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Original research

# The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial

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## HIGHLIGHTS

- Fibrin glues may reduce axillary wound discharge but results are not definitive.
- Low-thrombin fibrin glue reduces fluid produced in the axilla after breast surgery.
- Low-thrombin fibrin glue allows faster drain removal and shorter hospital stay.
- Overweight patients are ideal candidates to low-thrombin fibrin glue placement.
- Low-thrombin fibrin glue is not associated with higher risk of long-term lymphedema.

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## ABSTRACT

**Background**: Breast cancer surgery with axillary lymphadenectomy may be associated with prolonged stay of the drain in the axilla due to high wound output, which may require further treatments and prolong the length of stay, impairing quality of life. No definitive data are available concerning how to prevent this complication. Our aim was to assess the efficacy of a new low-thrombin fibrin glue in reducing the serous output from the axillary surgical wound in patients undergoing axillary node dissection for breast cancer, and its long-term effects on lymphedema. **Methods**: Sixty patients undergoing surgery between September 2012 and June 2013 were enrolled. Thirty patients received Artiss®(Baxter, UK) fibrin glue plus drainage, and 30 drainage alone. A multivariate analysis was performed to identify predictors of seroma, and subgroup analyses were performed. Lymphedema was assessed 12 months after surgery. **Results**: Patients who received fibrin glue had reduced serum output collected in the drain after surgery (94.3 ± 22.4 vs 176 ± 24.6 ml $p < 0.001$) and shorter length of postoperative hospital stay ($p = 0.001$). Incidence of seroma at 4-week follow-up did not differ between groups. At multivariate analysis, BMI ≥30 kg/m$^2$ was the only independent predictor of seroma formation (OR = 2.7, 95%CI 1.4–5.3; $p = 0.002$). Overweight patients receiving Artiss® had fewer seroma at 4-week follow-up compared with control overweight patients (0% vs 55.6%, $p = 0.03$). No differences were observed in lymphedema between groups (6.7% vs 10%, $p > 0.99$). **Conclusions**: Low-thrombin fibrin glue reduced the amount of fluid produced in the axilla after breast surgery. Overweight patients may be the ideal candidates for this treatment. Such sealant did not increase the rates of lymphedema.



## 1. Introduction

Breast cancer is the most common neoplastic disease in women worldwide. Axillary lymph node dissection plays an important role in the surgical management of breast cancer. Despite the trend toward breast-conserving treatments and the standardization of

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surgical techniques, the procedure is not free from complications [1].

The introduction of sentinel lymph node biopsy reduced the rate of complete axillary lymphadenectomy [2,3], but radical node dissection still has precise indications and represents a key clinical problem for the associated postoperative morbidity.

Potential complications are represented by lymphorrhea requiring delayed drain removal, seroma, hematoma, wound infection, bleeding and nerve lesion. These lead to patient discomfort, longer in-hospital stay, prolonged outpatient treatment, and increased costs of care [1–8].

Seroma is reported to occur in 15–81% of patients after node dissection [4–8]. It can require repeated aspirations and increase the risk of wound dehiscence, prolonged pain, infection, reduced limb mobility and prolonged time off-work [7,8], impairing quality of life. The etiology of seroma relies on extensive axillary lymph node dissection being responsible for blood and lymphatic oozing in the residual dead space [9]. Halsted suggested that the obliteration of dead spaces facilitated surgical recovery [10]. Several strategies have been attempted to reduce seroma, including suction drainage placement, closure of the axillary fossa by means of stitches to eliminate "dead spaces", application of external compression, and application of fibrin glue [4–6]. However, prolonged stay of the drain is a frequent cause of discomfort for the patients, although needed to avoid the seroma. Fibrin glue offers several advantages, such as less traumatic closure, reduction of pain, no need to remove stitches, and excellent esthetic results. Also, it creates a moist environment and is gradually metabolized by the surrounding tissue, without generating foreign body response [9,11].

Nevertheless, the results are not definitive, and the methodological and clinical diversity among studies makes it difficult to draw conclusions [12]. A new fibrin sealant has recently been introduced, Artiss® (Baxter, UK), characterized by a reduced thrombin concentration in comparison to other fibrin sealants. This results in polymerization of Artiss® taking approximately 60 s, allowing longer time to further manipulate the tissues before fixation, eventually further reducing residual dead spaces.

The purpose of this study was to evaluate the efficacy of low-thrombin fibrin glue (Artiss®, Baxter, UK) plus suction drain versus suction drain alone in reducing the serum output after axillary node dissection in patients with breast cancer, allowing faster removal of the suction drain without increasing the risk of seroma.

## 2. Materials and methods

This is a double blind, randomized, controlled clinical trial. All patients diagnosed with node positive T1–T3 breast cancer candidates to surgery with complete axillary lymph node dissection observed in our Unit between September 2012 and June 2013 were considered for enrollment in the present study. Patients were randomized to treatment with fibrin sealant plus a percutaneous vacuum drain versus percutaneous vacuum drain alone after axillary dissection. Patients were randomized by means of covariate adaptive randomization [13], meaning that several covariates were taken into account (age, body mass index [BMI], Eastern Cooperative Oncology Group score [ECOG], and American Society of Anesthesiologists score [ASA]) to avoid misbalances between groups. Surgery was performed by two experienced Senior Surgeons, and patients were equally distributed between operating teams. Both patients and surgeons who performed the postoperative assessment were blind to the procedure performed.

Our primary aim was to obtain a reduction of the serum discharge from the axilla collected in the vacuum drain, allowing its removal. Our secondary aims were to obtain reduction of seroma formation, shorter length of postoperative hospital stay, and similar rates of lymphedema in the long-term. Approval of the Ethical Committee was obtained. All enrolled patients gave written informed consent to be included and to complete long-term follow-up.

### 2.1. Inclusion and exclusion criteria

Inclusion criteria were as follows: female gender, age ≥25 years, absence of coagulopathy and/or liver disease, BMI ≤35 kg/m$^2$, indication to axillary lymph node dissection. All patients candidates for enrollment underwent preoperative needle biopsy to confirm diagnosis and CT scan to allow preoperative staging.

Patients who had undergone previous breast surgeries and those who did not meet inclusion criteria were excluded.

### 2.2. Intervention and follow-up

Artiss® consists of a dual-chamber pre-filled syringe that contains in a chamber the solution of coagulable proteins (aprotinin), in frozen form of 1 ml, 2 ml and 5 ml, and in the other chamber the thrombin solution (with calcium chloride) in frozen form of 1 ml, 2 ml and 5 ml, allowing to obtain a total volume of 2 ml, 4 ml and 10 ml of the product ready for use. The product is characterized by lower concentration of thrombin compared with other sealants. After axillary node dissection, patients were randomly assigned to either instillation of this low-thrombin fibrin glue and placement of a vacuum drain (Group A) or placement of vacuum drain alone (Group B). The former received 4 ml of fibrin glue spray into the axillary wound cavity before placing stitches.

The amount of serum drained was recorded daily. The total amount of fluid collected before drain removal and days needed to remove the drains were used for comparison between groups. Drains were removed when serum discharge did not exceed 30 ml during 24 h. Length of postoperative hospital stay was defined as hours elapsed between surgical procedure and discharge.

After discharge, patients were followed-up after 1, 2 and 4 weeks, undergoing clinical and ultrasonographic exam. Septic and neurological (pain, paresthesia) complications were recorded. Limb mobility was always assessed. Neurological pain was assessed by means of DN4 (Douleur Neuropathique 4) questionnaire [14], consisting of total 10 items grouped in 4 sections: seven items related to quality of pain (burning, painful cold, electric shocks) and its association to abnormal sensations (tingling, pins and needles, numbness, itching); three items related to neurological examination in the painful area (touch hypesthesia, pinprick hypesthesia, tactile allodynia). Each positive item is scored 1 while negative items are scored 0. The total score results from the sum of all 10 items, and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10. We also classified scores >0 and <4 as "minor disturbances".

Seroma was assessed 4 weeks postoperatively by means of ultrasonography.

Lymphedema was assessed 12 months after surgery in all included patients. Lymphedema was diagnosed and graded as reported by Petrek et al. [15]. Preoperatively we collected baseline measurements 10 cm above and 5 cm below the olecranon process on both the treated and contralateral upper extremities. The difference in measurement at follow-ups at the site of greatest difference was used to determine extent of lymphedema [16]. Lymphedema was defined as present if difference was >2 cm for either location.

### 2.3. Statistical analysis

Data are reported as mean ± standard deviation (SD), unless otherwise indicated. Continuous variables were analyzed by