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Effect of quilting on seroma formation in mastectomies: A meta-analysis☆

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ABSTRACT

Background: Seroma is the most common complication following mastectomy and can require several days of drainage and lead to delayed wound healing, longer hospital stays, and an increased financial and emotional burden. Seroma formation is not well understood and but there is good evidence that closing the dead space via quilting can help reduce seroma formation. This study assessed randomized controlled trials and reviewed current literature to elucidate if there is a strong association between quilting sutures and seroma formation.
Methods: A systematic search of 5 databases using search terms similar to "seroma", "quilting", "flap fixation", "random", and "mastectomy". Data was extracted and Medcalc software used to perform a meta-analysis of the primary outcome: incidence of seroma formation, as well as secondary outcomes: volume and duration of drainage.
Results: Eleven randomized controlled trials with 2009 patients were included. Quilting with sutures greatly reduced the incidence of seroma formation compared with conventional closure ($p < 0.001$, RR 0.367 [95% CI 0.25, 0.539]; $I^2 = 63.56\%$) as well as duration of drainage ($p = 0.015$, SMD -1.657, SE 0.680 [95% CI -2.991, -0.324]; 8 studies, $n = 1578$; $I^2 = 98.98\%$). Quilting did not significantly affect volume of drainage.
Conclusions: Quilting was found to be associated with lower seroma rates. Future studies should investigate the use of quilting in combination with other preventative techniques to search for a synergistic method that will further improve patient care.

1. Introduction

Over the past two decades, there has been an upward trend of women opting for a bilateral mastectomy for unilateral breast cancer, as well as for prophylaxis with no disease [1]. Because breast cancer is the most common cancer in females, the applications of the treatment of disease are wide. There is a growing patient population in need of mastectomies and therefore, it is crucial that surgeons find the technique most suitable to each individual patient to lessen the burden of the treatment process.

One complication of breast surgery is seroma formation, or a buildup of serous fluid that accumulates in dead space in the place of excised tissue [2]. Seroma formation rates vary widely among studies but are considered one of the most common complications following mastectomies and can greatly add to the discomfort of the patient [3,4]. Not only can seromas require several days of drainage, delay wound healing, and increase the length of hospital stays, but they can also put the patient at higher risk for infection and skin necrosis. This, in turn, puts greater financial strain on the patient, in addition to the already taxing experience that comes with a diagnosis of breast cancer and subsequent treatment plan.

The mechanism for seroma formation remains unclear. Although it was originally thought that seroma was lymph or blood, histochemistry revealed vast differences. McCaul et al. analyzed seroma fluid and lymph in post-mastectomy patients, and found that seroma fluid contained more granulocytes and monocytes than lymphocytes, as well as higher levels of protein, albumin, globulin, cholesterol and calcium than lymph [5]. Al-Gaithy and Ayuob performed immunohistochemistry of seromas from post-mastectomy rabbits and found a large number of inflammatory cells when compared with non-seromatous tissue from the same animal. They also found lymphocytes and macrophages producing angiogenic factors and a majority of defective new vessels lacking basement membranes and endothelial linings. They concluded that defective neovascularization may be an underlying cause of the seroma formation. In addition to studies that have suggested neovascularization [6–8], Petrek et al. suggested that the number and extent of axillary lymph node involvement affected seroma formation [9], while others

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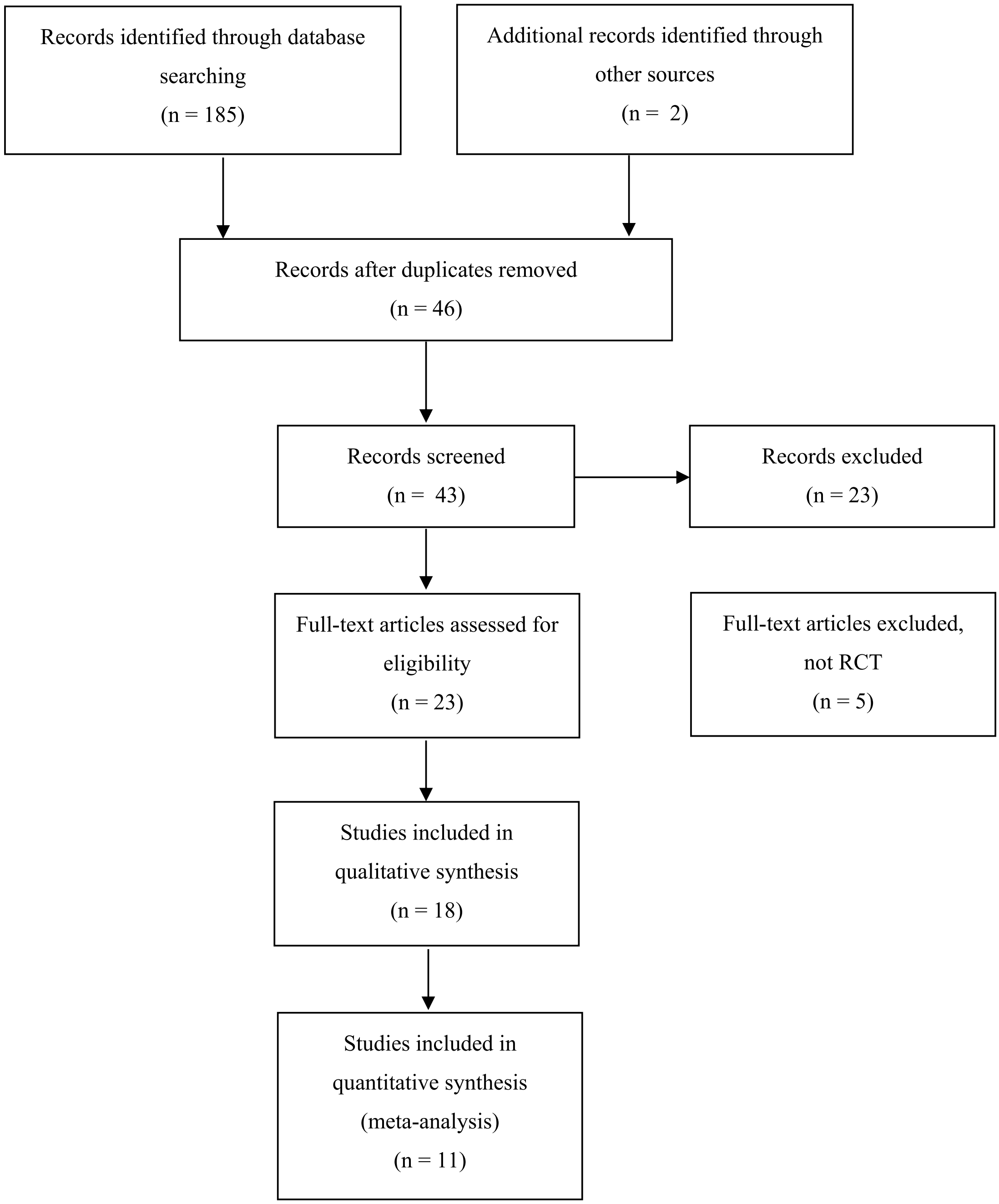

Fig. 1. PRISMA flow chart of study selection process. *RCT,* randomized controlled trial.

discuss fibrinolytic activity and inflammatory mediators as contributors [6,8,10–13].

Although the cause for seroma formation is unknown, risk has been extensively researched. A review by Kuroi et al. found several associations with seroma formation, such as obesity, hypertension, longer operation time, lack of drainage, electrocautery use, and drainage volume in the first 3 post-operative days [14]. Some studies found that patients over the age of 60 were at higher risk for seromas [15–17] while others found no such difference [18,19].

Along with risk factors, studies have attempted to elucidate seroma prevention strategies, like the use of sharp or ultrasonic dissection [20–24], and introduction of talc into the wound cavity [25,26].

Dead space seems to be one of the most problematic risk factors and is generally accepted to be worsen seroma formation. Widely used techniques [2] that attempt to reduce of dead space include the use of closed suction drains [27–29], fibrin sealants [30,31], negative pressure wound therapy [32], and quilting sutures [29,30,33–42].

In suction drainage, a tube attached to a vacuum is inserted into the wound site and kept in place with a few sutures to remove matter from the dead space [2]. He et al.'s meta-analysis found that insertion of a suction drain into the axilla following axillary lymph node dissection significantly reduced seroma formation when compared with no drainage, but still increased the length of hospital stays. Similarly, a review found that closed suction drains significantly reduce incidence of seroma following abdominal, breast, and face surgeries. High- or low-pressure suction can be used to remove unwanted buildup of fluid. In a RCT, Lin et al. found that low pressure suction drainage resulted in fewer complications and lower costs than high pressure suction drainage. Earlier RCTs found no difference between high and low vacuum suction, recommending low suction, as it required shorter hospital stays [43–45].

Another option for reducing seroma formation is fibrin sealants. These adhesives use fibrinogen, thrombin, aprotinin, and calcium chloride to cause overlying tissue to adhere to underlying tissue, effectively closing the dead space. Although more expensive, the fibrin sealants were found to reduce length of stay, and therefore overall cost of treatment [2].

Negative wound pressure therapy, or vacuum assisted closure, is a technique that uses a vacuum attached to a sealed dressing that is placed on the wound. While still a relatively new intervention, studies show that negative pressure wound therapy reduces surgical site complications and cost in high-risk patients [46]. A meta-analysis by Cagney et al. found that when compared with conventional wound dressing, negative wound pressure therapy reduced the incidence of seroma formation across seven RCTs.

Lastly, quilting sutures, otherwise known as flap fixation, attempt to mechanically diminish dead space by suturing the skin to the fascia of the underlying muscle [2]. Published techniques in closing post-mastectomy vary slightly, with differences in whether the fascia is preserved or whether the suturing begins medially or laterally, absorbable monofilament or polyfilament sutures, number of centimeters between each suture and number of rows of sutures. Regardless of specific technique, most authors also included a low-pressure suction drain [37, 47–49].

Studies that analyze the effect of quilting sutures have some of the strongest evidence for seroma reduction in patients undergoing modified radical mastectomies. A recent review [50] showed that there may be an advantage to using quilting sutures, but there has yet to be published a convincing analysis regarding prevention of seromas in mastectomies. By including only randomized controlled trials of mastectomies and modified radical mastectomy (MRM), we attempt to analyze randomized controlled trials to elucidate the role quilting may play in seroma prevention.

2. Materials and methods

This meta-analysis was conducted in accordance with the guidance of the Cochrane handbook and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

2.1. Focused question

In female patients undergoing mastectomies and MRM, is there evidence that quilting, compared with conventional closure, affects seroma formation?

Patient, Intervention, Comparison, Outcome (PICO) Question.

P (Population): Female patients undergoing mastectomies or MRM.

I (Intervention): Quilting suture.

C (Comparison): Conventional closure.

O (Outcome): Seroma formation.

2.2. Search strategy

On December 31, 2020, a search was conducted in 5 databases: Web of Science, Pubmed, ClinicalTrials.gov, Cochrane Library, and Google Scholar, as denoted in Fig. 1. The full texts of all potentially relevant articles were obtained. The reference lists for included articles were reviewed for further potentially relevant papers. Final lists of included articles were compared, and disagreements resolved by discussion.

We used MeSH headings and subheadings in various combinations, supplemented with free text to increase sensitivity. Keywords related to the surgical technique, such as "quilting" and "flap-fixation," were combined with the search term "seroma." A comprehensive and sensitive search strategy was adapted from the Cochrane Database of Systematic Review.

2.3. Study selection criteria

This review considered human randomized controlled trials with at least 20 female participants per experimental arm. Trials that assessed MRM, simple mastectomy with axillary lymph node dissection, axillary drainage, quilting sutures, or flap fixation with sutures compared with conventional wound closure (control) were eligible for inclusion. Studies pertaining to breast reconstruction, latissimus dorsi flap, other wound closures (glue), drug administration, or lack of drainage were excluded. Studies that looked at more variables than quilting versus conventional had data extracted for analysis that only pertained to the study question. Other systematic reviews or meta-analyses, observational, retrospective, or nonrandomized trials and animal studies were excluded from this study. There were no date or language limitations placed on the search; however, all included articles are in English.

2.4. Data extraction

Details of study design and statistics relating to the outcomes of interest were extracted. Where data was missing or unclear, the corresponding author was contacted by email and if no reply was received, 4 weeks later all possible authors were contacted in addition to re-contacting the corresponding author. Missing data was imputed, as described below.

2.5. Outcomes

The primary outcome was incidence of seroma formation. Secondary outcomes included total volume of drainage (mL) and duration of drainage (days).

2.6. Risk of bias assessment

The risk of methodological bias and quality of evidence was assessed based on the GRADE tool guidelines for each outcome, as summarized in Table 2. All 11 articles offered level I evidence (randomized controlled trials; n = 2009). Risk of bias was assessed by the five questions outlined by the Cochrane Handbook. These include bias arising from: the randomization process, deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. Three studies show high certainty of evidence and eight studies show moderate certainty of evidence due to factors such as randomization process or missing information. Studies with high risk of bias remained in the study when they had no other concerning characteristics.

2.7. Data analysis

To maintain a high level of evidence, only randomized controlled trials were included. For the duration of drainage outcome, three studies did not include standard deviations. Additionally, two studies did not include standard deviations for total volume of drainage. For these studies, data from remaining studies were plotted in Microsoft Excel (mean v. SD) and a line of best fit based on an R squared value was produced. Missing standard deviations were imputed from the equation for the line of best fit. The meta-analysis was conducted using MedCalc software using a random effects model.

3. Results

3.1. Study selection

We identified 187 articles (Web of Science: 33, PubMed: 26, Clinicaltrials.gov: 3, Cochrane Library: 121, Google Scholar: 2), out of which 23 were potentially eligible. Following screening, 11 RCTs were included[48,49,51–60]. Eight studies assessed total volume of drainage

Table 1
Characteristics of included studies.

Study	Study Design	Randomization Technique	Type of Surgery	Number of participants		Patient Characteristics					
						Mean Age		Mean BMI		Tumor	
				Q	C	Q	C	Q	C	Q	C
Khater et al., 2015	RCT	Computer-generated random number	Mastectomy + axillary clearance	60	60	46 ± 7	44 ± 8	30.5 ± 1.8	30.9 ± 1.5	Size: 35 ± 6 mm Grade: I:8 II/III:52	Size: 34 ± 7 mm Grade: I: 11 II/III:49
Najeeb et al., 2018	RCT	"Randomly divided"	MRM	35	35	46.26 ± 9.23	42.77 ± 10.55	<40	<40	Stage: II: 55 III: 15 Grade: I: 8 II: 37 III:25	
Arafa et al., 2019	RCT	Computer-generated random number	MRM	69	69	44.82 ± 7.29*	48.97 ± 9.36*	28.06 ± 5.09*	27.01 ± 5.31*	Stage: I: 18 II: 38 III: 13	Stage: I: 14 II: 39 III: 16
Awad et al., 2019	RCT	Computer generated random allocation	MRM	400	400	n/a	n/a	n/a	n/a	Stage: II-IIIa	
Thu Myint et al., 2020	RCT	Independent statistician via computer-based system	Mastectomy + level 2 axillary dissection	70	70	49.60 ± 11.73	51.34 ± 11.29	26.21 ± 5.4	25.35 ± 5.4	Size: 51.9 ± 16.92 mm	Size: 50.3 ± 14.94 mm
Sakkary, 2012	RCT	"Randomly divided"	MRM	20	20	51 (37–62)	54 (38–72)	Stated homogenous		Stage: T1: 1 T2: 15 T3: 4 T4: 0 N0: 12 N1: 6 N2: 2 Grade: II: 16 III: 4	Stage: T1: 1 T2: 10 T3: 6 T4: 3 N0:6 N1:10 N2:4 Grade: I: 15 II: 5
George et al., 2011	RCT	Computer-generated randomization tables	MRM	40	40	51.43 ± 9.83		25.11 ± 3.68		Mean Nodes: 16.88 Positive Nodes: 4.3	Mean Nodes: 15.85 Positive Nodes: 3.83
Gong et al., 2010	RCT	Randomly ordered sealed envelopes opened immediately prior to mastectomy	MRM	101	100	49.83 ± 9.47	60.63 ± 9.16	21.7 ± 2.97	22.08 ± 3.03	Mean Nodes: 15.45 ± 5.72 Positive Nodes: 43%	Mean Nodes: 14.06 ± 3.44 Positive Nodes: 32%
Seenivasagam et al., 2013	RCT	Computer pre-generated randomization list: block randomization, factorial design	(MRM or BCS) with level 3 axillary dissection	49	48	48	50	24.8	25.4	Stage: T1: 4 T2: 29 T3: 4 T4: 7	Stage: T1: 4 T2: 20 T3: 5 T4: 15
Ozaslan et al., 2010	RCT	Patients numbered at hospitalization: even = group 1, odd = group 2	MRM	50	50	51.8 ± 10.9	48.1 ± 11.4	27.1 ± 4.1	28.2 ± 4.7	Mean Nodes: 25.4 ± 9.8 Metastatic Nodes: 3.8 ± 5.8	Mean Nodes: 25.2 ± 10.3 Metastatic Nodes: 3.2 ± 6.9
de Rooij et al., 2020	RCT, double blinded	Web-based randomization program (ALEA): 30 min before wound closure. Stratified block randomization	MRM or simple mastectomy or mastectomy with sentinel node dissection	Q: 109 FF-G: 111	114	Q: 65.4 ± 13.6 FF-G: 65.2 ± 13.5	64.1 ± 12.6	Q: 28.0 ± 5.5 FF-G: 27.7 ± 4.9	27.4 ± 5.2	Q Stage: T0: 0 T1-2: 80 T3-4: 18 N0: 83 N1: 22 N2: 4 N3: 1 FF-G Stage: T0:1 T1-2: 88 T3-4: 13 N0: 82 N1: 27 N2: 3 N3: 1	Stage: T0:3 T1-2: 73 T3-4: 25 N0: 84 N1: 22 N2: 7 N3: 2

*$p < 0.05$.
Q: quilting (flap fixation with suture), FF-G: flap fixation with tissue glue, C: control (conventional wound closure), RCT: Randomized controlled trial, MRM: Modified radical mastectomy, BCS: breast conserving surgery.

Table 2
Risk of bias assessment.

Study	Certainty of evidence: GRADE		
	Seroma formation	Duration of Drainage	Volume of Drainage
Khater et al., 2015	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High
Najeeb et al., 2018	⊕⊕⊕x̂ Moderate[a]	n/a	n/a
Arafa et al., 2019	⊕⊕⊕⊕ High	n/a	n/a
Awad et al., 2019	⊕⊕⊕x̂ Moderate[b]	⊕⊕⊕x̂ Moderate[b]	⊕⊕⊕x̂ Moderate[b]
Thu Myint et al., 2020	⊕⊕⊕x̂ Moderate[d]	⊕⊕⊕x̂ Moderate[d]	⊕⊕⊕x̂ Moderate[d]
Sakkary, 2012	⊕⊕⊕x̂ Moderate[ab]	⊕⊕⊕x̂ Moderate[abc]	⊕⊕⊕x̂ Moderate[ab]
George et al., 2011	⊕⊕⊕x̂ Moderate[b]	⊕⊕⊕x̂ Moderate[bc]	⊕⊕⊕x̂ Moderate[b]
Gong et al., 2010	⊕⊕⊕x̂ Moderate[a]	⊕⊕⊕x̂ Moderate[ac]	n/a
Seenivasagam et al., 2013	⊕⊕⊕x̂ Moderate[b]	⊕⊕⊕x̂ Moderate[b]	⊕⊕⊕x̂ Moderate[b]
Ozaslan et al., 2010	⊕⊕⊕x̂ Moderate[a]	⊕⊕⊕x̂ Moderate[a]	⊕⊕⊕x̂ Moderate[a]
de Rooij et al., 2020	⊕⊕⊕⊕ High	n/a	⊕⊕⊕⊕ High

[a] Risk of bias in randomization process.
[b] Risk of bias in underreporting characteristics of participants.
[c] Risk of bias due to missing standard deviation data.
[d] Risk of bias due to missing data.

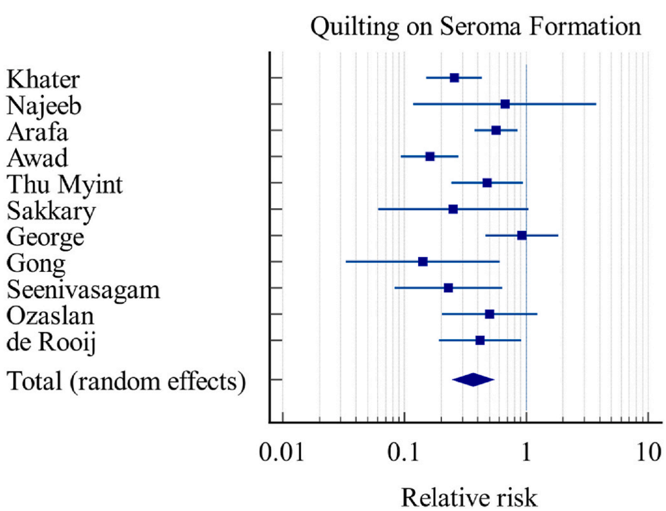

Fig. 2. Effect of quilting versus control on seroma formation across 11 RCTs. Relative risk less than 1 signifies quilting decreases seroma formation (protective effect of quilting). *p < 0.001.

on seroma formation, 8 studies assessed the correlation between duration of drainage and seroma formation, and all 11 studies investigated the number of participants with seroma formation. Among the RCTS, seromas were considered an accumulation of fluid at the surgical site requiring drainage.

3.2. Study characteristics

The studies ranged from 40 to 800 participants. Most of the studies reported on homogenous characteristics, except Awad et al. [53]. Table 1 shows mean age, BMI, and tumor characteristics that each article reported. Other characteristics, such as hypertension, smoking, and diabetes mellitus were reported in various studies without being

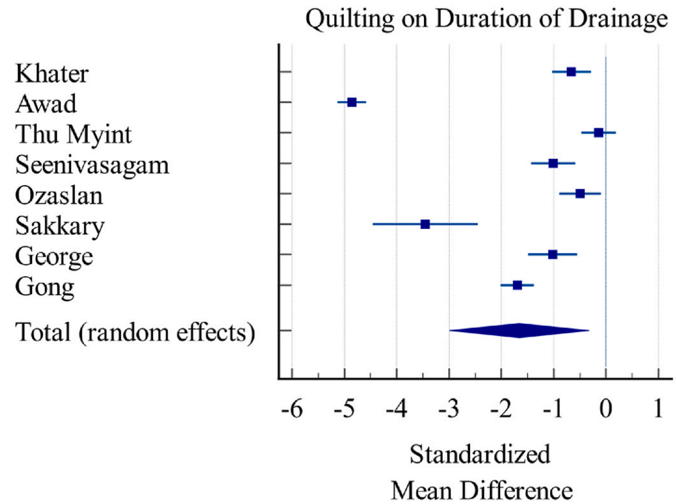

Fig. 3. Effect of quilting versus control on duration of drainage across 8 RCTs. Standard mean differences less than zero signify quilting decreases duration of drainage (improvement). *p = 0.015.

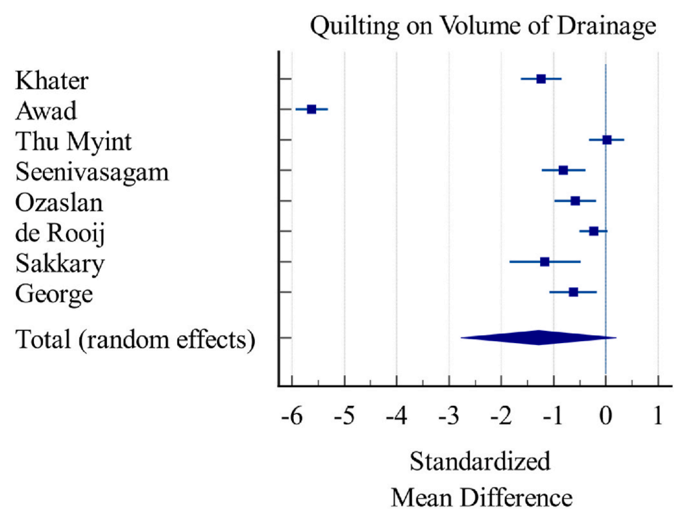

Fig. 4. Effective of quilting versus control on volume of drainage across 8 RCTs. No significant effect demonstrated.

consistently reported across all studies, and so were not included in this analysis for simplicity. All of the studies compared female adults undergoing MRM or simple mastectomy with or without axillary node dissection with quilting sutures (intervention) versus conventional closure (control).

One study, de Rooij et al. [48], compared 3 groups: quilting with sutures, quilting with tissue glue, and the conventional closure. Seenivasagam et al. [59] compared quilting with sutures, compression dressing and control. In these trials, we extracted data for the analysis pertaining only to quilting with sutures versus control. However, characteristics of the interventions were extracted and can be found in Table 1.

3.3. Effects of the intervention

Effect sizes varied between the studies, with some outliers, so we used the random effects measure for all three calculations. Relative risk was calculated for effect of quilting with sutures on incidence of seroma formation. When calculating relative risk of total random effects, the effect of quilting on the number of seromas was statistically significant ($p < 0.001$), indicating quilting with sutures greatly reduced the incidence of seroma formation compared with conventional closure. However, there was moderate heterogeneity among the studies (RR 0.367 [95% CI 0.25, 0.539]; 11 studies, $n = 2009$; $I^2 = 63.56\%$; Fig. 2).

Similarly, quilting with sutures decreased the duration of drainage. In a continuous measure meta-analysis for duration of drainage, total random effects were statistically significant ($p = 0.015$); however, the studies were calculated to be almost completely heterogenous (SMD -1.657, SE 0.680 [95% CI -2.991, −0.324]; 8 studies, $n = 1578$; $I^2 = 98.98\%$; Fig. 3).

Quilting with sutures did not affect the total volume of drainage ($p = 0.09$, SMD -1.287, SE 0.758 [95% CI -2.774, 0.2]; 8 studies, $n = 1600$; $I^2 = 99.23\%$; Fig. 4).

Heterogeneity may have been caused by the variation in the amount of days drains were kept in place. Some studies removed the drains on a specific day regardless of volume of drainage or had difference preferences for appropriate time to drain removal. Additionally, in regard to variables that have been previously shown to affect seroma outcomes, studies varied on reporting on tumor grade, stage, and lymph node involvement, with some reporting only average size of tumors. Studies also differed in how they reported patient age and used varying statistical tests.

4. Discussion

In this meta-analysis, we aimed to clarify the effects of quilting on seroma formation, duration, and volume of drainage. Our analysis provides strong evidence that the use of quilting sutures was related to a significant reduction in seroma formation in patients having undergone mastectomies.

While our meta-analysis focused on seroma formation, it is important to consider why we did not find quilting to reduce the volume of drainage. In addition to the size of the dead space, it has been suggested that the formation of seromas is stimulated by damage to lymphatics via tumor infiltrate or during the surgery [61]. In a RCT, Yetim et al. [62] found that gentamycin sponge implant to the axillary surgical area decreased seroma rate as well as volume of drainage, suggesting microbes may play a role in the volume of drainage. These are two factors that closure of dead space alone would not eradicate.

Although we found closure of dead space reduced seroma formation, we cannot conclude whether drains should be maintained as standard practice. Existing literature finds the advantage of drains to be ambiguous with respect to decreasing seroma formation, especially when taken in context with disadvantages, such as patient discomfort and longer hospitalization times [63]. A large meta-analysis by Kosins et al. [64] that considered drainage in various surgeries found drains decreased seroma formation in various surgeries including axillary lymph node dissection, but had no effect on cesarean delivery, abdominal wound procedures, and surgeries on obese patients. This may signal a lack of strong evidence to emphatically support the use of drains in standard practice.

It is presumed that the mechanism of quilting in controlling seroma formation is to decrease the space into which fluids can leak. However, studies show that not all techniques for minimizing dead space have the same significant effect. De Rooij et al. found quilting to be more beneficial when compared with fibrin tissue glue [48]. This may be due to fibrin glue clotting nearby blood vessels, expediting tissue hypoxia. It is well established that dead space is hypoxic and tissue hypoxia leads to neo-angiogenesis [65]. Proangiogenic cytokines have also been found in post-mastectomy seromas [66–68]. However, Al-Gaithy and Ayuob looked at post-mastectomy rabbits with seromas and found defective neovasculature [6], an important inducer of fluid accumulation.

Furthermore, matrix metalloproteinase-2 (MMP-2) has been studied in the setting of seroma in post-mastectomy patients. During wound healing, IL-6 induces MMPs to degrade extracellular matrix components. A lack of MMPS leaves debris, leading to granulation tissue, and enhancing the accumulation of seroma fluid [67,69,70].

Although the pathogenesis of seroma formation remains unclear, there may be several options to decrease post-operative morbidity. However, patient-controlled variables (such as hypertension, obesity, depression) can be exceedingly difficult to manage, stressing the importance for surgeons to continue honing their skills and searching for techniques that will result in the best possible outcome for the patient.

The results of this study suggest that quilting with sutures may be preferred over conventional closure to minimize seromas, and subsequently reduce further complications, financial costs, and other discomforts to patients undergoing mastectomies.

4.1. Generalizability

It may be difficult to generalize the findings of this study to a procedure that is not a mastectomy in a female patient. Additionally, risk factors including hypertension [5], high BMI, and diabetes [14], thought to increase seroma formation are usually excluded from RCTs. Therefore, patients with comorbidities may not necessarily benefit from these techniques and surgeons should carefully consider patient demographics when assessing the best course of action.

4.2. Limitations

Several limitations are associated with this study. Three studies did not report standard deviation data for volume and/or duration of drainage; data was imputed [56–58]. Most of the experimental groups were relatively small ($n < 100$). Three studies included more than 100 participants per group and four studies included 50 or more participants per group. In addition, seromas were defined differently between studies based on detection methods. Some considered seromas only if they required multiple drainage sessions while others used ultrasonography, a much more precise tool that can find seromas that need no drainage[71].

5. Conclusion

This meta-analysis supports the use of quilting with sutures to reduce seroma formation in female patients undergoing mastectomy. Future large scale RCTs should investigate the use of quilting in combination with other preventative measures, such as fibrin sealants.

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