Cyanoacrylate Adhesive Reduces Seroma Production After Modified Radical Mastectomy or Quadrantectomy With Lymph Node Dissection—A Prospective Randomized Clinical Trial

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Abstract

The accumulation of fluid, a seroma, is a frequent complication of breast surgery. The present study examined the use of a cyanoacrylate adhesive, which was applied at the operative field after removal of the breast and lymph nodes. The results showed that seroma production was significantly less with cyanoacrylate adhesive. Thus, cyanoacrylate adhesive can contribute to the reduction of seromas after mastectomy and decrease the duration of postoperative drainage.

Introduction: The accumulation of fluid, a seroma, is a frequent complication after modified radical mastectomy or quadrantectomy with lymph node dissection. The aim of the present study was to examine whether a new adhesive material made of cyanoacrylate can effectively provide a sealing coat to tissues and thus reduce the incidence of seroma significantly. Patients and Methods: The present prospective, randomized case-control study included 128 women with a breast cancer diagnosis and scheduled for modified radical mastectomy or quadrantectomy with lymph node dissection in Thessaloniki, Greece. In 64 patients (cases), a cyanoacrylate adhesive was applied at the operative field after removal of the tumor and lymph nodes; the remaining 64 patients served as the controls. Results: Seroma production ($P = .001$), drainage duration ($P = .001$), and drainage amount ($P = .001$) were all significantly less for cases than for controls. The results from a stepwise multiple regression model incorporating the use of adhesive, body mass index, tumor size, and number of infiltrated lymph nodes were significant and able to explain 51.6% of the variability in seroma amount. Conclusion: The results of our study have demonstrated that the cyanoacrylate adhesive can contribute to the reduction of seromas produced after mastectomy and subsequently decrease the duration of postoperative drainage and the frequency of seroma aspirations. However, because the pathogenesis of seroma formation is multifaceted and complex, further research of larger sample sizes is required to confirm the results of our study.

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Introduction

A seroma is a fluid collection in the wound other than pus or blood. Seromas often develop after operations that involve elevation of skin flaps and transection of numerous lymphatic channels, including modified radical mastectomy and lumpectomy plus axillary lymph node dissection. Seromas delay healing and increase the
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risk of wound infection. Extensive research has been performed in the field of postoperative reduction of seroma. However, none of these studies revealed any effective method to decrease the incidence of seroma formation.

The aim of the present study was to explore the effectiveness of a novel material, the cyanoacrylate adhesive Glubran 2, to reduce postoperative fluid accumulation, or seroma formation, after modified radical mastectomy or quadrantectomy with lymph node dissection. The assumed mechanism of action was that the adhesive would create a sealing coating in the operative field to occlude lymphatic leaks and limit the accumulation of fluid (and, thus, seroma formation).

Patients and Methods

Study Population

The study population consisted of 128 women with a diagnosis of breast cancer who underwent scheduled modified radical mastectomy (62 patients) or quadrantectomy with lymph node dissection (66 patients) at AHEPA University Hospital (Thessaloniki, Greece). In 64 patients, a cyanoacrylate adhesive was used in the operative field after removal of the tumor and lymph nodes; the remaining 64 patients served as the controls. The mean ± standard deviation SD patient age was 61.50 ± 10.57 years, the average body mass index (BMI) was 30.20 ± 4.39 kg/m², and the average breast weight was 507.23 ± 369.85 g. The exclusion criteria were age <18 years, local recurrence of breast cancer, clinically nonpalpable axillary lymph nodes, a known allergy to the materials used, immunosuppression, neoadjuvant therapy, steroid treatment, clotting disorders, diabetes mellitus, cardiovascular disorders, a history of chest radiation, scheduled immediate breast reconstruction, and pregnancy or lactation. All participants signed an informed consent form, and the Hellenic National Bioethics Commission approved the present study.

Sample Size

The statistical power of the trial was defined at 80% (1 − β = 0.8) and statistical significance at α = 0.05. Using these parameters, the required sample size was calculated at 128 patients.

Cyanoacrylate Adhesive

The cyanoacrylate adhesive Glubran 2 has hemostatic and adhesive properties, and its administration, once solidified, provides an effective antiseptic barrier. It has a yellowish, transparent appearance. It rapidly polymerizes on contact with living tissue in liquid environments and forms a thin elastic membrane of high tensile strength, which guarantees the firm bonding of tissues. The membrane adapts seamlessly to the anatomy of the tissue and is waterproof and not affected by blood or other organic fluids. The polymerization time depends on the type of tissue in contact with the material, the amount and composition of fluids present, and the quantity of product applied. When applied correctly, solidification begins within 1 to 2 seconds, and the process concludes within 60 to 90 seconds, at which point it has obtained its maximum mechanical resistance. After solidification, it no longer retains adhesive properties; therefore, no possibility exists of further unwanted adhesions.

Procedure

The study used a randomized design with parallel groups. All surgical operations involved the same type of incision, with lymph node dissection performed at a standard level (levels I and II) using electrocautery. After surgical removal of the tumor and lymph nodes, the adhesive was placed in both operative fields (i.e., the region of the resected breast tumor and the axillary area).

All mastectomies were performed by the same team of surgeons, using principally identical methods. The entire field was checked to ensure that complete hemostasis had been achieved. Two large closed-suction drains were inserted through puncture wounds into the lower axilla. One catheter was brought across the thoracic wall from the puncture wound to the region of the resected breast tumor (drain A). The other catheter was placed in the axillary area, close to the axillary vein (drain B). The drainage tubes were not removed until the daily drainage had diminished to 30 mL/day. A bulky pressure dressing was applied at the end of the operation.

We measured the daily drainage amount of both drains and the quantity of serum underneath the skin flaps, which was aspirated with a sterile syringe and needle as needed, and the duration of drainage. In the case of quadrantectomy and lymph node dissection, the serum was aspirated either from beneath the skin flaps of the lumpectomy site or from the axillary area. The patients were not permitted to abduct the arm on the side of the operation for 5 to 7 days. The participants were discharged on postoperative day 5 ± 2, regardless of drainage tube removal and were routinely followed up on postoperative days 10 ± 1 and 15 ± 2.

Statistical Analysis

The program IBM SPSS Statistics, version 22, was used for the analysis, and the level of significance was set at P = 0.05. Descriptive statistics were calculated for all variables of interest. After using the Kolmogorov-Smirnov assessment for normality, all necessary analyses culminating in the creation of a stepwise multiple regression model were performed, including t tests, Mann-Whitney U tests, Spearman correlations, analyses of covariance, and Wald χ² tests. The assumptions tested before the creation of the model were those of homoscedasticity, lack of collinearity, no or little autocorrelation and outliers, and linear relationship among the variables.

Results

All patients enrolled completed the study. The somatometric data and operation characteristics per group are listed in Table 1. The drainage duration was significantly lower for the cases (2.51 ± 0.89 days) than for the controls (3.63 ± 1.62 days; U = 1231.5; P = .000). The amount of aspirated seroma was significantly less for the cases (155.77 ± 103.35 mL) than for the controls (457.81 ± 435.51 mL; U = 1180.5; P = .000). The formation of seromas was significantly lower for the cases (1298; P = .000). Age (r = 0.416; P = .000), BMI (r = 0.490; P = .000), breast weight (r = 0.362; P = .000), operative time (r = 0.379; P = .000), tumor size (r = 0.451; P = .000), and number of infiltrated lymph nodes (r = 0.304; P = .000) all correlated significantly with the amount of seroma fluid produced.
possibly, reoperations, which eventually increase the postoperative complications can lead to repeated visits to the surgeon and, formation of seromas.3-17 Seromas can develop in the dead space however, ridden with complications, with the most common the choice in most cases. Surgical intervention at the axillary region is, that forms under the skin the axillary region.14,18-24 It can predispose to surgical site infection, quadrantectomy with lymph node dissection2 are the methods of the treatment of the disease. Modiﬁed radical mastectomy and quadrantectomy with axillary dissection5-7 are the surgical techniques intended for dead space closure.31 However, it appears that although the use of these interventions can reduce the risk of seroma formation, all the methods described to date have signiﬁcant disadvantages, and none has proved sufﬁciently effective.32

The present study enrolled patients undergoing modiﬁed radical mastectomy or quadrantectomy and axillary dissection using a surgical cyanoacrylate adhesive. Analysis of our results showed that the amount and duration of drainage and the total amount of collected seroma ﬂuid (including aspirated seromas, when needed) were signiﬁcantly reduced in the cases compared with the controls. Speciﬁcally, seroma accumulation was reduced by 51.6% in the cases.

These ﬁndings can be explained because cyanoacrylate adhesive quickly polymerizes into a thin elastic ﬁlm with high tensile strength and tightly adheres to the tissue on which it has been applied. Consequently, the use of cyanoacrylate adhesive during mastectomy creates a strong sealing coating that can prevent seroma formation, either in the form of exudate from resected tissue or as lymph from transected lymphatic channels. Because of its properties, cyanoacrylate adhesive might have a longer and more permanent effect on tissues than the frequently used ﬁbrin glue.30 The systematic use of this tissue sealant can prevent several of the postoperative complications that result from the formation of seroma. Speciﬁcally, it signiﬁcantly reduces the number of postoperative visits, the requirement of reinsertion of new drainage tubes, and the necessity for repeat surgery.

Moreover, the signiﬁcantly reduced duration of drainage in the case group compared with the control group (2.51 vs. 3.63 days) contributed to a better quality of life postoperatively. It has been widely accepted that postoperative wound drainage has a substantial negative effect on patients’ well-being, restricting their normal daily activities, such as dressing, bathing, and sleeping and delaying their return to work.33

The results from the present study also revealed that a signiﬁcant correlation was present between the amount of seroma ﬂuid produced and the following variables: BMI, breast weight, tumor size, operative time, and number of inﬁltrated lymph nodes.

Extensive research has been performed to discover an effective method to reduce the postoperative accumulation of seroma ﬂuid. These methods include the use of ultrasonic shears,28 special stitches,29 ﬁbrin glue,30 ﬁbrin sealant, and bovine thrombin at some stage during lymphadenectomy and the use of different surgical techniques intended for dead space closure.31 However, it appears that although the use of these interventions can reduce the risk of seroma formation, all the methods described to date have signiﬁcant disadvantages, and none has proved sufﬁciently effective.32

A stepwise multiple regression model was applied to examine whether the use of cyanoacrylate adhesive, BMI, tumor size, and number of inﬁltrated lymph nodes could predict the amount of seroma ﬂuid produced postoperatively. The model results were statistically signiﬁcant [F(4,123) = 32.79; P = .000] and explained 51.6% of the seroma amount variability. All independent variables signiﬁcantly contributed to the model (P ≤ .001).

The accepted stepwise multiple regression equation was as follows: seroma amount = (9.04 \times \text{BMI}) + (42.82 \times \text{tumor size}) + (52.88 \times \text{use of adhesive}) + (4.60 \times \text{number of inﬁltrated lymph nodes}) − 353.37.

The variables examined but excluded from the model because they had no predictive value for seroma formation were age, operative time, resected breast weight, and number of lymph nodes removed. Figure 1 shows the relationships among the continuous variables used in the model, and Figure 2 demonstrates their differences with regard to the case and control groups.

### Discussion

Breast cancer has the greatest prevalence among noncutaneous cancers for women in developed countries and is, after lung cancer, second in mortality. Surgery continues to have an important role in the treatment of the disease. Modiﬁed radical mastectomy and quadrantectomy with lymph node dissection are the methods of choice in most cases. Surgical intervention at the axillary region is, however, ridden with complications, with the most common the formation of seromas.3-17 Seromas can develop in the dead space that forms under the skin ﬂaps, at both the site of mastectomy and the axillary region.14,18-24 It can predispose to surgical site infection, wound dehiscence, ﬂap necrosis, and even sepsis.25,26 These complications can lead to repeated visits to the surgeon and, possibly, reoperations, which eventually increase the postoperative costs, prolong the period of recovery, delay administration of adjuvant therapy, and, ﬁnally, negatively affect patients’ psychological well-being.17,27

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.67 ± 10.36</td>
<td>61.34 ± 10.86</td>
<td>.994</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.50 ± 3.44</td>
<td>31.90 ± 4.61</td>
<td>.000</td>
</tr>
<tr>
<td>Breast weight (g)</td>
<td>541.41 ± 358.57</td>
<td>473.14 ± 380.53</td>
<td>.037</td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>108.56 ± 37.47</td>
<td>124.89 ± 44.79</td>
<td>.042</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>1.13 ± 0.52</td>
<td>1.01 ± 0.50</td>
<td>.097</td>
</tr>
<tr>
<td>Removed lymph nodes (n)</td>
<td>20.68 ± 5.64</td>
<td>14.67 ± 3.95</td>
<td>.000</td>
</tr>
<tr>
<td>Inﬁltrated lymph nodes (n)</td>
<td>4.29 ± 2.38</td>
<td>3.24 ± 2.78</td>
<td>.000</td>
</tr>
<tr>
<td>Drainage duration (days)</td>
<td>2.51 ± 0.89</td>
<td>3.63 ± 1.62</td>
<td>.000</td>
</tr>
<tr>
<td>Seroma drained (mL)</td>
<td>155.77 ± 103.35</td>
<td>457.81 ± 435.51</td>
<td>.000</td>
</tr>
<tr>
<td>Seroma aspirated (mL)</td>
<td>25.46 ± 27.14</td>
<td>94.69 ± 109.26</td>
<td>.000</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation.

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The results from the present study also revealed that a signiﬁcant correlation was present between the amount of seroma ﬂuid produced and the following variables: BMI, breast weight, tumor size, operative time, and number of inﬁltrated lymph nodes.

The contribution of a high BMI to increased seroma ﬂuid production has also been reported in several other studies2,6,25,33 and can be considered one of the most important factors in seroma formation. The published data regarding breast weight as a risk factor for seroma formation are insufﬁcient. In the present study, however, we found a signiﬁcant positive correlation between the size of the removed breast and the amount of accumulated seroma ﬂuid, which can be explained by the larger dead space created below the skin ﬂaps when a larger part of the breast is removed. The tumor size has been identiﬁed as a risk factor in only 1 other study.9 Thus, more extensive investigations are required.

Woodworth et al17 reported that an increased operative time can lead to formation of a greater amount of seroma ﬂuid. The risk of seroma ﬂuid accumulation is 2.5 times greater after radical modified
mastectomy, which requires a considerably longer operative time, than after quadrantectomy with lymph node dissection.\textsuperscript{6,11,34} However, in our study, the operative time was significantly shorter for the cases than for the controls. This finding can be explained by the use of a surgical glue in the cases that has hemostatic properties, in addition to the adhesive qualities, leading to less time required for hemostasis and reducing the operative time in the case group.

Moreover, the number of lymph nodes removed and the number of infiltrated lymph nodes were found to be significantly greater in the cases than in the controls. A greater number of removed lymph nodes, including infiltrated ones, would be expected to be associated with increased seroma production.\textsuperscript{32} However, such a finding was not confirmed in our study, which, again, can be attributed to the use of cyanoacrylate adhesive in our case patients.

Finally, multiple regression analysis, performed to identify the variables with the greatest predictive value for seroma production, resulted in a predictive model incorporating BMI, tumor size, adhesive use, and number of infiltrated lymph nodes. The model explained 51.6% of seroma amount variability. All these independent variables contributed statistically significantly to the model. The variables of age, operative time, breast weight, and number of removed lymph nodes were ultimately excluded from this model, because they did not contribute significantly to the predictive model of seroma formation.

Abbreviation: BMI = body mass index.
Conclusion

The results of the present study indicate that the use of cyanoacrylate adhesive in modified radical mastectomy or quadrantectomy with lymph node dissection can contribute to the reduction of seromas produced postoperatively, decreasing the duration of postoperative drainage and the frequency of required seroma aspirations. Accordingly, the use of cyanoacrylate adhesive is a safe, easily applicable, and effective tissue sealant and can be recommended for patients with a high risk of seroma formation after surgery for breast cancer. However, because the pathogenesis of seroma formation is complex, further research and larger sample sizes are required to confirm the results of our study and open a new horizon for research on the treatment of this frequent complication.

Clinical Practice Points

- The most common complication after breast surgery is seroma formation, which can predispose to surgical site infection, wound dehiscence, flap necrosis, and, even, sepsis, leading to repeated visits to the surgeon, reoperations, increased postoperative cost, longer recovery period, and delay in the administration of adjuvant therapy.
- Extensive research has been performed to discover an effective method to reduce postoperative seroma formation, including ultrasonic shears, special stitches, fibrin glue, fibrin sealant, and bovine thrombin at some stage during lymphadenectomy and different surgical techniques intended for the closure of the dead space. However, all these methods have significant disadvantages and none has proved sufficiently effective.
- The present study examined the use of a cyanoacrylate adhesive at the operation field after modified radical mastectomy or quadrantectomy with lymph node dissection.
- Our results showed that cyanoacrylate adhesive can potentially contribute to the reduction of seroma fluid produced
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postoperatively, decreasing the duration of postoperative drainage and the frequency of required seroma aspirations.

- The use of cyanoacrylate adhesive might be recommended for patients with a high risk of seroma formation after surgery for breast cancer.

Disclosure

The authors declare that they have no competing interests.

References