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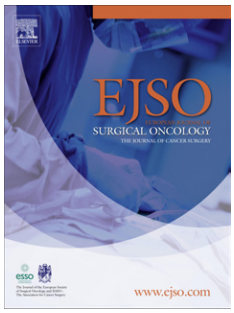

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Prevention of seroma formation after axillary dissection in breast cancer:
a systematic review.

A.J.M. van Bemmel [1,2], C.J.H. van de Velde [1], R. F. Schmitz [2], G.J. Liefers [1]

1 Department of surgery, Leiden University Medical Centre, the Netherlands
2 Department of surgery, Groene Hart Hospital Gouda, the Netherlands

Background: The most common complication after breast cancer surgery is seroma formation. It is a source of significant morbidity and discomfort. Many articles have been published describing risk factors and preventive measures. The aim of this paper is to provide a systematic review of studies and reports on risk factors and preventive measures. Surgery lies at the core of seroma formation; therefore focus will be placed on surgical ways of reducing seroma.
Methods: A computer assisted medline search was carried out, followed by manual retrieval of relevant articles found in the reference listings of original articles.
Results: 136 relevant articles were reviewed. Though the level of evidence remain varied several factors,type of dissection, tools with wich dissection is carried out, reduction of dead space, suction drainage, use of fibrin glue and octreotide usage, have been found to correlate with seroma formation and have been shown to significantly reduce seroma rates.
Conclusion: Seroma formation after breast cancer surgery can not be avoided at present. There are however several methods to minimize seroma and associated morbidity. Future research should be directed toward the best ways of reducing seroma by combining proven methods.
Keywords: Seroma, breast cancer, lymphadenectomy, risk factors, prevention.

Introduction

Seroma formation, an abnormal collection of serous fluid, is known for being the most common complication following breast cancer surgery. Viewed by some surgeons as a necessary evil, it accounts for prolonged patient discomfort which translates as pain, delayed wound healing, skin flap necrosis and infection.[1 2] Additional financial burden is caused by late onset seroma formation; which in most cases requires multiple visits with manual evacuation of accumulated fluid.
With incidence rates varying from 15 up to 90 percent there is extensive literature on this subject. [3 4 5] Consensus however is lacking with respect to pathophysiology as well as preventive measures. This article provides an up to date review of available literature in an attempt to clarify seroma formation. Pathophysiology and preventive measure will be discussed. Emphasis will be placed on surgical aspects, as it is surgery that lies at the root of seroma formation.

Pathogenesis

Although not yet fully understood the pathogenesis of seroma formation has been linked to several precipitating factors. [6] The dead space created by dissected tissue is filled with serous fluid.[7] This fluid changes composition in the days following surgery. At first it simulates lymph like fluid with blood clots, indicating broken lymph and blood vessels due to the dissection. A few days later it imitates an exsudate, which seems to be formed as the body reacts to the acute inflammatory condition following surgery.[8] Skin flaps, the result of

dissecting through different layers of tissue, which already had to adhere to the irregular chest wall are further hindered by seroma.[9] This leads to a prolonged primary wound union process.[10] Lymphatic and blood vessels which are damaged by the operation start to ooze blood and lymphatic fluid, which adds to the seroma, as the patient resumes moving her arm.[11] The pathophysiology for seroma formation seems to be multifactorial with surgery at its core. [12]

Materials and methods

Articles were collected via a computer assisted medline search up to February 2010, and additional references were found in bibliographies of these articles. As reference terms 'seroma', 'lymphadenctomy' 'breast cancer', 'mastectomy' and 'lymphocele' were used in combination with the following search strategy: (("seroma"[MeSH Terms] OR "seroma"[All Fields]) OR ("lymphocele"[MeSH Terms] OR "lymphocele"[All Fields])) AND (("lymph node excision"[MeSH Terms] OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields]) OR ("mastectomy"[MeSH Terms] OR "mastectomy"[All Fields])) Included articles were limited to studies published in English. Randomized controlled trials, prospective studies, retrospective studies as well as smaller descriptive studies were selected from the list of found articles and extensively reviewed. Quality of evidence was categorized according to the levels of evidence and grades of recommendation as used by the Oxford centre of Evidence –based Medicine.

Results

Risk factors

A multitude of research has tried to provide characteristics of patients at risk of developing seroma formation after breast cancer surgery. Bodyweight and hypertension have shown to be significant influencing factors for seroma formation. [13 14 15] Age, number of lymph nodes and extent of lymph nodes involved remain controversial factors as some studies show significant seroma formation [16 17 18 19 20] while others found no significant association.[21 22 23 24] The following factors were shown to have no significant influence on seroma formation: tumour size, neoadjuvant therapy, smoking, breast size, diabetes mellitus. [25 26]

Surgical risk factors

There are several factors concerning surgical involvement in the formation of seroma. First and foremost is the type of dissection carried out. The more extensive the dissection will be the more blood and lymphatic vessels will be damaged; resulting in larger seroma formation. This was shown when studies compared modified radical mastectomy with mastectomy and modified radical mastectomy with wide local excision and axillairy dissection. [15 16 17 27] When modified radical mastectomy was compared to breast conserving therapies results were mixed. Yet breast conserving therapies have an overall lower seroma formation. [28 29 30 31] Axillary dissection has been shown to negatively influence seroma formation. With the introduction of sentinel lymph node biopsy a means to assess the need for axillary dissection has become available. Sentinel lymph node biopsy has been associated with significantly lower seroma formation in comparison to axillary dissection. [12 32] Not only is the actual dissection, and with that the damage to lymphatic and blood vessel, smaller with dissection of one sentinel node, it also prevents in many cases the need for a larger dissection. Interesting to note is that a recent RCT showed that concurrent axillairy dissection, when needed after sentinel node biopsy, is better to be carried out in a secondary procedure. Patients who

underwent concurrent axillary dissection in the same operation as the sentinel lymph node biopsy had significantly more seroma formation in comparison to patients who underwent two separate procedures.[33]

The choice of instruments with which surgery is performed has also been shown to influence seroma formation. Electrocautery for haemostasis is the preferred method due to decreased operating time and reduced blood loss. It has however been linked with significantly more seroma formation when compared to knife dissection. [34 35 36 37 38]Other techniques include argon diathermy, laser scalpel and ultrasonic tools. All of the aforementioned show equal amounts of seroma formation when compared with knife dissection, yet every technique reports better haemostasis. [23 39 40 41 42 43 44 45 46 47] A recent prospective study which used the electrothermal bipolar vessel sealing system showed promising result. 60 patients with locally advanced breast cancer (T2 or T3) were treated by modified radical mastectomy with axillary dissection. All operations were carried out by the same surgical team using the electrothermal bipolar vessel sealing system. No seroma formation was found in 60 patients with haemostasis reported equal to electrocautery.[48]

Preventive measures

Suction drains, first described in 1947, have brought forth many an article.[49] When compared to no drain usage suction drainage resulted in significantly lower seroma formation.[50 51 52 53] The negative pressure applied by the drain is thought to obliterate the dead space left after excision, thus facilitating skin flap apposition and enforcing wound healing. Negative pressure is also thought to reduce wound dehiscence, necrosis, wound infection and seroma formation.[54 55 56 57 58] Whether this negative pressure is applied by a single drain or multiple drains at several locations does not seem to affect seroma formation.[26 59 60] The amount of suction, high or low pressure and active or passive suction, used by the drain is also of no consequence on seroma formation.[61 62 63 64 65 66 67] With respect to the type of drain used, a flat type drain with multiple channels has been show to correlate with lower seroma formation. [27 57] The duration of drainage is also subject to discussion. It has been shown that 74% of total seroma formation is drained in the first 48 hours postoperative. [68] Recent studies have shown that volume drained in the first 48 hours predicts seroma formation. [69 70 71] However studies comparing removal after max 3 days postoperative, with removal ranging form 6 until 16 days postoperative, have not been associated with significant decrease of seroma formation.[45 47 72 73 74 75 76 77 78 79 80]. No significant seroma increase has been correlated to leaving the hospital with a drain in situ.[81 82 83 84 85 86 87]

Shoulder immobilisation has been thought to decrease seroma formation. Multiple studies however have shown that immobilisation of the shoulder does not correlate with a decrease in seroma formation. [8 88 89 90 91 92] Active shoulder exercise however, such as physiotherapy, has been linked with decreased seroma formation when the exercise was postponed until at least one week after surgery.[93 94 95 96 97]

External compression dressings in the axilla have claimed to reduce the dead space created after surgery. Nevertheless studies have shown that they do not reduce seroma formation. The idea of axillary padding in the reduction of seroma formation has long been forfeited. [98 99]

Surgical prevention

Due to the lack of fibrinogen found in aspirated serous fluid, the hypothesis was raised that fibrin enriched fluid could decrease seroma formation. [6 100] Although a few small studies have shown promising result, [101 102 103 104 105] a multitude of large trials report that fibrin glue does not reduce seroma formation. [11 106 107 108 109 110 111 112 113 114] Recent trials, though

limited in patient numbers, show reduced seroma formation however no differences are observed. [103] [115] [116] A recent trial using fibrin glue also did not show a decrease in seroma formation; however it did show significantly reduced drainage duration and overall drain output. [117]

Another investigated chemical means for obliterating dead space has been tetracycline sclerotherapy. Although successful in decreasing seroma formation the process proved too painful for patients to endure, while another study showed a high rate of infection. [118] [119] [120] [121] [122]

The secretion suppressing qualities of octreotide have led to its study in the decrease of seroma formation. A large randomized controlled trial showed a significant decrease in seroma formation after surgery in comparison to controls. [123] [124] [125]

The dead space left after surgery seems to be one of the key factors in the formation of seroma. Research has gone toward obliterating dead space, not only by chemical means but also by using a mechanical way. [1] [126] [127] Flap fixation to reduce dead space has been performed in many different places: axilla, skin edge, in the line of wound closure and at the site of flaps. [46] [128] [129] [130] Many different techniques and materials were used in the fixation: skin to fascia, mattress type sutures, through the skin sutures, subcutaneous sutures, sutures approximating the axillary aponeurosis to proximate muscle, flaps to underlying muscle and buttress sutures. These sutures were made using surgical silk, fine cotton thread and absorbable thread. [9] [14] [131] [132] These techniques were carried out after various forms of breast cancer surgery: breast conserving therapy, radical and extended mastectectomy and functional axillary lymphadenctomy. [3] [19] [133] All of the used techniques showed a significant decrease in seroma formation. Interesting to note is that two recent studies showed that after flap fixation there was no need for suction drainage. No increase in seroma formation was found after flap fixation without drain when compared to drain usage. [55] [134] While cosmetic appearance after fixation was reported to be satisfactory, the downside of fixation can be found in increased operating time required. Increases have been reported up to 20 minutes. [20] [46] [135] [136]

Discussion

Seroma formation is the most common complication after breast cancer surgery. With an incidence of up to 90 percent seroma formation is a common problem. Left untreated it can lead to delayed wound healing, pain, skin necrosis and infection. This literature research has not found a single way to prevent seroma formation; however there are many proven methods to significantly reduce seroma formation.

Several factors have been linked to seroma formation. The dissection creates a large dead space with skin flaps in different layers and damage to lymphatic and blood vessels. The spilled fluids, which leak trough the damaged lymphatic and blood vessels as patients resume their daily routine, is collected in the dead space area. The skin flaps, which already had a hard time adhering to the irregular underlying tissue, are further hindered by this accumulation of fluid leading to secondary wound union. Seroma is maintained through this secondary wound union as the space where this fluid accumulates is not reduced rapidly enough.

Every woman undergoing breast cancer surgery is at risk for creating seroma yet it has been demonstrated that some factors correlate with an increase of aforementioned risk. Increased bodyweight and hypertension have shown to be significant influencing factors for seroma formation. Not all risk factors however are patient related, the type of surgery corresponds with seroma formation; the more extensive the dissection the more blood and lymphatic vessels will be damaged, resulting in increased seroma formation. Aside form the type of surgery the tools with which to perform said operation have also been show to alter seroma

formation. Though electrocautery provides an excellent means for haemostasis, it also significantly increases seroma formation. At present there are other techniques available, argon diathermy, laser scalpel, ultrasonic tools and bipolar, which show better haemostasis compared to knife dissection, with significantly lower seroma rates. The type of dissection to be carried out is linked to the stage of disease, however the tools with which to operate can be chosen.

At present no means to prevent seroma is readily available, yet ways for reducing seroma formation are widely available. Suction drainage, thought to reduce dead space trough negative pressure, significantly lowers seroma formation after surgery. A single flat type drain with multiple channels used for 48 hours produces the best results. Though 48 hours in hospital stay is irregular after breast cancer surgery, patients can also be discharged with drain in situ as this did not increase seroma rates. Use of the arm at the affected site has been linked to seroma formation since it pressures lymph and blood towards the damaged lymph and blood vessels. Restricting the use of aforementioned arm however has not decreased seroma formation, yet has led to disability of the shoulder. No immediate physiotherapy correlated with decreased seroma rates. Therefore patients should be encouraged to use their arm in normal routines; physiotherapy on the other hand should be started at least one week after surgery. Compression dressings, which were thought to decrease dead space extracorporeal, have been demonstrated to cause no effect on seroma formation.

The reduction of dead space after surgery can be achieved through chemical and mechanical means. The chemical way, through either fibrin enriched fluid tetracycline or octreotide, shows promise of reducing seroma formation yet it has its shortcomings. Fibrin enriched compounds have shown seroma reduction in smaller studies but in large randomized trials effect seems to be missing. Tetracycline showed significant seroma reduction yet the present method of administering proved too painful. Octreotide, a secretion suppressing compound equal to somatostatine, showed significant seroma reduction. At present however this was only shown in one study. Mechanical means of reducing seroma through minimizing dead space have proven to be very successful. All of the different methods, using different materials after different kind of operations, show significantly lower seroma rates. While cosmetic results have been reported to be acceptable there is a cost however: operating time is increased by as much as 20 minutes.

With incidence as high as 90% seroma is a given for these patients. There are however measures that can be taken significantly reduce seroma, through good use of drains and mechanical dead space closure as well as other means such as delaying physiotherapy. At present we recommend, especially in patients with increased risk factors, to utilize a combination of proven seroma reducing measures. Future research concerning decreasing seroma should be directed towards the reduction of seroma formation through the combined use of proven seroma reduction methods.

Conflict of interest

There are no conflicts of interest.

Table 1 Risk factors per level of evidence

Grade		***Direction of association***	
	Increase	No association	Decrease
Level 1	none	none	none
Level 2	Body weight extended radical mastectomy	Duration of drainage Immobilization of the shoulder LN status Intensity of negative suction Use of fybrinolysis inhibitor Number of LN's	Sentinel LN biopsy Suction drainage Octreotide use
Level 3	Hypertension Multiple holes type drains No drainage Operation time Use of electrocautery	Use of adhesive glue Use of laser scalpel Use of argon diathermy Use of pressure garment Breast size Diabetes mellitus Smoking Neoadjuvant therapy	Suture fixation techniques Use of ultrasonic scissors Use of electrothermal bipolar vessel system Extent of dissection Postponed active shoulder exercise Tetracycline sclerotherapy
Level 4	none	Age Tumor Size Total drainage volume	none

Table 2 Randomized controlled trials

Dead space reduction through fixation

Year	Author	n	Intervention	Incidence of seroma%
1990	Hamy	53	Surgical wadding vs none	27 vs 80
1993	Coveney	40	Suture fixation vs none	25 vs 85
2002	Purushotham	375	Suture fixation without drain vs conventional surgery	47 vs 51

Suction drainage

Year	Author	n	Intervention	Incidence of seroma %
1973	Morris	53	suction drainage vs static drainage	12 vs 29
1979	Britton	46	high vacuum vs low vacuum drainage	not significant
1988	Cameron	40	drain vs no drain	10 vs 15
1991	Inwang	84	drain removal at 5th vs < 20 ml	49 vs 28
1992	Petrek	65	single vs multiple drains	not significant
1992	Somers	227	suction drain vs no drain	73,1 vs 89,1
1992	Terrel	84	axillary drainage vs axillary and pectoral drainage	19 vs 13
1992	Parikh	100	drain removal at 3d vs 6th POD	not significant
1995	Heurn	78	low versus high vacuum drainage	30 vs 42
1997	Ackroyd	120	drain removal at 5th vs < 30 ml	29 vs 25
1998	Zavotsky	46	suction drain vs no drain	8,3 vs 50
1999	Kopelman	90	drain removel 3d POD vs < 35 ml	21 vs 2
2001	Gupta	121	drain removal 5th vs 8th POD	48 vs 28
2003	Puttawibul	60	axillair drainage vs axillairy and pectoral drainage	20 vs 37
2004	Dalberg	250	drain removal at first POD vs < 40 ml	48,5 vs 22,2
2005	Soon	87	drain vs no drain	94 vs 96
2005	Chintamami	85	half versus full vacuum drainage	2,8 vs 4
2005	Baas-Vrancken	100	short versus long term postoperative drainage	76 vs 64

Shoulder immobilisation

Year	Author	n	Intervention	Incidence of seroma %
1979	Flew	64	7 days immobilisation vs excercise starting 2d POD	7 vs 20
1990	Petrek	57	mobilization from 2nd POD vs 5th POD	not significant
1990	Janssen	144	excercise from 1st POD vs 8 days of immobilization	not significant
1996	Browse	67	10 days immobilization vs none	31 vs 43
1998	Abe	116	mobilization from 1st POD vs 7th pod	significant

Shoulder excercise

Year	Author	n	Intervention	Incidence of seroma %
1997	Schultz	163	shoulder excercise form 1st POD vs 7th POD	38 vs 22
2005	Shamley	444	Delayed vs early shoulder excercise	27 vs 46

Compression dressing

Year	Author	n	Intervention	Incidence of seroma %
1998	Chen	40	14 days compression dressing vs none	0 vs 4,8
1999	O'hea	135	Compression dressing vs conventional dressing	2,9 vs 1,8

Fibrin glue

Year	Author	n	Intervention	Incidence of seroma %
1993	Uden	53	fibrin glue vs none	64 vs 53
1995	Vaxman	40	fibrin glue vs none	20 vs 5
1998	Gilly	108	fibrin glue vs none	2 vs 1.7
2000	Dinsmore	27	fibrin glue vs none	43 vs 23
2001	Moore	79	fibrin glue vs none	16 vs 29
2001	Berger	60	fibrin glue vs none	39 vs 42
2003	Ulusoy	54	fibrin glue vs none	18 vs 11
2003	Langer	55	fibrin glue vs none	4 vs 3
2004	Jain	116	fibrin glue vs none	38 vs 26
2004	Mustonen	40	fibrin glue and fibrinolysis inhibitor vs none	not significant
2005	Johnson	82	fibrin glue without drainage vs drainage	36,8 vs 45,5

Octreotide

Year	Author	n	Intervention	Incidence of seroma %
2003	Carcoforo	261	octreotide subcutaneously vs none	significant

Tetracycline

Year	Author	n	Intervention	Incidence of seroma %
2000	Rice	62	tetracycline vs none	53 vs 22

Bovin thrombine

Year	Author	n	Intervention	Incidence of seroma %
1997	Burak	101	bovine thrombin vs none	37 vs 40

Surgical prevention

Year	Author	n	Intervention	Incidence of seroma %
1993	Wyman	40	laser scalpel vs scalpel	50 vs 55
1996	Kerin	50	aron diathermy vs scalpel	12 vs 17
1998	Porter	80	electrocautery vs scalpel	38 vs 13
2004	Lumachi	92	ultrasound scissors vs scissors and ligation	20 vs 40
2005	Purushotham	298	SLND vs ALND	11 vs 24
2006	Mandar	160	electrocautery vs scalpel	88,3 vs 82,2

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