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ORIGINAL ARTICLE – BREAST ONCOLOGY

Effects of Fibrin Sealant on Seroma Reduction for Patients with Breast Cancer Undergoing Axillary Dissection: Meta-Analysis of Randomized Controlled Trials

Ya-Ting Chang, MS[1], Shen-Liang Shih, MD, MSc[2,3], El-Wui Loh, PhD[4,5,6], and Ka-Wai Tam, MD, PhD[5,6,7,8]

[1]School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [2]Cancer Center, Yuan's General Hospital, Kaohsiung, Taiwan; [3]Department of Health Business Administration, Meiho University, Pingtung, Taiwan; [4]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [5]Center for Evidence-Based Health Care, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [6]Cochrane Taiwan, Taipei Medical University, Taipei, Taiwan; [7]Division of General Surgery, Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [8]Division of General Surgery, Department of Surgery, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

ABSTRACT

Background. Seroma formation is common in patients with breast cancer after axillary dissection. Fibrin sealant, containing fibrinogen and thrombin, has been developed to improve wound healing. We conducted a systematic review and meta-analysis to evaluate the efficacy of fibrin sealants in reducing seroma among patients with breast cancer undergoing axillary dissection.

Methods. We searched the PubMed, EMBASE, and Cochrane Library databases for randomized controlled trials (RCTs) published up to April 2020. Pooled estimates of the outcomes were computed using a random-effects model. The primary outcomes were incidence and volume of seroma, while the secondary outcomes were volume and duration of drainage, incidence of infection, and length of hospital stay.

Results. We reviewed 23 RCTs that included 1640 patients. Compared with the control group, the fibrin sealant group had no significant differences in the incidence of seroma, length of hospital stay, or incidence of surgical site infection. Significant intergroup differences were discovered in lower volume of seroma (weighted mean difference [WMD] − 71.88, 95% confidence interval [CI] − 135.58 to − 8.19), volume of drainage (WMD − 73.24, 95% CI − 107.32 to − 39.15), and duration of drainage (WMD − 0.84, 95% CI − 1.50 to − 0.19).

Conclusions. Fibrin sealants provide limited benefits in reducing the volume of seroma and the volume and duration of drainage. Therefore, after shared decision making, surgeons may apply fibrin sealants to patients with breast cancer undergoing axillary dissection.

Breast cancer is the most commonly diagnosed cancer and the second leading cause of death among women. In 2018, 2.09 million cases and approximately 0.63 million deaths worldwide were estimated.[1] In mastectomy and breast-conservation surgeries, axillary lymph node dissection (ALND) is essential for the staging and treatment of patients with positive nodes; however, complications may occur afterwards, including seroma, delayed drain removal, wound infection, hematoma, and nerve injury, leading to longer hospital stays, higher morbidity, and greater patient discomfort.[2]

Ya-Ting Chang and Shen-Liang Shih contributed equally to this work.

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K.-W. Tam, MD, PhD
e-mail: kelvintam@h.tmu.edu.tw

Seroma formation is the most frequent complication, with 15–80% incidence in node dissection.[3,4] Seroma is defined as palpable fluid collection under the wound and required aspiration because of high output, or after removal of the drain, which can delay wound healing and increase the risk of wound infection.[5] Therefore, various approaches have been used to prevent seroma:axillary dead-space stitching, external compression, use of an ultrasound cutting device, use of a suction drainage system, application of bovine thrombin, and tetracycline sclerotherapy;[6–9] however, which method is most effective at decreasing the incidence of seroma remains controversial.

Fibrin sealants, as a form of glue or patch, are highly concentrated solutions of fibrinogen and other cryoglobulins and have been developed for more than a century.[10] These sealants increase hemostasis and cell adherence, reduce the number of transactions of small vessels and lymphatics, promote fibroblast growth, and accelerate fibroblast duplication during ALND; thus, fibrin sealants theoretically reduce the likelihood of seroma formation and enhance wound healing.[3,11,12] Fibrin sealants may be beneficial for breast cancer surgery.

Reviews have reported that fibrin sealants have the potential to reduce the likelihood of seroma, but the results have been inconclusive because limited trials have been conducted.[13,14] Several studies have recently been published;[15] therefore, the present study evaluated the effects of fibrin sealant on seroma incidence and fluid accumulation in patients with breast cancer after mastectomy or lumpectomy involving axillary dissection by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs).

MATERIALS AND METHODS

Inclusion Criteria

We included RCTs investigating the effect of fibrin sealant application among patients with primary breast cancer who underwent ALND. In addition, these trials had to clearly report the patient inclusion and exclusion criteria, surgical techniques employed, and fibrin sealant used. Our exclusion criteria were (1) patients had not received lumpectomy or mastectomy for breast cancer (e.g. only breast tumor sampling was conducted); (2) patients had received only sentinel node biopsy; (3) patients had received breast reconstruction; (4) patients had received neoadjuvant therapy; and (5) duplicate reporting of patient cohorts.

Search Strategy and Study Selection

Relevant RCTs published before April 2020 were identified by searching the PubMed, EMBASE, and Cochrane Library databases. The following Medical Subject Heading search terms were used: (*fibrin glue OR fibrin sealants OR fibrin tissue adhesive OR fibrin patches) AND (breast surgery OR axillary dissection OR mastectomy OR lumpectomy OR lymphonodectomy).* The 'related articles' function in PubMed was used to broaden the search, and all retrieved abstracts, studies, and citations were reviewed. In addition, we identified other relevant studies by searching the reference lists of the relevant articles and by contacting experts in the field. Finally, we searched for unpublished studies using the ClinicalTrials.gov registry (https://clinicaltrials.gov/). No language restrictions were applied. The systematic review described herein was accepted by the PROSPERO online database (CRD42016047059).

Data Extraction

Baseline and outcome data were independently extracted by two reviewers (YTC and SLS). The reviewers extracted data regarding the study design, study population characteristics, inclusion and exclusion criteria, surgical techniques, fibrin sealants, intraoperative and postoperative parameters, and complications. The individually recorded decisions of the two reviewers were compared, and any disagreement was resolved by a third reviewer (KWT). Authors of the RCTs were contacted for additional information when necessary.

Methodological Quality Appraisal

Two reviewers (YTC and SLS) independently assessed the methodological quality of each RCT by using the revised tool for assessing risk of bias in randomized trials (RoB 2.0).[16] Five domains were assessed: bias arising from the randomization process; bias due to deviation from the intended intervention; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported results. Each RCT was awarded an overall risk of bias according to the highest risk calculated for the trial.

Outcomes and Statistical Analysis

The primary outcomes were incidence of seroma and total volume of seroma, while the secondary outcomes were total volume and duration of drainage, incidence of surgical site infection, and length of hospital stay. All data were entered into, and analyzed using, the Review Manager version 5.3.5 (Cochrane Collaboration, Oxford, UK).

A meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] When necessary, standard deviations were estimated from the provided confidence interval (CI) limits or standard errors.[18] The effect sizes of the continuous outcomes were reported as the weighted mean difference (WMD), whereas the binary outcomes were reported as the risk ratio (RR). The precisions of the effect sizes were reported as 95% CIs. Pooled estimates of the WMD and RR were computed using the DerSimonian and Laird random-effects model.[19]

Cochrane Q tests and I^2 statistics were used to evaluate the statistical heterogeneity and inconsistency in treatment effects among the included studies, respectively. Statistical significance was set at $p < 0.1$ for the Cochrane Q tests. Statistical heterogeneity was assessed by performing the I^2 test, with I^2 quantifying the proportion of the total outcome variability attributable to the variability between the studies. Subgroup analyses were also performed by pooling estimates for similar patient subsets among trials when possible.

RESULTS

Randomized Controlled Trial Characteristics

Electronic supplementary Fig. 1 presents a flowchart describing the RCT screening and selection process. Our initial search strategy yielded 802 citations, 668 of which were excluded on the basis of the criteria used for screening titles and abstracts; thus, we retrieved the full text of 134 studies. Most of these were excluded from our final review for the following reasons: 7 had repeated content; 1 had a cohort that overlapped with another included RCT; 33 were animal trials; 12 evaluated the effects of fibrin sealants on patients with cancers other than breast cancer; 26 recruited patients with breast cancer who did not undergo ALND; 2 enrolled patients with adjuvant therapy before breast surgery; 4 employed different treatments for patients with breast cancer; 14 evaluated the effects of fibrin sealants other than wound healing effects; and 12 were not RCTs. The remaining 23 RCTs were finally selected for inclusion in our study.[3,11,15,20–39].

The characteristics of the 23 RCTs meeting our requirements are summarized in Table 1. The trials, which were published from 1993 to 2018, recruited patients with primary breast cancer who underwent lumpectomy or mastectomy with ALND. The patient sample sizes ranged from 21 to 142 patients, and the mean number of total lymph nodes removed ranged from 7.1 to 25.77 nodes. Regarding fibrin sealant use, Tisseel or Tissucol fibrin glue was used in 11 RCTs,[11,21,25,27,32–38] one of which used an additional fibrinolysis inhibitor.[32] Hemaseel fibrin glue was used in one RCT,[30] the Greenplast kit fibrin glue was used in one RCT,[28] Artiss low-thrombin fibrin glue was used in one RCT,[15] Quixil fibrin glue was used in one RCT,[20] and a fibrin patch, either TachoComb H[22] or TachoSil,[39] was used in two RCTs. In the other RCTs, fibrin glue was made from the researchers' own kits.[3,24,26,29,31] In the analyzed

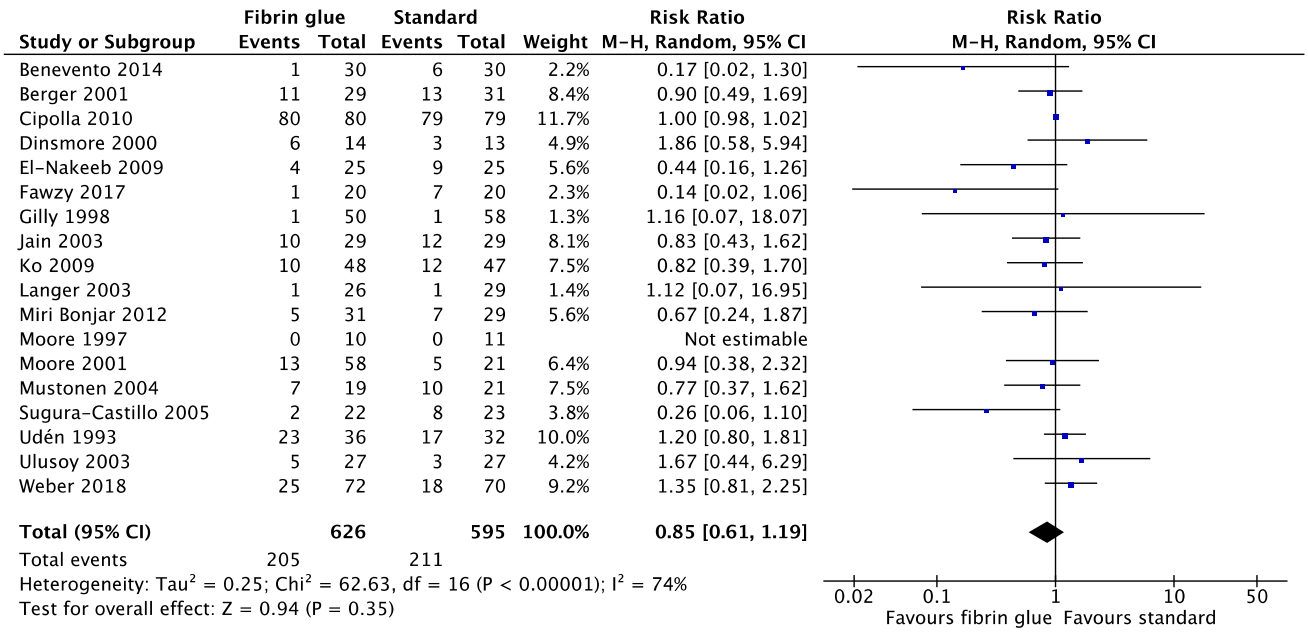

FIG. 1 Forest plot comparing fibrin sealants and the control, where the outcome is incidence of seroma. *M-H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

TABLE 1 Characteristics of the included RCTs

Author, year	No. of patients	Age, years[a]	Surgery type and location	No. of nodes removed	Intervention	Criterion for drainage removal (mL/24 h)
Benevento et al., 2014[15]	F: 30 C: 30	F: 56.4 ± 11.4 C: 57 ± 14.8	F: 7 M, 23L C: 9 M, 21L	F: 24 ± 4.6 C: 23.7 ± 5.8	F: Artiss (Baxter, Newbury, UK), 4 mL C: Standard closure	< 30
Berger et al., 2001[22]	F: 29 C: 31	F: 56 ± 12.6 C: 61.5 ± 11.5	F: 11 M, 18L C: 8 M, 23L	Not provided	F: TachoComb H (Nycomed Pharma AS, Denmark) C: Standard closure	< 70
Cipolla et al., 2010[3]	F: 80 C: 79	F: 59.1 ± 13.93 C: 58.8 ± 10.87	F: 33 M, 47L C: 33 M, 46L	F: 16.6 ± 4.70 C: 17.4 ± 7.40	F: Fibrin glue, 2 mL C: Standard closure	< 80
Dinsmore et al., 2000[23]	F: 14 C: 13	F: 62.3 ± 2.1 C: 64.5 ± 2.8	F: 14 M C: 13 M	F: 16.7 ± 1.3 C: 16.8 ± 1.5	F: Fibrinogen, 25.47 mg/mL, 5 mL C: Standard closure	< 30
El Nakeeb et al., 2009[24]	F: 25 C: 25	Not provided	F: 25 M C: 25 M	Not provided	F: Fibrin glue, 8 mL C: Standard closure	< 30
Fawzy et al., 2017[26]	F: 20 C: 20	F: 43.35 ± 9.90 C: 43.25 ± 9.10	F: 20 M C: 20 M	F: 16.45 ± 3.17 C: 16.35 ± 2.97	F: Fibrinogen, 65 mg/mL C: Standard closure	Not provided
Gilly et al., 1998[25]	F: 50 C: 58 (2 male)	F: 60.6 ± 10.8 C: 62.5 ± 11.5	F: 6 M, 44L C: 11 M, 47L	F: 10.6 ± 2.1 C: 10.8 ± 2.5	F: Tissucol (Immuno, Vienna, Austria), 2 mL C: Standard closure	All removed after 6 days
Giofferè Florio, et al., 1993[21]	F: 12 C: 12	Not provided	F: 6 M, 6L C: 6 M, 6L	Not provided	F: Tissucol C: Standard closure	Not provided
Jain et al., 2004[27]	F: 29 C1: 29 C2: 58	F: 62.3 ± 12.3 C1: 62.3 ± 12.3 C2: 61.9 ± 13.2	F: 19 M, 10L C1: 12 M, 17L C2: 36 M, 22L	F: 7.6 ± 3.1 C1: 7.6 ± 3.1 C2: 7.1 ± 2.8	F: Tisseel (Baxter, Newbury, UK), 2 mL with no drain C1: Closure with no drain C2: Closure with drain	< 50
Ko et al., 2009[28]	F: 47 C: 48	F: 48.5 ± 8.7 C: 47.9 ± 7.7	F: 47L C: 48L	F: 12.6 ± 5.6 C: 12.5 ± 6.0	F: Greenplast kit (Green Cross, Seoul, South Korea), 2 mL C: Standard closure	< 30
Langer et al., 2003[11]	F: 26 C: 29	F: 60.8 (34–88)[b] C: 56.3 (37–82)[b]	F: 18 M, 8A C: 13 M, 16A	F: 19.4 (0–48[b] C: 19.5 (11–30)[b]	F: Tisseel (Baxter, Glendale, CA, USA), 2 mL C: Standard closure	< 30 for 2 days
Miri Bonjar et al., 2012[30]	F: 31 C: 29	F: 58.3 ± 10.7 C: 57.5 ± 11.2	F: 21 M, 9L C: 20 M, 10L	F: 14.7 ± 4.7 C: 14.2 ± 3.4	F: Hemaseel (Haemacure, Sarasota, FL, USA), 4 mL C: Standard closure	< 30
Moore et al., 1997[12]	F: 10 C: 11	Not provided	F: 10 M C: 11 M	F: 14.7 ± 2.8 C: 13.7	F: Fibrinogen, 40 mg/mL C: Standard closure	< 40
Moore et al., 2001[29]	F1: 19 F2: 19 F3: 20 C: 21	F1: 58 ± 16 F2: 51 ± 9 F3: 59 ± 16 C: 56 ± 14	M, L	Not provided	F1: Fibrinogen, 75 mg/mL 4 mL F2: Fibrinogen, 75 mg/mL 8 mL F3: Fibrinogen, 75 mg/mL 16 mL C: Standard closure	< 40
Mustonen et al., 2004[32]	F: 19 C: 21	F: 67.5 ± 13.6 C: 66.1 ± 12	F: 19 M C: 21 M	Not provided	F: Tisseel, 2 mL + fibrinolysis inhibitor, 2 mL C: Standard closure	< 50
Ruggiero et al., 2009[33] and 2008	F: 45 C: 45	Not provided	F: 15 M, 30L C: 15 M, 30L	Not provided	F: Tisseel/Tissucol (Baxter, Deerfield, IL, USA), 2 mL C: Standard closure	< 100
Ruggiero et al., 2014[34]	F: 40 C: 40	Not provided	F: 10 M, 30L C: 10 M, 30L	Not provided	F: Tisseel/Tissucol (Baxter, Deerfield, IL, USA), 2 mL C: Standard closure	< 100
Segura-Castillo et al., 2005[20]	F: 22 C: 23	F: 48.36 ± 8.9 C: 52.87 ± 9.74	F: 22 M C: 23 M	Not provided	F: Quixil (Biomedical International, Miami, FL, USA), 10 mL C: Standard closure	< 50
Tasinato, 1993[35]	F: 66 C: 61	F: 49 ± 22 C: 47 ± 19	Not provided	F: 20.2 C: 20.8	F: Tissucol C: Standard closure	Not provided

TABLE 1 continued

Author, year	No. of patients	Age, years[a]	Surgery type and location	No. of nodes removed	Intervention	Criterion for drainage removal (mL/24 h)
Udén et al., 1993[36]	F: 36	F: 73 (42–89)[b]	F: 36 M	Not provided	F: Tisseel, 2 mL	< 100
	C: 32	C: 70 (40–84)[b]	C: 32 M		C: Standard closure	
Ulusoy et al., 2003[37]	F: 27	F: 51.37 ± 2.35	F: 27 M	F: 21.61 ± 1.87	F: Tisseel, 4 mL	< 20
	C: 27	C: 50.88 ± 2.11	C: 27 M	C: 25.77 ± 2.11	C: Standard closure	
Vaxman et al., 1995[38]	F: 20	F: 55.6 ± 12	M, L	F: 10.8 ± 5.1	F: Tisseel/Tissucol, 5 mL	< 10
	C: 20	C: 56.2 ± 10		C: 9.3 ± 3.9	C: Standard closure	
Weber et al., 2018[39]	F: 72	F: 59 (48–70)[c]	F: 72L	F: 16.0 (12.0–22.0)[c]	F: TachoSil (Takeda Pharmaceuticals International)	< 30
	C: 70	C: 56 (47–70)[c]	C: 70L	C:18.5 (14.0–24.0)[c]	C: Standard closure	

[a]Data are expressed as mean ± SD unless otherwise indicated

[b]Mean (range)

[c]Median (interquartile range)

F fibrin sealant group, *C* control group, *M* modified radical mastectomy, *L* lumpectomy, *A* axillary lymph node dissection alone, *RCTs* randomized controlled trials, *SD* standard deviation

Fibrinogen concentration: Artiss: 91 mg/mL; Tissucol/Tisseel: 70–110 mg/mL; Hemaseel: 75–115 mg/mL; Quixil: 100 mg/mL; TachoSil: 5.5 mg/cm^2

Fibrin patch: TachoComb H, TachoSil

RCTs, drain removal was performed if the targeted drainage volume was lower than a certain cut-off, ranging from 10 to 100 mL over 24 h.

The RCTs compared the effects of fibrin sealants with standard drainage with that of a control treatment, except for Jain et al.,[27] who compared the effects of fibrin glue without drainage, closure without drainage, and standard closure; the data for the first two of these groups were included in our meta-analysis.[27] Moreover, Moore et al. evaluated these effects against the control of different doses of fibrin sealant, i.e. 4, 8, and 16 mL.[29] Fibrin glue spraying was performed in all trials, but Berger et al. and Weber et al. used a fibrin patch in the wound before closure.[22,39] The amount of fibrin glue applied ranged from 2 to 16 mL.

The methodological quality of the included RCTs is summarized in electronic supplementary Table 1. All RCTs reported acceptable methods of randomization, and all except six[3,11,30,33,34,37] adequately described their allocation concealment method. We judged that there was a low risk of bias due to missing outcome data for all RCTs because either no participants who were recruited were lost or missing data were input appropriately.[3,22,28] Complications were mentioned in all but four RCTs.[20,21,24,35] No bias was discovered in selection of the reported results. Overall, the included RCTs were concluded to have low risks of bias.

Incidence of Seroma Formation

Seroma formation was reported in 18 of the included RCTs.[3,11,15,20,22–32,36,37,39] These trials evaluated a total of 1221 patients, of whom 626 were randomized to the fibrin sealant group. Seroma was defined as palpable fluid collection under the wound and required aspiration after removal of the drain. In the study by Moore et al., the incidences of seroma in the three study groups treated with different amounts of fibrin glue were combined and then compared with the incidence in the control group.[29] Our pooling results revealed a lower incidence of seroma in the fibrin group (RR 0.85, 95% CI 0.61–1.19) than in the standard group, but the result was nonsignificant (Fig. 1).

Total Volume of Seroma Aspiration

Nine of the included RCTs reported the total volume of seroma aspiration after closed catheters were removed.[3,15,24,27,30,32,36,37,39] Two of these reported the mean but not the standard deviation, CI, or range[16,30] and were thus excluded from our pooling. The pooling result revealed that the total volume of seroma aspiration was significantly lower in the patients receiving fibrin sealant than in the controls (WMD − 71.88, 95% CI − 135.58 to − 8.19) [Fig. 2].

Total Drainage Volume

The total drainage volume in a closed suction was reported in 21 RCTs.[3,11,15,20–26,28,29,31–39] In the study by Moore et al., the authors only reported the results for some patients, therefore the incomplete data were not included in our meta-analysis.[29] The pooling result showed that the total drainage volume was significantly lower in the

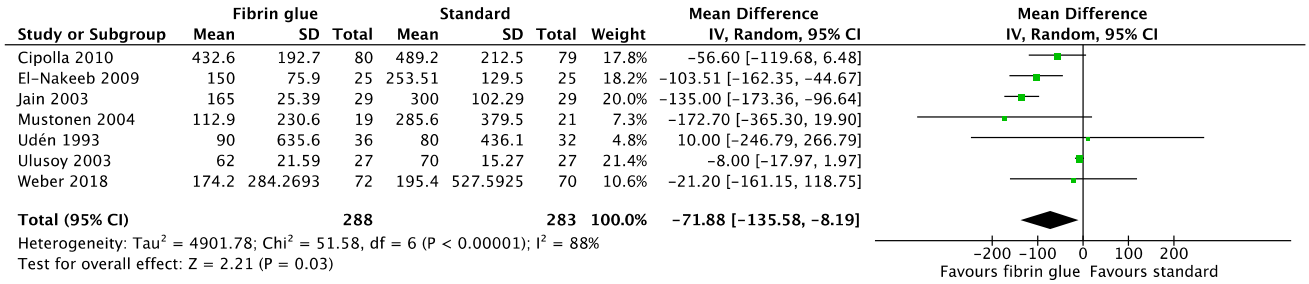

FIG. 2 Forest plot comparing fibrin sealants and the control, where the outcome is total volume of seroma aspiration. *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of variance

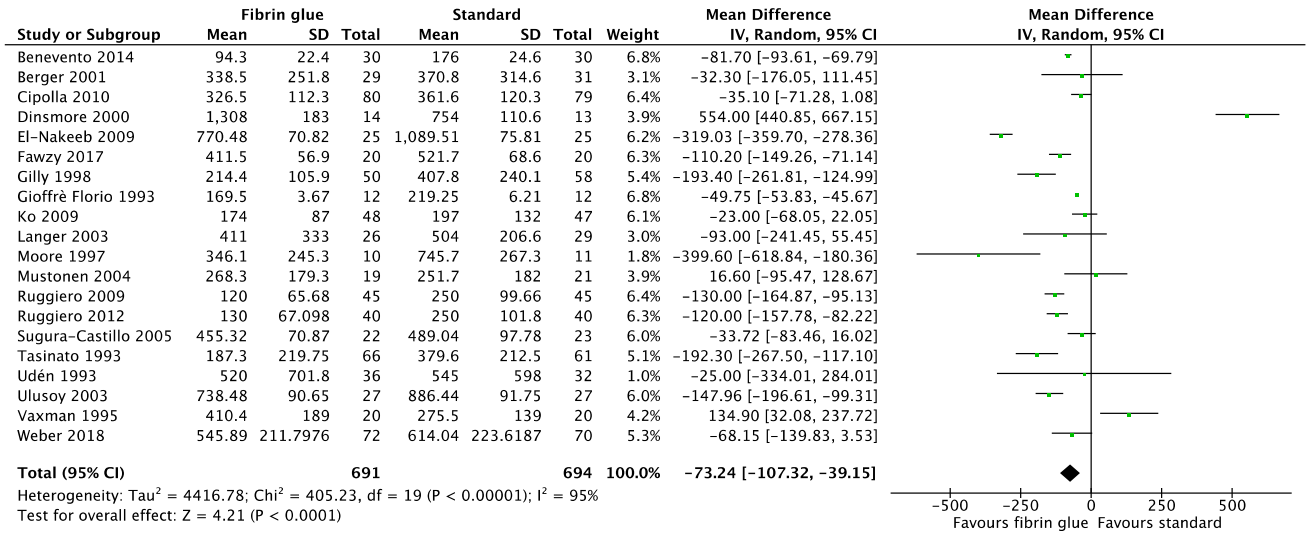

FIG. 3 Forest plot comparing fibrin sealants and the control, where the outcome is total drainage volume. *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of variance

patients receiving fibrin sealant than in the controls (WMD − 73.24, 95% CI − 107.32 to − 39.15) [Fig. 3].

Duration of Drainage

The duration of drainage was reported in 16 RCTs.[3,11,15,21–24,26,28,31,32,35–39] The criteria for drainage removal were different among the trials and are shown in Table 1. Florio et al. reported only the means and not the standard deviation, CI, or range.[21] The data format in this RCT was different to that in the other RCTs and thus the RCT was excluded from our pooling. Finally, 15 studies were considered eligible for further meta-analysis.[3,11,15,22–24,26,28,31,32,35–39] Wb et al. reported only the daily amount of drainage, from which the total duration of drainage was calculated for further meta-analysis.[39] The pooling results demonstrated that the total drainage duration was significantly lower in the patients receiving fibrin sealant (WMD − 0.84, 95% CI − 1.50 to − 0.19; $p = 0.01$) [Fig. 4].

Length of Hospital Stay

Length of hospital stay was reported in 10 RCTs.[15,22,25,26,31–33,36,38,39] Two reported only the mean and not the standard deviation, CI, or range[33,36] and were thus excluded from our pooling. In total, eight trials were considered eligible for further meta-analysis.[22,25,26,31,32,38,40,41] The pooling results revealed that although the fibrin sealant group had a shorter length of hospital stay than the standard group, the result was non-significant (WMD − 0.49, 95% CI − 1.22 to 0.24) [Fig. 5].

Incidence of Surgical Site Infection

Surgical site infection was reported in 16 of the included RCTs.[3,11,15,23,25–30,32–34,36,37,39] In the study by Moore et al.,[29] the incidence of surgical site infections in the three study groups treated with different amounts of fibrin glue were combined and compared with that in the control group. Our pooling results indicated no significant

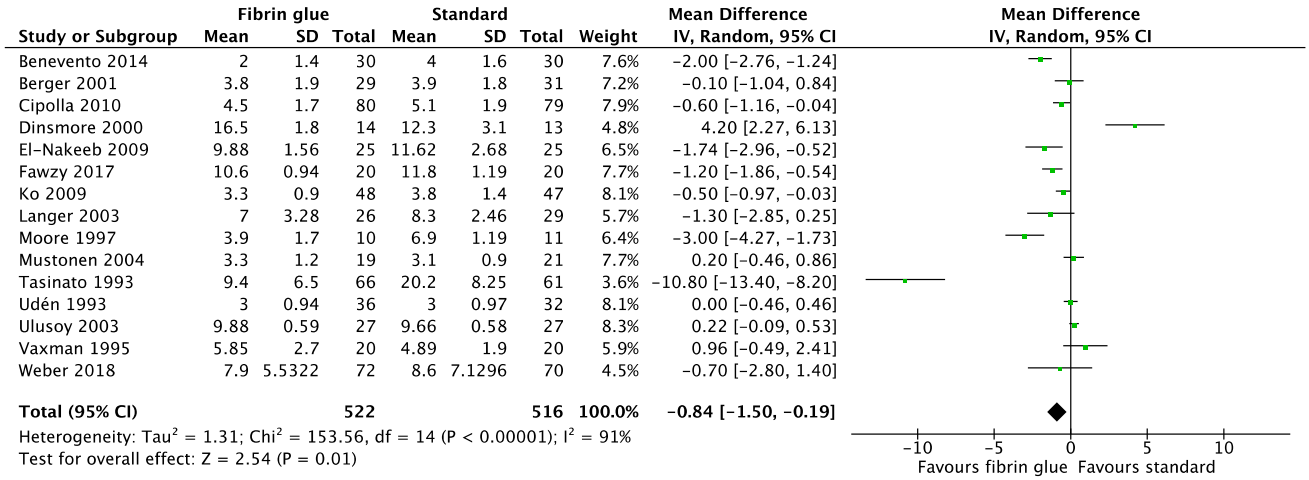

FIG. 4 Forest plot comparing fibrin sealants and the control, where the outcome is drainage duration. *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of variance

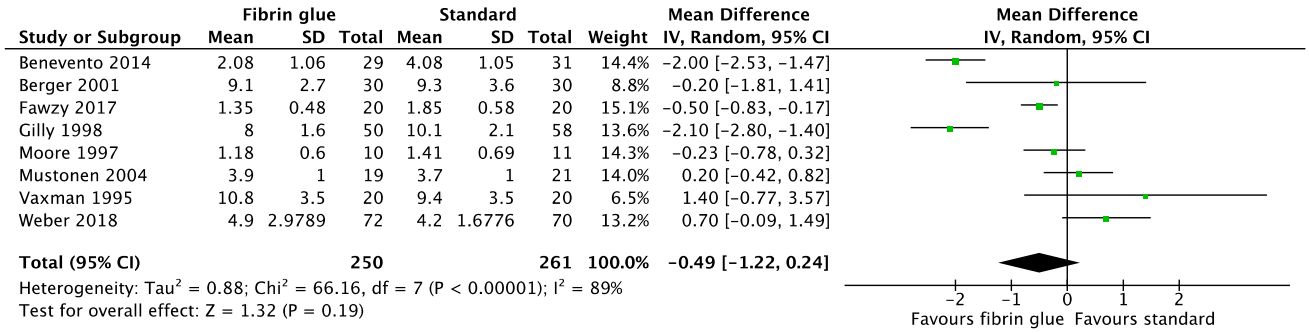

FIG. 5 Forest plot comparing fibrin sealants and the control, where the outcome is length of hospital stay. *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of variance

difference in the incidence of surgical site infection between patients receiving fibrin sealant and the controls (RR 0.84, 95% CI 0.54–1.30 [Fig. 6].

DISCUSSION

Our results revealed that fibrin sealants did not significantly reduce the incidence of seroma, likelihood of surgical site infection, or length of hospital stay in patients undergoing breast surgery with axillary dissection; however, fibrin sealant did show some benefits in reducing the total volume of seroma and the volume and duration of drainage. Therefore, fibrin sealant has limited benefits in improving postoperative quality for patients with breast cancer.

The benefits of fibrin sealants have been known for many years and they have been used in other surgeries. In patients with melanoma who underwent lymph node dissection, the use of fibrin sealants significantly reduced the volume and duration of drainage.[40] Additionally, in patients with gynecologic cancer who underwent pelvic lymph node dissection, the volume of drainage was significantly reduced in the fibrin group.[41] However, no consensus has been reached regarding the positive effect of fibrin sealants on treatment-related morbidity among patients with breast cancer. Several studies and trials have evaluated the effects of fibrin sealants in latissimus dorsi flap fixation, but no significant advantages of applying fibrin sealant were demonstrated.[42–44] In the present analysis of patients with breast cancer undergoing ALND, the fibrin sealant group was demonstrated to have lower volume of seroma and lower volume and duration of drainage compared with the standard group, and are considered major outcomes in many studies.

The effects of sealant may depend on fibrinogen concentration. A low concentration could result in a weaker effect of the fibrin sealant.[26] In our included RCTs, all but three applied fibrin sealant with a fibrinogen concentration

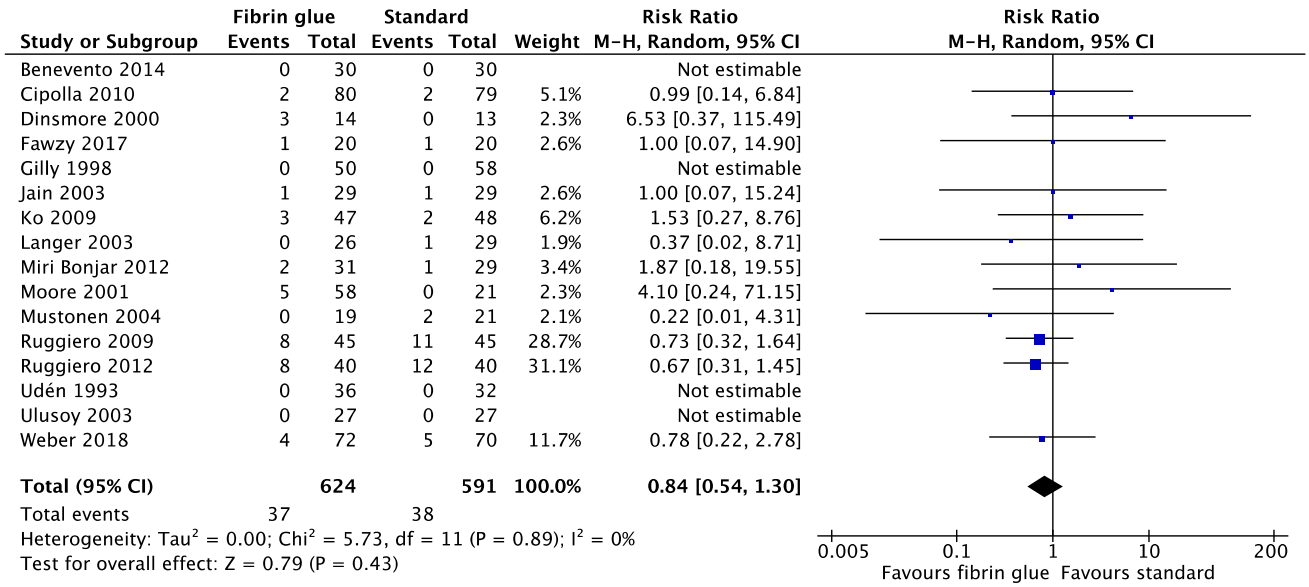

FIG. 6 Forest plot comparing fibrin sealants and the control, where the outcome is incidence of surgical site infection. *M-H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

of more than 75 mg/mL; Dinsmore et al.,[23] Moore,[31] and Fawzy et al.[29] adopted a fibrinogen concentration of 25.47, 40, and 65 mg/mL, respectively. Among all the RCTs, Dinsmore et al.[23] obtained the poorest outcome in terms of drainage volume and duration reduction in the fibrin group compared with the controls, whereas Moore[31] and Fawzy et al.[26] reported that fibrin sealant had a significant negative effect on seroma likelihood. Consequently, we suspect that the fibrinogen concentration should be higher than 25.47 mg/mL if its benefits are to be achieved. The optimal fibrinogen concentration must be evaluated in future trials.

Regarding the form of fibrin sealant, several studies investigating the use of nonliquid fibrin sealant patches obtained a greater benefit than when glue was employed.[39] In our study, two included RCTs[22,39] compared the effects of fibrin patches with controls, but the effects on seroma incidence and drainage appeared to be no different from those determined in the other RCTs.

The number of lymph nodes that are removed is related to the incidence and volume of seroma. In our study, fewer than 10 nodes were removed from patients in two RCTs.[27,38] In the study by Jain et al., a lower seroma volume was discovered in the fibrin group than in the controls.[27] Moreover, in three trials, fibrin sealant was discovered to reduce drainage volume in patients who had more than 20 nodes removed.[16,35,37] Thus, fibrin sealants can have benefits for patients with breast cancer undergoing axillary dissection regardless of the number of nodes removed in surgery.

The RCTs included in our meta-analysis exhibited considerable heterogeneity. First, the types of breast surgery were not identical among the studies. Mastectomy was performed in some, whereas lumpectomy was performed in others. Second, the formulation or brand of fibrin sealant differed among the RCTs, potentially resulting in differing wound healing efficacy. Finally, the observed variation may have also been due to different criteria for diagnosing or detecting seromas and performing drainage. For example, the criteria of drain removal differed among the RCTs. In the study by Udén et al.,[36] the drain could be removed when the drainage rate was < 100 mL/day, whereas most of the studies had a stricter criterion of < 30 mL/day. Finally, as described previously, the means of evaluating the length of hospital stay, seroma formation, volume of seroma, and total volume and duration of drainage differed among the trials. These differences explained the observed heterogeneity.

This study had several limitations. First, the trials included did not separate the outcomes by type of surgery (i.e. mastectomy or lumpectomy), thus limiting the implications of our findings for specific groups of patients. Second, patients who underwent neoadjuvant therapy or breast reconstruction were not included in our study; therefore, the benefits of fibrin sealants for these patients remain unknown. Third, we did not include patients who underwent sentinel lymph node biopsy; the effectiveness of fibrin sealants in this scenario must also be confirmed.

CONCLUSIONS

This meta-analysis revealed that the application of fibrin sealants to the surgical site in breast cancer surgery with axillary dissection has limited benefits in reducing seroma, with few positive results in decreasing volume and duration of drainage. Therefore, considering little impact of fibrin sealants in increasing postoperative quality, and considering their high cost, applying fibrin sealants will not be recommended as a standard procedure in breast cancer patients. However, based on different patients' expectations and affordability, shared decision making with patients regarding the use of fibrin sealants is worthwhile, as opposed to essential.

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