroma formation with fibrin glue and proposed that the additional cost of fibrin glue was worthwhile with regard to improved postoperative outcomes. Bailey et al likewise showed a significant reduction in drainage duration, but the effect of fibrin glue on rate of seroma formation was not statistically significant. Cha et al showed some clinical improvement in drainage duration with fibrin glue; however, this was not statistically significant. Llewellyn-Bennet et al also found no significant improvement in rate of seroma formation following the use of fibrin glue. Interestingly, Hart et al found no significant improvement in drain duration or seroma formation with the use of fibrin glue but did find significant improvement in these outcomes with the use of quilting sutures. Even though some of the individual studies supported the use of fibrin glue as a method to reduce seroma formation and decrease drainage, the pooled results of these studies overall did not support the role of fibrin glue in seroma reduction, and only weakly supported a reduced duration of drainage when fibrin glue is used in conjunction with quilting in breast reconstruction. It would therefore be of interest for additional studies to compare the outcomes of seroma formation and drainage duration following quilting sutures versus fibrin glue, as Hart et al were the only study we came across that directly compared those two interventions.
Limitations to this study, as with any meta-analysis, include the inherent heterogeneity of included studies whether due to surgeon, patient, or investigator-dependent factors. Additionally, there were few articles that directly compared the impact of fibrin glue on the outcomes of seroma rate formation and drainage duration following breast reconstruction. More work is needed on this topic to expand the understanding of the benefits or lack thereof of fibrin glue on breast reconstruction outcomes following mastectomy.

Conclusion

Seroma formation continues to be a complication of surgical procedures involving DIEP and LD flaps. Our review shows that existing literature supports that using fibrin glue is not associated with a significant decrease in the rate of seroma formation, and weakly supports a reduction in the duration of drainage when fibrin glue is used with quilting in DIEP and LD flap donor sites. This work can thus be used to guide the operative management of breast reconstruction patients and allow clinicians to make more guided decisions that will aid in reducing the incidence of seroma. Possible usage of fibrin glue, therefore, continues to be largely at the clinician’s discretion.

Conflict of Interest

None declared.

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