Reducing seroma formation and its sequelae after mastectomy by closure of the dead space

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Original article

Reducing seroma formation and its sequelae after mastectomy by closure of the dead space: The interim analysis of a multi-center, double-blind randomized controlled trial (SAM trial)

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ABSTRACT

Objective: The main objective of this double-blind randomized controlled trial (RCT) was to assess seroma formation and its sequelae in patients undergoing mastectomy. Patients were randomized into one of three groups in which different wound closure techniques were applied: 1) conventional wound closure without flap fixation (CON) 2) flap fixation using sutures (FF–S) and 3) flap fixation using an adhesive tissue glue (FF-G).

Background: Seroma formation is still a bothersome complication after mastectomy. Flap fixation seems promising in reducing seroma formation. Various flap fixation techniques remain to be analyzed, including long-term outcome measures.

Methods: This trial was conducted in three different hospitals between June 2014 and November 2016. Patients were allocated to one of three groups. The primary outcome was the number of seroma needle aspirations. Secondary outcomes were (surgical site) infections, number of outpatient clinic visits, shoulder function, postoperative pain, patient-reported cosmesis and skin dimpling.

Results: A total of 187 patients were randomly assigned to CON (n = 61), FF-S (n = 64) and FF-G (n = 62). The number of seroma aspirations was significantly higher in CON when compared to both flap fixation groups (p = 0.032), with no difference between FF-S and FF-G. Secondary outcomes showed no statistical differences between all groups. The higher number of outpatient clinic visits in CON was considered to be of clinical importance (CON = 27 (44.3%), FF-S = 19 (30.6%) and FF-G = 21 (34.4%)).

Conclusions: Mastectomy followed by flap fixation with either sutures or adhesive tissue glue reduces the number of seroma aspirations when compared to simple wound closure.

1. Introduction

Post mastectomy seroma is a bothersome complication for both the patient and breast surgeons. The cited incidence of seroma formation is highly variable and ranges from 3% to more than 90% [1–4]. A possible explanation for this large discrepancy is the subjective grading of seroma by surgeons.

Seroma is a serous fluid that contains blood plasma and/or lymph fluid and accumulates between the pectoral muscle and skin flaps and in the axillary space after mastectomy. Many articles describe the risk factors and causes of seroma formation such as axillary clearance, the type of breast surgery performed and the use of electrocautery during surgery [3–7]. Seroma formation often leads to repeated seroma aspirations, (surgical site) infections and frequent visits to the outpatient clinic. It can furthermore lead to significant discomfort for patients, delayed wound healing and skin flap necrosis [1,8,9].

In recent years, an increasing number of publications have

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focused on preventing seroma formation, all of which seem to have one common denominator: closing the dead space following mastectomy [10]. Closed suction drainage, quilting of the skin flaps or application of adhesive tissue glue are all methods that have been described when closing the dead space [9,11–20]. To date, there are three published prospective randomized trials demonstrating a significant reduction in seroma formation when flap fixation was applied using sutures compared to conventional wound closure [21–23]. In 1993, Coveney et al. [21] showed a significant reduction in seroma formation and fewer complications in patients treated with flap fixation compared to conventional wound closure. A recent review published by van Bastelaar et al. [24] showed that mechanical flap fixation played a key role in reducing seroma formation. They concluded that a prospective randomized controlled trial is needed to evaluate which form of flap fixation is superior.

To date, no studies have shown any further benefit in reducing seroma related complications (reducing infection and outpatient visits) after flap fixation [25]. To the best of our knowledge, this is the first study to describe long-term outcome measures such as patient-reported cosmesis and skin dimpling after the application of sutures or adhesive tissue glue in flap fixation. Maintaining shoulder function after mastectomy is important for patient well-being. It has rarely been described in studies evaluating flap fixation after mastectomy. The possible effect of flap fixation on shoulder function and mobility remains unclear. While Coveney et al. [21] showed faster recovery of the functional range of shoulder motion in patients treated with flap fixation, how these results were obtained was unclear.

The main objective of this randomized controlled trial was to assess seroma formation and its sequelae in patients undergoing mastectomy with or without axillary clearance. Patients were randomized into one of three groups: 1) conventional wound closure without flap fixation 2) flap fixation using sutures and 3) flap fixation using adhesive tissue glue.

2. Methods

2.1. Study design

The SAM-trial (Seroma reduction After Mastectomy) is a prospective, double-blind, randomized controlled trial conducted at three different district hospitals in the Netherlands (Zuyderland Medical Center Sittard, Albert Schweitzer Hospital Dordrecht, and St Jansgasthuis Hospital Weert). This study commenced on 14 June 2014. The study protocol was approved by the local institutional scientific review board and registered at ClincalTrial.gov, identifier: NCT03305757. Participants were recruited from the surgical breast cancer units after the work up for suspected invasive breast cancer or ductal carcinoma in situ (DCIS). Patients were informed and included after signing for informed consent. Permuted block randomization with random block sizes was performed. Randomization took place during the surgical procedure using a web-based randomization program (ALEA), 30 min before wound closure. Patients were allocated to 1 of 3 treatment arms: 1) Conventional wound closure (CON), 2) Flap fixation using sutures (FF—S), or 3) Flap fixation using ARTISS adhesive tissue glue (FF-G). A low suction drain was placed in all patients. Patients were blinded throughout the duration of the trial. The surgeon performing follow-up assessments was also blinded as this was never the same surgeon who had performed the procedure.

2.2. Participants

Female patients older than 18 years of age were eligible for inclusion if they had an indication for mastectomy with or without a sentinel lymph node biopsy or axillary clearance. Patients undergoing direct breast reconstruction were excluded. Patients unable to comprehend implications and extent of the study and therefore unable to sign for informed consent were excluded.

2.3. Surgery

All surgical procedures and clinical assessments were conducted by experienced breast cancer surgeons (at least five years experience in breast cancer surgery). During surgery, the nipple-areola complex was removed and dissection of the skin flaps was performed using electrocautery. Removal of the breast tissue from the pectoral muscle included removal of the prepectoral fascia. One low suction drain was placed in all patients before closure of the skin. Before closure, the extent of the skin flaps was measured from cranial to caudal and from medial to lateral (in cm). Depending on the surgeon's preference, absorbable monofilament sutures (Monocryl 3.0 or V-loc 30 cm) were used to close the skin edges.

1) Conventional wound closure

After completion mastectomy, no form of flap fixation was applied.

2) Flap fixation using sutures

After completion mastectomy, multiple rows of individual intermittent absorbable polyfilament sutures (Vicryl 3.0) were placed at 4–5 cm intervals on the skin flaps in order to approximate them to the pectoral muscle. The dead space of the axillary area was not reduced, due to the surgical difficulty of closing this space. The total number of sutures, including the number of rows, was noted. Care was taken to prevent dimpling of the skin.

3) Flap fixation using ARTISS adhesive tissue glue

After completion mastectomy, a 2 mL adhesive tissue glue spray was applied to both the skin flaps and pectoral muscle. This was sufficient to cover the full wound surface. Before application of the glue, both the skin flaps and pectoral muscle surfaces were carefully dried. After spraying the glue, compression of both skin flaps was applied to the underlying muscle.

2.4. Training

To standardize the surgical procedure, detailed instructions on the three closure techniques were given to all breast surgeons.

2.5. Drain policy

In all patients, one low suction drain was placed in the mastectomy gutter, lateral to the pectoral muscle before flap fixation or wound closure. The drain was connected to a low suction drain bottle. Drain output was noted daily. In patients undergoing mastectomy without axillary clearance, drain removal was performed when daily production was less than 50 mL or after a maximum of 48 h, irrespective of drain output. In patients undergoing mastectomy with axillary clearance, drain removal was performed when daily drain output was less than 50 mL or after a maximum of five days, irrespective of drain output. The length of drain use was longer in this group as axillary clearance is a known risk factor for seroma formation (19, 26).

2.6. Follow-up

Follow-up was performed until one year after surgery. Patients were evaluated two weeks, six weeks, three months, six months and twelve months postoperatively. The primary and secondary outcome measures were assessed during all follow-up appointments. Participating patients could leave the study at any time for any reason without any consequences.

2.7. Primary outcome

The number of seroma aspirations was the primary outcome of the SAM-trial. There were well-defined, strict indications on when to perform seroma aspirations. The mere presence of seroma did not warrant seroma aspiration. The three indications for seroma aspiration were defined as follows; 1) wound healing at risk due to seroma (seroma leakage, wound break down, skin necrosis) 2) pain or discomfort caused by large amounts of seroma and characterized by tenseness of the skin, or 3) contaminated/infected seroma which warranted seroma aspiration to treat the infection. In cases in which seroma aspiration was performed due to infection, patients were treated with a one-week course of amoxicillin/clavulanic acid 500/125 mg three times daily. If seroma was aspirated, the volume of aspirated fluid was noted in the case report form (CRF).

2.8. Secondary outcome

Secondary outcomes were measured during the first postoperative year and included, infections (determined by the need for antibiotics), additional outpatient clinic visits, shoulder function (measured using the DASH questionnaire including a baseline score), patient-reported cosmesis, dimpling (assessed by a breast surgeon) and patient-reported postoperative pain (measured using a 1–10 Likert scale). Details about the secondary outcomes are reported in the study protocol [27].

2.9. Sample size calculation

For the SAM-trial a sample size of 112 patients per treatment arm was calculated to ensure a power of 0.90 for detecting a difference of 20% in the need for seroma aspirations. The sample size was calculated based on an ordinal regression using alpha = 0.025 and beta = 0.10.

2.10. Statistical analysis

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0). Baseline characteristics were presented as mean, standard deviation (SD) and range for continuous variables and frequencies and percentages for categorical variables. Missing data were imputed using stochastic regression imputation to prevent a loss of statistical power. The imputed values were drawn using predictive mean matching.

Both the number of seroma aspirations and the number of additional outpatient clinic visits were dichotomized into yes/no after inspecting the distribution. To compare proportions between groups we used the chi-squared test or, if deemed appropriate, Fisher's exact test. In case of significant differences, logistic regression analysis with dummy-variables was used to test for differences between combinations of the three groups. Means of continuous variables were compared using a one-way analysis of variance (ANOVA). A p-value of less than 0.05 was considered significant.

2.11. Interim analysis

A planned interim analysis was adopted in the protocol for the SAM trial. The reason for the interim analysis was to assess early superiority in one of the flap fixation arms. In the case of interim superiority, early trial termination would take place. Unblinding was not necessary as the interim analysis included patients (n = 187) that had completed one year of follow up.

3. Results

Between June 2014 and November 2016, 187 patients were included in the trial. The majority of the non-enrolled patients underwent direct breast reconstruction, excluding them from participation. The 187 patients were allocated to one of the three arms; CON (n = 61 (33%)), FF-S (n = 64 (34%)) and FF-G (n = 62 (33%)). Three patients were later excluded from the analysis due to missing data: two patients had no follow-up data at all and one patient changed hospitals six weeks after surgery. A flow diagram of the SAM-trial is shown in Fig. 1. Demographics and clinical data are presented in Table 1. Outcome data are presented in Tables 2 and 3.

In the FF-S study group, the mean number of suture rows used was 4.7 [2–8] and the mean number of sutures used was 20 [5–34].

3.1. Primary outcome

In total, 25 (13.6%) patients underwent one or more seroma aspirations (Table 2). Significantly more patients underwent seroma aspiration when flap fixation was not applied (CON = 23.0%, FF-S = 8.1% and FF-G = 9.8%, p = 0.032). A significant difference in seroma aspirations between CON and FF-S was observed (odds ratio [OR] = 0.29 (95% confidence interval [CI]: 0.10–0.88, p = 0.028), the difference in seroma aspirations between CON and FF-G was not significant although of clinical importance (OR = 0.37,

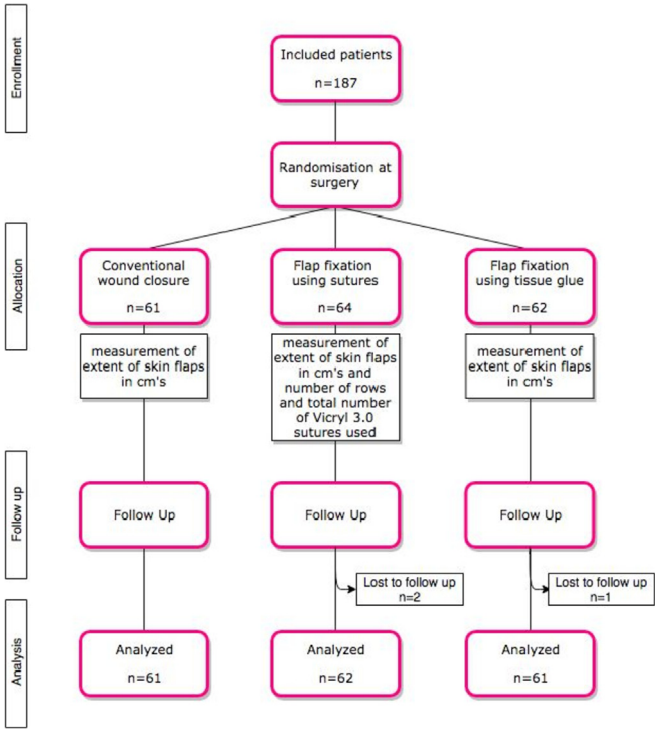

Fig. 1. Flowchart SAM-trial.

Table 1
Baseline and surgery characteristics of patients undergoing conventional wound closure (CON), flap fixation using sutures (FF–S) and flap fixation using adhesive tissue glue (FF-G).

	CON (N = 61)	FF-S (N = 62)	FF-G (N = 61)
cT			
x	1 (1.6)	1 (1.6)	1 (1.6)
Is	7 (11.5)	6 (9.7)	6 (9.8)
1/2	35 (57.4)	45 (72.6)	47 (77.1)
3/4	18 (29.5)	10 (16.1)	7 (11.5)
cN			
0	45 (73.8)	46 (74.2)	44 (72.1)
1	10 (16.4)	14 (22.6)	15 (24.6)
2	6 (9.8)	2 (3.2)	2 (3.3)
Age[a]	63.2 ± 12.5	65.6 ± 13.5	64.8 ± 12.4
Charlson Comorbidity Index[a]	4.2 ± 1.6	4.5 ± 1.9	4.4 ± 1.7
BMI[a]	27.1 ± 5.1	27.3 ± 5.3	27.7 ± 4.4
Anticoagulation	7 (11.5)	14 (22.6)	16 (26.2)
Smoking	18 (29.5)	17 (27.4)	10 (16.4)
Neoadjuvant chemotherapy	16 (26.2)	12 (19.4)	15 (24.6)
Axillary lymph node dissection	22 (36.1)	18 (29.0)	20 (32.8)
Clinically node positive	16 (26.2)	16 (25.8)	17 (27.9)
Wound surface (cm^2) [a, b]	198.1 ± 61.9	192.4 ± 50.5	185.9 ± 51.3

[a] Continuous variables are presented as mean ± SD. Categorical variables in number (%).
[b] The wound surface was considered to be shaped like a horizontal diamond and was calculated from the measurements of the skin flaps (from medial to lateral and from cranial to caudal).

95% CI: 0.13–1.03, p = 0.057). There was no difference in seroma aspirations between both flap fixation groups (FF-G and FF-S, OR 0.804, p = 0.731).

The number of seroma aspirations per patient showed a statistically significant difference between the three study groups, favoring flap fixation (Table 2). In total, there were eight patients that received more than one seroma aspiration of which six patients were in the CON group. Only two patients received more than two aspirations (range 3 and 24). Both of these patients were allocated to the conventional closure technique.

The mean volume of aspirated seroma showed no significant difference between the three study groups. Although it is not statistically significant, the higher volume of aspirated seroma in the CON group is certainly of added clinical value.

3.2. Secondary outcomes

Patients not treated with flap fixation visited the outpatient clinic more often (CON = 27 (44.3%), FF-S = 19 (30.6%) and FF-G 21 (34.4%), p = 0.270). Although not statistically different, the difference between the three study groups is of clinical importance. The same applies to patients who visited the outpatient clinic more than 3 times (CON = 8 (13.1%), FF-S = 3 (4.8%) and FF-G = 3 (5.9%)). In total, 23 (12.5%) patients were treated with antibiotics; there were, however, no statistical differences between the three study groups (p = 0.709). In twelve (6.5%) patients antibiotic treatment was prescribed due to infected seroma. The distribution of these patients in the three groups showed no statistical difference (CON = 7 (58.3%), FF-S = 2 (16.7%) and FF-G = 3 (25%), p = 0.138). No differences in shoulder function between the three study groups were observed. After a year, all mastectomy patients showed a slight deterioration of the shoulder function, regardless of the method of wound closure. Dimpling was observed in all three study groups, however, no significant differences were observed. There was a decrease in the number of patients with dimpling one year postoperatively. The same applies to cosmesis, which showed no

Table 2
Primary outcome.

	CON (N = 61)	FF-S (N = 62)	FF-G (N = 61)	p-value
Seroma aspiration (dichotomous)	14 (23.0)	5 (8.1)	6 (9.8)	0.032
Seroma aspiration (categorical)	47 (77.1)	57 (91.9)	55 (90.1)	0.048
a) no aspiration	8 (13.1)	5 (8.1)	4 (6.6)	
b) 1 aspiration	6 (9.8)	0 (0)	2 (3.3)	
c) >1 aspiration				
Volume seroma aspiration (ml) [a]	470 [785]	420 [310]	275 [706]	0.498

*Continuous variables are presented as means ± SD, one way ANOVA. Categorical variables in numbers (%), Pearson Chi-Square.
[a] Calculated among patients that underwent one or more seroma aspiration(s), presented as medians [interquartile range], Kruskal Wallis test.

Table 3
Secondary outcomes.

	CON (N = 61)	FF-S (N = 62)	FF-G (N = 61)	p-value
Drain output (ml)	279.7 ± 234.4	261.8 ± 217.3	230.3 ± 238.0	0.488
Additional outpatient clinic visits (dichotomic)	27 (44.3)	19 (30.6)	21 (34.4)	0.270
Additional outpatient clinic visits (categorical)	34 (55.7)	43 (69.4)	40 (65.6)	0.297
• No additional	19 (31.1)	16 (25.8)	18 (29.5)	
• 1-3 additional	8 (13.1)	3 (4.8)	3 (5.9)	
• >3 additional				
(Surgical Site) Infection	9 (14.8)	8 (12.9)	6 (9.8)	0.709
Reoperation	4 (6.6)	3 (4.8)	6 (9.8)	0.547
Readmission	5 (8.2)	4 (6.5)	4 (6.6)	0.915
Postoperative pain 10 days	3.10 ± 2.13	3.87 ± 2.74	3.33 ± 2.27	0.177
DASH Baseline (mean)	13.1 ± 17.5	16.4 ± 18.2	12.0 ± 14.0	0.322
DASH 1 year	19.5 ± 22.1	24.8 ± 19.8	21.8 ± 22.8	0.400
Dimpling 3 months[a]	15 (24.6)	17 (27.4)	17 (27.9)	0.906
Dimpling 1 year[b]	10 (16.4)	11 (17.8)	14 (23.0)	0.622
Cosmesis 3 months[a]	6.20 ± 2.39	6.35 ± 2.44	6.69 ± 2.20	0.498
Cosmesis 1 year[b]	7.00 ± 2.20	6.85 ± 2.37	7.10 ± 2.30	0.839

*Continuous variables are presented as means ± SD, one way ANOVA. Categorical variables in numbers (%), Pearson Chi-Square.
[a] 2 patients had undergone reconstructive surgery.
[b] 35 patients had undergone reconstructive surgery.

differences between the three study groups. A slight improvement was seen after one year in all study groups. See Table 3 for all secondary outcomes.

4. Discussion

The current interim analysis of this study demonstrated that closure of the dead space using flap fixation, using either sutures or adhesive tissue glue in patients undergoing mastectomy, significantly reduces the need for seroma needle aspirations (CON = 23.0%, FF-S = 8.1% and FF-G 9.8%, p = 0.032).

For many years seroma formation has been a controversial topic in breast cancer surgery. Considerable research has been done concerning the pathophysiology; the exact mechanism of seroma formation, however, remains unclear [12,14,28]. Application of closed suction drainage has had a pivotal position in reducing seroma formation during the last decades. More recently, research has focused on reducing seroma formation by closing the dead space, where the scientific body of evidence favoring flap fixation after mastectomy has shown a substantial gain [7,17–24,29]. Coveney et al. [21] published the first prospective study in which flap fixation was performed using sutures. This led to a significant reduction of seroma formation. We believe that closure of the dead space is the key to reducing or even completely diminishing seroma formation. Recently, van Bastelaar et al. [20] published the first (retrospective) study comparing two different methods of flap fixation (sutures versus adhesive tissue glue) compared to conventional wound closure. This study showed a significant reduction in seroma formation and seroma aspirations in patients undergoing flap fixation.

Seroma formation and its bothersome sequelae are of clinical importance as it leads to patient discomfort. It is often seen as the underlying cause of infections, additional outpatient clinic visits, delayed wound healing and even surgical reinterventions [11]. In contrast to the results published by Eichler et al. [30], our results demonstrate no decrease in the rate of reoperations when patients were treated with one of the flap fixation techniques. The frequency of readmission and postoperative pain rate showed no statistical differences, although patients treated in the FF-S group seemed to have slightly higher postoperative pain scores.

Axillary clearance has been reported as a predictive factor for seroma formation, with the highest incidence of seroma formation in patients undergoing a modified radical mastectomy [4,5]. This can probably be explained by the fact that the dead space in the axillary space cannot be closed properly. Only two studies focused on closing the axillary space [17,23]. In our interim analysis, only half the number of patients was included, and, therefore, no subgroup analysis was performed between mastectomy with or without axillary clearance.

The percentage of SSI's here varied from 10% to 15% and were in line with the numbers reported by van Bastelaar et al. [24]. The range of previously published SSI rates differs greatly from 1% to 26% [31]. Ten Wolde et al. [17] showed an 80% SSI decrease in patients undergoing mastectomy and axillary clearance treated with flap fixation. In the current study, the number of patients developing SSI's was highest in the group without flap fixation but this was not significantly different (CON = 14.8%, FF-S = 12.9% and FF-G = 9.8%). This could be due to the fact that all patients were treated with prophylactic antibiotics prior to surgery.

The effect of flap fixation on shoulder mobility has been prospectively studied by Coveney et al. [21]. They reported a faster recovery of shoulder mobility in mastectomy patients treated with flap fixation. The latest studies [17–19] reporting on flap fixation after mastectomy did not mention postoperative shoulder motion or shoulder function. Many authors describe the potential loss of shoulder motion due to tightening of the skin on the pectoral muscle. This has, however, never been extensively analyzed. In the current study, baseline and one year follow up scores did not significantly differ between the three groups. It seems clear that flap fixation has no adverse effect on the subjectively reported shoulder function one year after surgery. All groups showed the same modest rise in DASH score measurements postoperatively. Mastectomy could possibly cause a slight, insignificant decline in shoulder motion.

This is the first prospective study to report on dimpling of the skin and patient-reported cosmesis after flap fixation. Dimpling of the skin had previously been cited as possibly disadvantageous when using sutures for flap fixation [17]. Special care was taken to avoid skin dimpling. All surgeons were individually trained in placing the sutures correctly. The results showed no differences in dimpling of the skin one year after surgery between the three groups (CON = 16.4%, FF-S = 17.8% and FF-G = 23.0%). Surprisingly, there seems to be more skin dimpling in the group undergoing flap fixation with adhesive tissue glue, though not significant. Skin dimpling seems to decrease over time with patients showing less skin dimpling one year after surgery when compared to three months after surgery.

There seems to be a similar effect when analyzing patient-reported cosmesis. In all three closure techniques, the Likert scale scores increased gradually from three months up to one-year follow-up. The mean cosmesis score of all patients was seven with no significant difference between the three study groups. It should be acknowledged that 19% of all patients had undergone breast reconstruction one year after surgery. This could lead to a certain degree of bias in these results.

This study has certain limitations. For instance, the subjective method used for evaluating cosmesis (patient reported outcome) makes it difficult to reliably compare scores among patients. Several methods have been described to objectively evaluate cosmetic outcome [32]. A further limitation is that no subgroup analysis has been performed to scrutinize the effect between mastectomy with or without axillary clearance. In this interim analysis, only half the number (n = 187) of the total power calculation (n = 336) was included, potentially increasing the risk of underestimating the results.

Strengths of this study are its prospective, randomized nature and the objective way of assessing seroma formation. The fact that both patients and the breast surgeon performing the follow-up assessments were blinded, makes this study unique. The most important finding of this interim analysis is the decreased need for seroma aspirations in patients undergoing any form of flap fixation after mastectomy. Another important finding is that there are no drawbacks regarding shoulder function, cosmesis, or skin dimpling when flap fixation is applied after mastectomy. The final results of the SAM-trial will further report on other long-term outcome measures such as cost-effectiveness and quality of life.

5. Conclusion

Mastectomy followed by flap fixation with either sutures or adhesive tissue glue reduces the number of seroma needle aspirations compared to patients undergoing simple wound closure. The use of adhesive tissue glue and sutures seems to be equally effective. Though not significant, patients undergoing flap fixation seem to require fewer visits to the outpatient clinic postoperatively. Flap fixation has no negative effects on shoulder function, cosmesis or skin dimpling. Completion of the SAM-trial will give additional information regarding costs and quality of life.

Conflicts of interest

All authors declared that they had no conflict of interest.

Research involving human participants and/or animals:

Ethical approval: All procedures performed in this study were in accordance with the ethical standard of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local institutional scientific review board and registered at ClincalTrial.gov, identifier: NCT03305757.

Declarations of interest

None.

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