Effect of topical application of tranexamic acid on reduction of wound drainage and seroma formation after mastectomy

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Objectives
Formation of a seroma most frequently occurs after mastectomy and axillary surgery. Prolonged drainage is troublesome as it increases the risk for infection and can significantly delay adjuvant therapy. Topical tranexamic acid as an antifibrinolytic agent may control fluid accumulation in the dead space under the skin flaps and in the axillary fossa after mastectomy. The aim of this study was to investigate whether moistening a wound surface with tranexamic acid reduces bleeding and fibrinolysis and therefore reduces the total wound drainage after mastectomy and also the incidence of hematoma or seroma formation.

Patients and methods
We conducted a prospective cohort study on 115 patients with breast cancer who underwent modified radical mastectomy. Topical tranexamic acid was used to moisten the area in some patients to assess its effect on total wound drainage and seroma formation in follow-up period of 1 month.

Results
The amount of wound drainage was significantly lower in the study group as compared with the control group (798.06±107.3 vs. 1067.1±188.6 ml; $P<0.005$). The duration of drainage was also lower in the study group as compared with the control group (9.85±1.66 vs. 11.67±1.9 days; $P<0.005$). Eight (12.3%) patients in the study group had seroma formation after removal of drains as compared with six (12%) patients in the control group. Three (4.6%) patients of the study group had wound infection compared with one (2%) patient in control group; wound was managed by local drainage and antibiotics.

Conclusion
Tranexamic acid was tolerated without any adverse effects in all patients, and is valuable in reducing the amount and duration of wound drainage after mastectomy without having any effect on the rate of seroma formation.

Keywords:
mastectomy, seroma formation, topical tranexamic acid

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Introduction

Seroma formation is the most frequent complication after mastectomy. The exact etiology of seroma formation remains controversial but certain factors like extent of mastectomy, extent of lymph node dissection, and methods of surgical dissection influence the amount and duration of seroma formation. Several interventions have been reported with the aim to reduce seroma formation such as use of compression bandage, suction drains [1], flap fixation with sutures [2], sclerotherapy [3], and fibrin glue [4] to obliterate the dead space. However, none of them proved to be effective in controlling the seroma formation absolutely.

Fibrinolytic activity of the plasmin system in serum and lymph may contribute to fluid accumulation in the dead space under the skin flaps and in the axillary fossa after mastectomy. Fibrin complexes already formed within and around vessels may result in further leakage of blood and lymph from the vessels. Tranexamic acid is a synthetic antifibrinolytic agent that inhibits fibrinolysis by blocking the lysine-binding sites on plasminogen, thereby preventing the activation of plasminogen to plasmin. Tranexamic acid also has a direct antiplasmin action, inhibiting fibrin degradation [5].

Intravenous administration of tranexamic acid during major surgery has been shown to reduce the need for blood transfusion by 32–37%, as well as measurable postoperative bleeding by 34%. However, its effect on the risk of thromboembolic events is uncertain and an increased risk remains a theoretical concern. It is still not recommended for routine use during most surgical

procedures. Safety concerns have included thrombosis, renal impairment, and increased risk of seizures associated with high doses (above 2 g) [6].

Tranexamic acid can be administered orally or intravenously, but topical use is being reported increasingly. Topical application of tranexamic acid provides a high drug concentration at the site of the wound and a low systemic concentration [7]. Studies from cardiac and orthopedic surgery have shown an equal or superior effect of topical compared with intravenous tranexamic acid on both bleeding and transfusion requirement [8].

In previous studies, topical tranexamic acid was instilled mainly as a bolus into confined spaces such as a joint, the mediastinum, or the pericardium, or applied to accessible wounds using soaked gauze. A few studies have described simple moistening of a wound surface [9]. The aim of this study was to investigate whether moistening a wound surface with tranexamic acid reduces bleeding and therefore reduces the total wound drainage after mastectomy and also the incidence of hematoma or seroma formation.

Patients and methods

Study population

Institutional Review Board approval was obtained. This study was a prospective nonrandomized trial conducted between January 2016 and March 2018. The patients comprised 115 women aged 18 years or older, with breast carcinoma (ductal or lobular) of any stage and for whom MRM had been recommended. Patients were excluded if they had any history of thromboembolic events, severe varicose veins, coagulation disorders, or receiving anticoagulant drugs. Patients with no measurable drain volume were also excluded.

Study groups and endpoints

All patients received guidance and provided signed informed consent. The patients underwent MRM (Patey or Madden), with level III axillary dissection. Three surgical oncologists with a minimum of 5 years of experience in breast cancer surgery performed the procedures.

During the induction of anesthesia, all patients prophylactically received 2 g of prophylactic antibiotic intravenously. The same method for dissection by electrocautery was used in all patients. In 65 cases (study group I), topical tranexamic acid was used after resection, whereas in group II (control group), 50 patients did not receive tranexamic acid.

As the specific mode of topical application of tranexamic acid has not been published previously, the concentration of tranexamic acid needed to achieve an antifibrinolytic effect was unknown. To ensure a sufficiently high concentration, the tranexamic acid was diluted only to a volume sufficient to moisten a fairly large wound surface: 20 ml moistens at least 1500 cm^2. The surgeon applied directly on wound a solution previously prepared of one ampoule (5 ml) of tranexamic acid (100 mg/ml) diluted in 15 ml of normal saline, so the prepared solution thus contained 20 ml of 25 mg/ml tranexamic acid.

In all patients, a continuous vacuum suction drain with a 600-ml capacity reservoir was used. Two suction drains were placed in the surgical bed, and occlusive dressings were placed over the surgical wounds. All patients were clinically discharged between 24 and 36 h postoperatively and given medical guidance about caring for the surgical wound and handling the drain, along with a card on which to note the daily drainage volume.

The measurements of the daily drainage were recorded; the drain was subsequently removed when wound drainage was less than 40 ml/24 h. On the 14th postoperative day, all of the stitches were removed. The patients with seroma accumulation were evacuated, the axilla was punctured, and the volume was measured. The local postoperative complications (necrosis of the breast skin flap, seroma, hematoma, and infection of the surgical wound) were evaluated at two time-points: on the 14th and 13th postoperative days.

The study has been reported in line with the STROCSS criteria [10].

Data analysis

Demographic, clinical, and treatment-related variables were recorded on a standardized form. SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. The study population was characterized using descriptive statistics. As most of the quantitative variables did not adhere to the normal distribution curve according to the Kolmogorov–Smirnov test, nonparametric tests were chosen for analysis of the differences among these variables. Comparisons between unpaired groups were carried out by means of Mann–Whitney when

the variables were numerical. The χ^2-test or Fisher's exact test was used to compare qualitative variables and risks. The risk was investigated using the odds ratio. We used a nonexploratory multivariate analysis model.

Results

Patients' age, BMI, tumor size, neoadjuvant chemotherapy status, total number of lymph nodes isolated, and the mean±SD duration of surgery were nearly similar in both groups (Table 1).

The mean amount of wound drainage was significantly lower in the study group as compared with the control group (798.06±107.3 vs. 1067.1±188.6 ml; $P<0.005$). The mean duration of drainage was also lower in the study group as compared with the control group (9.85 ±1.66 vs. 11.67±1.9 days; $P<0.005$); this difference was significant (Table 2).

There was no significant difference in the study and control groups in relation to the amount of wound drainage in patient those received neoadjuvant chemotherapy and those who did not received neoadjuvant chemotherapy. It was also observed that there is no significant reduction in wound drainage in relation to number of lymph nodes isolated in both groups.

Postoperative complications are shown in Table 2. None of the patients in the study group and control group had flap necrosis. Eight (12.3%) patients in the study group had seroma formation after removal of drains as compared with six (12%) patients in the control group. All patients with seroma formation in the control group were managed by single aspiration, whereas those in the study group, six patients required only single aspiration whereas two patients required aspirations twice. Three (4.6%) patients of the study group had wound infection compared with one (2%) patient in the control group; wound was managed by local drainage and antibiotics.

Tranexamic acid was tolerated by all patients in the study group, without any adverse effects.

Discussion

Formation of a seroma most frequently occurs after mastectomy and axillary surgery. Prolonged drainage is troublesome as it increases the risk for infection and can significantly delay adjuvant therapy. Because the true etiology of a seroma is unknown, a multifactorial-causation hypothesis has been accepted. Obliteration of dead space with various flap fixation techniques, use of sclerosants, fibrin glue and sealants, octreotide, and pressure garments has been attempted with conflicting results, and none have been consistent. A detailed analysis of the use of drains showed there is evidence for reduced seroma formation after early drain removal [11].

In previous studies, topical tranexamic acid was instilled mainly as a bolus into confined spaces such as a joint, the mediastinum, or the pericardium, or applied to accessible wounds using soaked gauze. A few studies have described simple moistening of a wound surface [12]. Although most topical hemostatic agents can cover only a small surface area, tranexamic acid diluted in saline can moisten large areas, such as after

Table 1 Comparison of both groups regarding patient and tumor characteristics

Patients' characteristics	Group I (*n*=65)	Group II (*n*=50)	*P* value
Age (mean±SD) (years)	45.96±7.06	47.87±6.54	0.102
BMI (mean±SD)	32.4±3.04	33.02±2.39	0.089
Tumor size [*n* (%)]			
T1	39 (60)	31 (68)	0.109
T2	26 (40)	19 (32)	0.093
Received neoadjuvant chemotherapy [*n* (%)]	16 (24.6)	11 (22)	0.413
Total number of lymph nodes isolated (mean±SD)	16.37±3.56	15.63±2.98	0.308
Duration of surgery (mean±SD) (min)	70.45±9.03	63.39±11.4	0.122

Table 2 Comparison of both groups regarding postoperative variables

	Group I (*n*=65)	Group II (*n*=50)	*P* value
Amount of wound drainage (mean±SD) (ml)	798.06±107.3	1067.1±188.6	<0.005
Duration of wound drainage (mean±SD) (days)	9.85±1.66	11.67±1.9	<0.005
Seroma formation [*n* (%)]	8 (12.3)	6 (12)	0.508
Wound infection [*n* (%)]	3 (4.6)	1 (2)	0.790
Flap necrosis/hematoma	0	0	–

massive weight loss surgery, or in patients with mastectomies [13].

The authors hypothesized that topical application of tranexamic acid within the dead space after mastectomy and axillary evacuation is effective in controlling the amount of postoperative fluid output; therefore, it could permit early drain removal and less seroma formation and wound infection and early adjuvant treatment.

Amount of fluid drained was significantly less in the study group as compared with the control group, and the closed suction drains were also removed early in the study group as compared with the control group ($P<0.001$). The stage of breast carcinoma, neoadjuvant chemotherapy, and total number of nodes dissected did not affect the amount of drained fluid or seroma formation. Although the amount and duration of drain output was less in the study group as compared with the control group, seroma formation after removal of drains was more in the study group as compared with the control group (12.3 vs. 12%).

None of the patients in both groups had either flap necrosis or hematoma. Three (4.6%) patients developed wound infection in the study group, and two of them required repeated aspiration of seroma. Moreover, one (2%) patient in the control group developed wound infection after seroma formation and aspiration.The total wound drainage is reduced and drains can be removed early, but there is increase in the incidence of seroma formation, which was resistant to simple aspiration owing to which the overall complication rates were nearly equal in both groups.

The possible explanation is that tranexamic acid was used only for single dose, which resulted in less amount of fluid output in early postoperative period, but there was increase in seroma formation when drug effect was stopped, and by that time, drains have been removed.

Tranexamic acid is inexpensive. Its cost-effectiveness has been thoroughly documented in orthopedic surgery [6]. Even after operations where bleeding is less common, repeated topical application of tranexamic acid through drains may be tried in outpatient visits to study the effect on late seroma formation in further studies.

Conclusion

Tranexamic acid was tolerated without any adverse effects in all patients and is valuable in reducing the amount and duration of wound drainage after mastectomy without any effect on the rate of seroma formation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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