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REVIEW ARTICLE

Seroma Formation after Mastectomy: Pathogenesis and Prevention

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Abstract Post mastectomy seroma remains an unresolved quandary as the risk factors for its formation have still not been identified. Seromas of the axillary space following breast surgery can lead to significant morbidity and delay in the initiation of adjuvant therapy. Various techniques and their modifications have been practiced and published in English literature, but there seems to be no consensus. In this article, all aspects of seroma formation from pathogenesis to prevention including drug therapies have been discussed.

Keywords Breast · Cancer · Surgery · Drains · Octreotide · Morbidity

Introduction

Seroma is a collection of serous fluid in the dead space of post-mastectomy skin flap, axilla or breast following modified radical mastectomy (MRM) or breast conserving surgery (BCS) and is the commonest early sequel [1]. However, there is inconsistency in the definition of seroma across published works. This presumed complication, albeit usually of minor consequence, may prolong recovery, length of hospital stay and over stretch health budget. The reported incidence of seroma formation varies widely between 15 and 18% [2]. There are several factors implicated in seroma formation like the extent of lymph node clearance, number of positive nodes, the use of postoperative radiation and whether intraoperative lymphatic channel ligation was done or not, but opinion differs as to their individual role in its pathogenesis [2, 3]. The main pathophysiology of seroma is still poorly understood and remains controversial. The optimal ways to reduce the incidence of seroma formation are unknown.

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Pathogenesis

The pathogenesis of seroma has not been fully elucidated. Seroma is formed by acute inflammatory exudates in response to surgical trauma and acute phase of wound healing [4]. Oertli et al. [5] believed that the fibrinolytic activity contribute to seroma formation. Petrek et al. [6] in a prospective randomized trial showed that the most significant influencing factors in the causation of seroma were the number and extent of axillary lymph node involvement. However, Gonzalez et al. [7] and Hashemi et al. [8] reported that the only statistically significant factor influencing the incidence of seroma formation was the type of surgery. They reported higher seroma rate in MRM than following wide local excision and axillary dissection (BCS). Factors such as age of the patient, obesity, tumor size and neoadjuvant therapy did not influence the incidence of seroma formation in the three mentioned studies. Extensive dissection in mastectomy and axillary lymphadenectomy damages several blood vessels and lymphatics and the subsequent oozing of blood and lymphatic fluid from a large surface area when compared with breast conserving surgery leads to seroma [9].

Seroma accumulation elevates the flaps from the chest wall and axilla there by hampering their adherence to the tissue bed. It thus can lead to significant morbidity such as wound hematoma, delayed wound healing, wound infec-

tion, wound dehiscence, prolonged hospitalization, delayed recovery and initiation of adjuvant therapy [4].

Prevention and Reduction of Seroma Formation

There are several techniques in practice that have been reported to prevent or reduce seroma formation, but no single method has been shown to be consistently and reliably effective. They can be discussed as (1) surgical techniques, (2) the use of sealants and sclerotherapy, (3) compression dressing, (4) the use of drains, (5) shoulder exercise (delayed vs early) and (6) the role of Octreotide.

Surgical Techniques

It s believed that meticulous attention applied to techniques of breast surgery to minimize the leakage from dissected blood vessels and lymphatics and to obliterate the dead space may reduce the incidence of seroma formation [10]. There are several surgical techniques that have been used with this respect, but there are conflicting results in their effectiveness at reducing the incidence and volume of seroma.

Tissue Dissection Techniques

Tissue dissection techniques in breast cancer surgery have been implicated as a major factor that influences the incidence and volume of seroma formation. As Kakos and James [11] in the 1970s suggested the use of electrocautery for breast dissection, it has been shown to decrease incision time, reduce blood loss and transfusion requirements but may be associated with increased wound complications. Ultrasonic dissection is well known in hepatic and cardiovascular surgeries and may create less thermal injuries than electrocautery. Kontos et al. [12] reported low incidence of seroma accumulation in patients where harmonic scalpel was used. Galatius et al. [13] showed that the time to removal of drain was significantly lower in the ultrasonic dissection group as a result of reduction in the total amount of drainage after axillary dissection. Wyman and Rogers [14] reported reduced blood loss using laser scalpel for MRM but has no other overall advantage over the conventional surgical technique for mastectomy. Argon enhanced electrosurgery has been shown to reduce intra-operative blood loss and postoperative transfusion requirements. Ridings et al. [15] did show that argon enhanced electrosurgery also decreased the incidence of seroma formation, whereas Kerin et al. [16] failed to show the difference in postoperative seroma drainage between argon enhanced electrosurgery and conventional diathermy. Therefore, there seems to be evidence against the use of electrocautery in breast surgery because of the degree of thermal trauma and inflammation followed by increase in the incidence of seroma formation. This fact is again supported by a study by Porter et al. [17] which concluded that the use of electrocautery to create skin flaps in mastectomy reduced blood loss but increased the rate of seroma formation. There are inconsistent and inconclusive results on the beneficial role of alternative dissection techniques using ultrasonic scissors and laser scalpel over electrocautery or sharp dissections. These in addition have obvious cost implications.

Wound Closure to Reduce or Obliterate Dead Space

Surgical techniques to reduce or obliterate the dead space following breast surgery and axillary dissection have been shown to reduce the incidence of seroma formation. Historically, Halstead suggested obliteration of the dead space particularly in the axilla to facilitate wound healing [17]. More recently, Chilson et al. [18] reported a significant decrease in the incidence of post mastectomy seromas ($p=0.038$) and the number of postoperative clinic visits for aspiration of seroma ($p=0.0001$) when flap tacking was carried out. Coveney et al. [19] showed significantly less drainage in the group of patients where skin flaps were sutured down to the chest wall muscles compared to just conventional skin flap closure. Classe et al. [20] showed that axillary padding with the use of axillary aponeurosis alternative to closed suction drain after axillary lymphadenectomy with early discharge. They reported 22.2% seroma rate in 207 of their patients. Published reports did not address the additional operating time and cosmetic implications in this surgery, where cosmesis is one of the important considerations. Various authors have reported different techniques with claimed similar efficacy, but it is difficult to draw any conclusion as the studies are non-randomized, vary in closure techniques and some have additional procedures.

The Use of Sealants and Sclerotherapy

Fibrin glue and other sealant agents have been shown in murine experimental models to reduce seroma formation after mastectomy [21]. However, there are conflicting results on the effect of fibrin glue in reducing seroma formation after breast surgery and axillary lymphadenectomy. Sanders et al. [22] noted that excessive concentration of fibrinogen in fibrin glue may be counterproductive as it may adversely affect wound healing, but in clinical practice

it significantly reduces the overall seroma formation, earlier drain removal and reduced length of hospital stay. Other investigators, however, have refuted this effect and reported that neither fibrin sealants for bovine thrombin have any significant effect on reduction of seroma formation and daily drainage [23, 24].

Jain et al. [25] opined is their study that usage of drain after application of fibrin sealant probably led to instability of clot formation and thereby non-significant advantage of fibrin sealant in other studies. However, Cipolla et al. [26] concluded that the higher cost of fibrin glue, cumbersome technique involved in its application and higher aspirate volume indicated that it has no advantage over the use of routine drain after breast surgery. The other sclerosant used to obliterate dead space following was tetracycline. The first study of tetracycline sclerotherapy in the prevention of seroma formation after mastectomy was by Sitzmann et al. [27] and they reported a significant reduction in the volume of seroma within 48 h of its application is all five patients. The same effectiveness of tetracycline in reducing seroma formation was shown by Nichter et al. [28]. However, other authors reported from randomized clinical trials that tetracycline sclerotherapy had no effect at reducing seroma formation and was associated with severe postoperative pain compared with the control group [29, 30]. The efficacy of fibrin glue and other sealants in reduction of the incidence of seroma over simple closure with or without drain, therefore is yet to be proved. The use of sclerotherapy has been abandoned and has no role in seroma reduction.

Compression Dressing

External compression dressing to the chest wall and axilla to obliterate the dead space has been traditionally used to reduce the incidence of seroma formation. Compression dressing generally has been abandoned, as there is only anecdotal evidence in support of its use after surgery for breast cancer. O'Hea et al. [31] in their randomized trial found that compression dressing failed to reduce the seroma formation and instead increased its incidence. Besides conflicting efficacy the other problems with compression dressing are discomfort and low tolerance by the patients.

The Use of Drains

The use of drains after surgery for breast cancer is probably the most investigated and at the same time most controversial of all the techniques aimed at preventing or reducing the incidence of seroma formation. A drain is used routinely after breast cancer surgery with the understanding that it will reduce or prevent seroma accumulation. Suction drainage was introduced in 1947 by Murphy with the expectation that it will apply negative pressure and obliterate the dead space after excision of breast tissue and axillary dissection [32]. The influence of negative pressure causing skin flap opposition to the chest wall may facilitate wound healing reduce the incidence of wound infection, wound dehiscence or flap necrosis and prevent seroma formation [33]. There are however, controversies correlating to the optimal suction pressure, number of drains, duration of drainage or in fact whether the drain should be used at all following breast cancer surgery [34].

Drain Versus No Drain

Drain continues to be used after breast excisions and axillary dissection in spite of the fact that there is no clear evidence that it totally reduces the incidence of seroma formation. There are authors who do not insert drain after breast cancer surgery because of the belief that it does not prevent seroma formation and is associated with increased wound complications, patient's discomfort and prolongs hospital care [35, 36]. Talbot and Magarey [37] grouped 90 consecutive patients who had axillary dissection for breast cancer into those with prolonged drainage, short drainage and no drain and reported the difference in the complication rates or the duration of fluid accumulation in these three groups. Patients with no drain inserted required more frequent aspiration. They concluded that early drain removal or avoidance of drain following axillary lymphadenectomy facilities early discharge but have no effect on either wound complications or the duration of axillary accumulation. Zavotsky et al. [38] showed significant extra visits for aspiration of seroma (p=0.002) in the undrained group and significantly increased incidence of pain in the drained group (p=0.0062).

Suction Versus Passive Drainage

Suction drain is known to obliterate the dead space left after breast surgery for cancer therapy preventing accumulation of seroma [36]. However, the incidence of seroma formation has been found to be higher when suction drains were used compared with passive drains, whereas some other investigators reported no significant difference correlating to the rate of seroma between the two types of drains [39, 40]. In contrast, the incidence of seroma was unacceptably high when suction drain were not used in a study by Kopelman et al. [41].

Single Versus Multiple Drains

Most surgeons tend to use more than one drain after mastectomy and axillary dissection and at least two: one at

the axilla and the other at the chest wall. However, there are few studies to compare the use of single and multiple drains in breast surgery for breast cancer. Terrell and Singer [42] reported that the use of two drains (axilla and chest wall) is not superior to that of one drain in the axilla in preventing seroma formation in their 84 inpatients. Petrek et al. [43] randomized 65 patients undergoing axillary dissection or MRM for stage I (or) II carcinoma into one or four suction drains into the axilla. Both groups had a drain in their chest wall dead space. The use of multiple drains in the axilla conferred no advantage as they did not affect the amount and duration of drainage compared with single drain. They therefore recommended the use of a single drain to the axilla after lymphadenectomy.

Length of Drainage (Early Vs Late)

The reported postoperative hospital stay following breast cancer surgery in the UK about a decade ago was 5 to 7 days [44]. Most surgeons tend to remove the drain when the drainage volume was less than 20–50 ml and this may take up to 10 days but increasingly in practice, patients are discharged early with the drain insitu. Kopelman et al. [41] recommended that drain may be removed if the drainage volume within the first three postoperative days is less than 250 ml, as keeping them longer insitu did not protect against seroma formation. Gupta et al. [33] in a prospective randomized study grouped patients into 5-day and 8-day drainages after MRM and showed that removal of drain on the fifth post operative day was safe but was associated with an increase in incidence of seroma aspiration and volume. Dalberg et al. [45] in a large multicentre Swedish randomized trial showed that early removal of drain shortened the hospital stay without risking high incidence of seroma formation and other wound complication. However in cases when there is persistent seroma production, increasingly is practice, drains are left insitu to be managed in the community.

Shoulder Exercise (Delayed Vs Early)

Several authors have implicated the role of early shoulder exercise in the pathogenesis of seroma formation after breast cancer surgery and strategies aimed at reduction of seroma formation included delaying postoperative shoulder exercise with added benefit of improved wound healing. Early active postoperative ipsilateral arm movement has been shown to increase seroma formation, whereas delayed shoulder exercise reduce the incidence of seroma without adversely affecting long term shoulder function [46]. In a recent systematic review of delayed versus immediate postoperative exercise following surgery for breast cancer, Shamley et al. [47] showed that current evidence from 12 randomized controlled trials supports the use of delayed arm exercise programme (p=0.00001) to reduce seroma formation. Delayed controlled shoulder exercise programme is superior to immediate postoperative movement at reducing seroma and there is no evidence that this affects long term shoulder function.

The Role of Octreotide

Octreotide is a long acting somatostatin analogue which suppresses secretion and its role is well documented in reduction of gastrointestinal tract secretions by reduction of splanchnic flood flow. It has also been used to control lymphorrhoea resulting from thoracic duct injury, chylous ascites and after radical neck dissection [48]. It has been shown in animal models to reduce local inflammatory reaction, which is one of the pathophysiological mechanisms implicated in seroma formation and probably can have a direct effect on the lymphatic circulation by reduction of lymph production. Carcoforo et al. [49] in a prospective trial randomized 261 consecutive patients following axillary dissection for breast cancer into treatment group who received 0.1mg octreotide subcutaneously thrice a day for 5 days starting on the first postoperative day and the control group who received no treatment. In the control group, the mean volume of seroma was 94.6+19 mL/day and the average duration was 16.7+3.0 days, where as in the treatment group, the mean volume of seroma was 65.4+21.1 ml/day (p<0.0001) and the average duration was 7.1+2.9 days (p<0.0001). They found no significant difference in the wound infection and hematoma rates between the two groups and concluded that octreotide may be used successfully for the treatment of seroma following axillary dissection and potentially in its prevention.

Conclusion

It appears that seroma formation after breast cancer surgery is a persistent problem much to the annoyance of surgeon and patient alike, in spite of advances in surgical techniques and hemostasis. Present evidence clearly attributes increase in the incidence of postoperative seroma to electrocautery because of increased thermal trauma. However, reduction of peroperative blood loss makes electrocautery indispensable because alternatives such as ultrasonic and laser dissection have cost implications.

As the exposure of raw area to a relatively less pressurized dead space appears to be yet another pathophysiological factor besides thermal trauma, techniques of

obliteration of dead space, therefore seem to be advantageous. Various methods thus can be used to obliterate this dead space including tacking of the flaps of mastectomy to the chest wall or the use of surrounding soft tissue to fill in after conserving surgery. Use of sealants appears promising but yet to be unequivocally proved, whereas compression dressing has been largely abandoned. The use of drains to evacuate collection in the dead space is probably the most controversial. Evidence has shown that short term use of drainage system prevents seroma or at least reduces its incidence compared with no drainage. Closed suction drain is preferred and provides better flap apposition to the chest wall and promotes healing. However, low suction drain cause less seroma volume, less duration of seroma flow, earlier drain removal and shorter length of hospital stay. Possible usage of drain and subsequent duration of drainage and suction pressure therefore, remains largely to the clinician's discretion.

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