Safety and Efficacy of Local Tranexamic Acid for the Prevention of Surgical Bleeding in Soft-Tissue Surgery: A Review of the Literature and Recommendations for Plastic Surgery

Kjersti Ausen, M.D., Ph.D.
Reidar Fossmark, M.D., Ph.D.
Olav Spigset, M.D., Ph.D.
Hilde Pleym, M.D., Ph.D.

Trondheim, Norway

**Background:** Although high-bleed surgery routinely utilizes the antifibrinolytic drug tranexamic acid, most plastic surgical procedures are conducted in soft tissue with low-volume bleeding. Unease regarding possible systemic adverse effects prevents widespread systemic use, but local use of tranexamic acid is gaining popularity among plastic surgeons. Randomized controlled trials on topical use of tranexamic acid are mainly from high-bleed surgeries, and few studies address the effect in soft tissue. This article reviews the scientific evidence regarding local use of tranexamic acid in soft-tissue surgery, discusses pharmacological effects and possible adverse reactions, and presents recommendations for use in plastic surgery.

**Methods:** A systematic search of databases for studies on local use of tranexamic acid in soft-tissue surgery was performed. Randomized controlled trials were included for a systematic review on effect; a narrative review regarding other clinically relevant aspects is based on extensive literature searches combined with the authors’ own research.

**Results:** Fourteen randomized controlled trials, including 1923 patients, were included in the systematic review on local use of tranexamic acid in soft-tissue surgery.

**Conclusions:** Local use of tranexamic acid may reduce blood loss comparably to intravenous prophylactic use with negligible risk of systemic adverse effects, but high-quality randomized controlled trials are few. Prolonged exposure to high local concentrations is discouraged, and direct contact with the central nervous system may cause seizures. No single superior means of administration or dosage is supported in the literature, and lowest effective dose is unknown. There may not be one single ideal dosing regimen, but rather many possibilities adaptable for different surgical situations. (Plast. Reconstr. Surg. 149: 774, 2022.)

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wound ruptures. Keeping surgical bleeding to a minimum is, thus, beneficial for both patient and provider. Fear of bleeding may also prevent plastic surgeons from using adequate thromboprophylactic measures as addressed by the American Society of Plastic Surgeons Venous Thromboembolism Prevention Task Force.

In surgery, a balance between coagulation and fibrinolysis is needed to prevent bleeding yet maintain circulation. If fibrinolysis exceeds coagulation, bleeding may occur despite adequately performed hemostasis. While meticulous surgical technique, use of cautery, and local infiltration of wound edges with adrenaline can largely control bleeding in soft-tissue surgery, bony tissue cannot be infiltrated or manipulated to the same extent. Measures such as hypotensive anesthesia and pharmacological aids are, therefore, used to control bleeding in bony tissue.

Antifibrinolytic drugs have been the only available pharmacological means of a general reduction of bleeding with an acceptable safety profile in patients without coagulation deficiencies. Tranexamic acid is a synthetic low-cost antifibrinolytic drug manufactured and approved for intravenous and oral use, and systemic prophylactic use reduces both bleeding volume and transfusion needs by 30 to 40 percent. Although large studies have found little evidence of a prothrombotic effect from tranexamic acid, contradictory studies do exist. Moreover, a dose-dependent increase in seizures has been documented from intravenous use of tranexamic acid in cardiac surgery. Fear of possible adverse effects has, therefore, limited routine systemic use to surgery with expected high-volume bleeding and frequent need of blood transfusions; this includes mostly surgery affecting skeletal structures, such as joint arthroplasties, craniomaxillofacial surgery, and cardiac surgery, with its associated thoracotomy, use of cardiopulmonary bypass, and high-dose anticoagulation. Use in burns is not established, probably because of uncertainties regarding adverse effects of tranexamic acid during ongoing hyperfibrinolysis.

An alternative to systemic use of tranexamic acid is local administration, which may provide sufficient drug concentrations at the wound surface with negligible risk of systemic adverse effects. Three meta-analyses on the use of topical tranexamic acid in surgery all demonstrate a significant reduction of blood loss and transfusion needs without any increase in adverse events. However, in the two first meta-analyses by Ker et al. in 2013 and Montroy et al. in 2018, only two of 29 and three of 66 studies, respectively, addressed surgery conducted in soft tissues. In the latest meta-analysis, by Teoh et al. in 2020, seven of 71 studies addressed soft-tissue surgery.

The term “plastic surgery” encompasses exceedingly diverse procedures. Both systemic and topical use of tranexamic acid have already been explored in plastic surgical fields that involve skeletal structures such as rhinoplasty, craniomaxillofacial, and orthognathic surgery. Yet, the larger bulk of plastic surgery takes place in soft tissue, and the effect of tranexamic acid according to type of tissue may be as clinically relevant as the effect in specific procedures.

Local use of tranexamic acid has been adopted by influential plastic surgeons and is receiving increasing attention. Four published reviews on the use of tranexamic acid in plastic surgery since 2016 have, however, only identified a total of three randomized controlled trials on topical use, with two in orthognathic surgery and only one in soft tissue (i.e., reduction mammoplasty).

The aim of this article is to provide insight on the pharmacological effects and adverse effects of tranexamic acid, review the current scientific evidence regarding local use in soft-tissue surgery, and present recommendations for use of tranexamic acid in plastic surgery.

**METHODS**

To describe the effect of local tranexamic acid in soft tissue, a systematic literature search was performed. The narrative review regarding other clinically relevant aspects is based on extensive literature searches combined with the authors’ own research and clinical experience.

**TRANEXAMIC ACID: EFFECTS BEYOND ANTIFIBRINOLYSIS**

Fibrinolysis is executed by the proteolytic enzyme plasmin. Plasmin also triggers platelet activation and thus increases platelet consumption. Plasmin inhibition will thus reduce bleeding both by reducing fibrin degradation and by preserving platelets.

Plasminogen is the inert precursor of plasmin. Plasminogen has multiple binding sites for the amino acid lysine. Binding to a lysine residue on the surface of fibrin, or to plasminogen receptors on a variety of cells, induces a conformational change in plasminogen to allow activation. Tissue-plasminogen activator released from damaged endothelium co-docks with plasminogen bound to fibrin. This co-docking aids the activation of plasminogen to plasmin, and proteolytic degradation...
of fibrin ensues (Fig. 1). In a variety of cells and tissues, plasminogen bound to plasminogen receptors is activated by urokinase-type plasminogen activators. Plasmin/plasminogen and plasminogen activators are involved in multiple physiological and pathophysiological processes outside of the fibrinolytic system. These include cell adhesion, migration and signaling, inflammation, wound debridement, and tissue remodeling.

Tranexamic acid is a synthetic analogue of lysine that blocks the lysine binding site on plasminogen, thus preventing the activation of plasminogen to plasmin (Fig. 1, below, right). Tranexamic acid can also block urokinase-type plasminogen activator. Tranexamic acid may therefore affect many processes related to surgery and wound healing other than fibrinolysis. The clinical implications of these complex interactions are insufficiently explored.

Lysine analogues can also act as competitive antagonists to inhibitory neurotransmitters acting on glycine and GABA receptors in the central nervous system and thus cause hyperexcitability. This is a plausible explanation for the increase in seizures observed after high-dose intravenous administration in cardiac surgery. Direct application of tranexamic acid onto the central nervous system can lead to generalized seizures and even death.

**CONSIDERATIONS REGARDING TRANEXAMIC ACID TISSUE CONCENTRATION, ADMINISTRATION FORM, AND DOSE**

A tissue concentration of at least 10 µg/ml tranexamic acid is needed to significantly inhibit fibrinolysis.
fibrinolysis. A single intravenous dose of 10 to 15 mg/kg will keep plasma concentration above 10 µg/ml for 1 to 3 hours and may have little risk of adverse effects, such as venous thromboembolism or seizures. Although much higher dosing has been practiced, particularly in cardiac but also craniomaxillofacial surgery, there is little clinical support for increased effect with high dosing, and the reports of a dose-dependent increase in seizures is changing dosing practice. Tissue and synovial fluid tranexamic acid concentrations match those in plasma, whereas cerebrospinal fluid concentration reaches approximately 10% of plasma concentration. Concentrations will, however, remain high for a longer period in tissue than in plasma, possibly because of strong binding to plasminogen, and time to peak concentration and retention time may vary among tissues.

The lowest effective concentration for local use is unknown. It is also unclear whether topical effect is determined by drug concentration, total drug dose, and/or a combination of concentration and contact time. In a meta-analysis by Montroy et al. on topical use of tranexamic acid, the effect on transfusion needs was not affected by dose; drug concentrations ranged from 1 to 100 mg/ml. Even the lowest concentration of 1 mg/ml solution will expose the wound surface to a concentration 100-fold stronger than what is considered the lowest inhibitory concentration in plasma. The effect of tranexamic acid may possibly be achieved through both prolonged exposure to low concentrations and short exposure to high concentrations.

Topical use of tranexamic acid is mostly applied at the end of a surgical procedure and, thus, cannot influence perioperative bleeding. Systemic administration of tranexamic acid before the initiation of surgery may be preferred when there is a risk of significant intraoperative hemorrhage, if a clear intraoperative view is essential, or if the procedure itself may trigger hyperfibrinolysis and platelet aggregation (e.g., through the use of cardiopulmonary bypass). When choosing systemic administration of tranexamic acid, adherence to recommended dose would be prudent.

**EFFECT OF LOCAL TRANEXAMIC ACID IN SOFT-TISSUE SURGERY**

**Literature Search Strategy and Study Selection**

With assistance from a Medical Research Librarian, we searched Medline, PubMed, Embase, The Cochrane Central Register of Controlled Trials, The Web of Science Core Collection, Google Scholar, and ClinicalTrials.gov from inception through March 20, 2020, for studies comparing the effect of local administration of tranexamic acid in surgery to either placebo or standard of care. The full electronic search strategy is provided in the Appendix. (See Appendix, Supplemental Digital Content 1, which shows the search strategy systematic review from March 20, 2020, http://links.lww.com/PRS/E932.) Search result and selection process are presented in Figure 2. Two authors (K.A. and R.F.) independently reviewed the retrieved results using the following inclusion criteria: (1) study population receiving local use of tranexamic acid in connection with a surgical procedure, (2) human studies, and (3) abstract or full-text article published. Orthopedic or cardiac studies and minor procedures, such as dental extractions or biopsies, were excluded. A full-text review of remaining publications was performed, and reference lists of relevant publications were screened. Randomized controlled trials were identified for final analyses for the systematic review. Other studies were included for the narrative review.

**Data Collection**

In the randomized controlled trials, type of procedure, study sample size, tranexamic acid concentration, volume applied, mode of administration, and comparator were recorded for each study. Outcome data included blood loss, transfusion requirements, postoperative major bleeding requiring intervention, and surgeon satisfaction with the surgical field.

**RESULTS**

Twenty-two randomized controlled trials investigating the effect of local use of tranexamic acid outside of cardiac and orthopedic surgery were identified. Fifteen addressed soft-tissue surgery. According to the type of soft-tissue surgery, the randomized controlled trials were classified as “superficial tissue” or “inner organs.” Seven studies of tranexamic acid application in superficial soft tissues were identified, five with topical administration (Table 1) and two with local infiltration (Table 2). Eight studies addressed inner organs, four of which were performed in open surgery (Table 3) and four in minimally invasive surgery (Table 4). Thus, 14 studies from soft-tissue surgery, including a total of 1923 patients, were included. Eight randomized
controlled trials from craniomaxillofacial (i.e., orthognathic and endoscopic sinus) surgery\textsuperscript{71-78} were identified; one study was excluded because of inadequate information.\textsuperscript{78} These studies are presented separately as they may be of interest to surgeons in associated fields (Table 5) but are not discussed in detail in this review.

Among the randomized controlled trials from soft-tissue surgery, two randomized controlled trials in reduction mammaplasty\textsuperscript{31} and mastectomy\textsuperscript{58} came from our group and were designed to assess the effect of topical application of tranexamic acid in soft tissue relevant to plastic surgery. The mode of application was moistening the wound surface with tranexamic acid 25 mg/ml, leaving a thin film of fluid only, as demonstrated in this video: https://www.youtube.com/watch?v=-8MAE3NAHfQ. Both studies found a 30 to 40 percent reduction in postoperative bleeding.

Removal of adenoids in children represents a model of superficial wounds. Albirmawy et al.\textsuperscript{57} poured a bolus of 10 ml of undiluted 100 mg/ml tranexamic acid into the nasopharynx and left it for 5 minutes; they then gradually suctioned nasopharyngeal fluid for another 5 minutes. They found a 27 percent reduction in blood loss.

The pockets created in pacemaker/defibrillator surgery resemble implant pockets in plastic surgery.
surgery. Parisi et al.\textsuperscript{59} irrigated 100 pockets with undiluted 100 mg/ml tranexamic acid or placebo and found hematomas needing intervention in two tranexamic acid patients (4 percent) versus 12 placebo patients (24 percent). Although this study has been published as an abstract only, the reduction in hematomas is particularly interesting, as all patients were on anticoagulants.

In all four randomized controlled trials on topical tranexamic acid in superficial soft-tissue procedures, postoperative hemorrhage requiring intervention was more frequent in the placebo group than in the tranexamic acid group (Table 1). When combining the four randomized controlled trials, active intervention because of postoperative hemorrhage was needed in three of 379 patients (0.8 percent) receiving tranexamic acid versus 21 of 379 patients (5.5 percent) receiving placebo.

Two randomized controlled trials in superficial tissue used tissue infiltration of tranexamic acid instead of topical application (Table 2). In Mohs microsurgery, Zilinsky et al.\textsuperscript{61} found that a mixture of 50 mg/ml tranexamic acid and 1% lidocaine was effective in reducing bleeding.

### Table 1. Randomized Controlled Trials on Local Use of Tranexamic Acid in Soft-Tissue Surgery: Superficial Tissue, Topical Application

| Reference, Year, Publication Type | TXA Group (total sample size) | Procedure | Concentration of TXA, Volume, Mode of Administration | Comparator | Bleeding\* | Postoperative Hemorrhagic Incidence/Intervention/Transfusion† |
|----------------------------------|-------------------------------|-----------|------------------------------------------------------|------------|-----------|----------------------------------------------------------|
| Ausen 2015, article\textsuperscript{31} | 28 (56) | Reduction mammoplasty | 25 mg/ml, 20 ml, topical moistening | 20 ml saline as placebo | Drain production at 24 h (ml) median (range) TXA 12.5 (0–44) vs placebo 20.5 (0–100), \( p = 0.038 \) | Hematoma warranting reoperation before drain removal (n): TXA = 0 vs placebo = 2 |
| Ausen 2019, article\textsuperscript{58} | 101 (202) | Mastectomy | 25 mg/ml, 20 ml, topical moistening | 20 ml saline as placebo | Drain production at 24 h (ml) mean (95% CI): TXA 110 (97–123) vs placebo 144 (122–167), \( p = 0.01 \) | Hematoma warranting reoperation before drain removal (n): TXA = 1 vs placebo = 7 |
| Albirmawy 2013, article\textsuperscript{57} | 200 (400) | Adenoidectomy in children | 100 mg/ml, 10 ml, topical bolus left for 5 minutes before suction removal. | 10 ml saline as placebo | Intraoperative blood loss (ml) TXA 19 ± 2.5 vs placebo 26 ± 4.3, \( p = 0.003 \) | Postoperative hemorrhage (n): TXA = 5 vs placebo = 12; Nasal packing needed: TXA = 1 vs placebo = 4. Transfusion TXA = 0 vs placebo = 2 |
| Parisi 2013, conference abstract\textsuperscript{59} | 50 (100) | Subcutaneous pocket for cardiac pacemaker | 100 mg/ml, 10 ml, topical irrigation | No irrigation as control | Not measured | Presence of hematoma within 15 days (n): TXA = 2 vs control = 1; Surgical revision needed: TXA = 1 vs control = 8 |

\( \text{TXA, tranexamic acid; CI, confidence interval.} \)

\*Values are mean ± SD unless otherwise stated.

†Values (n) are number of patients unless otherwise stated.

### Table 2. Randomized Controlled Trials on Local Use of Tranexamic Acid in Soft-Tissue Surgery: Superficial Tissue, Local Infiltration

| Reference, Year, Publication Type | TXA Group (total sample size) | Procedure | Concentration of TXA, Volume, Mode of Administration | Comparator | Bleeding\* | Postoperative Hemorrhagic Incidence/Intervention/Transfusion |
|----------------------------------|-------------------------------|-----------|------------------------------------------------------|------------|-----------|----------------------------------------------------------|
| Zilinsky 2019, article\textsuperscript{61} | 60 (127) | Mohs microsurgery in head/neck | Lidozone 20 mg/ml diluted 1:1 with 100 mg/ml TXA | Lidozone 20 mg/ml diluted with saline as placebo | Ratio of dressing blood stain to surgical wound size TXA = 1.8 vs placebo = 2.5, \( p < 0.001 \) | Not assessed |
| Sagiv 2018, article\textsuperscript{60} | 17 (34) | Upper blepharoplasty | Lidozone 20 mg/ml diluted 1:1 with 100 mg/ml TXA | Lidozone 20 mg/ml diluted with saline as placebo | No difference in blood weight in pads or cautery time | No significant difference in ecchymoses |

\( \text{TXA, tranexamic acid.} \)

\*Values are mean ± SD unless otherwise stated.
lidocaine significantly reduced the dressing blood stain–to–wound size ratio by 28 percent compared to lidocaine diluted with saline. Sagiv et al. did not find statistically significant differences using the same solution in a possibly underpowered study in upper eyelid blepharoplasty.

Randomized controlled trials from open surgery on inner organs find both reduced bleeding volumes and transfusion needs from topical use of tranexamic acid (Table 3). Sabry et al. performed lung decortication surgery, which may be comparable to capsule/scar tissue excisions. They applied 100 ml of 30 mg/ml tranexamic acid into the thoracic cavity.

Two randomized controlled trials investigated the effect of topical tranexamic acid in open hysterectomy and myomectomy, which may reflect the effect of topical tranexamic acid in muscle. In open hysterectomy, Sallam and Shady combined irrigation and an intraabdominal bolus using 20 mg/ml tranexamic acid, whereas in open myomectomy, Shady et al. applied 20 mg/ml tranexamic acid by means of a soaked gauze compressing the myoma bed for 5 minutes. In open prostatectomy, Pourfakhr et al. irrigated the wound bed with 5 ml of undiluted 100 mg/ml tranexamic acid. In sum, these randomized controlled trials from open surgery on inner organs report a 34 to 40 percent reduction of blood loss, and 19 of 401 tranexamic acid patients (4.7 percent) versus 53 of 401 placebo patients (13.2 percent) needed transfusion.

In minimally invasive procedures (Table 4), adding tranexamic acid to the irrigation fluid (final concentrations of 0.2 to 1 mg/ml) reduced blood loss in transurethral prostate surgery, percutaneous nephrolithotomy, and hysteroscopic myomectomy by 24 to 38 percent.

The visibility of the surgical field influences both operative result and safety. In nephrolithotomy, Bansal and Arora found that irrigation fluid volume spent was halved when tranexamic acid was added to the fluid, and the risk of vessel injury requiring angioembolization was also significantly reduced. Rasheedy et al. reported three cases of uterine instrumental perforation during hysteroscopic myomectomy associated with poor operative field visibility in the placebo group.

**Cocktail Solutions: Adding Tranexamic Acid to Local Anesthetics or Tumescent**

Intraarticular tranexamic acid combined with adrenaline has shown superiority to tranexamic acid alone in reducing blood loss in joint arthroplasties.

Namazi first suggested adding tranexamic acid to tumescence solution both for hair transplantation and liposuction. Fernau reported adding 1 mg/ml tranexamic acid to tumescence and infiltrating flanks in a blinded paired randomized fashion and found consistently less bruising on the tranexamic acid side. In rhytidectomies,
Schroeder and Langsdon\(^8^2\) used local anesthetics or tumescence containing 10 mg/ml tranexamic acid and found a 70 percent reduction in drain output on the first day in a recent retrospective cohort study; Couto et al.,\(^8^3\) Nayak and Linkov,\(^2^5\) and Kochuba et al.\(^8^4\) reported reductions in operating time and drain production in rhytidectomy using tumescence with only 0.75 to 2 mg/ml tranexamic acid. In rhinoplasty, Brown et al.\(^8^5\) have reported adding tranexamic acid to the local anesthetic solution in addition to using intravenous tranexamic acid. Randomized controlled trials on the use of tranexamic acid in rhinoplasty generally address systemic administration.\(^2^0,2^2\)

In the four randomized controlled trials by our group and Zilinsky’s group\(^3^1,5^8,6^0,6^1\) (Tables 1 and 2), the effect of tranexamic acid alone as a hemostatic was examined, although both groups normally use cocktails with both lidocaine and adrenaline. More research is needed on a possible synergy between adrenaline and tranexamic acid for hemostasis in soft tissue.

**LOCAL INFILTRATION OR TOPICAL APPLICATION?**

Although local infiltration may provide higher and longer-lasting levels of tranexamic acid in the tissue,\(^2^5\) infiltrated tranexamic acid may not reach the raw wound surface to the same extent as free-flowing, topically applied tranexamic acid. Although topical (i.e., intraarticular) application of tranexamic acid has been proven noninferior to intravenous administration in orthopedic surgery,\(^8^6,8^7\) studies assessing infiltration are few and find less effect.\(^8^8,8^9\)

In liposuction, systemic or infiltrative administration are the only options. In larger open surgery, complete contact between raw wound surface and tranexamic acid is more easily achieved through moistening than infiltration. In surgery with smaller wound areas, such as dermal surgeries, rhinoplasties, face lifts, and blepharoplasties, sufficiently large volumes of cocktail solutions may be injected to ensure contact between tranexamic acid and raw wound and provide a longer-lasting depot effect. Dosing and practicality may guide mode of administration.\(^9^0\)

**SYSTEMIC ADVERSE EFFECTS AFTER TOPICAL APPLICATION?**

None of the three meta-analyses on topical use of tranexamic acid found any difference in incidence of possible systemic adverse events.\(^1^6-1^8\) Tissue concentration after intravenous
administration quickly matches that of plasma, and local administration resulting in a peak plasma concentration above 10 µg/ml can thus theoretically provide an antifibrinolytic concentration in other tissues. Plasma concentrations after topical administrations have mostly been investigated using single measurements at single time-points, and peak plasma concentrations have therefore been largely unknown. In a pharmacokinetic study in patients undergoing abdomino-plasties, moistening these large wound surfaces with 25 mg/ml tranexamic acid or instilling a 200-mL bolus of 5 mg/ml tranexamic acid generally produced lower peak serum concentrations than 10 µg/ml. However, systemic concentration may be proportional to topical drug concentration and dose and may also be influenced by tissue vascularity and contact time. In knee arthroplasties, plasma concentrations reaching 10 to 20 µg/ml have been demonstrated both after a 500-mg intraarticular dose with prolonged drain clamping and after a 3-g dose without drain clamping.

**LOCAL ADVERSE EFFECTS AFTER LOCAL USE?**

As discussed previously, tranexamic acid should never be applied topically onto the
central nervous system, as this may cause convulsions.41–43,79,98 High doses of tranexamic acid, as provided by topical application, may also inhibit glutamate receptors, which are present in various tissues.98 Human receptors with affinity for lysine analogues and the consequences of such bindings are inadequately explored.

Studies on the local toxicity of tranexamic acid have mainly been conducted on cartilage, tendon, and synovial tissue, but our group and others have investigated the effect on keratinocytes and fibroblasts in vitro.95,103–105 Short exposures even to high doses seem well-tolerated, as do prolonged exposures to concentrations below 10 mg/ml. The threshold value for toxicity may lie around 25 mg/ml given several hours of exposure, such as after intraarticular administration.99,100,102 In soft tissue, a physiological dilution of the drug may ensue faster.

Adverse effects may not only be caused by excessively high concentrations. Tranexamic acid in cancer treatment was investigated in the 1980s because of an observed inhibitory effect of tranexamic acid on tumor invasiveness and vascularization.106 Our group made the unexpected observation that prolonged exposure to high concentrations of topical tranexamic acid caused lack of re-epithelialization and even nontoxic epithelial detachment in an ex vivo human skin wound model.95 We have also observed an unexplained increase in seroma in patients undergoing mastectomy with axillary lymph node clearance; to our knowledge, this is the first description of a possible clinically relevant adverse effect after topical tranexamic acid.58 The possible effect by tranexamic acid on cell adherence and migration caused by mechanisms linked to plasminogen/plasmin outside of the fibrinolytic system may explain these observations.35 In vivo, drugs will be physiologically diluted, and a prolonged exposure of several days from laboratory studies does not translate into clinical practice.

Topical tranexamic acid may, however, also have positive effects other than reduced bleeding; documented beneficial effects include reduction of inflammatory response in surgery,107,108 and a reduction of melasma and erythema in dermatology.109,110 Tranexamic acid enemas in colorectal anastomosis surgery may prevent collagenolysis and anastomotic leakage.111 In animal models, fibrin glue containing tranexamic acid gave fewer intraabdominal adhesions,112,113 and topical tranexamic acid reduced healing in tendons but increased healing in fractures.115,116 The plethora of processes involving plasminogen/plasmin/urokinase-type plasminogen activator warrants further investigations regarding potential adverse and beneficial effects of topical tranexamic acid.

CONCLUSIONS

Local use of tranexamic acid may reduce blood loss comparably to intravenous prophylactic use with negligible risk of systemic adverse effects. It may also prevent reoperation because of hematoma. Tranexamic acid should, however, never come into contact with the central nervous system, as it may cause convulsions. Although prolonged exposure to high concentrations is discouraged, no single superior means of administration or dosage is supported in the literature, and lowest effective dose is unknown. There may not be one single ideal dosing regimen, but rather many possibilities adaptable for different surgical situations. Tranexamic acid in local anesthetics/tumescence with added adrenaline may be beneficial for both topical and infiltrative use. Systemic administration of tranexamic acid may, however, be beneficial for surgery with hard-to-control perioperative bleeding, particularly surgery involving bony structures. More high-quality studies are needed to determine whether efficacy and safety differ among the various methods of administration, and we look forward to future publications as the plastic surgical community continues to explore the use of tranexamic acid.

Kjersti Ausen, M.D., Ph.D.
Section for Plastic and Reconstructive Surgery
Clinic of Surgery
St. Olav’s University Hospital
P.O. Box 3250 Torgarden
N-7006 Trondheim, Norway
kjerstiausen@gmail.com

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REFERENCES

1. Murphy RX Jr, Alderman A, Gutowski K, et al. Evidence-based practices for thromboembolism prevention: Summary of the ASPS Venous Thromboembolism Task Force Report. Plast Reconstr Surg. 2012;130:168e–175e.

2. Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of
41. Furtmüller R, Schlag MG, Berger M, et al. Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther. 2009;329:118-17.

42. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. Ann Neurol. 2016;79:18-26.

43. Patel S, Robertson B, McConachie I. Catastrophic drug errors involving tranexamic acid administered during spinal anaesthesia. Anaesthesia 2019;74:904-914.

44. Andersson L, Nilsson IM, Colleen S, Granstrand B, Melander B. 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.

45. Eriksson O, Kjellman H, Billbrant A, Schonnang M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol. 1974;7:375-380.

46. Kirksey MA, Wilson LA, Fiasconaro M, Poeran J, Liu J, et al. Diffusional pharmacokinetics of tranexamic acid during cardiopulmonary bypass: A meta-analysis of randomized trials. BMC Anesthesiol. 2019;19:129.

47. Guo J, Gao X, Ma Y, et al. Different dose regimens and administration methods of tranexamic acid in cardiac surgery: A meta-analysis of randomized trials. J Oral Maxillofac Surg. 2015;73:129–133.

48. Goobie SM, Staffa SJ, Meara JG, et al. BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319–2331.

49. Fergusson DA, Hébert PC, Mazer CD, et al.; BART Investigators. A double-blind, placebo-controlled, randomized clinical trial. Crit Care. 2010;14:R157.

50. Parisi Q, Messano L, Santamaria M, Alessandri F. Pocket irrigation with tranexamic acid reduces the risk of hematoma formation in patients on anticoagulant therapy submitted to pacemaker/defibrillator surgery. Eurosurge. 2013;15:171.

51. Sagiv O, Rosenfeld E, Kalderon E, et al. Subcutaneous tranexamic acid in upper eyelid blepharoplasty: A prospective randomized pilot study. Can J Ophthalmol. 2018;53:600-604.

52. Zilinsky I, Barazani TB, Visentin D, Ahuja K, Martinowitz U, Haik J. Subcutaneous injection of tranexamic acid to reduce bleeding during dermatologic surgery: A double-blind, placebo-controlled, randomized clinical trial. Dermatol Surg. 2019;45:759-767.

53. Falbe-Hansen J Jr, Jacobsen B, Lorenzen E. Local application of an antifibrinolytic in tonsillectomy. A double-blind study. J Laryngol Otol. 1974;88:565-568.

54. Pourfakhr P, Gatai E, Gooran S, et al. Local administration of tranexamic acid during prostatectomy surgery: Effects on reducing the amount of bleeding. Nephron Mon. 2016;8:e4090.

55. Sabry MM, Sallam AA, Elgehaly AS, Abdelwahab AA. Evaluation of local intra-pleural application of tranexamic acid on postoperative blood loss in lung decortication surgery, a prospective, randomized, double-blind, placebo-controlled study. Ann Card Anaesth. 2018;21:409-412.

56. Sallam HF, Shady NW. Reducing blood loss during abdominopelvic hysterectomy with intravenous versus topical tranexamic acid: A double-blind randomized controlled trial. J Obstet Gynaecol India 2019;69:173-179.

57. Shady NW, Sallam HF, Fahmy H. Reducing blood loss during open myomectomy with intravenous versus topical tranexamic acid: A double-blinded randomized placebo-controlled trial. Middle East Fertility Society Journal 2018;23:225–231.

58. Abdullah A, Javed A. Does topical tranexamic acid reduce post-turp hematuria: A double blind randomized control trial. Urology 2012;81:2922.

59. Bansal A, Arora A. A double-blind, placebo-controlled randomized clinical trial to evaluate the efficacy of tranexamic acid in irrigant solution on blood loss during percutaneous nephrolithotomy: A pilot study from tertiary care center of North India. World J Urol. 2017;35:1223–1240.

60. Rani R, Mittal S, Choubey SK, Pipara G. Use of tranexamic acid as a topical agent to reduce bleeding during TURP: A novel technique! Int J Sci Res. 2018;7:66–68.

61. Rashedeey R, Makled A, Abou-Gamrah A, Guima H. Intravenous instillation of tranexamic acid in hysteroscopic myomectomy: A double-blind, placebo-controlled, parallel-group randomized clinical trial. Journal of Minimally Invasive Gynecology 2019;16:16.

62. Athanasiadis T, Beule AG, Wormald PJ. Effects of topical antifibrinolytics in endoscopic sinus surgery: A novel technique! Int J Sci Res. 2017;21:737–742.

63. Baradaranfar MH, Davudnia MH, Mahmoudi H, et al. The effect of topical tranexamic acid on bleeding reduction during functional endoscopic sinus surgery. Iran J Otorhinolaryngol. 2017;29:69–74.

64. Eftekharian H, Vahedi R, Karagah T, Tahrizi R. Effect of tranexamic acid irrigation on perioperative blood loss during orthognathic surgery: A double-blind, randomized controlled clinical trial. J Oral Maxillofac Surg. 2015;73:129–133.

65. Jahanshahi J, Hashemian F, Pazira S, et al. Effect of topical tranexamic acid on bleeding and quality of surgical field.
during functional endoscopic sinus surgery in patients with chronic rhinosinusitis: A triple blind randomized clinical trial. Plast Reconstr Surg 2014;133:1044–77.

Kavepradab P, Apiapan B, Rummasak D. Does tranexamic acid in an irrigating fluid reduce intraoperative blood loss in orthognathic surgery? A double-blind, randomized clinical trial. J Oral Maxillofac Surg. 2011;69:e186–e189.

Shehata A, Ibrahim MS, Abd-El-Fattah MH. Topical tranexamic acid versus hot saline for field quality during endoscopic sinus surgery. The Egyptian Journal of Otolaryngology 2014;40:327–331.

Amal Da T. Evaluation of topical tranexamic acid to control bleeding following endoscopic sinus surgery—A one year hospital based clinical trial. Cochrane Central Register of Controlled Trials. 2012. Available at: https://www.cochranelibrary.com/central/doi/10.1002/centr/1415759/full. Accessed January 28, 2022.

Yu Z, Yao L, Yang Q. Tranexamic acid plus diluted-epinephrine versus tranexamic acid alone for blood loss in total joint arthroplasty: A meta-analysis. Medicine (Baltimore) 2017;96:e7095.

Namazi MR. Practice pearl: A novel anesthetic solution for decreasing the blood loss at the recipient site of hair transplantation (Namazi solution). Aesthetic Plast Surg. 2007;31:415.

Namazi MR. Practice pearl: Using ‘Namazi solution’ for decreasing the formation of bruises in liposuction. J Cutan Aesthet Surg. 2014;7:69–70.

Schroeder RJ 2nd, Langsdon PR. Effect of local tranexamic acid on hemostasis in rhytidectomy. Facial Plast Surg Aesthet Med. 2020;22:195–199.

Couto RA, Charafeddine A, Sinclair NR, Nayak LM, Zins JE. Local infiltration of tranexamic acid with local anesthetic reduces intraoperative facelift bleeding: A preliminary report. Aesthet Surg J. 2020;40:587–593.

Kochuba AL, Coombs DM, Kwicijon JG, Sinclair NR, Zins JE. Prospective study assessing the effect of local infiltration of tranexamic acid on facelift bleeding. Aesthet Surg J. 2021;41:391–397.

Brown S, Brown T, Tessone A. Role of tranexamic acid in rhinoplasty. Plast Reconstr Surg Glob Open. 2019;7:12.

Li J, Zhang Z, Chen J. Comparison of efficacy and safety of topical versus intravenous tranexamic acid in total hip arthroplasty: A meta-analysis. Medicine (Baltimore) 2016;95:e4689.

Sridharan K, Sivaramakrishnan G. Tranexamic acid in total knee arthroplasty: Mixed treatment comparisons and recursive cumulative meta-analysis of randomized, controlled trials and cohort studies. Basic Clin Pharmacol Toxicol. 2018;122:111–119.

Arun-Kumar V, Naresh-Babu J. Is there a role for preoperative local infiltration of tranexamic acid in elective spine surgery? A prospective randomized controlled trial analyzing the efficacy of intravenous, local infiltration, and topical administration of tranexamic acid. Global Spine J. 2021;11:21–27.

Virani SR, Dahapute AA, Panda I, Bava SS. Role of local infiltration of tranexamic acid in reducing blood loss in peritrochanteric fracture surgery in the elderly population. Malays Orthop J. 2016;10:26–30.

Cho MJ, Rohrich RJ. The role of tranexamic acid in plastic surgery: Review and technical considerations. Plast Reconstr Surg. 2018;142:842–9.

De Bonis M, Cavaliere F, Alessandri F, et al. Topical use of tranexamic acid in coronary artery bypass operations: A double-blind, prospective, randomized, placebo-controlled study. J Thorac Cardiovasc Surg. 2000;119:575–580.

Krohn CD, Sorensen R, Lange JE, Riise R, Bjornsen S, Brostad F. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. The European Journal of Surgery Supplement: = Acta Chirurgica Supplement 2003;588:57–61.

Nadeau R, Howard J, Ralley F, Somerville L, Naudie D. Systemic absorption of intravenous and topical tranexamic acid in primary total hip arthroplasty. Orthopaedic Proceedings 2016;98-B:56.

Wong J, Abishiami A, El Beheiyy 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.

Eikebrokk TA, Vassmyr BS, Aussen K, Gravastrand C, Spigset O, Pukstad B. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. BJ Clin Pharmacol. 2019;3:840–851.

Sa-ngasoongsong P, Chanplakorn P, Wongsak S, et al. An in vivo study of low-dose intra-articular tranexamic acid application with prolonged clamping drain method in total knee replacement: Clinical efficacy and Safety. Biomed Res Int. 2015;2015:164206.

Jules-Elysee KM, Tseng A, Sculco TP, et al. Comparison of topical and intravenous tranexamic acid for total knee replacement: A randomized double-blinded controlled study of effects on tranexamic acid levels and thrombogenic and inflammatory marker levels. J Bone Joint Surg Am. 2019;101:2120–2128.

Lecker I, Wang DS, Kaneshwaran K, Mazer CD, Orser BA. High concentrations of tranexamic acid inhibit ionotropic glutamate receptors. Anesthesiology 2017;127:89–97.

McLean M, McCulll K, Smith IDM, et al. Tranexamic acid toxicity in human periarticular tissues. Bone J Res. 2019;8:11–18.

Parker JD, Lim KS, Kieser DC, Woodfield TBF, Hooper GJ. Is tranexamic acid toxic to articular cartilage when administered topically? What is the safe dose? Bone Joint J. 2018;100-B:404–412.

Sitek P, Wysocka-Wycisk A, Kepski F, Kroli D, Bursig H, Dylag S. PRP-fibrinogen gel-like chondrocyte carrier stabilized by TXA-preliminary study. Cell Tissue Bank. 2013;14:135–140.

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.

Bergenholtz A, Gustafson GT, Hänström L. The effect of antifibrinolytic agents on wound healing in vitro. Experientia 1977;33:254–256.

Cox S, Cole M, Mankarious S, Tawil N. Effect of tranexamic acid incorporated in fibrin sealant clots on the cell behavior of neuronal and nonneuronal cells. J Neurosci Res. 2005;72:734–746.

Fürst W, Banerjee A, Redl H. Comparison of structure, strength and cytocompatibility of a fibrin matrix supplemented either with tranexamic acid or aprotinin. J Biomed Mater Res B Appl Biomater. 2007;82:109–114.

Sundbeck A, Alpsten M, Appelgren L, Karlsson L, Månsson LG, Peterson HI. Influence of tranexamic acid on tumour blood flow. Anticancer Res. 1981;1:141–148.

Lei YX, 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.

Wu KT, Siu KK, Ko JY, Chou WY, Kuo SJ, Hsu YH. Tranexamic acid reduces total blood loss and inflammatory response in computer-assisted navigation total knee arthroplasty. Biomed Res Int. 2019;2019:5207517.
109. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: A clinical trial with histological evaluation. *J Eur Acad Dermatol Venereol*. 2013;27:1035–1039.

110. Zhu JW, Ni YJ, Tong XY, Guo X, Wu XP, Lu ZF. Tranexamic acid inhibits angiogenesis and melanogenesis in vitro by targeting VEGF receptors. *Int J Med Sci*. 2020;17:903–911.

111. Jacobson RA, Williamson AJ, Wienholts K, et al. Prevention of anastomotic leak via local application of tranexamic acid to target bacterial-mediated plasminogen activation: A practical solution to a complex problem. *Ann Surg*. 2021;274:e1038–e1046.

112. Wiseman D, Lyachovetsky Y, Keidan I, Trout JR, Nur I. The effect of tranexamic acid in fibrin sealant on adhesion formation in the rat. *J Biomed Mater Res B Appl Biomater*. 2004;68:222–230.

113. Wiseman DM, Meidler R, Lyachovetsky Y, Kurman E, Horn S, Nur I. Evaluation of a fibrin preparation containing tranexamic acid (Adhexil) in a rabbit uterine horn model of adhesions with and without bleeding and in a model with two surgical loci. *Fertil Steril*. 2010;93:1045–1051.

114. Çıraklı A, Gürgör PN, Uzun E, Erdem H, Çankaya S, Baş O. Local application of tranexamic acid affects tendon healing negatively in the late period. *Eklem Hastalik Cerrahisi*. 2018;29:20–26.

115. Çevik HB, Eceviz E, Çilingir Kaya OT, Ercan F, Çeçen GS. The effect of topical and systemic tranexamic acid on fracture healing in rats. *Acta Orthop Traumatol Turc*. 2020;54:207–212.

116. Degirmenci E, Ozturan KE, Sahin AA, Yılmaz F, Kaya YE. Effects of tranexamic acid on the recovery of osteochondral defects treated by microfracture and acellular matrix scaffold: An experimental study. *J Orthop Surg Res*. 2019;14:105.