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Burns

Topical Tranexamic Acid on Donor Wounds in Burn Patients: A Randomized Placebo-controlled Trial

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Background: Patients with major burn injuries are prone to massive blood loss owing to tangential excision of burn wounds and donor skin harvesting. In general, topical application of the antifibrinolytic drug tranexamic acid (TXA) to surgical wounds reduces bleeding; however, its effect on bleeding and re-epithelialization in superficial wounds of burns has not been explored.

Methods: This study aimed to investigate the therapeutic potential of topical TXA in reducing blood loss and its effect on wound re-epithelialization in burn surgery. Split-thickness skin graft donor wounds in burn patients were paired and randomized to topical application of either TXA (25 mg/mL) or placebo. Endpoints were postoperative bleeding as measured by dressing weight gain per cm^2 wound area, blood stain area per wound area, and visual evaluation of bleeding in the dressings. Healing time was recorded to analyze the effect on wound re-epithelialization.

Results: There was no significant difference in bleeding or time to re-epithelialization between the TXA and placebo wounds. A post hoc subanalysis of wounds with dressing weight gain above the median, showed a significant difference in favor of TXA. However, use of tumescence may have influenced end points. No significant adverse events related to the study drugs were observed.

Conclusions: This study demonstrates that topical application of TXA (25 mg/mL) to split-thickness skin graft donor wounds does not delay re-epithelialization. Although a reduction in bleeding is suggested, further studies are needed to determine the role of topical TXA in reducing bleeding in burn surgery. *(Plast Reconstr Surg Glob Open 2024; 12:e6074; doi: 10.1097/GOX.0000000000006074; Published online 22 August 2024.)*

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INTRODUCTION

Patients with major burn injuries are prone to massive blood loss due to the tangential excision of burn wounds and donor skin harvesting. Historic quantitative estimates suggest blood loss of 5%–15% of the total blood volume per 1% burn excised and grafted.[1–4] This is a cause of concern because significant blood loss and subsequent transfusions are associated with major morbidity and mortality.[5,6] Interventions such as tourniquets, vasoconstrictors, tumescence, electrocautery, and hemostatic agents have reduced bleeding in burn surgery; however, a consensus regarding the optimal treatment protocol has not been established.[7]

Antifibrinolytic drugs prevent dissolution of clotted blood, thereby reducing bleeding. Tranexamic acid (TXA) is the most commonly used antifibrinolytic drug.[8] Intravenous (IV) administration of TXA in surgical settings can reduce bleeding and the need for blood transfusions by approximately one-third.[9,10] Prophylactic use has become commonplace, particularly in cardiac and orthopedic surgery, and seems exceedingly safe in

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elective surgery.[11–13] However, it is uncertain whether TXA increases the risk of venous thromboembolism (VTE) in patients with potentially disturbed coagulation, particularly in trauma patients and those who have undergone significant bleeding.[14–18] Although observational and retrospective studies have revealed coagulopathy and platelet dysfunction in acute burns, adequately powered prospective studies investigating the association between TXA and risk of thrombosis in burns are lacking.[19]

Topical administration of TXA is an alternative to systemic administration. Although off-label, topical administration may provide therapeutic concentrations on the wound surface with negligible systemic concentrations.[20] Instillation into joints and the mediastinum has shown effects equal to those of IV administration in orthopedic and cardiac surgery.[21] Our group previously demonstrated a similar effect from simple moistening of a wound surface with 25 mg per mL TXA.[22,23] This method may be particularly applicable in burn surgery. However, a possible drawback of local administration is cell toxicity. In an ex vivo human skin wound model, re-epithelialization was inhibited by prolonged exposure to high concentrations of TXA.[24] No such inhibitory effect was present with short-term exposure to even undiluted (100 mg/mL) TXA or prolonged exposure to concentrations below 20 mg per mL, indicating that diluted TXA is unlikely to affect wound re-epithelialization.[24]

This study aimed to evaluate whether topical TXA (25 mg/mL) reduces blood loss or affects wound re-epithelialization in homogenous superficial wounds created from split-thickness skin graft (STSG) harvesting in burn surgery.

METHODS

This single-center, double-blinded randomized controlled trial (RCT) was registered at ClinicalTrials.gov (NCT02918201) and approved by the Norwegian Medicines Agency (16/07752-14) and the Regional Committee for Medical and Health Research Ethics in Mid Norway (2016/831 and 2020/6808). The trial was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

Study Population

Patients admitted to the National Burn Center at Haukeland University Hospital in Bergen, Norway, between January 2021 and April 2022, who were older than 18 years of age and had burn injuries that required treatment with at least two separate donor sites for STSG, were included by three burn surgeons participating in the study. The exclusion criteria were a known allergy to TXA and pregnancy or breastfeeding. Eligible patients or their next of kin received oral and written information about the study before surgery and signed a consent form. For those who were unable to provide informed consent at the time of inclusion and who consented by next of kin, additional written consent was obtained when the patient was medically competent to consider inclusion.

Takeaways

Question: Does topical tranexamic acid reduce bleeding or affect wound re-epithelialization in split-thickness skin graft donor wounds in burn surgery?

Findings: In this first randomized controlled trial on topical tranexamic acid in burns, we have demonstrated that topical use does not delay wound healing. Although a reduction in bleeding is suggested, it was not clinically significant.

Meaning: Topical use of tranexamic acid in burn surgery does not delay wound healing and may have a potential in reducing bleeding.

Intervention

Before trial initiation, the three surgeons participating in the study received training regarding protocol surgical technique. Three pilot patients were included to ensure standardization of intervention. In each patient included in the study, one or more paired donor sites were created using the Zimmer Air dermatome with 0.01" cutting depth and 4-inch-wide plate. The donor wounds were primarily placed on the lower extremities or abdomen. Before harvesting, all donor sites were infiltrated with a tumescent (saline-epinephrine solution 2 µg/mL), in accordance with our institutional standard of care. Paired wounds were of comparable size, depth, and location and were labeled "A" and "B." The wounds' location and label were documented in a separate study form for each wound pair. A study nurse not involved in the operation prepared two identical vials of 20 mL saline, marking them "A" and "B." A sealed numbered study envelope stated which vial should receive TXA. In the study drug vial, 5 mL of saline was replaced with 5 mL of 100 mg per mL TXA, yielding a solution of 25 mg per mL TXA. Both vials received 0.1 mL epinephrine 1 mg per mL, yielding an epinephrine concentration of 5 µg per mL to match the hemostatic saline-epinephrine solution applied topically to donor wounds at our burn center. The sets of vials and the corresponding study ID numbers were delivered to the operating theater.

After skin graft harvesting, donor wounds were immediately and temporarily covered with gauze soaked in 5 µg per mL saline-epinephrine solution, in accordance with standard of care.

At the time of epinephrine gauze removal, the study donor sites were smeared with the entire volume of respective study solutions, and gloves were changed between each application to avoid cross-contamination. The study wounds were then covered with an innermost nonabsorbent layer of Vaseline gauze and five dry surgical gauzes to absorb the blood and exudate. The weight of a single dry gauze was consistent (27.5 g). The dressings were marked "A" and "B" according to the drug vials used. On the extremities, a circular elastic bandage loosely secured the five study gauzes. On the trunk, the dressings were held in place using a loose and elastic tubular net bandage. No occlusive bandages were used, as vapor from one study wound could then be absorbed by the gauzes overlying the other wound.

On the first postoperative day, the dressings were removed, except for the innermost Vaseline gauze. The wound surface area and the area of the blood stain on the innermost gauze were measured. Dressing weight gain was calculated by weighing the five dry gauzes and subtracting the dry weight (137.5 g). The paired gauzes were then visually assessed for bleeding. This was photo documented for later direct comparison by two of the participating surgeons. We used the intensity of the color and number of layers stained as markers. Contamination of blood and oozing from neighboring donor wounds were noted. In instances where the surgeons differed in opinion, the photographs were reassessed for consensus. Registration of first postoperative day data was performed by one of the participating surgeons along with a study nurse, all of whom were blinded.

Until wound healing at approximately 3–4 weeks, the participants were monitored for possible adverse events and postoperative complications.

Randomization

Computer-generated randomization in blocks of 10 and 6, production of corresponding sealed study envelopes, and organization of electronic case report forms were provided by the Clinical Research Unit of St. Olav's University Hospital, Trondheim, Norway. Sealed envelopes were sent to the burn center at Haukeland University Hospital, where randomization instructions were executed by a study nurse who was otherwise not connected to the surgical procedures or patient follow-ups. All participants and personnel involved in surgery, follow-up, data collection, and statistical analysis were blinded to the randomization.

Study Endpoints

The primary endpoint was postoperative bleeding, defined as the net weight gain of the dressings per wound area. The secondary endpoints were blood stain to wound area ratio and visual comparison of the amount of blood between paired dressings. All variables were recorded on the first postoperative day. Additional secondary outcomes were time to re-epithelialization, defined as no oozing in the dressings, and the occurrence of complications, such as wound infections and thromboembolic events. This information was obtained by investigators participating in dressing changes and by extraction from patients' medical records. For patients discharged from the hospital before complete re-epithelialization, additional data was collected through video consultations.

Statistical Analysis

A 25% or more reduction in bleeding in TXA donor wounds was considered clinically significant. A delay in healing time or an increase in infection rate of 25% or more was also considered clinically significant. The SD was uncertain, as few similar studies exist but were estimated to be 0.4, based on previous effect studies.[22,23] As each patient was his or her own control, using a paired samples *t* test to detect a difference of 0.25, and a standard deviation of 0.4, α of 0.05, and power of 0.80, a sample size of 23 wound pairs was needed.[25] We chose to include a total of 36 wound pairs for additional power in case of technical difficulties, because previous effect studies did not use the same surrogate variables for bleeding used in this study. Continuous data were analyzed using the paired samples *t* test for normally distributed data and Wilcoxon signed-rank test for nonnormally distributed data. Categorical data were analyzed using the chi squared test. We analyzed the results for each wound pair as separate cases (Table 1) and for each patient as separate cases, using average variable scores for the wound pairs within the same patient (Table 2).

RESULTS

Twenty-four patients (36 wound pairs) were enrolled in the study. One patient was excluded because the study drug was not administered due to technical error. The final dataset consisted of 23 patients with 35 wound pairs (Fig. 1). Five wound pairs had blood stains that had reached the edges of the gauzes or bled through all five gauzes, indicating insufficient dressing material and a possible loss of fluid. Therefore, we conducted a post hoc analysis excluding wounds with blood overflow (Table 3). All continuous data were nonnormally distributed, and the Wilcoxon signed-rank test was used for these analyses. Conducting a paired sample *t* test on the log-transformed data did not change the overall results.

Overall, there was no significant difference in the variables used to assess bleeding [dressing weight gain per cm^2 wound surface, blood stain area-to-wound area ratio, and observer visual comparison of the amount of blood in the dressing material (Tables 1–3)]. However, when conducting a post hoc subanalysis of wounds where the placebo wound had a dressing weight gain equal to or above the median, the difference in dressing weight gain per cm^2 was significantly in favor of TXA in all three versions of the analyses (Tables 1–3, *P* value range 0.016–0.041), albeit not with the 25% difference which we had set as a clinically relevant level. There was a nonsignificant trend toward a smaller blood stain area-to-wound area ratio in the TXA wound. Similarly, visual assessment of the dressing material more often rated placebo dressings as having absorbed the most blood (Fig. 2). However, the difference was significant only after excluding wounds with potentially significant errors due to blood overflow (Table 3).

There was no difference in the time to re-epithelialization between TXA and placebo wounds (Tables 1–3). A local wound infection was noted in both TXA and placebo wounds in five wound pairs, and solely in the TXA wound in two wound pairs. The difference was not significant ($P = 0.75$, chi-squared test). One patient experienced a pulmonary embolism 2 weeks after inclusion, and one patient experienced a thrombus in association with a central venous catheter.

DISCUSSION

This is the first RCT on topical use of TXA in burn patients. Only two case reports and one prospective observational study have been published on topical use in burns.[26–28] The main strength of the study is the

Table 1. Results Analyzed by Wound Pairs

	All Wound Pairs (n = 35)*			Wound Pairs ≥ Median Bleeding (n = 18)†		
	TXA	Placebo	*P*	TXA	Placebo	*P*
Wound surface area, cm^2 (mean ± SD)	206±67	209±72	0.792	177±67	189±76	0.418
Dressing weight gain, g per cm^2 wound surface (mean ± SD)	0.35±0.19	0.38±0.21	0.120	0.46±0.21	0.52±0.20	0.016
Blood stain to wound area ratio (mean ± SD)	1.53±0.68	1.60±0.78	0.228	1,72±0.87	1.79±0.96	0.177
Dressing with most blood (n (%))	TXA: 9/35 (25.7) Placebo: 13/35 (37.1) Similar: 13/35 (37.1)		0.549	TXA: 5/18 (27.8) Placebo: 9/18 (50.0) Similar: 4/18 (22.2)		0.467
Days to re-epithelialization (mean ± SD)	18.5±10.2	18.3±9.9	0.109	19.5±10.2	19.1±9.8	0.109

*Complete material, each pair of wounds calculated individually.
†Post hoc separate analysis for high bleed placebo wounds with dressing weight gain per wound cm^2 ≥ median.

Table 2. Results Analyzed per Patient

	All Participants (n = 23)*			Patients with ≥ Median Bleeding (n = 12)†		
	TXA	Placebo	*P*	TXA	Placebo	*P*
Dressing weight gain, g per cm^2 wound surface (mean ± SD)	0.38±0.20	0.42±0.23	0.065	0.50±0.20	0.58±0.21	0.031
Blood stain to wound area ratio (mean ± SD)	1.58±0.75	1.66±0.86	0.375	1.63±0.79	1.78±1.10	0.213
Dressing with most blood (n (%))	TXA: 5/23 (21.7) Placebo: 9/23 (39.1) Similar: 9/23 (39.1)		0.197	TXA: 3/12 (25.0) Placebo: 5/12 (42.0) Similar: 4/12 (33.0)		0.317
Days (n) to re-epithelialization (mean ± SD)	17.9±8.1	17.7±8.1	0.109	18.8±8.0	18.3±8.1	0.109

*Complete material, using mean values for the sum of TXA and placebo wounds in each participating patient.
†Post-hoc separate analysis for high bleed placebo wounds with dressing weight gain per wound cm^2 ≥ median.

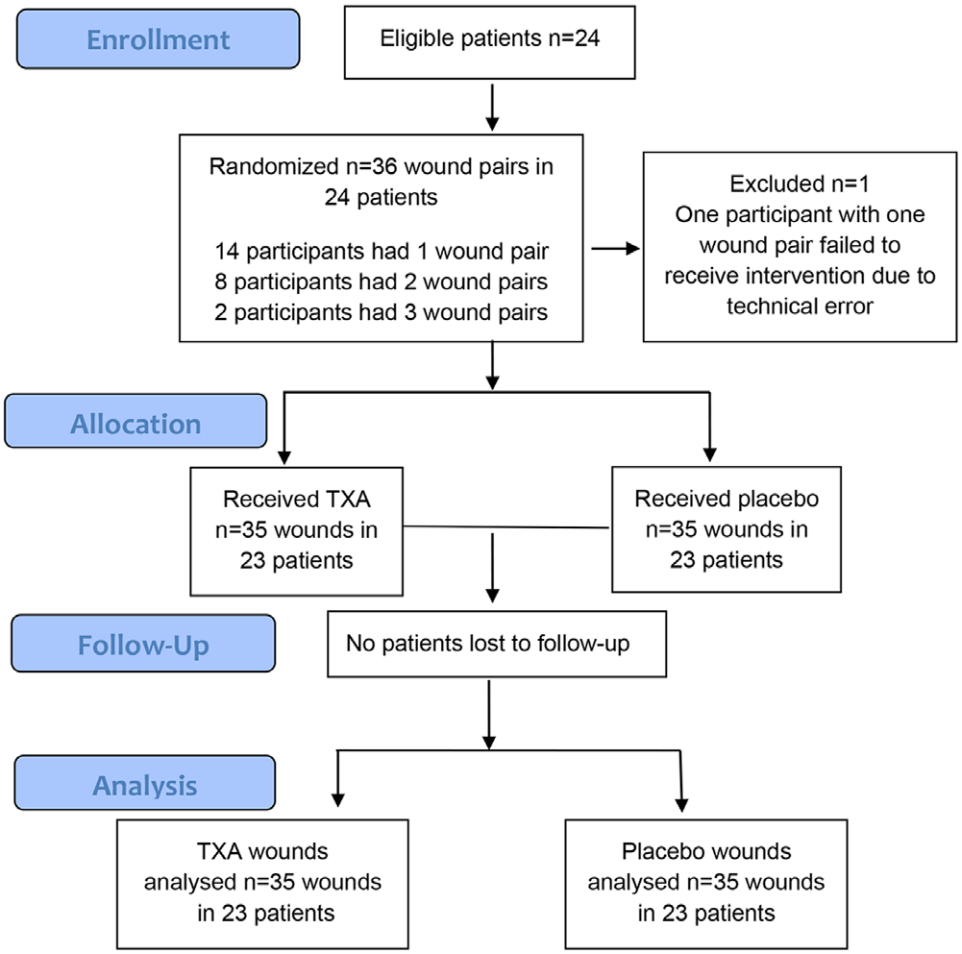

Fig. 1. CONSORT diagram for the study.

double-blind RCT design and within-patient randomization for optimizing homogeneity of study wounds. Furthermore, this study adds to safety data in burns, as it demonstrates that topical TXA 25 mg per mL does not delay re-epithelialization, nor does it lead to any other adverse effects. However, this pilot study failed to demonstrate a clinically relevant reduction in bleeding from topical use of TXA in the selected patient population, which we postulate may be due to flaws in study size and design.

A major limitation of this study is the indirect measurement of wound bleeding. Estimating blood loss during surgery is difficult, and, to date, there is no gold standard method. Gravimetric estimation leads to underestimation of blood loss[29] and does not separate blood from other fluids. If topical TXA were applied to all wounds in a patient, appropriate formulas could have been used to assess systemic blood loss. However, this was not an option given the within-patient randomization of relatively small wounds. Notably, blood loss estimation formulas may also be uncertain and tend to overestimate the blood loss.[29]

A major confounding factor in our study is the use of tumescence infiltration. The study institution infiltrates donor sites with a saline-epinephrine hemostatic solution which effectively reduces bleeding. In addition, the solution contributes to the volume absorbed by overlying dressing material. The amount of tumescence infiltration was not registered. As most of the fluid in dressing material with the least amount of blood could have been primarily transudate and infiltration fluid, a post hoc separate assessment of the wounds with dressing weight above median in the placebo wounds was conducted, assuming that these wounds bled more. In this population, topical TXA reduced dressing weight. Of note, our post hoc analysis and assumptions were done in the aftermath of the technical difficulties encountered in this pilot study. Ideally, the study should have been performed in a study population where the use of tumescence has not been introduced. However, we did not find it ethically sound to remove an effective standard of care.

Another limitation of this study is the rather coarse and subjective determination of a "healed wound." Though not an established and validated end point for burn wound healing, as such is lacking, we defined the wound as healed when the wound appeared with a dry surface and was no longer oozing in the dressings. Alternatively, histological examination would require multiple biopsies, but we did not deem such an intervention appropriate for

this pilot study. The study suggests that 25 mg per mL of topical tranexamic acid does not significantly affect re-epithelialization. Still, conclusions cannot be finally drawn regarding the effect of TXA on other scar properties such as tensile strength.[30,31]

Our study encountered further technical difficulties. When visually assessing the dressing material, blood had sometimes reached the edges of the gauze and/or bled through all five gauzes. This led to an uncertainty regarding the actual amount of fluid absorbed by the study gauzes, since fluid may have been absorbed by adjacent dressing or bandage material. In addition, in cases of more extensive burn injuries, we were forced to place the donor wounds in proximity because of the lack of available donor skin. In these instances, we sometimes experienced contamination of blood and fluid from neighboring donor wounds. In retrospect, additional dressing materials should be added to each wound.

Two patients included in our study experienced vascular occlusive events: one pulmonary embolism 2 weeks postoperatively and one venous thrombus associated with a central venous catheter. As the total wound surface area exposed to TXA was very small in our study, a systemic concentration above the therapeutic threshold value for antifibrinolytic effects is very unlikely.[20] However, the study was not powered to evaluate the risk of venous thromboembolism (VTE). Although there seem to be benefits from intravenous TXA in certain trauma situations,[14,32] there is little research on its use in burns. Walsh et al addressed this issue in 2014, pointing out the complexity of burn patients with an associated increased risk of VTE.[33] To our knowledge, three RCTs[34–36] and three retrospective studies[37–39] on the use of IV TXA in burn surgery have been published. All the studies reported significantly reduced transfusion requirements. However, the sample sizes were small and insufficient for evaluating the potential effect of TXA on VTE. Only Dominguez et al[37] found any vascular occlusive events but without significant differences between the TXA and placebo groups.

Based on the mechanism of action of TXA and current knowledge regarding the possible increased risk of VTE that intravenous TXA poses on traumatized patients,[15] topical TXA may be a sound alternative in burn patients, as it results in lower plasma concentrations and reduced risk of systemic effects. However, systemic drug concentration is expected to be proportional to the dose applied[40] and may also be influenced by the surface area, tissue vascularity, and duration of exposure. In vitro studies have suggested that fibrinolysis is significantly inhibited by a plasma concentration of approximately 10 µg per mL in adults.[41] Moistening of the wound surface after abdominoplasty with 20 mL of TXA (25 mg/mL) resulted in a peak serum concentrations of 5.2 ± 2.6 µg per mL.[20] Hence, covering an extensive burn with large volumes of TXA (25 mg/mL) is likely to lead to concentrations above the threshold value for systemic therapeutic effects, thereby theoretically increasing the risk of VTE. As concentrations as low as 1 mg per mL have been found to be effective in wound irrigation, lower concentrations and, possibly, other modes of administration,

Table 3. Results Analyzed after Excluding Wound Pairs with Blood Overflow

	All Wound Pairs (n = 30)*			Wound Pairs ≥ Median Bleeding (n = 15)†		
	TXA	Placebo	*P*	TXA	Placebo	*P*
Dressing weight gain, g per cm² wound surface (mean ± SD)	0.34 ± 0.19	0.37 ± 0.20	0.199	0.44 ± 0.21	0.51 ± 0.20	0.041
Blood stain to wound area ratio (mean ± SD)	1.50 ± 0.58	1.50 ± 0.50	0.854	1.66 ± 0.74	1.63 ± 0.58	0.551
Dressing with most blood (n (%))	TXA: 6/30 (20.0) Placebo: 13/30 (43.3) Similar: 11/30 (36.7)		0.201	TXA: 2/15 (13.3) Placebo: 9/15 (60.0) Similar: 4/15 (26.7)		0.035
Days to re-epithelialization (mean ± SD)	19.1 ± 10.9	18.8 ± 10.7	0.109	20.1 ± 11.1	19.5 ± 10.7	0.109

Wound pairs with blood overflow (n = 5) excluded from total number of wound pairs (n = 35).
*Complete material, each pair of wounds calculated individually.
†Post-hoc separate analysis for high bleed placebo wounds with dressing weight gain per wound cm² ≥ median.

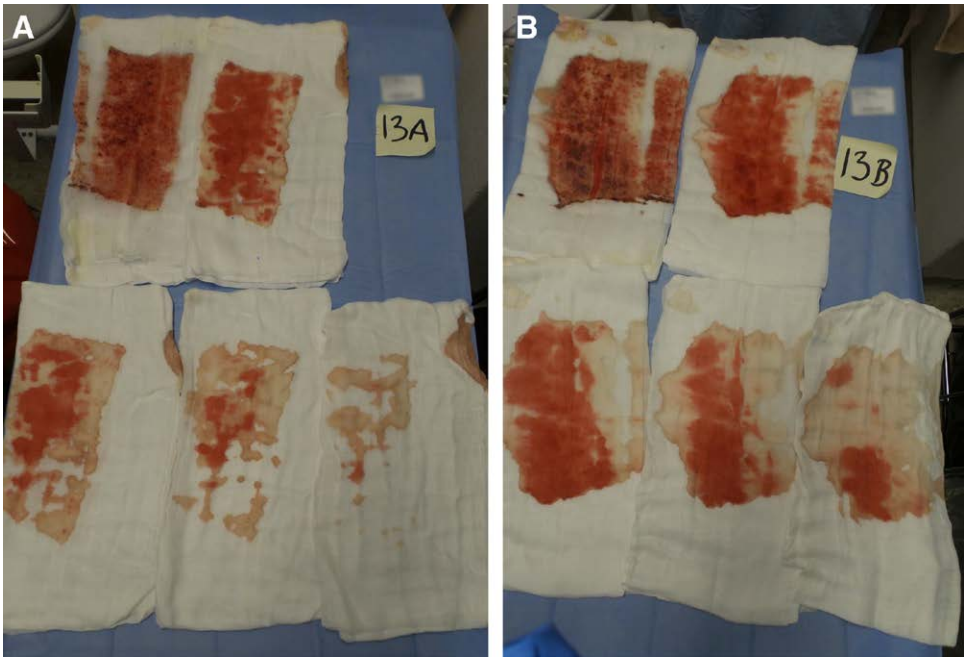

Fig. 2. Photo documentation of dressing material that covered paired STSG donor wounds for visual comparison of bleeding.

such as moistening the innermost dressing,[28] may be prudent in burn surgery.

CONCLUSIONS

Topical use of TXA in burn surgery does not delay wound re-epithelialization. Our study failed to demonstrate a clinically significant reduction in bleeding when topical TXA was applied to STSG donor wounds infiltrated with tumescence. Further studies are needed to explore the role of topical TXA in donor wounds, grafted wound areas, and superficial wounds. The limitations in methodology and the confounding factors of this first pilot RCT may conceal a potential benefit from topical use of TXA in burn surgery.

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DISCLOSURES

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REFERENCES

1. Steadman PB, Pegg SP. A quantitative assessment of blood loss in burn wound excision and grafting. *Burns.* 1992;18:490–491.
2. Snelling. Quantitative evaluation of blood loss during excision and grafting of bum wounds. *Bull Clin Rev Bum Inj.* 1984;1:44.
3. Warden GD, Saffle JR, Kravitz M. A two-stage technique for excision and grafting of burn wounds. *J Trauma.* 1982;22:98–103.
4. Pasch S, Joolukuntla A, Hauck E, et al. 797 estimated blood loss in burns: a quality metric that defies measurement? *J Burn Care Res.* 2020;41:S235–S235.
5. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA.* 2003;289:959–962.
6. Johnson DJ, Scott AV, Barodka VM, et al. Morbidity and mortality after high-dose transfusion. *Anesthesiology.* 2016;124:387–395.
7. Israel JS, Greenhalgh DG, Gibson AL. Variations in burn excision and grafting: a survey of the American Burn Association. *J Burn Care Res.* 2017;38:e125–e132.
8. Elena Scarafoni E. A systematic review of tranexamic acid in plastic surgery: what's new? *Plast Reconstr Surg Glob Open.* 2021;9:e3172.
9. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ.* 2012;344:e3054–e3054.
10. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database Syst Rev.* 2013;23:CD010563.

11. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*. 2014;349:g4829.
12. Ng WCK, Jerath A, Wasowicz M. Tranexamic acid: a clinical review. *Anestezjol Intensywna Ter*. 2015;47:339–350.
13. Heyns M, Knight P, Steve AK, et al. A single preoperative dose of tranexamic acid reduces perioperative blood loss: a meta-analysis. *Ann Surg*. 2021;273:75–81.
14. 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.
15. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86:20–27.
16. Myers SP, Neal MD. Venous thromboembolism after tranexamic acid administration: legitimate risk or statistical confounder? *ANZ J Surg*. 2020;90:425–426.
17. Roberts I, Shakur-Still H, Afolabi A, et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395:1927–1936.
18. Devereaux PJ, Marcucci M, Painter TW, et al;POISE-3 Investigators. Tranexamic acid in patients undergoing noncardiac surgery. *N Engl J Med*. 2022;386:1986–1997.
19. Pidcoke HF, Isbell CL, Herzig MC, et al. Acute blood loss during burn and soft tissue excisions: an observational study of blood product resuscitation practices and focused review. *J Trauma Acute Care Surg*. 2015;78:S39–S47.
20. Ausen K, Pleym H, Liu J, et al. Serum concentrations and pharmacokinetics of tranexamic acid after two means of topical administration in massive weight loss skin-reducing surgery. *Plast Reconstr Surg*. 2019;143:1169e–1178e.
21. 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.
22. Ausen K, Fossmark R, Spigset O, et al. Randomized clinical trial of topical tranexamic acid after reduction mammoplasty. *Br J Surg*. 2015;102:1348–1353.
23. 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.
24. Eikebrokk TA, Vassmyr BS, Ausen K, et al. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. *BJS Open*. 2019;3:840–851.
25. Paired t-test [online tool]. Available at http://www.biomath.info/power/prt.htm. Accessed June 9, 2023.
26. Tang YMJ, Chapman TWL, Brooks P. Use of tranexamic acid to reduce bleeding in burns surgery. *J Plast Reconstr Aesthet Surg*. 2012;65:684–686.
27. Barsun A, Sen S, Palmieri TL, et al. Reducing postburn injury anemia in a Jehovah's witness patient. *J Burn Care Res*. 2014;35:e258–e261.
28. Mohan A, Vishwanath G, Rajendran N. A study to evaluate reduction in blood loss by topical application of tranexamic acid in burn wound surgery. *J Mar Med Soc*. 2021;23:129–134.
29. Gerdessen L, Meybohm P, Choorapoikayil S, et al. Comparison of common perioperative blood loss estimation techniques: a systematic review and meta-analysis. *J Clin Monit Comput*. 2021;35:245–258.
30. Cox S, Cole M, Mankarious S, et al. Effect of tranexamic acid incorporated in fibrin sealant clots on the cell behavior of neuronal and nonneuronal cells. *J Neurosci Res*. 2003;72:734–746.
31. Björlin G, Nilsson IM. The effect of antifibrinolytic agents on wound healing. *Int J Oral Maxillofac Surg*. 1988;17:275–276.
32. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg*. 2012;147:113–119.
33. Walsh K, Nikkhah D, Dheansa B. What is the evidence for tranexamic acid in Burns? *Burns*. 2014;40:1055–1057.
34. Jennes S, Degrave E, Despiegeleer X, et al. Effect of tranexamic acid on blood loss in burn surgery: a preliminary study. *J Burn Care Rehabil*. 2003;24:S59–S59.
35. Bhatia N, Sen I, Kumari K, et al. Impact of single dose intravenous tranexamic acid on peri-operative blood transfusion requirements in burn patients: a prospective, randomized trial. *Egypt J Anaesth*. 2017;33:251–255.
36. Ajai KS, Kumar P, Subair M, et al. Effect of single dose intravenous tranexamic acid on blood loss in tangential excision of burn wounds—A double blind randomised controlled trial. *Burns*. 2022;48:1311–1318.
37. Domínguez A, Alsina E, Landín L, et al. Transfusion requirements in burn patients undergoing primary wound excision: effect of tranexamic acid. *Minerva Anestesiol*. 2017;83:353–360.
38. Tapking C, Hundeshagen G, Kirchner M, et al. Tranexamic acid reduced blood transfusions in acute burn surgery: a retrospective case-controlled trial. *Burns*. 2022;48:522–528.
39. Cook S, Carney B, Lodge M, et al. The use of tranexamic acid to reduce blood loss in pediatrics burns: our institute's experience. Australia and New Zealand Burn Association 42nd Annual Scientific Meeting 2018. Available at https://slideplayer.com/slide/14346805/. Accessed June 12, 2023.
40. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010;92:2503–2513.
41. Andersson L, Nilsoon IM, Colleen S, et al. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci*. 1968;146:642–658.