

REVIEW ARTICLE

Seroma Formation after Breast Cancer Surgery: What We Have Learned in the Last Two Decades

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Formation of a seroma most frequently occurs after mastectomy and axillary surgery. Prolonged drainage is troublesome as it increases the risk for infection and can significantly delay adjuvant therapy. Seroma has been defined as serous fluid collection under the skin flaps or in the axillary dead space following mastectomy and/or axillary dissection. Because the true etiology of a seroma is unknown, a multifactorial-causation hypothesis has been accepted. Surgical factors include technique, extent of dissection and the surgical devices used for dissection. Obliteration of dead space with various flap fixation techniques, use of sclerosants, fibrin glue and sealants, octreotide, and pressure garments have been attempted with conflicting results and none have been consistent. Early movement of the shoulder during the postoperative period may increase the formation of seroma, although delayed physiotherapy decreases the formation of seroma. A detailed analysis of the use of drains showed that use of single or multiple drains, early or late removal, and drains with

or without suction are not significantly different for the incidence of seroma. Although there is evidence for reduced seroma formation after early drain removal, very early removal within 24 hours seems to increase formation of seroma. No patient or tumor factors seem to affect seroma formation except body mass index and body weight. Consensus is lacking among studies/trials with different groups producing conflicting evidence. Besides a few established factors such as body mass index, the use of electrocautery for dissection, early drain removal, low vacuum drains, obliteration of dead space, and delayed shoulder physiotherapy, most of the hypothesized causes have not been demonstrated consistently. Thus, seroma remains a threat to both the patient and surgeon. Recurrent transcutaneous aspiration remains the only successful management.

Key Words: Breast neoplasms, Lymph node excision, Mastectomy, Seroma

INTRODUCTION

Breast cancer has remained the second leading cause of cancer death among women worldwide over the past three decades [1] and contributes significantly to cancer surgical load. Surgical treatment for breast cancer includes breast conservation therapy and mastectomy with or without axillary dissection depending on disease stage. Seroma formation is the most frequent postoperative complication seen after mastectomy and axillary surgery with an incidence of 3% to 85% [2]. It is so common that it is now believed to be a side effect of surgery rather than a complication. Associated morbidity in the form of prolonged drainage is not only troublesome to

the patient but can also significantly impact treatment by delaying adjuvant therapy and increasing the risk for infection [2]. A reoperation may be necessary for cases of longstanding persistent seroma [3]. This review updates the various factors thought to contribute to seroma formation and the probable interventions that may be of help to reduce incidence.

PATHOPHYSIOLOGY

Seroma after breast surgery is defined as a serous fluid collection that develops under the skin flaps or in the axillary dead space following mastectomy and/or axillary dissection. The origin of seroma remains unclear but several risk factors and predictors are age, breast size, comorbid conditions, presence and number of malignant nodes in the axilla, previous surgical biopsy, and use of heparin or tamoxifen [4-6]. It has been hypothesized that seromas form as an exudate from an acute inflammatory reaction following surgical trauma [6] to increase serous fluid collection in response to increased

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Received: May 29, 2012 Accepted: October 23, 2012

fibrinolytic activity in serum and lymph [7]. Low fibrinogen levels in seromas compared with those in plasma during the postoperative period [8] support the hypothesis that seroma most likely originates from lymph [9]. Seroma formation is influenced by an array of surgical techniques and devices [10-13]; thus, leading to varying incidence of seroma in different studies.

FACTORS RELATED TO SURGERY

Techniques

Surgical treatment for breast cancer has undergone a paradigm shift from Halstead's radical mastectomy to breast conservation. It has been demonstrated that radical mastectomy increases seroma formation compared with that of simple mastectomy [14,15], but the association is inconclusive when radical mastectomy is compared with modified radical mastectomy (MRM) [14]. Conversely patients undergoing MRM have a significant increased incidence of seroma formation when compared to those who have breast conservation surgery [16]. Preservation or removal of the pectoral fascia has no effect on the incidence of seroma [17]. It has also been observed that immediate breast reconstruction following MRM decreases seroma formation when compared to a delayed procedure [18]. The number of removed lymph nodes probably does not influence seroma formation [19,20]. A randomized controlled trial by Purushotham et al. [21] demonstrated that sentinel lymph node biopsy is associated with significantly less seroma formation than that of conventional axillary dissection.

Surgical devices

Various electro-mechanical devices are used during surgery to reduce blood loss and operating time. These include electrocautery, laser scalpel, argon diathermy, ultrasonic scalpel, ultrasonic scissors, and vessel sealing systems. All of these devices have been investigated in an effort to reduce seroma formation. Randomized trials have shown that the use of electrocautery for dissecting flaps is significantly associated with increased seroma formation when compared to that of scalpel dissection [12,22]. However, no individual study has shown a significant effect on seroma formation with or without the use of a laser scalpel [23], argon diathermy [13], or an ultrasonic scalpel [24]. Ultrasonic scissors resulted in reduced seroma formation in a randomized controlled trial comparing level I and II axillary dissection using either ultrasound scissors or surgical scissors with ligation [25]. An Italian group compared the bipolar vessel sealing system with conventional surgical dissection and found no difference in the duration of the surgical procedure, total drainage fluid volume, drainage

duration, or postoperative adverse events between the groups in a randomized trial [26]. Interestingly, a significant increase in seroma was observed in the vessel sealing system group. However other studies have reported improved results with use of a vessel sealing system. One of these was a prospective study [27], in which the results were compared with historical data, and decreased drainage duration and hospital stay were observed. Another retrospective study concluded that the drainage duration is significantly shorter with the use of a vessel sealing system but not the cost of treatment. The benefit in terms of fluid loss also remains to be demonstrated [28]. The differences in outcomes probably reflect differences in study methods; thus, further randomized trials with larger sample sizes are required.

OBLITERATION OF DEAD SPACE

Mechanical

Different techniques have been employed to obliterate the dead space (under flaps and the axilla) to reduce seroma formation. Halsted first advocated creating a short superior flap and suturing it with interrupted silk to the fascia below the first rib and skin grafting the remaining part of the defect [29]. In 1951, Orr [30] used tension sutures tied over rubber tubing bolsters to tack flaps to the chest wall. In 1953, Keyes et al. [31] used through and through sutures to attach the skin flaps to the chest wall. Besides these techniques, suturing of flaps with subcutaneous tissue [32], avoiding use of axillary drains following breast conservation therapy [33], and obliterating axillary dead space by muscle approximation [34,35] have all been tried for reducing seroma formation. Coveney et al. [36] compared suturing skin flaps to underlying muscle with conventional skin closure and observed a lower incidence of seroma formation in the flap suture group, although flap suturing did add to total operating time. A recent randomized study [37] compared a combination of skin flap suturing, ligation of lymphatics and obliteration of axillary dead space to conventional skin closure after mastectomy. As a result, the incidence of seroma formation decreased to 2% with the combination of techniques. Although effective, the authors stated that it was impossible to determine which of the three techniques, or any combination, actually produced the observed effect. Mechanical pressure has also been applied to obliterate dead space following surgery. The use of a pressure garment does not reduce postoperative drainage and has low tolerance and a higher complication rate [38,39].

Chemical

Fibrin glue [40], light activated fibrin sealant [41], and trans-

dermal photo-polymerized adhesive [42] reduce seroma formation after mastectomy in animal models. Use of a fibrinolysis inhibitor was based on the hypothesis that fibrinolytic activity in serum and lymph might contribute to fluid accumulation. Sanders et al. [43] reported that fibrinogen and thrombin concentrations in the fibrin sealant are proportional to the reduction in seroma formation. However, no significant difference in the incidence of seroma formation occurred with the use of fibrin glue in human studies [44-46]. In contrast, Vaxman et al. [46] demonstrated in a randomized trial that use of fibrin glue actually increases seroma formation rate. The advantage of using fibrin glue comes from three other studies that demonstrated significantly reduced total seroma drainage [47], early drain removal [48], and reduced hospital stay [49]. Most of these studies had a limitation of a relatively small sample size. A reduction in postoperative drainage and hospital stay were observed following use of fibrin glue, but it did not affect delayed seroma formation [49]. However, the use of fibrin glue or peri-operative and postoperative administration of a fibrinolysis inhibitor does not reduce seroma formation [50].

Various sclerosants have also been used to prevent and manage seroma. A number of agents have been investigated in rat models, including marine mussel protein [51] and the Gram-positive anaerobe *Corynebacterium parvum* [52]. In humans, seromadesis has been reported with talc [53] and hypertonic saline [54]. Although successful, both of these reports were based on the experience of one patient. The most commonly reported sclerosant in the literature is tetracycline, and, similar to fibrin glue, some reports found it useful [55-57] whereas others did not [58,59]. Two prospective, randomized trials from the Mayo clinic evaluated the use of tetracycline. They first used tetracycline postoperatively, administering it into wound cavities via drains in patients who had undergone mastectomy [59]. This trial was aborted early due to severe pain experienced following the tetracycline administration with no associated benefit. A second trial administered tetracycline intra-operatively [58] and found no difference in postoperative pain between the groups but also found no difference in seroma formation. The non availability of tetracycline has led to the use of erythromycin as a sclerosant, which is commonly used in pleurodesis [60]. Ali-Khan et al. [61] showed that erythromycin was useful in one case of breast surgery and three cases of inguinal bloc dissection complicated by refractory seroma formation.

Somatostatin receptors have been discovered in the lymphatic tissue within and outside the gastrointestinal tract [62] and are thought to reduce lymph production when stimulated, although the precise mechanism of action responsible for this effect is not well understood. Octreotide, a long acting and 20

times more potent synthetic analogue of somatostatin has been used successfully to combat chylous ascites and lymphorrhoea following thoracic duct injury. Studies have demonstrated a benefit when administering octreotide following axillary lymph node dissection to reduce the to the duration and volume of lymphorrhoea [63]. However further trials are required to establish its true significance.

SHOULDER FUNCTION AND PHYSIOTHERAPY

Shoulder dysfunction is a common complication of mastectomy [64], and it is necessary to mobilize the shoulder early to prevent this complication. It was thought that early shoulder mobilization led to increased seroma formation and this hypothesis was supported by a systematic review of 12 randomized controlled trials (RCTs) of which six were included in a meta-analysis [65]. The study showed that a delayed shoulder exercise program reduces seroma formation (odds ratio, 0.4; 95% confidence interval, 0.2-0.5; $p=0.00001$) but no differences were found for drainage volume or hospital stay. Conversely, a number of RCTs have demonstrated no difference in seroma formation between early (within 1-2 days postoperatively) or late (by 5-7 days postoperatively) shoulder movement [20,66-68]. Temporary immobilization of the shoulder using a collar and cuff [20] or sling [66] has been attempted with an aim to reduce seroma formation but was not found to be beneficial. Thus, the present evidence does not support shoulder immobilization.

Another parallel issue is whether active shoulder mobilization through physiotherapy has any effect on seroma formation. A number of reports comparing delayed physiotherapy, even until removal of the drain showed less total wound drainage, shorter drainage period, and a shorter hospital stay without any difference in the functional range of movement in the longer term [68-70]. Rodier et al. [71] and van der Horst et al. [72] found no significant difference in seroma production to production following early or delayed physiotherapy. Thus delayed physiotherapy may reduce seroma formation at the expense of mild short-term shoulder dysfunction but without long term restriction of movement.

DRAINS

The use of drains has been a common practice to obliterate the dead space created after surgery [73,74]. The use of closed suction drainage in patients who underwent mastectomy accelerates wound healing and is also associated with a lower incidence of wound infection, necrosis, and breakdown [75,76]. A study by Bourke et al. [77] found no difference between

using closed suction wound drainage and corrugated wound drainage in 51 patients who underwent simple mastectomy [78]. In a study by Whitfield and Rainsbury [79], no significant difference was observed between suction and closed siphon drainage on the formation of seroma. The choice of the number of drain tubes used has been studied. Two randomized trials reported that use of multiple drains does not confer any significant advantage on either the amount or duration of seroma drainage [80,81].

Studies comparing the intensity of negative drain suction have shown mixed results. In a study of 46 patients who underwent mastectomy, randomized between high vacuum drain and low vacuum drain, seroma drainage and postoperative hospital stay was longer in the low vacuum system group than that in the high vacuum system possibly because the high vacuum drain led to more efficient flap approximation to the chest wall [82]. In contrast, van Heurn and Brink [83] found that the mean volume evacuated was significantly lower from a low vacuum system, which led to early drain removal in 76 patients who underwent axillary dissection with breast-conserving surgery. Bonnema et al. [84] compared high versus low vacuum drainage, in 141 patients undergoing modified radical mastectomy, lumpectomy with axillary dissection or axillary dissection alone. No significant difference was observed in the volume of axillary fluid produced, drainage duration or wound complication rates between the two groups. High vacuum drains had a higher incidence of vacuum loss but a lower incidence of leakage around the drain. Thus, no strong evidence is available to recommend high or low pressure suction to reduce seroma formation.

Discharge with drain *in situ*

Patients can be safely discharged with drains *in situ* with adequate patient education and coordination of inpatient and outpatient facilities, including telephone contacts [85,86]. Acceptance rates for early discharge with drains *in situ* vary between 24% and 41% [86,87]. Interestingly, patients who choose early discharge tend to be significantly younger, are living with another adult, and are more likely to have had breast-conserving surgery [88]. A number of studies have evaluated the effect of different days of postoperative discharges [86,88-92]. Early discharge from the hospital with the drain *in situ* does not appear to be associated with any untoward events [87,90, 93]. Holcombe et al. [86] reported a lower seroma rate in the early discharge with drain *in situ* group (18%), compared to a standard treatment group (34%) and a reduction in median hospital stay of 5 days in a series of patients who underwent axillary dissection. However no significant decrease in seroma rates was observed with early discharge at a mean of

4.3 days [92]. Orr et al. [91] reported discharging 72 patients who had undergone total mastectomy and axillary dissection, segmental mastectomy and axillary dissection, or total mastectomy alone at a mean of 2.9 days. The seroma rate was as low as 11%. High seroma rates (45-67%) have been observed in patients who received mastectomy and were discharged the day following surgery [94,95].

Concerns expressed in the early discharge group of patients include personal care, bed posture, dressing themselves, fatigue, loneliness, pain, and worries about the wound and the arm [87]. Despite these factors, studies have shown that patient acceptance of early discharge with drains *in situ* remains good [87,91]. However, some reports have expressed mixed results and no compelling evidence points to a uniform reduction in seroma rate following early discharge with a drain *in situ*, although discharge within a day of surgery has been fraught with a higher rate of seroma formation.

Early drain removal

It is common practice to remove drains when drainage decreases to a minimal volume (20-50 mL) in the preceding 24 hours to minimize seroma formation [96]. It has been shown that 48 hours after surgery, as much as 74% of the total volume of seroma has been drained [97]. It has also been observed that drains may be safely removed after axillary dissection, if the total drainage during the first 3 days is less than 250 mL [98]. Somers et al. [19] studied 108 patients who underwent level one or two axillary node dissection, whose drains were removed on the first postoperative day regardless of drainage volume and the patients were discharged. No significant difference was observed with respect to drainage volume at the time of drain removal, subsequent mean number of aspirations, and time to resolution of seromas. Parikh et al. [99] randomized 100 patients who underwent mastectomy with axillary clearance to drain removal at either 3 or 6 days postoperatively. More seroma fluid was collected in the group whose drain was left *in situ* longer, but no difference in the volume, number, or duration of percutaneous aspirations was observed once the drain was removed. Inwang et al. [100] randomized 84 patients to drain removal on day 5 to drain removal when drainage was less than 20 mL over 2 consecutive days and found no significant difference in the mean number of aspirations required, wound complications or cosmesis. Yii et al. [101] compared drains removed at 48 hours to a "standard" removal group. No significant difference in drainage at 48 hours and no significant difference in seroma frequency were observed. Liu and McFadden [102] removed drains at 23 hours postoperatively in 50 patients who underwent axillary lymphadenectomy. Only a 2% seroma rate was observed, as

49 out of the 50 patients had no symptomatic seroma. Thus, there appears to be good evidence in favor of early drain removal.

No wound drainage

When drainage and no drainage were compared in patients who underwent lumpectomy and axillary dissection [19], short duration closed suction drainage appeared advantageous for decreasing the incidence and degree of seroma formation and did not seem to delay early hospital discharge. Cameron et al. [103] studied 40 patients who received axillary drainage and 20 who were allocated to no drain. The results showed a significantly higher rate of seroma formation in the undrained group (45% vs. 10%). Jeffrey et al. [104] reported safe axillary dissection without drainage after breast-conserving surgery, although this required frequent seroma aspiration. All seromas resolved clinically within 1 month or within 4 months on ultrasonographic examination. Siegel et al. [105] also reported that axillary dissections combined with breast-conserving surgery can be performed safely without axillary drainage. Zavotsky et al. [106] demonstrated that axillary node dissection can be managed with or without a drain. More aspirations in the no-drain group were required (50%) compared to that in the drain group (8.3%), but no difference was observed in the complication rate and the pain rating was significantly less in the no-drain group.

PATIENT FACTORS

Although a number of surgical technique-related factors have been described to play a role in seroma formation, most patient and tumor-related factors have been shown consistently to have no significant association with seroma formation. A number of studies have attempted to associate patient and tumour characteristics to postoperative seroma formation. Body weight [2,107] and body mass index [108] are associated with increased seroma formation, whereas no consistent association has been found between seroma formation and hormone receptor status [26,107], axillary nodal status, lymph node positivity [18,20,107] or disease stage and grade [18,26]. Similarly, no consistent association has been found between seroma formation and the presence of anemia, smoking, diabetes mellitus, or breast size [14]. Tumor size and location, histological type, site of the disease and specimen weight are not associated with increased seroma formation [26,109].

CONCLUSIONS

Seroma formation is a side effect of breast or axillary surgery rather than a complication but can delay patient recovery and

cause unpleasant symptoms. Patient and tumor-related factors have no significant bearing on seroma formation except possibly body weight and body mass index, which seem to be directly proportional to seroma formation. Physical closure of the dead space appears to reduce seroma rate, but studies have failed to address the issues of cosmesis, and shoulder movement restrictions and these add to the operating time. Evidence for the use of fibrin glue remains controversial. Thrombin spray, sclerotherapy and mechanical pressure do not reduce seroma drainage. Shoulder immobilization is of no advantage to the patient, but it appears that delaying shoulder physiotherapy reduces drainage. Drains should be used, but the number of drain tubes or a low pressure system does not decrease the formation of seroma. However, low vacuum drains in the axilla result in less seroma formation, earlier drain removal and earlier discharge. High pressure vacuum drains in the axilla may promote increased drainage due to flap irregularity and poor flap adherence. High pressure vacuum drains appear safe and acceptable to discharge many patients early with drains *in situ*, if adequate patient counseling and nursing support are provided. Seroma formation can be safely considered on an outpatient basis by multiple percutaneous aspirations.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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