Ann Surg Oncol (2021) 28:2599–2608
https://doi.org/10.1245/s10434-020-09225-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Reducing Seroma Formation and Its Sequelae After Mastectomy by Closure of the Dead Space: A Multi-center, Double-Blind Randomized Controlled Trial (SAM-Trial)

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ABSTRACT

Background. Seroma is a common complication after mastectomy, with an incidence of 3% to 85%. Seroma is associated with pain, delayed wound healing, and additional outpatient clinic visits, leading potentially to repeated seroma aspiration or even surgical interventions. This study aimed to assess the effect of flap fixation using sutures or tissue glue in preventing seroma formation and its sequelae.

Methods. Between June 2014 and July 2018, 339 patients with an indication for mastectomy or modified radical mastectomy were enrolled in this randomized controlled trial in the Netherlands. Patients were randomly allocated to one of the three following arms: conventional wound closure (CON, $n = 115$), flap fixation using sutures (FFS, $n = 111$) or flap fixation using tissue glue (FFG, $n = 113$). The primary outcome was the need for seroma aspiration. The secondary outcomes were additional outpatient department visits, surgical-site infection, shoulder function and mobility, cosmesis, skin-dimpling, and postoperative pain scores.

Results. Flap fixation after mastectomy leads to fewer seroma aspirations than conventional wound closure (CON 17.5% vs FFS 7.3% vs FFG 10.8%; $p = 0.057$), with a significant difference between flap fixation with sutures and conventional wound closure (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.16–0.89; $p = 0.025$). Flap fixation has no significant negative effect on surgical-site infections, shoulder function and mobility, cosmesis, skin-dimpling, or postoperative pain.

Conclusion. Flap fixation using sutures leads to a significant reduction in aspirations of post-mastectomy seromas. The authors strongly advise surgeons to use sutures for flap fixation in patients undergoing mastectomy. (ClinicalTrials.gov no. NCT03305757).

Preregistration. The trial was registered after enrollment of the first participant. However, no specific explanation exists for this except that through the years more importance has been given to central trial registration. Our research team can ensure that after enrollment of the first participant, no changes were made to the trial, analysis plan, and/or study design.

Seroma formation is a common complication after mastectomy, with an incidence of 3% to 85%.[1–4] Seroma can cause pain and patient discomfort, and can lead to wound complications such as surgical-site infections

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-020-09225-8) contains supplementary material, which is available to authorized users.

First Received: 2 June 2020
Accepted: 17 September 2020;
Published Online: 19 October 2020

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(SSIs), wound dehiscence, and skin flap necrosis. When adverse events occur, additional outpatient clinic visits generally are required for treatment of seroma-related complications. Depending on the severity of the complications, seroma aspiration or even surgical intervention may be necessary. Extensive research has been performed to understand the etiology so seroma formation can be reduced after breast cancer surgery.

It is assumed that obliteration of the dead space that forms after mastectomy reduces seroma formation.[5,6] The best technique for achieving this goal, however, remains a subject of debate.

Various techniques are used to dissect the skin flaps such as electrocautery, laser scalpel, argon diathermy, and ultrasonic scalpel. The use of electrocautery is associated with seroma formation compared with scalpel dissection alone.[6] No specific method of skin flap dissection has proved to be beneficial in reducing seroma formation.[6–8]

The various techniques for closing the dead space by means of flap fixation have been extensively analyzed. Studies of flap fixation show promising results in terms of reducing the need for aspirations in case of clinically significant seroma.[9–15] A retrospective cohort study conducted by Van Bastelaar et al.[16] showed that flap fixation using tissue glue yielded results similar to those from flap fixation using sutures. It is believed that both techniques reduce the dead space by sealing the skin flaps to the pectoral muscle. This could reduce lymphatic leakage and limit the accumulation of fluid.

A recent systematic review of flap fixation techniques used to reduce seroma formation and its sequelae showed that mechanical flap fixation seems to reduce seroma formation after mastectomy with or without axillary clearance.[17] However, no well-powered, randomized, controlled trials have evaluated all aspects of seroma formation and its sequelae.

This is the first double blind, randomized controlled trial to compare the effect of flap fixation on seroma formation after mastectomy between sutures, tissue glue, and a conventional wound closure technique. We hypothesized that obliteration of the dead space after mastectomy prevents seroma formation and its sequelae, and that it is beneficial for patients undergoing mastectomy. After an earlier interim analysis, this report describes the full results.[18]

MATERIALS AND METHODS

Study Design

The Seroma Reduction After Mastectomy (SAM) Trial was a double-blind, randomized controlled trial. Eligible patients who provided informed consent were allocated to one of three groups. The first group underwent conventional wound closure, whereas the second group underwent flap fixation using sutures, and the third group underwent flap fixation using ARTISS tissue glue.

Setting and Patient Selection

Patients were recruited from four different breast clinics in the Netherlands (Atrium Medical Center Heerlen, Orbis Medical Center Sittard [later Zuyderland Medical Center after the merger of the former two], Albert Schweitzer Hospital Dordrecht, and St. Jans Gasthuis Hospital Weert). Patients with an indication for mastectomy or modified radical mastectomy due to invasive breast cancer or ductal carcinoma in situ (DCIS) were eligible for inclusion. Patients undergoing breast-conserving therapy or primary breast reconstruction were excluded. Patients were recruited from June 2014 to July 2018.

Interim Analysis

An interim analysis of the SAM trial was performed to detect the superiority of one of the flap fixation arms.[18] At that time (n = 187), no superiority was detected in either of the flap fixation techniques. Thus, premature abortion of this trial was not necessary.

Randomization, Blinding, and Treatment Allocation

Randomization was achieved using a web-based randomization program (ALEA, Software for Randomization in Clinical Trials). The patients were randomized on the day of surgery 30 min before wound closure. Stratified block randomization using randomly selected block sizes (6/9/12) with an allocation ratio of 1:1:1 was performed. Randomization was stratified per site. The patients were blinded throughout the trial. At the 1-year follow-up evaluation, the patients were informed about the treatment group to which they had been allocated. During follow-up visits, the patients were evaluated by surgeons other than the one who had performed the operation. Thus, the evaluating surgeon also was blinded to treatment allocation.

Study Interventions

All procedures were performed by experienced breast surgeons. The nipple-areola complex was removed, and dissection of the skin flaps was performed using electrocautery. The breast tissue, including the prepectoral fascia, was removed from the pectoral muscle. In all the patients, the extent of the skin flaps was measured (in centimeters) from medial to lateral and from cranial to caudal. With

these measurements, the wound area was calculated under the assumption that it resembled an ellipse ($A = \pi \times a \times b$; see Fig. 1). For skin closure, the edges were sutured using absorbable monofilament sutures (Monocryl 3.0 or V-loc 30 cm) depending on the surgeon's preference.

Flap Fixation Using Sutures After the mastectomy, the skin flaps were sutured onto the pectoral muscle using polyfilament absorbable sutures (Vicryl 3.0) placed at 4- to 5-cm intervals in two or three rows depending on the extent of the skin flaps. Care was taken to prevent dimpling of the skin. The axillary area was not approximated.

Flap Fixation Using Tissue Glue The skin flaps in this group were anchored using fibrin tissue glue (ARTISS, Baxter, IL, USA). First, the study ensured that the skin flaps and pectoral muscle surface were dried with an air spray. Subsequently, ARTISS tissue glue was applied as a spray using 2 ml on both skin flaps and the underlying muscle. After positioning of the skin flaps, compression was applied for 3 min.

Conventional Wound Closure After mastectomy and measurement of the skin flaps, no form of flap fixation was performed. The skin was closed in a conventional manner using an absorbable skin suture.

Drain Policy In all patients, one low suction drain was placed before flap fixation or skin closure. The drain was positioned in the mastectomy gutter lateral to the pectoral muscle and connected to a low-suction drain bottle (Armstrong Medical, Coleraine, UK). Drain output was recorded daily. For patients undergoing mastectomy with axillary clearance, the drain was removed when the volume was less than 50 ml per 24 h, or after a maximum of 5 days. In case of mastectomy without axillary clearance, the drain was removed when the volume was less than 50 ml per 24 h or after a maximum of 48 h.

Follow-up Evaluation Follow-up evaluation was performed for 1 year postoperatively. The patients were evaluated at 1 week (postoperative visit), 6 weeks, 3 months, 6 months, and 1 year after surgery. During these visits, the primary and secondary outcomes were evaluated. At any moment during the trial, the patients could decide to stop participating in the study.

FIG. 1 Formula for calculating wound area

Primary Outcome

The number of seroma aspirations performed during the first postoperative year was the initial primary outcome. This parameter was chosen because it was considered to be the most relevant and objective assessment of clinically significant seroma. Seroma needle aspirations were performed under strict criteria and only when one of the following conditions were met:

1. Seroma causing delayed wound healing and leading to wound breakdown, leakage of lymph fluid, and/or skin flap necrosis.
2. Pain or discomfort caused by large amounts of seroma, characterized by tenseness of the skin.
3. Contaminated or infected seroma warranting seroma aspiration to treat the infection. In these cases, the patients also were treated with antibiotics for 1 week (amoxicillin/clavulanic acid 500/125 mg three times daily).

When needle aspiration was performed, the amount of aspirated fluid (mL) was noted on the case report form.

Secondary Outcomes

Surgical-Site Infection Surgical-site infection is an infection occurring after surgery in the part of the body where the surgery took place. Signs of SSI include drainage of pus from the surgical wound, spreading redness, increased pain or swelling, and fever. In this study, SSI was considered to be present if antibiotics were needed with or without seroma aspiration or in cases that warranted surgical drainage during the first year postoperatively.

Additional Outpatient Clinic Visits If patients required additional hospital visits (emergency room or outpatient clinic) during the first postoperative year due to seroma or seroma-related consequences, this was documented.

Shoulder Function and Mobility Shoulder function and mobility were assessed at baseline and at every follow-up visit during the first year after surgery using the Disability of Arm, Shoulder, and Hand (DASH) questionnaire (validated Dutch version), a validated tool for assessing shoulder function disability.[19] The questionnaire results in a score between 0 (no disability) and 100 (most severe disability).

Cosmesis and Dimpling of the Skin Cosmesis of the chest wall as reported by the patient and skin-dimpling assessed by the blinded surgeon were evaluated at every follow-up visit during the first postoperative year. The patients were asked to grade the self-perceived cosmetic aspect of their chest wall on a Likert scale from 1 to 10.

Postoperative Pain Patient-reported postoperative pain was evaluated at every follow-up assessment and measured on a Likert scale from 1 to 10.

Sample Size Calculation

Estimation of the sample size was based on ordinal regression following assumptions of the distribution of the outcome variable. Using an alpha of 0.025 (correction for 2 comparisons with 3 study groups, comparison of both flap fixation groups with conventional wound closure), 90% power, and an odds ratio or 2.67 (corresponding to an absolute difference of 20% in the need for seroma aspirations), the sample size was estimated to be 112 patients per study group. Therefore, plans were made for a sample size of 336. A p value lower than 0.05 was considered proof of statistical significance.

Statistical Analysis

All analyses were performed using SPSS (IBM SPSS statistics for Windows, version 25, New York, USA). Baseline characteristics are presented as mean ± standard deviation and range for continuous variables and as frequencies and percentages for categorical variables. Missing data were imputed using stochastic regression imputation to prevent a loss of statistical power and to decrease the likelihood of biased treatment effects. The imputed values were drawn using predictive mean-matching.

After inspection of their distribution, both the number of seroma aspirations and the number of additional outpatient clinic visits were dichotomized into yes or no. Logistic regression analysis was used to test whether the proportion of patients who needed seroma aspirations differed between FFS and FFG with the conventional technique. Using multivariable logistic regression analysis, the study corrected for potential confounding by intervention group, age, Charlson Comorbidity Index, body mass index (BMI), wound surface, smoking, use of anticoagulants, axillary clearance, or neoadjuvant chemotherapy. Pearson's Chi square test was used to test the difference in categorized aspiration needs. Logistic regression analysis was subsequently used to assess associations between characteristics and the need for seroma aspirations. Analysis of variance (ANOVA) and logistic regression were used to compute differences between groups in terms of continuous outcome measures and binary secondary outcome variables, respectively.

RESULTS

The study enrolled 339 patients between June 2014 and July 2018. The 339 patients were allocated to one of three study arms: conventional closure (CON; n = 115, 33.9%), flap fixation with sutures (FFS; n = 111, 32.7%), or flap fixation with tissue glue (FFG; n = 113, 33.3%). Primary breast reconstruction was one of the main reasons why patients were excluded from this study. Furthermore, five patients were excluded from the analysis because of too many missing data to be considered for imputation. Two of these patients had no follow-up data at all (one patient withdrew from the study directly after surgery, and one patient died of abdominal sepsis caused by a bowel perforation 5 days after surgery). Three patients were lost to follow-up evaluation 6 weeks after surgery. A flowchart of the SAM trial is shown in Fig. 2. Patient characteristics are shown in Table 1.

Primary Outcome

Seroma aspiration was performed for 40 patients (12%). Compared with the conventional closure group, fewer patients underwent seroma aspiration when flap fixation with sutures and tissue glue was applied (CON 17.5% vs FFS 7.3% vs FFG 10.8%; p = 0.057; Table 2). This difference, however, was significant only between FFS and CON (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.16–0.89; p = 0.025; Table 3). No difference in seroma aspirations was found between the two flap fixation groups (FFG vs FFS: OR, 1.5; p = 0.371).

The univariate logistic regression analysis showed that axillary clearance and neoadjuvant chemotherapy significantly increased the odds of undergoing seroma aspiration (Table 3). Increasing wound surface was associated with a significantly higher risk of seroma aspiration (OR, 1.05; range, 1.01–1.09). When these variables were combined in a multivariable logistic regression analysis, axillary clearance proved to be the only significant independent factor increasing the likelihood of a need for seroma aspiration. Subgroup analysis between patients with and without axillary clearance showed no significant difference in seroma aspiration between the flap fixation groups (Table 4).

Secondary Outcomes

Drain Output Volume. Total postoperative drain output volume did not differ significantly between the three

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CONSORT 2010 SAM Trial Flow Diagram

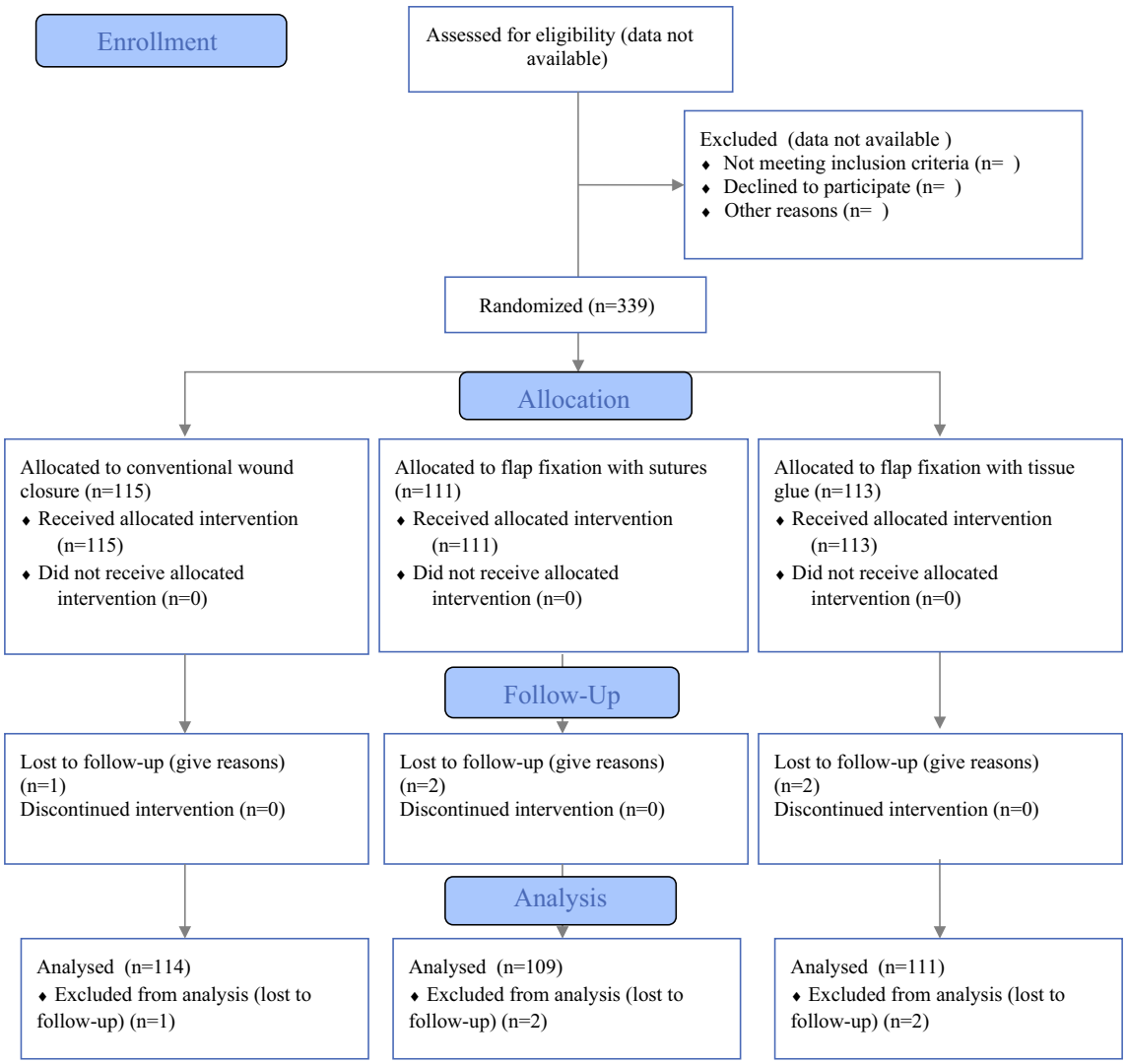

FIG. 2 Flowchart of the Seroma Reduction After Mastectomy (SAM) Trial

groups (CON 316.2 ± 302.9 ml vs FFS 246.0 ± 285.1 mil vs FFG 256.3 ± 285.6 ml; $p = 0.151$).

Additional Outpatient Visits Additional hospital visits were required for 130 (38.9%) of the patients. The patients not treated with flap fixation visited the outpatient clinic more often (CON 54 [47.3%] vs FFS 35 [32.1%] vs FFG 41 [36.9%]; $p = 0.057$). The difference was significant for the patients undergoing flap fixation with sutures compared with the patients who had conventional wound closure ($p = 0.020$).

Surgical-Site Infection Antibiotics were used to treat 56 patients (19.5%). The distribution between the three groups showed no significant difference (CON 19.3% vs FFS 12.8% vs FFG 18.0%). Although nonsignificant, the

TABLE 1 Patient and baseline characteristics

	CON (n = 115) n (%)	FFS (n = 111) n (%)	FFG (n = 113) n (%)
Mean age (*years*)	64.1 ± 12.6	65.4 ± 13.6	65.2 ± 13.5
Mean CCI	4.7 ± 1.9	4.8 ± 2.0	5.0 ± 2.3
Mean BMI	27.4 ± 5.2	28.0 ± 5.5	27.7 ± 4.9
Anticoagulation	17 (14.7)	27 (24.3)	27 (23.8)
Smoking	23 (20.0)	25 (22.5)	16 (14.2)
Procedure			
Mastectomy	9 (7.8)	14 (12.5)	9 (7.9)
Mastectomy + SN	64 (55.6)	64 (57.7)	70 (61.9)
MRM	42 (36.5)	33 (29.5)	34 (30.1)
c			
T 0	3 (2.6)	0	1 (0.9)
x	1 (0.9)	1 (0.9)	3 (2.7)
Is	13 (11.3)	11 (10.0)	8 (7.1)
1–2	73 (63.5)	80 (72.7)	88 (77.9)
3–4	25 (21.7)	18 (16.4)	13 (11.5)
cN			
0	84 (73.0)	83 (75.5)	82 (72.6)
1	22 (19.1)	22 (20.0)	27 (23.9)
2	7 (6.1)	4 (3.6)	3 (2.7)
3	2 (1.7)	1 (0.9)	1 (0.9)
Neoadjuvant chemotherapy	29 (25.2)	19 (17.1)	21 (18.5)
Mean wound surface (cm^2)	286.6 ± 90.2	293.8 ± 71.2	284.0 ± 81.7

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as absolute numbers (%). All patient characteristics are equally allocated between the groups

CON, conventional wound closure; FFS, flap fixation using sutures; FFG, fixation using tissue glue; CCI, Charlson Comorbidity Index; BMI, body mass index; SN, sentinel node; MRM, modified radical mastectomy; cT0, benign tumors; Is, in situ

TABLE 2 Primary outcome: number of patients undergoing seroma aspiration per intervention group (%)

	CON (n = 114) n (%)	FFS (n = 109) n (%)	FFG (n = 111) n (%)	p Value
Seroma aspiration*s* (dichotomous)	20 (17.5)	8 (7.3)	12 (10.8)	0.057
No. of aspirations (*categorical*)				0.101
a. No aspiration	94 (82.5)	101 (92.7)	99 (89.2)	
b. Aspiration	9 (7.9)	6 (5.5)	7 (6.3)	
c. > 1 Aspiration	11 (9.6)	2 (1.8)	5 (4.5)	

Categorical variables reported as n (%), Pearson's Chi square

absolute 5% to 6% fewer SSI rate for flap fixation using sutures can be regarded as potentially of clinical importance.

Reoperation and Postoperative Pain The three groups did not differ significantly in terms of reoperation and postoperative pain (Table 5).

Shoulder Function No differences in shoulder function were observed between the three groups. All the patients showed a slight deterioration of their shoulder function and mobility 1 year postoperatively (Table 5).

Cosmesis and Dimpling No significant differences in cosmesis and dimpling were observed between the three groups. Cosmesis seemed to improve slightly 1 year after

TABLE 3 Logistic regression analysis: independent odds ratios for seroma aspirations for various factors

	Seroma aspiration *OR* (95% CI)	*p* Value
Intervention group		0.065
Conventional	–	–
FFS	0.37 (0.16–0.89)	0.025
FFG	0.57 (0.26–1.23)	0.152
Age (years)	1.01 (0.98–1.03)	0.693
CCI	1.04 (0.88–1.21)	0.669
BMI	1.02 (0.96–1.09)	0.532
Wound surface (per 10 cm^2)	1.05 (1.01–1.09)	0.013
Anticoagulation	0.77 (0.33–1.83)	0.561
Smoking	1.59 (0.73–3.47)	0.242
Axillary clearance	2.91 (1.49–5.69)	0.002
Neoadjuvant chemotherapy	2.08 (1.01–4.30)	0.047

OR, odds ratio; CI, confidence interval; FFS, flap fixation using sutures; FFG, fixation using tissue glue; CCI, Charlson Comorbidity Index; BMI, body mass index

surgery. The number of patients with skin-dimpling had decreased in all three study groups 1 year after surgery (Table 5).

DISCUSSION

This trial showed that flap fixation using sutures for patients undergoing mastectomy leads to a reduction in seroma aspirations from 18 to 7%. The smaller reduction of flap fixation with tissue glue to 11%, although potentially relevant clinically, was statistically nonsignificant.

Although the exact pathophysiology of seroma formation remains unclear, closing the dead space seems pivotal in reducing seroma formation.[1,2,5,6] During the past years, research has gradually focused on finding the best technique for closure of the dead space. Mechanical flap fixation seems to be a promising tool for achieving this.

Coveney et al.[20] were the first to publish a prospective study on flap fixation after mastectomy using sutures. Their study showed a significant reduction of seroma formation. Since this publication, several published studies have focused on either flap fixation using sutures or flap fixation using tissue glue.[6,10–12, 14] Van Bastelaar et al.[16] conducted a retrospective study comparing these two methods of flap fixation with conventional wound closure and demonstrated a significant reduction in seroma formation after mechanical flap fixation using either technique.

Objective quantification of seroma remains challenging for studies reporting on seroma formation. Seroma presents on a sliding scale, and reporting of seroma is observer dependent. Furthermore, not every seroma is clinically significant. For this reason, the current study chose seroma aspiration as the primary outcome. Consequently, only clinically significant seromas were analyzed. This was the first double-blind, randomized, controlled trial to compare the effect of flap fixation with conventional wound closure on seroma formation after mastectomy.

The group with conventional wound closure had more patients (10.5%) who exceeded three additional hospital visits than the groups with flap fixation (FFS group, 4.6%; FFG group, 5.4%). This difference was not statistically significant, but it might be considered clinically important. Furthermore, the 6.7% difference between the FFG and CON groups in the proportion of patients who needed seroma aspirations was not significant (OR, 0.57; 95% CI, 0.26–1.23; $p = 0.152$) but could be considered clinically meaningful. In the interim analysis, both flap fixation groups showed significantly fewer seroma aspirations than the conventional wound closure group. The final results, however, showed no significant difference in seroma aspiration for the flap fixation group with tissue glue. This could be explained by the fact that the calculation of sample size was based on detecting an absolute difference of 20% in seroma aspirations. Consequently, this study was insufficiently powered to detect smaller differences that still may be considered clinically meaningful.

TABLE 4 Subgroup analysis based on axillary clearance: no. of patients undergoing seroma aspiration (%)

Procedure	Total[a] *n* (%)	CON[b] *n* (%)	FFS[b] *n* (%)	FFG[b] *n* (%)	*p* Value[c]
Mastectomy ±SN	18/225 (8.0)	8/72 (11.1)	3/76 (3.9)	7/77 (9.1)	0.251
Modified radical mastectomy	22/109 (20.2)	12/42 (28.6)	5/33 (15.2)	5/34 (14.7)	0.225

CON, conventional wound closure; FFS, flap fixation using sutures; FFG, fixation using tissue glue; SN, sentinel node

[a]Total per procedure group

[b]Per intervention group

[c]*p* Value between different intervention groups

TABLE 5 Secondary outcomes

	CON (n = 114) n (%)	FFS (n = 109) n (%)	FFG (n = 111) n (%)	p Value
Mean drain output (ml)	316.2 ± 302.9	246.0 ± 285.1	256.3 ± 285.6	0.151
Additional OPD visits (dichotomous)	54 (47.3)	35 (32.1)	41 (36.9)	0.057
Additional OPD visits (categorical)				0.091
a. No additional	60 (52.3)	74 (67.9)	70 (63.0)	
b. 1–3 Additional	38 (33.3)	29 (26.6)	35 (31.5)	
c. > 3 Additional	12 (10.5)	5 (4.6)	6 (5.4)	
SSI	22 (19.3)	14 (12.8)	20 (18.0)	0.075
Reoperation	12 (10.5)	6 (5.5)	12 (10.8)	0.301
Postoperative pain at 10 days	3.3 ± 2.3	3.7 ± 2.5	3.4 ± 2.5	0.442
Mean DASH *at b*aseline	14.5 ± 18.6	16.8 ± 17.5	14.9 ± 17.1	0.590
Mean DASH *at* 1 year	21.4 ± 22.4	22.3 ± 19.9	21.2 ± 21.7	0.918
Cosmesis 3 months[a]	6.5 ± 2.4	6.3 ± 2.5	6.5 ± 2.2	0.719
Cosmesis 1 year[b]	6.7 ± 2.6	6.8 ± 2.3	6.9 ± 2.5	0.816
Dimpling of skin *at* 3 months[a]	26 (23.6)	25 (22.9)	29 (26.1)	0.806
Dimpling of skin *at* 1 year[b]	18 (15.8)	20 (18.3)	21 (18.9)	0.393

Continuous variables are presented as mean ± standard deviation, one-way analysis of variance (ANOVA), and categorical variables are presented as numbers, Pearson Chi square

CON, conventional wound closure; FFS, flap fixation using sutures; FFG, fixation using tissue glue; OPD, outpatient department; SSI, surgical-site infection; DASH, disability of arm, shoulder, and hand

[a]3 Patients had undergone reconstructive surgery

[b]47 Patients had undergone reconstructive surgery

This study included all mastectomy patients regardless whether axillary clearance was performed. Axillary clearance has proved to be a predictor for seroma formation and seroma aspiration, with the highest incidence among patients undergoing a modified radical mastectomy.[21,22] This could be explained by the dead space in the axilla, which is challenging to close adequately because of its three-dimensional shape. Furthermore, the higher frequency of lymph vessels in the axilla and consequently the greater lymph leakage after dissection in this area also could explain why axillary clearance is a predictor for seroma formation.

In this study, significantly more patients undergoing mastectomy with axillary clearance underwent seroma aspiration than patients who had no axillary clearance performed. A subgroup analysis between simple mastectomy and modified radical mastectomy showed that flap fixation with sutures is of clinical importance in both patient groups, resulting in fewer seroma aspirations. Although not statistically significant, the difference in seroma aspirations between the groups could be considered clinically meaningful, primarily for the axillary clearance group. Flap fixation using tissue glue seems to be more beneficial for patients undergoing modified radical mastectomy than for patients undergoing simple mastectomy.

The percentage of patients treated for SSI in this study varied from 13 to 19%, consistent with previous results published by Van Bastelaar et al.[16] Ten Wolde et al.[12] found an overall higher SSI rate of 28%, which decreased to 9% after flap fixation with quilting sutures.

The number of patients with SSIs in our study was similar to that of groups without flap fixation or flap fixation with tissue glue. This could be due to the fact that the group with flap fixation using sutures underwent fewer seroma aspirations, representing fewer clinically significant seromas. Furthermore, the patients undergoing flap fixation with sutures showed the lowest reoperation rate and had fewer additional outpatient visits.

Diminished shoulder function and mobility is a common complication after mastectomy.[6] There is a concern that flap fixation with sutures or tissue glue could lead to impaired shoulder mobility postoperatively as a consequence of securing the skin flaps to the pectoral muscle. No recent data are available on the effect that flap fixation has on postoperative shoulder function and mobility. Coveney et al.[20] previously reported faster recovery of shoulder mobility in mastectomy patients treated with flap fixation. Generally, we found a slightly diminished shoulder function in patients 1 year after mastectomy, with no significant

difference between the groups. This seems to be a consequence of mastectomy itself and not whether flap fixation was performed or not.

This is the first randomized controlled trial to report on patient-reported cosmesis and surgeon-reported dimpling of the skin after flap fixation. Securing the skin flaps to the pectoral muscle could lead to unwanted dimpling of the skin. All the surgeons in this trial were individually trained in placement of the subcutaneous sutures in the same fashion to ensure uniformity and prevention of skin-dimpling. No significant difference was found between the three groups in terms of skin-dimpling 1 year after surgery.

Besides dimpling caused by sutures, postoperative dimpling can remain after resorption of seroma due to the occurrence of fibrous scar tissue. Therefore, dimpling to some extent was observed in all three patient groups, with dimpling of the skin apparently improving over time and fewer patients showing dimpling 1 year after surgery than 3 months after surgery.

Flap fixation with tissue glue appears to lead to more skin-dimpling, albeit not a significant increase. Patient-reported cosmesis on the Likert scale showed no difference between the groups and a slight improvement for all the groups 1 year after surgery.

One limitation of this study was possible confounding due to neoadjuvant chemotherapy and axillary clearance. Axillary clearance and neoadjuvant chemotherapy have proven to increase the odds of patients undergoing seroma aspiration. Because these factors were slightly more prevalent in the patients who underwent conventional wound closure, it should be considered that this might have influenced the results.

A second limitation of this study was the possible bias of the improved patient-reported cosmesis 1 year after surgery. This improvement over time might have been biased by the fact that 14% of the patients had undergone secondary breast reconstruction during the first year after surgery. The subjective aspect of the patient-reported cosmesis made it difficult to compare these scores between patients. A more objective method of evaluating cosmesis might be considered for future studies. In addition, the relatively low incidence of the need for seroma aspirations and the subsequently smaller than anticipated between-group differences resulted in less statistical power. This may have caused clinically meaningful differences to go undetected.

CONCLUSION

Flap fixation after mastectomy with sutures leads to fewer patients requiring seroma aspiration compared with patients undergoing conventional wound closure or wound closure using tissue glue. With suture flap fixation, patients require fewer additional outpatient clinic visits postoperatively. Flap fixation has no negative effect on shoulder function mobility, skin-dimpling, or cosmesis. Therefore, we strongly advise surgeons to perform flap fixation using sutures for patients undergoing mastectomy. The effects of flap fixation on long-term quality of life and the cost effectiveness of the SAM trial are awaited.

DATA AVAILABILITY The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

DISCLOSURE There are no conflicts of interest.

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