Topical Tranexamic Acid in Breast Reconstruction: A Double-Blind Randomized Controlled Trial

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Background: Excess fluid accumulation (seroma/hematoma) around the breast implant after reconstruction can lead to significant complications. Topical administration of tranexamic acid (TXA) may reduce fluid accumulation and reduce postoperative complications. This trial aims to investigate whether TXA-treated mastectomy pockets will exhibit less postoperative fluid production and complications.

Methods: This paired, double-blind, randomized, controlled trial enrolled patients undergoing bilateral mastectomies with immediate direct-to-implant reconstruction. In each patient, one breast was randomized to receive 3 g of TXA (100 cc), and the other received 100 cc of normal saline. The blinded solutions were soaked in the mastectomy pocket for 5 minutes before implant placement. Postoperatively, daily drain outputs, complications, and baseline demographics were recorded.

Results: Fifty-three eligible patients, representing 106 breasts, were enrolled. All patients underwent bilateral nipple-sparing mastectomies. After randomization, TXA was placed in the right breast in 30 patients (56.6%). The use of topical TXA resulted in a mean drain output reduction of 30.5% (range, −83.6% to 26.6%). Drains on the TXA-treated breast were eligible for removal 1.4 days (range, 0 to 4 days) sooner than the control side. The TXA-treated group had three complications (5.67%) versus 15 (28.3%) in the control group (OR, 0.1920; $P = 0.0129$). Specifically, for operative hematomas, the TXA group had none (0%), versus three in the control group (5.7%) (OR, 0.1348; $P = 0.18$).

Conclusions: Soaking the mastectomy bed with 3% topical TXA before implant insertion leads to a decrease in drain output and a decrease in complications. Topical administration of TXA represents an option to decrease complications in alloplastic breast reconstruction. *(Plast. Reconstr. Surg.* 152: 699, 2023.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, I.

Breast cancer affects one in every eight women, many of whom will undergo treatment with mastectomy and implant-based breast reconstruction.[1] Breast cancer reconstruction has been shown to improve patient-reported outcomes in physical, psychosocial, and sexual well-being domains.[2] Even with advances in prosthetic devices, reconstructive techniques, and mastectomy flap quality, recent reviews have demonstrated that surgical complications can arise in up to 20% of alloplastic breast

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reconstruction cases.[3] Aside from complications arising from mastectomy flap skin necrosis, most complications arise from excess fluid accumulation around the breast implant, including blood or seroma fluid.[3] Residual blood, either from hematoma or generalized oozing, creates a proinflammatory environment which, in conjunction with the high osmotic potential of blood, draws fluid into the breast pocket, promoting seroma formation.[4,5] In addition, the residual hematoma is an excellent nidus for bacterial infection.[6] This excess fluid can lead to patients requiring urgent surgical drainage or becoming infected, or it can exacerbate eventual chronic inflammatory complications such as capsular contracture.[7] Although surgeons consistently strive for meticulous intraoperative hemostasis and place drains to minimize the fluid collection, the reported rates of seroma and hematoma following mastectomy with direct-to-implant (DTI) reconstruction remain at 6.7% and 3.4%, respectively.[8] In addition, drains themselves are cumbersome to the patients and may represent a source of bacterial contamination.[9]

One possible solution to reduce drain output and expedite removal is the application of topical administration of tranexamic acid (TXA). As an antifibrinolytic agent, TXA prevents the breakdown of formed blood clots, which helps to maintain hemostasis.[10] In addition, as mentioned above, TXA could also reduce fluid accumulation in the mastectomy pocket by reducing the osmotic load. This proposed paired, double-blind, randomized controlled trial (RCT) aims to compare postoperative fluid production and the incidence of complications in individual breasts (one breast randomized to topical TXA, and the other to topical saline) in patients undergoing bilateral mastectomy with immediate implant-based breast reconstruction.

PATIENTS AND METHODS

The study was undertaken with the approval of the clinical research ethics board of St. Mary's Hospital and Health Canada (HC6-24-c248414). Inclusion criteria included any consenting patient over 18 who underwent bilateral nipple-sparing mastectomy (NSM) with immediate implant-based reconstruction. Exclusion criteria consisted of any other form of reconstruction, previous thromboembolic disease, or patient preference. Starting in December of 2020, all eligible patients were recruited at the first of two preoperative visits, and informed consent was obtained. The primary outcome of the study was daily Jackson-Pratt (JP) drain outputs of the TXA-treated breast compared with control. Secondary outcomes included time to drain removal and surgical complications. Major complications (hematoma, pocket infection, seroma, mastectomy flap necrosis) required operating room surgical intervention, whereas minor complications (cellulitis, mild dehiscence) were treated in the clinic.

Statistical analysis was performed using IBM SPSS Version 24.0 (IBM Corp., Armonk, NY). Bivariate analysis was performed using *t* tests and the Fisher exact test to compare complication rates between subgroups.

Sample Size with or without Randomization

In collaboration with the Biostatistics Consulting Unit of the McGill University Health Centre, the study size was estimated to be 82 included breasts [$n = 41$ in the TXA group and $n = 41$ in the normal saline (NS) group]. This was calculated using a power of 80% and an alpha of 5%. To come to this calculation, the mean JP drain outputs were taken from the literature.[11,12] In addition, another RCT with similar methodology found there to be 39% reduction in drain outputs.[11,13] For a more realistic, yet meaningful analysis, a 20% reduction in drain output was selected.

The allocation was 1:1 given the sample population having bilateral mastectomies and the fact that each patient is a self-control. The included patients underwent bilateral mastectomy and DTI reconstruction, with each breast randomized to the treatment or control group. Before the start of surgery, the nonblinded charge nurse created both 100-cc solutions in bowls labeled A and B (one solution, 70 cc of NS and 3 g of TXA; and the other, 100 cc of NS). Three grams of TXA was selected because of prior literature demonstrating its effectiveness in comparison to other formulations.[11] The TXA solution is odorless and colorless. Once the case had commenced, the scrub nurse and the surgeons were completely blinded. At mastectomy completion, using an online platform (https://www.randomizer.org/), the breasts were randomized in a 1:1 allocation.

Data Collection with or without Follow-Up

Baseline demographics were documented at the time of preoperative consultation. Patients were followed up every week postoperatively for 1 month, and then every 6 months. On discharge from the hospital immediately following breast reconstruction, patients were taught to mark the daily drain outputs on a standardized JP drain output sheet that was collected at the time of JP removal. Drains

were eligible to be removed in the clinic on follow-up when the output was less than 25 cc for 2 consecutive days. If the drain was over 25 cc at follow-up, the patient would retain the drain for another week. Days until drain removal eligibility was calculated based on the drain sheets filled by the patient. Patients were unblinded after drains were removed and no further intervention was required.

Reconstructive Technique

Immediate DTI breast reconstruction was performed in the prepectoral plane as described previously without the use of any acellular dermal matrix or dermal substitute.[3] Two JP drains were placed laterally at sites previously injected with lidocaine 1% with epinephrine. After hemostasis and before implant placement, a randomized sponge (soaked in TXA solution or NS) was placed to contact the entirety of the surgical breast pocket surface; then, with manual pressure on the breast, the solution was extruded from the sponge. This does differ from previously described trials with the use of a moistened sponge, but helped control excess spillage of the solution.[11] Any residual solution was placed into the breast and left closed for 5 minutes. No TXA was administered intravenously. No nonsteroidal anti-inflammatory drugs were administered in the postoperative period. After 5 minutes, 100 cc of 10% povidone-iodine, triple antibiotic (1 g of cefazolin, 80 mg of gentamicin, and 50 000 IU of bacitracin), and NS (500 cc) solution was irrigated into the breast pocket before a no-touch implant placement. In addition, all adjunctive procedures [axillary lymph node dissection or sentinel lymph node biopsy (SLNB)] were performed through separate axillary incisions and did not communicate with the breast pocket.

RESULTS

Patient Demographics

Fifty-three patients, representing 106 breasts, participated in the trial. The mean age of the patients was 48 years (range, 30 to 70 years) with an average body mass index of 24.2 kg/m^2 (range, 19.5 to 28.7 kg/m^2). All patients were nonsmokers. One patient (1.9%) had a prior lumpectomy to her breast with subsequent radiation therapy. No patient had any significant comorbidity, including diabetes, or was on immunosuppressant medication (Table 1 and Figs. 1 and 2).

Surgical Demographics

All patients underwent bilateral NSM. Thirty patients (56.6%) underwent bilateral prophylactic mastectomies for a genetic mutation, whereas 23 patients (43.4%) were diagnosed with active cancer and underwent a contralateral prophylactic mastectomy and adjunctive lymph node procedures as a result. No patient underwent an axillary lymph node dissection.

Table 1. Patient and Surgical Demographics

Characteristic	Value (%)
No. of patients	53
No. of breasts	106
Age, yr	
Mean	48
Range	30–70
BMI, kg/m^2	
Mean	24.2
Range	19.5–28.7
Bilateral prophylactic	30 (56.6)
Unilateral active cancer with unilateral prophylactic	23 (43.4)
Prior lumpectomy	1 (0.9)
SLNB	23 (43.4)
ALND	0
Incision type	
Inferolateral	31 (58.5)
Wise pattern	22 (41.5)
TXA with SLNB	10 (18.8)
Implant size, cc	
Mean	355.7
Range	200–575

BMI, body mass index; ALND, axillary lymph node dissection.

Surgical Outcomes

Twenty-three patients (43.4%) underwent an SLNB performed through a separate incision. Of these 23, 10 (43.5%) had the SLNBs performed on the TXA-treated side, and 13 (56.5%), on the control side. In all patients, the same incision was used in bilateral breasts. Twenty-two patients (41.5%) underwent a bilateral Wise-pattern NSM mastectomy, and the remainder (58.5%) underwent a bilateral inferolateral incision. In all patients, identical implants were used on both sides (mean size, 355.7 cc). Mean follow-up time was 69.8 weeks.

Primary Outcome: Percentage Difference in Drain Output

The primary clinical outcome measured was the percentage difference in the total JP drain output between the TXA-treated and control breasts, for the duration they were bilaterally in place. After analysis of 53 patients, drain data were deemed usable in 43 patients (81.1%). Data were unusable because of inaccurate use of the provided drain sheet (n = 6), inaccurate reporting on all days (n = 3), or loss of drain sheet

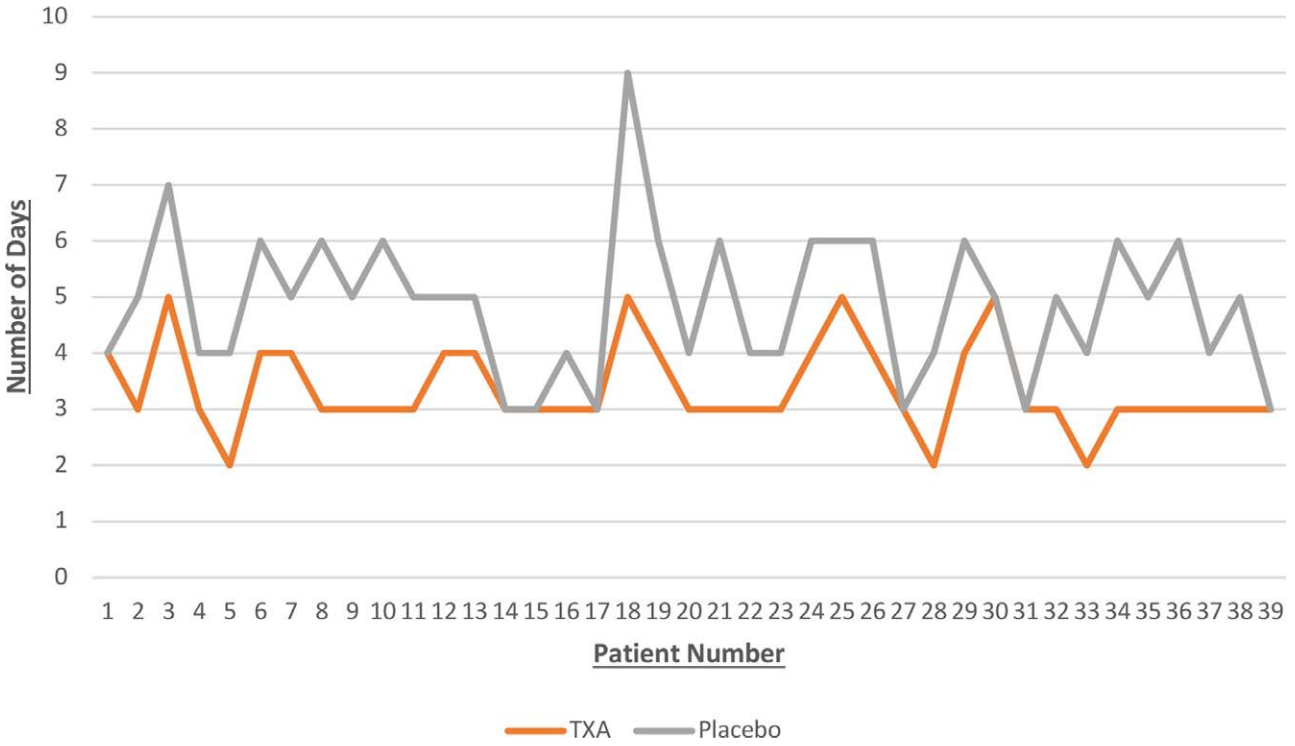

Fig. 1. Days difference until JP drain removal for TXA versus control.

(n = 1). The mean percentage reduction in the TXA-treated breasts was calculated to be 30.5% (range, −83.6% to 26.6%) compared with control breasts. Only one patient (2.3%) had more drainage on the TXA-treated breast compared with control.

Secondary Outcomes

Days until Drain Removal

Drains on the TXA-treated breast were eligible for removal 1.4 days (range, 0 to 4 days) sooner than control.

Surgical Complications

Overall, the TXA-treated group had three complications (5.67%) versus 15 (28.3%) in the control group (OR, 0.1920; P = 0.0129). Specifically, for operative hematomas, the TXA group had none (0%) versus three in the control group (5.7%) (OR, 0.1348; P = 0.18). All patients were followed up for at least 6 months; severe capsular contracture was seen in seven breasts in the control group compared with one in the TXA-treated group. Two of the cases (28.6%) of significant capsular contracture in the control group had undergone postmastectomy radiation therapy that may have contributed to the onset of capsular contracture. No significant capsular contracture occurred in bilateral breasts. Three complications occurred on the side on which an SLNB was performed, all without TXA. No complications (infection, cellulitis, lymphocele, hematoma) occurred directly in relation to the SLNB. Table 2 lists individual complications.

DISCUSSION

This paired, double-blinded, RCT demonstrated that the use of topical TXA in immediate breast reconstruction was associated with a decrease in JP drain outputs, decrease in overall complications, and decrease in the time until drain removal. TXA represents a safe, low-cost, and effective modality to help improve outcomes in breast cancer reconstruction.

Mean drain outputs vary heavily between patients because of many patient and surgical factors such as mastectomy weight, body mass index, excessive use of electrocautery, and use of acellular dermal matrix.[14] By creating a matched trial, these factors are all controlled, and each breast is compared with its contralateral side that is similar in volume, tissue composition, and surgical technique.

In breast surgery specifically, multiple articles describing TXA have recently been published. In two RCTs on breast reduction surgery and modified radical mastectomy, topical TXA was shown to decrease drain output significantly (110 mL versus 144 mL; P = 0·011) and clinically relevant hematomas.[11,12]

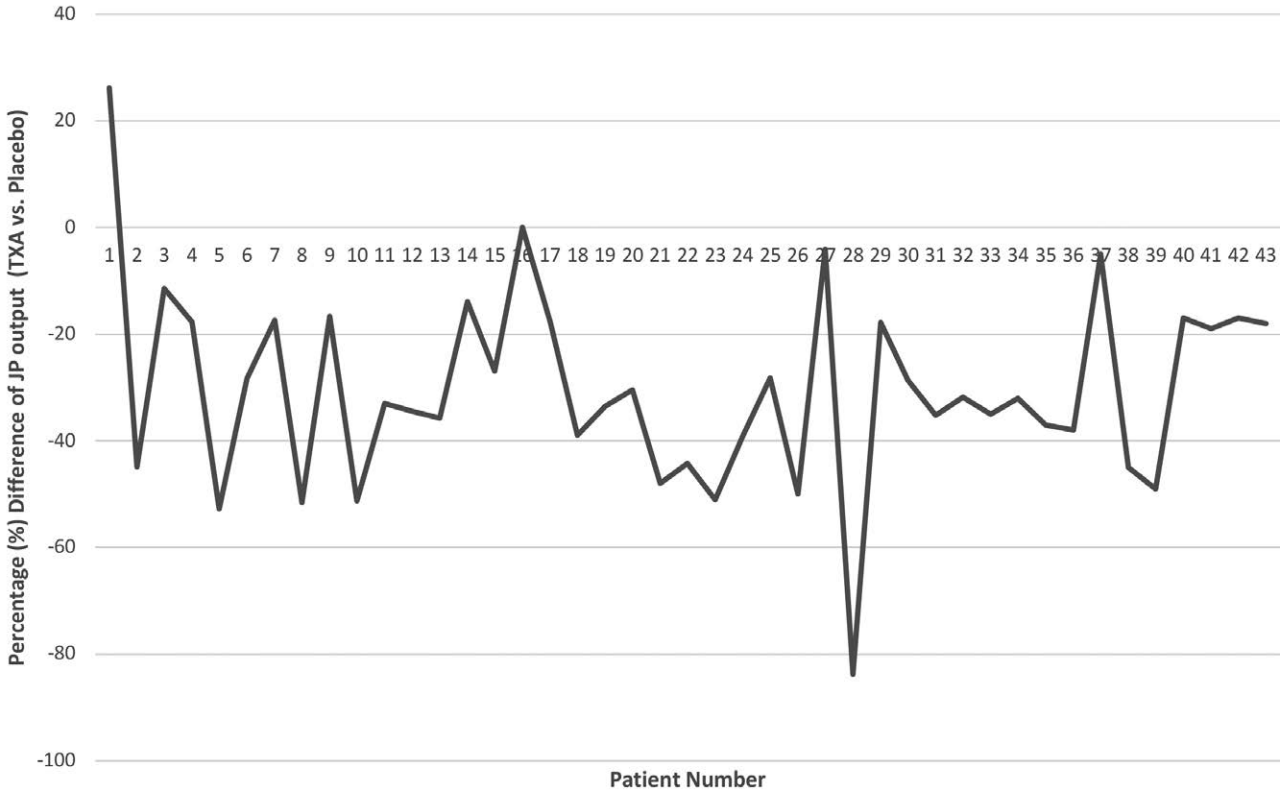

Fig. 2. Percentage difference in JP drain output for TXA versus placebo per patient.

Table 2. Surgical Complications

Complications	TXA Group (%)	Control Group (%)	*P*
Hematoma	0 (0.0)	3 (5.7)	0.24
Seroma	1 (1.9)	1 (1.9)	1.00
Pocket infection	1 (1.9)	4 (7.5)	0.36
Capsular contracture (Baker/Spear 3–4)	1 (1.9)	7 (13.2)	0.06
Mastectomy skin flap necrosis	0 (0.0)	0 (0.0)	1.00
Minor complications	0 (0.0)	0 (0.0)	1.00

One study in breast reduction surgery found a 39% reduction in drain fluid when TXA was used topically in breast reductions.[12] Mastectomies, however, include much more extensive dissection with increased interruption of blood supply to the skin. Another single-center, retrospective study examined topical TXA's effect in implant-based breast reconstruction.[15] Patients who received topical TXA were significantly less likely to develop postoperative seromas (7.5%) than patients who did not receive TXA (12.5%) ($P = 0.032$).[15] Furthermore, patients who received TXA also had their surgical drains removed significantly earlier (12.3 ± 4.3 days) than the patients who had not received topical TXA (13.1 ± 4.9 days) ($P = 0.024$). The rate of hematoma among patients who received TXA [$n = 3$ (0.8%)] was not significantly different from the patients who did not [$n = 5$ (1.8%)] ($P = 0.256$).[15] This article, however, did not control for mastectomy type, patient demographics, and reconstructive factors, which can all increase risk of bleeding and fluid production. In addition, this article demonstrated a difference in hematomas between the two groups, but was also not significant, likely because of the low incidence of these complications. Another article examined how topical TXA affected implant-based breast reconstruction and found that patients who received TXA were less likely to develop hematomas [$n = 1$ (0.46%)] than patients who did not [$n = 19$ (2.9%)].[16] In addition, the rate of seroma in the TXA group was lower [$n = 5$ (2.3%)] than in the group that did not receive TXA [$n = 28$ (4.3%)], although this was not statistically significant ($P = 0.093$).[16]

Mechanism of Action

TXA serves as an antifibrinolytic agent by reversibly binding four to five lysine receptor sites on plasminogen.[17] This reduces the conversion of plasminogen into plasmin, preventing fibrin degradation, and preserving the framework of

fibrin's matrix structure.[17] Therefore, TXA prevents the breakdown of already formed blood clots, which help ensure adequate hemostasis, but does not *cause* thrombosis, which is a critical consideration after surgery.[18] TXA also directly inhibits the activity of plasmin with weak potency and it can block the active site of urokinase plasminogen. By doing so, it will stabilize existing clots.[18] Lastly, TXA may also exert anti-inflammatory effects on the tissue by blocking plasmin activation of the complement cascade.[19] Studies have shown that TXA led to less up-regulation of proinflammatory genes and an increase in anti-inflammatory genes.[19–22]

The use of TXA in oral or intravenous forms has been limited to episodes and events where the risk of bleeding outweighs the low risk of thromboembolic events. In mastectomies, where the risk of hematoma is not uncommon, the topical administration may be still quite effective for local hemostasis without the systemic side effects, which are still very rare in oral/intravenous forms but need to be avoided, especially in the setting of malignancy.[23] The plasma concentration of topically applied TXA has been shown to be approximately 90% less than when the medication is administered intravenously.[23] TXA is also listed on the World Health Organization's List of Essential Medicines and is quite inexpensive.[24]

In one of the largest trauma trials to date, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 trial, the efficacy and safety of intravenous TXA was assessed in over 20,000 adult trauma patients, and no increase in thromboembolic events was reported.[24] In 32 of the 66 surgical trials on topical TXA, topical TXA was either poured or sprayed directly onto the operative site. Compared with control, the administration of topical TXA significantly reduced the odds of receiving a blood transfusion (OR, 0.29; $P < 0.001$), which was similar to intravenous administration.[25] The concentration of topical TXA used in the trials ranged from 1 to 100 mg/mL. The dosage of topical TXA did not influence effectiveness of topical TXA used in the trials ($P = 0.75$). Topical TXA resulted in a mean blood loss reduction of 276 mL compared with control.[25] In all studies, there was no difference between control for thromboembolism, stroke, myocardial infarction, or death.[25]

In breast reconstruction, most patients will receive drains that lead directly into the surgical pocket. With prolonged drain outputs and bleeding, patients are at higher risks of infection and bacterial seeding of the pocket.[26] This is likely attributable to the communication with skin flora. TXA in this case can decrease average drain output to be able to remove drains faster. In addition to hematoma and residual blood requiring operative intervention and increased risk of infection, the most common complication in implant-based breast reconstruction is capsular contracture. Although not significant ($P = 0.06$), there were seven significant contractures in the placebo group versus one in the TXA-treated group. Under normal circumstances, the implant is surrounded by a fibrous capsule that remains benign and presents no concerns. However, in response to sustained inflammation from a bacterial biofilm or proinflammatory substrates (blood), the capsule can become thickened and/or contract, culminating in capsular contracture.[7] In breast reconstruction, capsular contracture affects up to 8.7% of patients with prepectoral reconstruction and up to 13.9% of patients with subpectoral implants.[7] Despite the high incidence of capsular contracture, effective treatment remains elusive, with up to 54% of surgically managed capsular contracture cases recurring.[27] Topical TXA may not only provide significantly improved serosanguineous output but may exert its anti-inflammatory effects on the breast capsule, decreasing capsular contracture.

Topical use of TXA is still off-label, with no consensus regarding the optimal concentration, mode of application, or duration of contact. An unexpected finding of a possible negative effect of TXA on leakage of lymph was reported in one RCT on topical TXA in mastectomy wounds.[11] In the subgroup of patients receiving TXA who underwent lymph node clearance, TXA had a less beneficial effect on postoperative drain production; these patients were later significantly more likely to need seroma aspiration and had an increased cumulative seroma volume but no increase in chronic seroma. This, however, was not shown in any other study. TXA also may have unrecognized antiadhesive properties in higher concentrations.[11] TXA inhibits plasminogen, which is ubiquitous in tissue matrix and has numerous functions beyond the cleavage of fibrin.[11]

Dosing

In a recent systematic review on TXA in plastic surgery, the authors reviewed the possible dosing for topical administration. In one double-blind RCT, high-dose (3 g) topical TXA had higher potency in reducing blood loss after total knee arthroplasty compared with low-dose (500 mg)

TXA.[28] It showed a reduction of 43% without any significant complications.[28] In addition, the U.S. Department of Veterans Affairs released dosing guidelines for topical irrigation, including 3 g in a 100-mL dilution.[29] Also, in the orthopedic literature, TXA's effect on chondrocytes and normal epithelium was examined to characterize its effect on adjacent tissues.[30,31] It was determined that chondrocyte toxicity increased with both concentration and exposure with a 20- to 25-mg/mL dose being the threshold; however, the individualized cells were exposed for over 48 hours.[30,31] In this trial, the concentration used was 3000 mg/100 mL for limited exposure, which avoids the possible side-effect profile seen in this trial.

Limitations

One of the major limitations of the primary outcome was the patient-derived data reliability. Unfortunately, drain data were usable in only 81.1% of patients for a variety of reasons, as mentioned in the Results section. The investigators repeatedly reminded patients to keep track of their outputs, and each patient received teaching before discharge from the hospital, but this was not always the case. In addition, although the reconstructive procedure was indeed performed by a single reconstructive surgeon, the mastectomies were performed by a variety of general surgeons. Variations in skin flap thickness, mastectomy technique, experience of the oncologic surgeon, and prophylactic versus therapeutic mastectomy could bias many factors and complication rates. Moreover, each side of the patient represents an individual breast with some variation and can be subject to technical variation. Thin flaps can lead to increased complications including flap necrosis. Lastly, this study demonstrated that topical TXA was effective in DTI prepectoral reconstructions; however, further studies that use dermal substitutes, or a delayed reconstruction, will also need to be performed.

CONCLUSIONS

This paired, double-blind, RCT has shown that topical soaking of TXA into the mastectomy pocket before implant insertion leads to significantly decreased JP drain output, decreased JP drain insertion length, and decreased complications. This medication represents an inexpensive, safe, and effective adjunct that should be used in all alloplastic breast reconstructions. Future studies will continue to examine the long-term effects of TXA on outcomes and the breast capsule.

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DISCLOSURE

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REFERENCES

1. American Society of Plastic Surgeons. 2020 plastic surgery statistics report. Available at: https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-report-2020.pdf. Accessed February 9, 2022.
2. Pusic AL, Matros E, Fine N, et al. Patient-reported outcomes 1 year after immediate breast reconstruction: results of the Mastectomy Reconstruction Outcomes Consortium Study. *J Clin Oncol*. 2017;35:2499–2506.
3. Safran T, Al-Halabi B, Viezel-Mathieu A, Boileau JF, Dionisopoulos T. Direct-to-implant, prepectoral breast reconstruction: a single-surgeon experience with 201 consecutive patients. *Plast Reconstr Surg*. 2020;145:686e–696e.
4. Darwish A, Lui F. Physiology, colloid osmotic pressure. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK541067/. Accessed October 3, 2020.
5. Horst K, Eschbach D, Pfeifer R, et al. Local inflammation in fracture hematoma: results from a combined trauma model in pigs. *Mediators Inflamm*. 2015;2015:126060.
6. Casanova J, Sicam RVG, Moreira-Barros J, Huang KG. Late retroperitoneal hematoma with abscess formation following laparoscopic staging of endometrial cancer. *Gynecol Minim Invasive Ther*. 2018;7:31–32.
7. Safran T, Nepon H, Chu CK, et al. Current concepts in capsular contracture: pathophysiology, prevention, and management. *Semin Plast Surg*. 2021;35:189–197.
8. Chatterjee A, Nahabedian MY, Gabriel A, et al. Early assessment of post-surgical outcomes with pre-pectoral breast reconstruction: a literature review and meta-analysis. *J Surg Oncol*. 2018;117:1119–1130.
9. Khansa I, Khansa L, Meyerson J, Janis JE. Optimal use of surgical drains: evidence-based strategies. *Plast Reconstr Surg*. 2018;141:1542–1549.
10. Patel JN, Spanyer JM, Smith LS, Huang J, Yakkanti MR, Malkani AL. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. *J Arthroplasty* 2014;29:1528–1531.
11. Ausen K, Hagen AI, Østbyhaug HS, et al. Topical moistening of mastectomy wounds with diluted tranexamic acid to reduce bleeding: randomized clinical trial. *BJS Open* 2020;4:216–224.
12. Ausen K, Fossmark R, Spigset O, Pleym H. Randomized clinical trial of topical tranexamic acid after reduction mammoplasty. *Br J Surg*. 2015;102:1348–1353.
13. Meaidi A, Mørch L, Torp-Pedersen C, Lidegaard O. Oral tranexamic acid and thrombosis risk in women. *EClinicalMedicine* 2021;35:100882.

14. Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. *J Breast Cancer* 2012;15:373–380.
15. Weissler JM, Banuelos J, Alsayed A, et al. Topical tranexamic acid safely reduces seroma and time to drain removal following implant-based breast reconstruction. *Plast Reconstr Surg Glob Open* 2020;8(9 Suppl):9–10.
16. Weissler JM, Banuelos J, Jacobson SR, et al. Intravenous tranexamic acid in implant-based breast reconstruction safely reduces hematoma without thromboembolic events. *Plast Reconstr Surg.* 2020;146:238–245.
17. U.S. Food and Drug Administration. Lysteda (tranexamic acid) package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022430s009lbl.pdf. Archived (PDF) from the original on March 4, 2016. Accessed October 10, 2020.
18. Roberts I, Perel P, Prieto-Merino D, et al.; CRASH-2 Collaborators. Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *BMJ* 2012;345:e5839.
19. Later AF, Sitniakowsky LS, van Hilten JA, et al. Antifibrinolytics attenuate inflammatory gene expression after cardiac surgery. *J Thorac Cardiovasc Surg.* 2013;145:1611–1616, 1616.e1–1616.e4.
20. Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care* 2007;11:R117.
21. Lei YT, Xie JW, Huang Q, Huang W, Pei FX. The antifibrinolytic and anti-inflammatory effects of a high initial-dose tranexamic acid in total knee arthroplasty: a randomized controlled trial. *Int Orthop.* 2020;44:477–486.
22. Scarafoni EE. A systematic review of tranexamic acid in plastic surgery: what's new? *Plast Reconstr Surg Glob Open* 2021;9:e3172.
23. World Health Organization. Tranexamic acid (inclusion)—adults. Available at: https://www.who.int/selection_medicines/committees/expert/18/applications/tranexamic/en/. Accessed October 10, 2020.
24. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess.* 2013;17:1–79.
25. Montroy J, Hutton B, Moodley P, et al. The efficacy and safety of topical tranexamic acid: a systematic review and meta-analysis. *Transfus Med Rev.* 2018;32:165–178.
26. Chen CF, Lin SF, Hung CF, Chou P. Risk of infection is associated more with drain duration than daily drainage volume in prosthesis-based breast reconstruction: a cohort study. *Medicine (Baltimore)* 2016;95:e5605.
27. Swanson E. Open capsulotomy: an effective but overlooked treatment for capsular contracture after breast augmentation. *Plast Reconstr Surg Glob Open* 2016;4:e1096.
28. Tammachote N, Raphiphan R, Kanitnate S. High-dose (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg): a double-blind randomized controlled trial. *Eur J Orthop Surg Traumatol.* 2019;29:1729–1735.
29. pbm.va.gov. Clinical recommendations for using tranexamic acid for reducing blood loss and transfusion requirements in patients undergoing total knee or total hip arthroplasty. Available at: https://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Tranexamic_Acid_in_TKA_or_THA_Clinical_Recommendations.pdf. Accessed October 10, 2020.
30. Tuttle JR, Feltman PR, Ritterman SA, Ehrlich MG. Effects of tranexamic acid cytotoxicity on in vitro chondrocytes. *Am J Orthop (Belle Mead NJ)* 2015;44:E497–E502.
31. Eikebrokk TA, Vassmyr BS, Ausen K, Gravastrand C, Spigset O, Pukstad B. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. *BJS Open* 2019;3:840–851.