

Randomized clinical trial investigating the use of drains and fibrin sealant following surgery for breast cancer

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Background: Despite limited evidence, closed suction drainage is often used to reduce the risk of seroma formation after breast cancer surgery. The aim of this study was to evaluate the effect of drains and fibrin sealant on the incidence of seroma formation.

Methods: A total of 116 patients undergoing surgery for breast cancer were randomized to receive suction drainage (group 1; $n = 58$), or to receive no drain ($n = 58$). Patients allocated to receive no drain were further randomized to have fibrin sealant applied to the dissected area (group 2; $n = 29$), or to no intervention (group 3; $n = 29$). Outcome measures were incidence and volume of postoperative seroma, length of hospital stay and postoperative pain scores.

Results: There was no significant difference in the incidence of seroma between group 1 (15 of 58) and either group with no drains (ten of 29 in group 2; 12 of 29 in group 3). There was a significant reduction in hospital stay and postoperative pain scores in patients who did not have a drain. Following mastectomy without a drain, the use of fibrin sealant was associated with a significant reduction in the incidence and total volume of seroma (190 versus 395 ml; $P = 0.012$).

Conclusion: Drains did not prevent seroma formation, and were associated with a longer postoperative stay and higher pain scores after surgery for breast cancer. In patients who had mastectomy the use of fibrin sealant reduced the rate of seroma formation.

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Introduction

The treatment of early breast cancer (stages I and II) is excision of the primary tumour (wide local excision or mastectomy) with axillary lymphadenectomy. The most common postoperative complication is a fluid collection in the wound (seroma); the reported incidence is between 15 and 81 per cent^{1–5}. Seromas are often considered a minor complication but nonetheless may be a cause of significant distress and discomfort.

Most surgeons continue to use closed suction drainage following surgery for breast cancer although there is no clear evidence that the use of a drain significantly reduces seroma formation^{6,7}. There are no consensus guidelines for the use of postoperative drainage. Some clinicians suggest removing drains on the first postoperative day⁸, whereas others leave them *in situ* until the volume drained

falls below 50 ml/day^{9,10}. The average postoperative stay following surgery for breast cancer in the UK is 5–7 days^{11–13}; the presence of a drain often contributes to a delay in discharge. Some surgeons overcome this drawback by sending patients home with a drain in place and arranging frequent review by a breast care nurse¹³.

The term 'seroma' is derived from the assumption that the fluid is a filtrate of plasma. As such, it would be a protein-poor transudate or a lymphatic leak. Alternatively, seroma fluid might be a protein-rich exudate due to increased capillary permeability (characteristically observed during the inflammatory phase of wound healing)¹⁴. If this were the case, there is a theoretical risk that the presence of a drain might prolong and intensify the inflammatory phase of wound healing, facilitating seroma formation. There is therefore a sound physiological basis for the hypothesis that optimal surgical management after

breast surgery is to avoid drainage altogether. The use of fibrin sealant may help reduce exudation by sealing 'leaky' capillaries. Fibrin sealant has been shown to reduce seroma formation in animal models¹⁵⁻¹⁷. In human studies, fibrin reduced the amount of drainage following mastectomy when used in combination with a drain^{18,19}, but there are no data regarding the use of fibrin sealant alone.

The aim of this randomized study was to investigate the nature of seromas following breast surgery, and to evaluate the use of both drains and fibrin sealant.

Patients and methods

The study was a randomized clinical trial conducted at a single centre with a specialist breast unit. All patients were admitted under the care of one consultant.

Eligibility

The study received approval from the local research ethics committee. Patients presenting with newly diagnosed carcinoma of the breast who required primary excision and axillary lymphadenectomy were eligible. Recruitment commenced in March 2001 and finished in March 2003 when predetermined numbers had been enrolled. Patients were excluded if they did not undergo axillary dissection or had previous breast surgery, or were on anticoagulants. Written informed consent was obtained from all the study patients.

Randomization

Fig. 1 shows the CONSORT flow chart outlining the progress of patients through the study²⁰. One hundred and sixteen patients were randomized, 58 to the drain

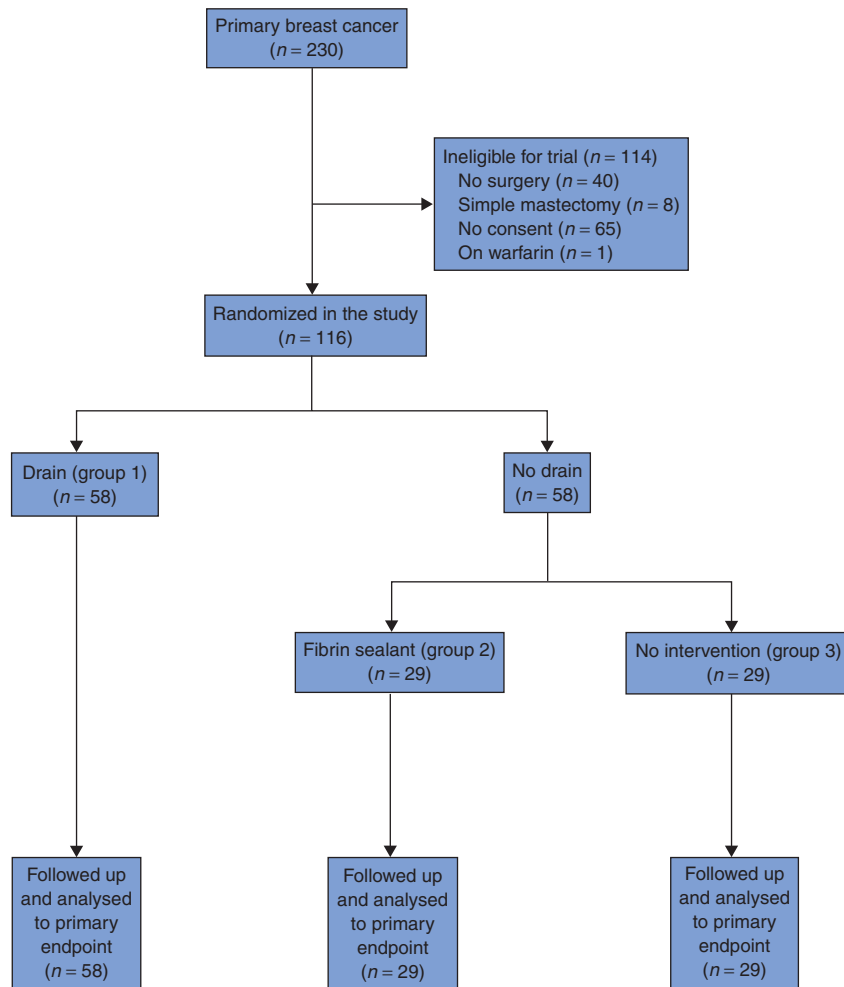


Fig. 1 Flow chart for study

group (group 1), and 58 to the no drain group. Of those in the latter group, 29 were further randomized to receive fibrin sealant (group 2) and 29 to receive no intervention (group 3). Randomization was achieved by means of computer-generated random numbers. A sealed envelope (sequentially numbered, opaque) was opened by the theatre nursing staff to reveal the randomization code to the operating surgeon at the end of the operation, immediately before wound closure. Patients in groups 2 and 3 were blinded regarding the use of fibrin sealant.

Operative protocol

A single consultant surgeon or a senior member of his team (associate specialist or specialist registrar working under consultant supervision) performed all operations. A level I and II axillary dissection was performed in all patients, and an effort made to ligate the major lymphatic vessels. The extent of axillary dissection was to the axillary vein superiorly, the medial border of pectoralis minor medially, the level of the fourth intercostal space inferiorly and the border of latissimus dorsi laterally, with preservation of the thoracodorsal neurovascular bundle and long thoracic nerve. Electrocautery was not used for dissection of skin flaps but was applied to cauterize small bleeding points. The axillary dissection was performed through a separate incision in patients who had a wide local excision and through the main primary incision in patients who had a mastectomy.

Patients in group 1 had a single 14-Fr vacuum drain (Medinorm[®]; Vanstraten Medical, Quierschied, Germany) inserted into the axilla. Drains were removed when drainage was less than 50 ml per 24 h. Patients in group 2 had no drain, but 2 ml fibrin sealant (Tisseel[®], Baxter Healthcare, Newbury, UK) was applied by means of a spray device (Tissomat[®]; Baxter Healthcare). The volume of Tisseel[®] used was sufficient to coat an area of 50 to 100 cm². The solution was prepared from four components: human pooled fibrinogen (75–115 mg/ml), aprotinin (3000 kallidinogenase-inactivator units/ml), human thrombin powder (500 units/ml) and calcium chloride (Ca²⁺ 40 µmol/ml). The fibrinogen and aprotinin were mixed in one vial, and the thrombin and calcium chloride in another. The contents of each vial were withdrawn into two syringes and were connected to the spray machine using the Duploject system (Baxter Healthcare). The solution was sprayed over all dissected areas of chest wall, skin flaps and axilla. Before closing the wound, skin flaps were compressed against the chest wall to remove excess air or fluid. Patients in group 3 simply had the wound closed, with no further intervention. Wound cavity closure

was not performed following wide excision. In patients who had a mastectomy skin flaps were not sutured to underlying muscle. The skin was closed with subcuticular continuous sutures or staples, and a compression dressing applied in all patients for the first 24 h after surgery.

Patient discharge and follow-up

Patients in group 1 were discharged after removal of the drain. Patients in groups 2 and 3 were discharged when ambulatory, and when analgesic requirements were met with oral preparations. A member of the surgical team examined the wound daily until discharge from hospital. Patients were seen in a dedicated breast clinic 1 week after surgery. Reviewing clinicians and breast care nurses were blinded to each patient's treatment group. Further follow-up visits were determined according to individual patient requirements; the majority of patients were seen 6 weeks and 3 months after surgery.

Outcome measures

The primary outcome measure was the incidence of symptomatic seroma. The wound was examined daily until discharge from hospital and during each clinic visit. A seroma was defined as a palpable fluid collection under the wound. Only clinically symptomatic seromas were aspirated and included in these data. Aspiration was performed using aseptic technique. For each patient, the total volume of aspirate and frequency of aspiration were recorded. On request, the breast care nurses visited patients at home between the scheduled clinic visits and performed wound aspirations as necessary. Fluid from the first aspiration of each seroma was sent for analysis of protein and lactate dehydrogenase (LDH) levels. The concentration of LDH can be used to accurately differentiate exudate from transudate^{21,22}. Fluid was considered exudate in nature when the protein concentration exceeded 30 g/l and the LDH level was greater than 400 units/l.

Secondary outcome measures were postoperative length of hospital stay and postoperative pain scores. In addition, all wound-related complications were recorded. Pain scores were recorded at 24 and 48 h after surgery in all groups, and at removal of the drain in group 1. Patients were asked to rate the intensity of pain on a visual analogue scale from 0 (no pain) to 10 (unbearable pain). Wound infection was defined as erythema, tenderness and/or purulent discharge from the incision site, and was treated with an oral antibiotic for 7 days.

Sample size and statistical analysis

The incidence of seroma formation was 25 per cent in this unit before the study. The power calculation was carried out by Power and PrecisionTM software (Biostat, Englewood, New Jersey, USA) using an equivalence test for proportion. This study had a power of 80 per cent to show that the seroma rate for the group without drainage was the same (neither lower nor higher) as that for the group with drains. This assumed that the seroma rates for the two groups were equal (at 25.0 per cent), and that a difference of 20 per cent or less was unimportant; the sample size needed in each group was 58, and α (one tailed) was set at 0.05. Data were stored using Excel (Microsoft Corporation, Redmond, Washington, USA) spreadsheet and statistical analyses were performed using SPSS[®] software version 10.0 (SPSS, Chicago, Illinois, USA). Analysis of the results was conducted on the basis of intention to treat. Qualitative data were compared using the Pearson χ^2 test or Fisher's exact test for small samples. Quantitative data were expressed as median (interquartile range) or mean(s.d.). The Mann-Whitney *U* test or Kruskal-Wallis test was used to compare non-parametric data where appropriate. $P < 0.050$ was considered statistically significant.

Results

Two hundred and thirty patients with primary breast carcinoma were identified during the study. Of these, 65 declined to participate, 40 did not undergo excision of primary tumour as initial treatment, eight did not have axillary lymphadenectomy and one was on warfarin, leaving 116 patients for randomization (Fig. 1). All patients completed the study and were followed to study endpoints. There were no significant differences between the drain and no drain groups with respect to age, type of operation, grade of operating surgeon, side of operation, number of lymph nodes removed or involved, and tumour size (Table 1).

Seroma

The incidence, frequency and volumes of seroma aspirated are shown in Table 2. There was no significant difference in the overall incidence of seroma between the drain group (group 1; 15 of 58) and either no drain groups (ten of 29 in group 2; 12 of 29 in group 3). The median total volume aspirated was significantly higher in group 3 than group 1 ($P = 0.008$) and group 2 ($P = 0.014$). The frequency of aspiration was also significantly higher in group 3 than in group 1 ($P = 0.029$) but not compared to group 2 ($P = 0.075$).

Table 1 Patient characteristics

	Drain (n = 58)	No Drain (n = 58)	P
Age (years)*	61.9(13.2)	62.3(12.3)	0.986†
Operation			
Mastectomy + axilla	36	31	0.541‡
WLE + axilla	22	27	0.475‡
Right : left	30 : 28	31 : 27	0.852‡
Surgeon			
Consultant	11	13	0.646†
Middle grade	47	45	
Tumour size (cm)*	2.5(1.3)	2.2(1.0)	0.122†
No. of nodes removed*	7.1(2.8)	7.6(3.1)	0.239†
No. of nodes involved*	1.3(2.4)	1.6(3.4)	0.844†

*Values are mean(s.d.), WLE; wide local excision. †Mann-Whitney test; ‡ χ^2 test.

The highest incidence of seroma and largest aspirate volumes occurred in patients who had undergone mastectomy from group 3 (no drain, no sealant). Comparison of patients who had undergone mastectomy from groups 2 and 3 revealed that the use of fibrin sealant was associated with a significant reduction in both the incidence of seroma ($P = 0.048$) and total volume aspirated ($P = 0.012$) (Table 2). However, there was no significant difference in the incidence of seroma or total volume aspirated between patients who had undergone mastectomy in groups 1 and 2 ($P = 0.317$ and $P = 0.563$, respectively).

Patients who underwent breast-conserving surgery without a drain or fibrin did not have a similarly high incidence of seroma. There were no significant differences in the incidence of seroma formation or total volumes aspirated between the three groups among patients who had wide local excision (Table 2).

There were no significant differences between groups 1, 2 and 3 in seroma protein content (median 36, 37 and 38 g/l respectively; $P = 0.863$, Kruskal-Wallis test) and LDH (median 860, 825 and 1053 units/l respectively; $P = 0.341$, Kruskal-Wallis test). The median (interquartile range) seroma protein and LDH concentrations for all patients combined were 37 (35–38) g/l and 855 (650–974) units/l respectively.

Pain score and length of stay

The use of drains was associated with a significant increase in pain scores as well as an increased duration of hospital stay (Table 3). The type of surgery (wide local excision or mastectomy) did not influence mean pain scores or duration of hospital stay within each study group. The mean(s.d.) pain score at the time of removal of the drain in group 1 was 3(1) cm.

Table 2 Incidence of seroma after breast surgery

	Drain (Group 1)	No drain, fibrin (Group 2)	No drain, no fibrin (Group 3)
All patients	58	29	29
Seroma	15	10	12
Total volume of aspirate (ml)*	140 (125–205)	165 (127–230)	300 (245–660)†
Frequency of aspiration*	1 (1–1)	1 (1–1)	2 (1–3)‡
After mastectomy	36	19	12
Seroma	9	8	10§
Total volume of aspirate (ml)*	150 (120–250)	190 (150–247)	395 (252–740)†
Frequency of aspiration*	1 (1–1)	1 (1–1)	2 (1–3)†
After wide local excision	22	10	17
Seroma	6	2	212
Total volume of aspirate (ml)*	140 (132–147)	115 (112–117)	160 (140–180)
Frequency of aspiration*	1 (1–1)	1 (1–1)	1 (1–1)

*Values are median (interquartile range). † $P < 0.050$ versus to groups 1 and 2 (Mann–Whitney test), ‡ $P < 0.050$ versus Group 1 (Mann–Whitney test), § $P < 0.050$ versus Groups I and II (Fischer's exact test).

Table 3 Pain scores and postoperative stay after surgery for breast cancer

	Drain ($n = 58$)	No Drain ($n = 58$)	P
Postoperative stay (days)	2.9(1.6)	1.9(0.9)	< 0.001
Pain score at 24 h	4.5(1.5)	3.2(1.9)	< 0.001
Pain score at 48 h	2.2(1.1)	1.4(1.2)	0.002

Values are mean(s.d.). Mann–Whitney test.

Complications

One patient in group 1 developed a wound infection that was treated with oral antibiotics and another patient suffered a small area of wound dehiscence that did not require intervention. One patient in group 2 developed a wound infection, and another had bleeding in recovery that needed re-exploration and drain insertion. One patient in group 3 developed a wound infection and needed oral antibiotic therapy. No patient required readmission.

Discussion

The results of this study confirmed that the use of drains following breast surgery did not prevent seroma formation, and was associated with a significant increase both in postoperative pain and hospital stay. In patients who underwent mastectomy, the absence of a drain was associated with an increase in seroma formation, but this was greatly reduced by the use of fibrin sealant. There was no benefit attributable to drainage or fibrin sealant in patients who had breast-conserving surgery.

The overall incidence of seroma in the present study was 31.9 per cent, comparable to other published values^{1–6}.

In the majority of patients, seromas cause minimal discomfort and resolve spontaneously, or after one or two aspirations. However, the presence of a seroma may result in anxiety, additional outpatient visits and delay in commencing adjuvant radiotherapy. Rarely, seromas result in skin flap necrosis, infection and lymphoedema²³. Various techniques have been used in an attempt to reduce seroma formation, including external compression²⁴, arm immobilization²⁵, flap-tacking sutures²⁶ and the avoidance of electrocautery²⁷. These methods can reduce the incidence of seroma but none has abolished the problem completely. Not surprisingly, the routine use of drains has remained standard practice^{5,28} in spite of well known disadvantages such as prolonged hospital stay^{6,11}.

Drains are usually left *in situ* until drainage is less than 50 ml in 24 h, which may take up to 10 days^{2,11}. Others have reported the use of multiple drains²⁹, or investigated the effects of low- or high-vacuum drainage³⁰, but without evidence of significant benefit. Some surgeons advocate early discharge with drains *in situ* to reduce hospital stay but this is associated with discomfort, problems of monitoring the drain in the community setting, and frequent visits to a family doctor. Many previous studies have demonstrated that postoperative drainage fails to prevent seroma formation; the incidence of seroma requiring aspiration ranges from 15 to 83 per cent following drain removal^{2–6}. In this study, the incidence of seroma after removal of drains was 25.9 per cent.

The present results suggest that patients undergoing breast-conserving surgery with axillary lymphadenectomy gain no benefit from the use of drains or fibrin sealant. Others have reported similar results. Siegel *et al.*⁷ reported a low incidence of symptomatic seroma (4.2 per cent) and concluded that it is not necessary to drain the axilla

following formal axillary breast dissection as part of breast-conserving surgery. Jeffrey *et al.*³¹ reported that seroma aspiration was required in 42 per cent of patients after breast-conserving surgery without drainage.

The incidence of seroma formation was much higher in patients who underwent mastectomy than in those who had breast-conserving surgery. This indicated that it was the wide area of chest-wall dissection, rather than the extent of axillary dissection, that contributed to seroma formation. Lack of a drain was associated with a high incidence of seroma after mastectomy, but the incidence, total volume of aspirate and frequency of seroma aspiration was halved with the use of fibrin sealant. The use of fibrin in animal models of mastectomy^{15–17} has consistently shown a reduction in seroma formation. However, previous studies of thrombin and fibrin sealant in humans reported conflicting results. Two studies^{18,19} demonstrated a reduction in drain volumes, but three others^{32–34} reported no significant difference in drainage volumes or seroma formation. All of these human studies employed a drain after the application of fibrin sealant. In the present study fibrin sealant was used without a drain. It is possible that the use of a suction drain immediately after the application of fibrin prevented stable clot formation and interfered with its capillary-sealing effects, accounting for the negative effects of previous studies.

The aetiology of seroma formation remains controversial. Some have suggested that it is a consequence of surgical disruption of lymphatics and capillaries with ensuing leakage of fluid into the dead space created by surgical dissection^{2,26}. Others have proposed that seromas are a consequence of inflammatory exudate¹⁴. This study showed high concentrations of proteins and LDH in fluid aspirates, suggesting that they are primarily exudate in nature^{19,20}. This finding was supported by the observation of high concentrations of IgG and leucocytes in seroma fluid by others¹⁴. In the setting of an inflammatory exudate, the presence of a drain may actually promote seroma formation by intensifying the inflammatory response.

There are various mechanisms by which fibrin sealant helps prevent the formation of seromas. Locally applied fibrin forms a strong bond that interlocks with the molecular structure of surgically damaged tissue and seals open tissue channels. Fibrin also provides significant adhesive strength and coapts the elevated skin flap to underlying tissues^{15,16}. It also promotes haemostasis and may prevent haematoma formation. The dose of sealant has to be optimal to achieve this outcome. The sealant effect is dependent on fibrinogen concentration, and clotting time on the thrombin concentration. Excessive concentrations of fibrin may reduce wound healing³⁵.

This study showed that neither drains nor the use of fibrin sealant abolished seroma formation totally, and that drainage was associated with a longer postoperative stay and higher pain scores. If the incidence of seroma is similar with or without use of drains then no drainage is obviously the treatment of choice as it is more convenient for the patient and has the added advantage of early discharge. This study suggests that no intervention is required in patients who undergo wide local excision, and that use of fibrin sealant without a drain is preferable to the use of drains in women undergoing mastectomy. The number of women in these subgroups was small, and further studies are required in women undergoing breast surgery.

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