Seroma Formation Following Breast Surgery – Incidence and Risk Factors

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ABSTRACT

Background

Seroma is perhaps the most common complications following breast surgery, with reported incidences as high as 85%. Even though it is such a common condition, its pathogenesis and risk factors are not well defined.

Objective

This study is set out to determine the incidence of seroma formation following simple mastectomy (SM), modified radical mastectomy (MRM) and axillary dissection (AD) on the University Hospital of Örebro; study the effect of age, prophylactic antibiotics, type of surgery, diabetes mellitus, smoking habits, bodyweight, postoperative infection and previous ipsilateral breast surgery on the incidence of seroma.

Method

150 patients, who underwent breast surgery at the University Hospital of Örebro, were included in this observational study. Their charts were studied in order to extract the clinical information. Binary logistic regression and Chi-2 test was used to determine the statistical significance.

Results

The incidence of seroma following breast surgery was 49% (74/150 patients). A statistically significant association was found between seroma formation and MRM (OR = 4,4, p = 0,009) as well as AD (OR = 0,36, p = 0,031). None of the other studied factors were found to significantly effect the incidence of seroma.

Conclusion

This study found that the incidence of seroma following breast surgery is 49% and that the type of surgery effects the incidence of seroma formation. MRM predisposes for seroma formation while AD reduces the risk.
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1 BACKGROUND

1.1 BREAST CARCINOMA

1.1.1 Epidemiology of Breast Carcinoma
Carcinoma of the breast is one of the most common forms of cancer in the population. Both men and women are effected, however women outnumber the men by far. In 2011 the prevalence of breast cancer in Sweden was 366 (men) and 94406 (women), at the same time the incidence of breast cancer in women was 176,8/100 000 [1]. By the year of 2014 the incidence of breast cancer in Sweden was 200/100 000 [2]. Breast cancer is commonly treated with surgery.

1.1.2 Etiology/pathogenesis of Breast Carcinoma
Carcinoma of the breast is a disease of multifactorial origin where heritage, hormonal influence on the mammary glands and lifestyle factors all contribute to the development. There are several established risk factors: early onset puberty, Hormone Replacement Therapy, alcohol and late onset menopause. In 5-10% of all breast cancers, heritage is the major etiological factor where BRCA1 and BRCA2 are common risk genes. Together inherited abnormalities in BRCA1 and BRCA2 are found in 2,5-5% of all breast cancers. [1]

Carcinoma of the breast arises from accumulation of mutations in the genome and follow a progression from precursor lesion to invasive cancer. The precursor lesions, Ductal Carcinoma in situ (DCIS) and Lobular Carcinoma in situ (LCIS). They both arise from the terminal ductal units and is confined within the basement membrane. LCIS is differentiated from DCIS by the discohesive growth, usually caused by a loss of E-cadherin. The invasive cancers are then categorized into special histologic subtypes (one third of the breast cancers) and the remaining are clumped together and called ductal of no special type (NST). However, the molecular characteristics of the tumor is of more clinical relevance. [3]

There are four molecular subtypes of breast cancer. They are luminal A, luminal B, HER2 and basal-like breast cancers. The luminal breast cancers are characterized by a high expression of hormone receptors (ER and PR). Luminal B is then separated from luminal A by the expression of HER2 and/or Ki67. Both luminal A and B constitutes roughly 70% of invasive breast carcinomas. HER2 is characterized by a high expression of HER2 and a rather low
expression of ER, PR and its associated genes. The HER2 subtype constitutes about 15% of invasive breast cancers and is likely to be high grade and node positive. On the other hand, the basal-like subtype is characterized by a high expression of basal epithelial genes and a low expression of ER and its associated genes as well as a low expression of HER2 and its associated genes. The basal type constitutes the last 15% of invasive breast cancers and is associated with the loss of function in BRCA1 and the cells are generally triple negative (ER, PR and HER2 negative). [4,5]

The molecular characteristics is of clinical significance in determining the treatment. For example, a HER2+ tumor is going to respond well to Herceptin-treatment whereas a HER2- would not. [4]

1.2 SURGICAL METHODS

1.2.1 Definition of Methods

Axillary dissection (AD) is the procedure where the axilla is opened in order to identify, examine or remove lymph nodes. [6] It is recommended to remove at least 10 lymph nodes.

Simple mastectomy (SM) is the removal of breast tissue only. Muscle tissue and lymph nodes are spared in this procedure. [7]

Modified radical mastectomy (MRM) is the removal of breast tissue and most of the axillary lymph nodes. However, the pectoralis major is spared. [8]

Generally, the size of the tumor is the determining factor when it comes to deciding upon a surgical method. Breast conservative surgery (partial mastectomy) is ruled out when the tumor is 4 cm or larger at its widest point of measure or when the ratio of the tumor size and breast size is so that an esthetical result is unattainable. Instead, mastectomy is chosen in those cases. Clearance of the axilla is performed if involvement of the sentinel node or other axillary lymph nodes is found either prior to surgery or after analysis of the sentinel node. [5,9]

Following the breast surgery, on the Department of Surgery at the University Hospital of Örebro, a drain is then put into place. It is removed when the volume drained no longer exceeds 100ml per 24 hours.
1.2.2 History of Breast Surgery
According to a review article by Cotlar et al, breast cancer surgery has seen a shift from a more radical approach to a more conservative one. Instead of a more routine use of modified radical mastectomy the current trend is to try to minimize the wound by performing more limited surgery. [10] This has resulted in the removal of the Sentinel node, which is the first lymph node and station the breast cancer is spread to.

1.3 Prophylactic Antibiotics
Before the year of 2012, the Department of Surgery in the University Hospital of Örebro, Sweden performed breast cancer surgery without prophylactic antibiotics. In 2012, breast cancer surgery patients started to routinely receive prophylactic antibiotics. The decision was based on SBUs report from 2010 which dictates that use of prophylactic antibiotics is indicated in breast cancer surgery but that no one antibiotic seems better than another. The antibiotic of choice on the University Hospital of Örebro is one peroral dose of Eusaprim Forte 160 mg/800 mg. Which was chosen after consideration of the pattern of resistance in Örebro. Eusaprim Forte has a similar spectrum to that of cephalosporins, which were avoided to not further breed ESBL-resistance. [11] The most common bacterial etiologies in postoperative breast infections are Staphylococcus Aureus and Escherichia Coli. [12]

1.4 Seroma

1.4.1 Epidemiology of Seroma
Seroma is the most common complication following breast surgery. [13] On the other hand, the reported range of incidence is widely scattered varying from 2 %- 85 %. [14-23] There are several possible explanations for the discrepancy in reported incidence. One of them is the use of different definitions of seroma in the studies. For example, seroma might be defined as an accumulation of liquids that is palpable; in the need of aspiration; or resulting in a minimum volume aspirated. [18]

1.4.2 Pathogenesis of Seroma
Although seroma is one of the most common complications following breast cancer surgery its pathogenesis remains inconclusive. There are several hypotheses, all with some support. One of the most mentioned hypotheses and perhaps the most accepted one is that surgery disrupts lymphatic channels which results in buildup of liquid, that is seroma. This hypothesis is backed up by studies in which the drained liquid was analyzed and compared to lymph.
On the other hand, there are studies that demonstrate an incongruity between lymph and seroma fluid. Analysis of the seroma fluid in other studies demonstrate lack of fibrinogen as well as protein, granulocyte and monocyte levels that are too high to be consistent with lymph and instead indicates that seromas could be the result of inflammatory exudates. There are also findings of increased levels of VEGF and decreased levels of endostatin in seroma fluid which could point to the conclusion that seroma could be the results of a physiological response in wound healing.

1.4.3 Risk Factors for Development of Seroma

Several etiological factors have been studied when it comes to seroma formation but many results are non-significant or have not been consistent in consequent studies.

Many surgical techniques and variables have been studied in order to determine any association to the formation of seroma. Ligation of lymph vessels and sealing of the dead space results in a significant reduction of seroma formation following MRM. Two other studies found that quilting (that is closing of the dead space) resulted in a decrease in seroma incidence from 78% and 80%, respectively, down to 20%. Axillary exclusion, which is the segregation of the axillary wound cavity from the mammary wound cavity through stitches, is another surgical technique that results in reduced incidence in seroma formation. The use of fibrin glue is another method that has been attempted in order to close the wound cavity in order to reduce seroma formation. One study demonstrated a non-significant improvement from an incidence of 20% to 3% using fibrin glue. To conclude, the size of the dead space does seem to correlate with increasing risk for seroma formation.

Different types of breast surgery appear to be differently associated with formation of seroma. Conservative breast surgery seems less likely to cause seroma compared to radical surgery. Another study however, found that AD resulted in a higher incidence of seromas than MRM.

The skill of the surgeon is factor that further effect the incidence. A variation in incidence rate between surgeons of 9%-47% has been reported. Also, the duration of the breast surgery is associated with incidence of seroma formation, an increase of 10 minutes on the duration correlates with a 30% increase in risk.

Sometimes, preoperative chemotherapy is used in order to reduce the size and extent of the cancer tumor before further treatment, in this case surgery. Preoperative chemotherapy could
be linked with an increase in seroma formation, although the results were not statistically significant. [17,21]

The linkage between lifestyle factors such as age, bodyweight, diabetes and smoking is rather inadequate. There are several studies that have looked at these factors but the results are either non-significant or contradicting. The search yielded six studies looking at the patients’ age in association to seroma formation. Three of those did not find any significant connection between age and seroma [17,20,21] but the other three found an association between increased age and seroma formation [25,30,31]. Three studies found an association between increased bodyweight and increased incidence of seroma [30,32,33] while a fourth study could not identify any association [20]. Diabetes mellitus has not been shown to correlate with any change in incidence of seroma formation. [20,32,34] Smoking, neither, has any significant association with the development of seroma. [32,34]

1.4.4 Complications Following Seroma
Although seroma itself is a complication following breast surgery it can also give rise to other complications. First and foremost, seromas can make the patient worried and uncomfortable. Secondly, seroma can lead to elevation of the wound flaps which in turn can disturb the wound healing. This can result in rupture of the wound, flap necrosis, infection, hematoma, delayed healing, prolonged hospital stay, delayed start of further treatment and delayed rehabilitation. [13,14] The connection between seroma and postoperative infection is unclear however. [22]

1.5 The Aim of This Study
This study will investigate the incidence of seroma following simple mastectomy (SM), modified radical mastectomy (MRM) or axillary dissection (AD) performed on the Department of Surgery on the University Hospital of Örebro. It will also investigate whether prophylactic antibiotics, the patients’ age, diabetes mellitus, smoking habits, bodyweight, postoperative infection, previous breast surgery or preoperative chemotherapy has any effect on the incidence of seroma.
2 MATERIAL AND METHODS

2.1 STUDY DESIGN
This is a retrospective cohort study investigating patients who underwent simple mastectomy (SM), modified radical mastectomy (MRM) or axillary dissection (AD) in 2011 and 2014 at the University Hospital of Örebro. In 2012 the Department of Surgery in Örebro changed their routine concerning administration of preoperative prophylactic antibiotics. Therefore, the patients who underwent surgery in 2014 received prophylactic antibiotics, namely Eusaprim Forte, while the patients in 2011 did not. The patient’s journals were studied for data on age, surgical procedure, postoperative seroma formation, number of aspirations, BMI, diabetes mellitus, smoking habits, preoperative chemotherapy, postoperative infection and previous breast surgery on the ipsilateral side.

2.2 SUBJECTS
A total of 150 patients were studied, 75 operated in 2011 and 75 operated in 2014. The inclusion criteria were that the patient underwent either SM, MRM or AD and the use of prophylactic antibiotics (2014) or the lack of use (2011). The first 75 patients operated on in each year that fulfilled those criteria were included in the study and their journals were further studied. The patient’s chart was studied for at least 30 days postoperative and even further, if any presence or suspicion of seroma formation. The studying of the charts was terminated if the patient underwent a second surgery in the operated area.

2.3 OUTCOME
Seroma, in this study, was defined as a postoperative accumulation of liquid either requiring aspiration or simply documented as a seroma by the doctor in charge of the follow up.

Data concerning smoking habits were interpreted such as if it was not documented that the patient smoked, the patient is assumed to not be smoking. If the patient smoked previously but now had stopped, it counts as no smoking.

Postoperative infection was defined by either one of two criteria. First, the patient had an infection affirmed by microbiological cultivation. Secondly, the patient was prescribed antibiotics with the intention to treat. If the patient was prescribed antibiotics as prophylaxis in order to prevent the development of an infection, it was not included in this study.
Previous breast surgery was defined as the patient having any history of previous surgery in the mammillary or axillary region on the ipsilateral side as the surgery that was studied in this report.

2.4 **Statistics**
The data was collected in Microsoft Excel 2013. Since the variables was constituted by one dependent as well as binary variable and multiple independent variables the software SPSS Statistics was used to run Binary Logistic Regression. Due to multicollinearity, AD, was excluded from the regression and instead a Chi-2 test was used. AD was excluded due to being the surgery least frequently performed in this project, thus having the smallest sample size. Results were deemed statistically significant when reaching a probability of 0,05 or lower.

2.5 **Ethics**
This study is a student project performed on the Department of Surgery at the University Hospital of Örebro and therefore no ethical approval was needed. Apart from that, the study was indeed performed on uninformed patients. However, all the data was handled anonymously and no information from any specific patient will be presented in this report.

3 **Results**

3.1 **Group Characteristics**
Data on patients’ BMI were lacking in many charts, not even half of the studied patients had data on BMI recorded. Therefore, the BMI variable was excluded from this study.

The total number of patients investigated was 150 ranging from 24-93 years of age with a mean age of 64.5 years, a median age of 64 years and a standard deviation of 14.7 years. Further group characteristics can be found in Table 1.

*Table 1. Group characteristics of studied patients.*

<table>
<thead>
<tr>
<th></th>
<th>Seroma</th>
<th>Non Seroma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>74</td>
<td>76</td>
<td>150</td>
</tr>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>64.9 (30-92)</td>
<td>64.1 (24-93)</td>
<td>64.5 (24-93)</td>
</tr>
<tr>
<td><strong>Prophylactic antibiotics</strong></td>
<td>40</td>
<td>35</td>
<td>75</td>
</tr>
</tbody>
</table>
3.2 Incidence of Post-Operative Seromas

A total of 74 patients went on to develop postoperative seromas, see Table 1. Thus the incidence of seroma formation following breast surgery is 49.3% (74/150) at the University Hospital of Örebro. Of the patients who developed seromas, 8% required no aspiration; 34% required a single aspiration; 45% required 2-5 aspirations and 13% required more than 5 aspirations.

*Table 2. Number of aspirations before resolution of the seroma.*

<table>
<thead>
<tr>
<th>Number of Aspirations</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>2 to 5</td>
<td>33</td>
</tr>
<tr>
<td>&gt;5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
</tr>
</tbody>
</table>

3.3 Risk Factors for Development of Seroma

Because of multicollinearity between SM, MRM and AD, AD was excluded from the regression and instead analyzed separately using the Chi-2 test.
Table 3. Odds Ratio, Confidence Interval and p-value for the surgical methods.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>0.36</td>
<td>0.14 to 0.94</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Table 4. Results of the Logistic Regression.

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95 % CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.001</td>
<td>0.98 - 1.02</td>
<td>0.93</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1.3</td>
<td>0.62 - 2.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>0.26 - 3.1</td>
<td>0.87</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.1</td>
<td>0.30 - 4.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Infection</td>
<td>3.4</td>
<td>0.94 - 12.3</td>
<td>0.061</td>
</tr>
<tr>
<td>PrevSurgery</td>
<td>1.3</td>
<td>0.55 - 2.9</td>
<td>0.59</td>
</tr>
<tr>
<td>PreopChemo</td>
<td>1.2</td>
<td>0.30 - 4.9</td>
<td>0.78</td>
</tr>
<tr>
<td>SM</td>
<td>2.7</td>
<td>0.84 - 8.4</td>
<td>0.095</td>
</tr>
<tr>
<td>MRM</td>
<td>4.4</td>
<td>1.4 - 13.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Constant</td>
<td>0.24</td>
<td></td>
<td>0.11</td>
</tr>
</tbody>
</table>

As is evident in Table 3 and Table 4, the only statistically significant variables are MRM and AD. The odds ratio for MRM equals 4.4 (95% CI 1.4 to 13.5), p = 0.009 and the odds ratio of AD equals 0.36 (95% CI 0.14 to 0.94), p = 0.031.

4 DISCUSSION

The aim of this study was to identify the incidence of seroma formation following breast surgery performed on the Department of Surgery on the University Hospital of Örebro. It was also to determine if any of the studied potential risk factors correlates with seroma formation in any way. Lastly, the background summarizes the current knowledge on seroma formation and related risk factors.

A total of 150 patients were retrospectively studied accordingly to the criteria previously mentioned. BMI as a variable was excluded due to lack of documentation. The other data was analyzed using a binary logistic regression. However, due to multicollinearity AD was excluded from the model and a Chi-2 test was used to determine a p-value.
The incidence of seroma formation was found to be 49%. This is within the range of previously reported incidences of seroma formation. [20-33] The reported range fluctuates heavily, which is probably partly explained by the definition of seroma and the diagnostic tools used. [18] Also, it is plausible that varying skills of the surgeons in minimizing the dead space and the duration of surgery could explain part of the difference in seroma incidences.

This study failed to identify any significant correlation between age and seroma formation. This appears to be in line with the previous research results which in 3 out of 6 studies indicate an increased risk of seroma formation with increased age whereas in the other 3 studies no significant correlation was found. [17,20,21,25,30,31]

No studies were found on the effect of prophylactic antibiotics on seroma formation. This study cannot find any significant correlation between prophylactic antibiotics and seroma formation.

In accordance with other research, the effect of diabetes mellitus on the development of seroma was not found to be statistically significant OR = 0,90 (CI 95% 0,26 to 3,1), p = 0,87. [20,32,34] By the same token, the effects of smoking were not statistically significant OR = 1,1 (CI 95% 0,30 to 4,3), p = 0,85. This also aligns with the previous research. [32,34]

Prevalence of postoperative infections might, according to the findings in this study, be related with an increase in seroma formation. 67% of the patients who developed postoperative infections also developed seromas, OR = 3,4 (CI 95% 0,94 to 12,3), p = 0,061. Although the results are not statistically significant there is certainly a trend for a positive association. This also reflects the prevailing information. [13,14]

The choice to study the effect of previous ipsilateral breast surgery on the incidence of seroma formation was made because of the prevailing idea that seroma results from damaged lymphatic vessels. A previous breast surgery might have had an impact on the integrity of the axillary lymphatic vessels and might therefore also have an effect on seroma formation. However, the results do not indicate any association between the two.

Preoperative chemotherapy’s effect on seroma development have been investigated previously, indicating a slightly increased albeit non-significant risk for seroma formation. [21] The results in this study are along the same line, OR = 1,2 (CI 95% 0,30 to 4,9), p = 0,78.

The type of surgery that the patient was subjected to does seem to affect the extent by which seroma formation occurs. No significant association could be found between SM and seroma formation.
formation. However, MRM does seem to significantly increase the incidence of seroma OR = 4.4 (CI 95% 1.4 to 13.5), p = 0.009. At the same time, AD does seem to significantly reduce the incidence of seroma OR = 0.36 (CI 95% 0.14 to 0.94), p = 0.031. Just like most of the previous research this indicates that the more tissue sparing surgery leads to the least seroma formation. [17,18,21] If one prescribes to the idea that seromas develop because of wounded lymphatics that leak lymph into the wound cavity then these results does make sense. The more conservative surgery does create the smallest wound and therefore the potential to disrupt lymphatics should be lower. This idea is in congruence with the results indicating that a larger incision and wound cavity correlates with an increase in seroma incidence. [15,17] This could also be a factor, along with the duration of the surgery, in the discrepancy in seroma formation between surgeons. [20,23] It is possible that the size of the incision or the size of the dead space varies among surgeons.

However, the pathogenesis of seroma is debated and there is currently no uniform model to explain seroma formation. It is proposed that seroma formation is either the byproduct of surgically disrupted lymphatics [15,24]or an inflammatory response in wound healing [15,25,26]. It might be possible that seroma is a phenomenon of multiple origin and not a single entity. After all, a seroma is only an accumulation of liquids of which the characteristics or origin is not specified. Part of all seromas could occur through disruption of axillary lymphatics. Whereas, some seromas occur because of inflammatory exudates which is part of the body’s healing mechanism and other seromas might develop because of other mechanisms. This might also explain why similarly performed studies sometimes demonstrates contraindicating results, the subtype of seromas might not have been equally represented.

The study is limited in its sample size and in order to acquire statistical significance more patients would have to be studied. Also, the documentation in the patients’ charts is of varying detail. This might have led to missed cases of infection, smoking, BMI et cetera, which then could have altered the outcome of this study. When it comes to BMI it was evident that the charts were lacking since a BMI was retrievable for only 69 out of 150 patients. Further, the statistical analysis is slightly unsatisfying because of the multicollinearity which forced the exclusion of AD from the regression. AD was therefore analyzed independently with the Chi-2 test and is therefore slightly vulnerable for confounding.
5 CONCLUSION

The results in this study determines that the incidence of seroma after breast surgery is 49% at the University Hospital of Örebro. Further, the type of breast surgery has an effect on the incidence of seroma, with MRM increasing the risk and AD reducing it. Regarding the other risk factors studied, no statistical significance was found. Therefore, more extensive studies regarding these potential risk factors are needed.

6 ACKNOWLEDGEMENT

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