OPEN

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.)

From the Section for Plastic and Reconstructive Surgery, Clinic of Surgery, Department of Clinical Pharmacology, and Clinic of Anesthesia and Intensive Care, St. Olav's University Hospital; and Departments of Circulation and Medical Imaging and Clinical and Molecular Medicine, Norwegian University of Science and Technology.

Received for publication July 23, 2020; accepted April 13, 2021.

DOI: 10.1097/PRS.0000000000008884

Although most plastic surgical procedures are not associated with major blood loss, bleeding causes swelling, bruising and pain, need for drains and bandage changes, and reoperations, and may increase the risk of infection and

Disclosure: *Dr. Ausen has received a Ph.D. grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology. None of the authors has a financial interest to declare in relation to the content of this article.*

Related digital media are available in the full-text version of the article on www.PRSJournal.com.

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.[1]

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.[2] 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.[3,4] Although large studies have found little evidence of a prothrombotic effect from tranexamic acid,[5–8] contradictory studies do exist.[9–11] Moreover, a dose-dependent increase in seizures has been documented from intravenous use of tranexamic acid in cardiac surgery.[12] 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[13,14] is not established, probably because of uncertainties regarding adverse effects of tranexamic acid during ongoing hyperfibrinolysis.[15]

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[16–18] 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[16] and Montroy et al. in 2018,[17] 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,[18] 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.[19–22] 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.[23–27] Four published reviews on the use of tranexamic acid in plastic surgery since 2016[19,21,26,28] have, however, only identified a total of three randomized controlled trials on topical use, with two in orthognathic surgery[29,30] and only one in soft tissue (i.e., reduction mammaplasty).[31]

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.[32] Plasmin also triggers platelet activation and thus increases platelet consumption.[33] 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,[34] induces a conformational change in plasminogen to allow activation.[35] 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

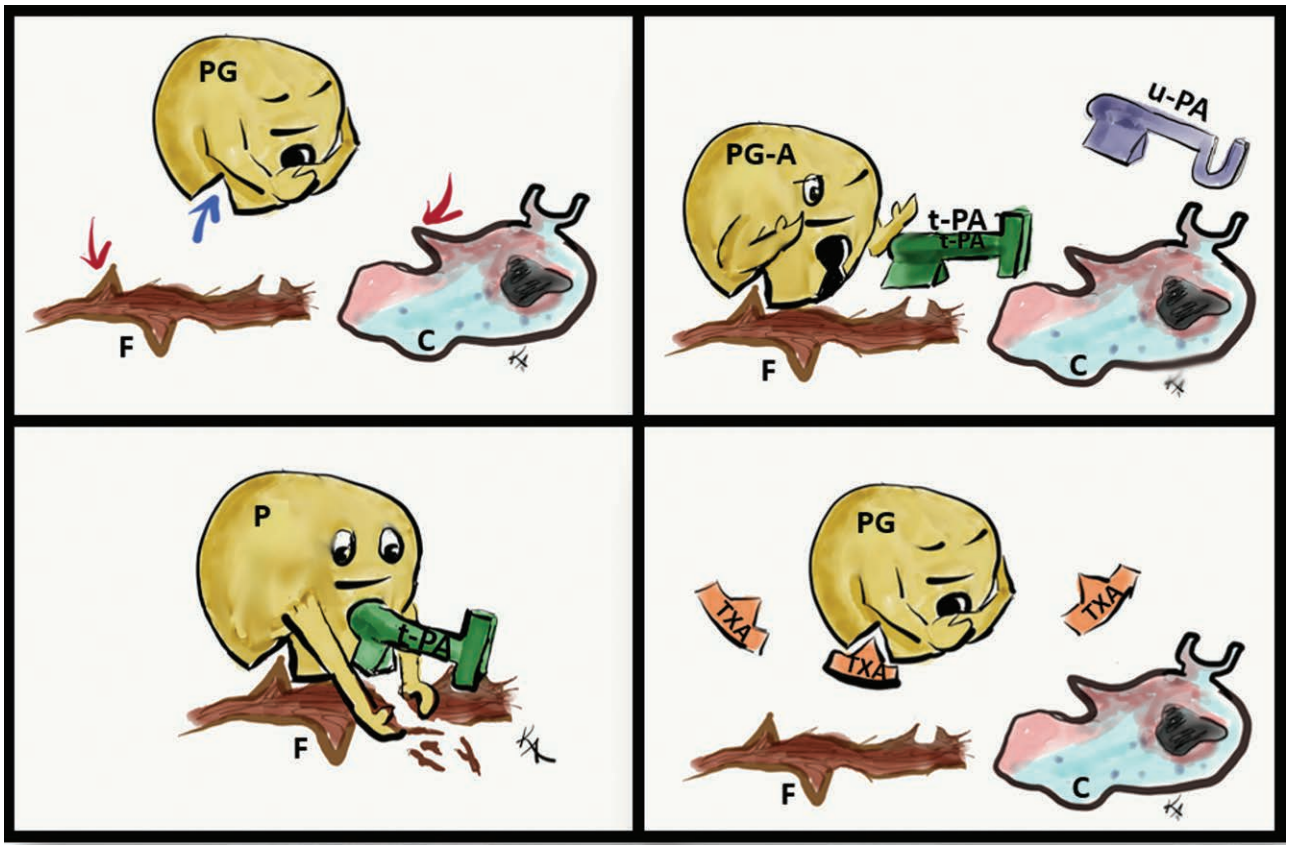

Fig. 1. (*Above, left*) Plasminogen is the inert precursor to plasmin. It is produced from the liver and released into the circulation. In its unbound circulating state, plasminogen has a closed activation-resistant confirmation. Lysine binding sites on plasminogen (*blue arrow*) facilitate docking to exposed residues of the amino acid lysine (*red arrows*) on the surface of both fibrin (*F*) and a variety of cells (*C*). (*Above, right*) Docking to a lysine residue causes a conformational change in plasminogen (*PG-A*) that allows for its activation by plasminogen activators. Tissue-plasminogen activator (*t-PA*) is present in vessel endothelium and released upon vessel injury. Urokinase-type plasminogen activator (*u-PA*) is present in all tissue. (*Below, left*) Co-docking of plasminogen and t-PA on fibrin transforms plasminogen into the proteolytic enzyme plasmin (*P*) and fibrinolysis ensues. Similarly, co-docking of plasminogen and u-PA on cell surfaces can provide cells with proteolytic properties. (*Below, right*) Tranexamic acid is a lysine analogue, and binding to the lysine binding site of plasminogen prevents its docking and, thus, its activation.

of fibrin ensues (Fig. 1). In a variety of cells and tissues, plasminogen bound to plasminogen receptors is activated by urokinase-type plasminogen activator. Plasmin/plasminogen and plasminogen activators are involved in multiple physiological and pathophysiological processes outside of the fibrinolytic system.[34,36] These include cell adhesion, migration and signaling, inflammation, wound debridement, and tissue remodeling.[35,37]

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*).[38] Tranexamic acid can also block urokinase-type plasminogen activator.[39] 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[40] and $GABA_A$[41] receptors in the central nervous system and thus cause hyperexcitability.[42] This is a plausible explanation for the increase in seizures observed after high-dose intravenous administration in cardiac surgery.[12] Direct application of tranexamic acid onto the central nervous system after accidental intrathecal injection has led to generalized seizures and even death.[43]

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.[44] A single intravenous dose of 10 to 15 mg/kg will keep plasma concentration above 10 μg/ml for 1 to 3 hours[45] and may have little risk of adverse effects, such as venous thromboembolism[3] or seizures.[46] Although much higher dosing has been practiced, particularly in cardiac but also craniomaxillofacial surgery,[19,47,48] there is little clinical support for increased effect with high dosing,[49,50] and the reports of a dose-dependent increase in seizures is changing dosing practice.[51] Tissue[44] and synovial fluid[52] tranexamic acid concentrations match those in plasma, whereas cerebrospinal fluid concentration reaches approximately 10% of plasma concentration.[53] Concentrations will, however, remain high for a longer period in tissue than in plasma,[44] possibly because of strong binding to plasminogen,[38] and time to peak concentration and retention time may vary among tissues.[44,54]

The lowest effective concentration for local use is unknown.[17] 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.[17] 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,[21] if a clear intraoperative view is essential,[55] or if the procedure itself may trigger hyperfibrinolysis and platelet aggregation (e.g., through the use of cardiopulmonary bypass).[56] 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).[31,57–62] One study was excluded because of nonstandardized drug preparation.[62] Eight studies addressed inner organs, four of which were performed in open surgery (Table 3)[63–66] and four in minimally invasive surgery (Table 4).[67–70] Thus, 14 studies from soft-tissue surgery, including a total of 1923 patients, were included. Eight randomized

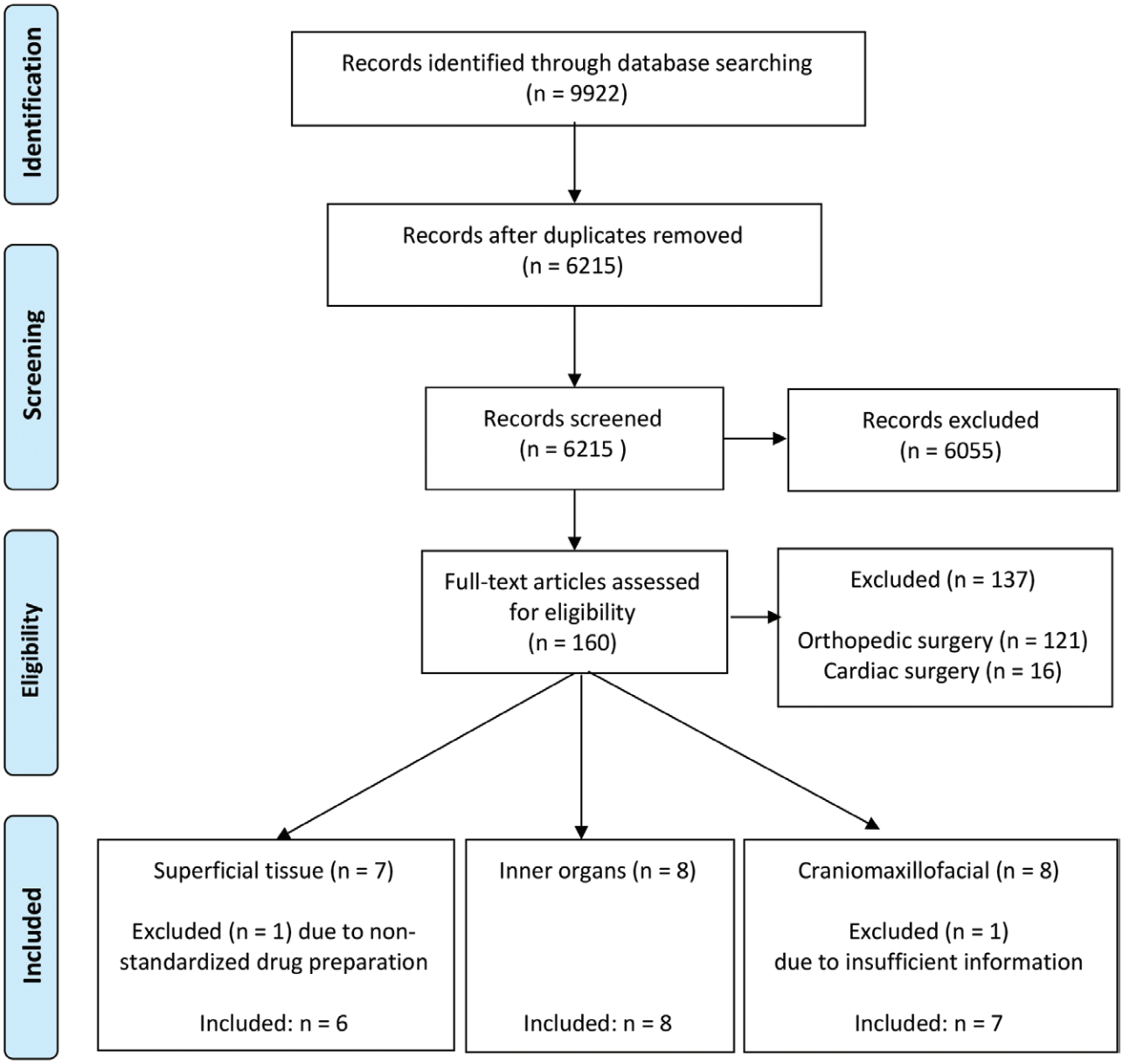

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the systematic review.

controlled trials from craniomaxillofacial (i.e., orthognathic and endoscopic sinus) surgery[71–78] were identified; one study was excluded because of inadequate information.[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[31] and mastectomy[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.[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

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[31]	28 (56)	Reduction mammaplasty	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[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[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[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 = 12. Surgical revision needed: TXA = 1 vs control = 8

TXA, tranexamic acid; CI, confidence interval.
*Values are mean ± SD unless otherwise stated.
†Values (*n*) are number of patients unless otherwise stated.

surgery. Parisi et al.[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.[61] found that a mixture of 50 mg/ml tranexamic acid and 1%

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[61]	60 (127)	Mohs microsurgery in head/neck	Lidocaine 20 mg/ml diluted 1:1 with 100 mg/ml TXA	Lidocaine 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[60]	17 (34)	Upper blepharoplasty	Lidocaine 20 mg/ml diluted 1:1 with 100 mg/ml TXA	Lidocaine 20 mg/ml diluted with saline as placebo	No difference in blood weight in pads or cautery time	No significant difference in ecchymoses

TXA, tranexamic acid.
*Values are mean ± SD unless otherwise stated.

Table 3. Randomized Controlled Trials on Local Use of Tranexamic Acid in Soft-Tissue Surgery: Inner Organs, Open Surgery

Reference, Year, Publication Type	TXA Group (total sample size)	Procedure	Concentration of TXA, Volume, Mode of Administration	Comparator	Bleeding*	Postoperative Hemorrhagic Incidence/ Intervention/ Transfusion†
Sabry 2018, article[64]	35 (70)	Lung decortication	30 mg/ml, 100 ml, poured into pleural cavity, drains clamped for 30–45 minutes	100 ml saline as placebo	Postoperative blood loss drain production at 48 h (ml); TXA = 383 ± 120 vs placebo = 633 ± 164	Transfusion need (units of transfused blood) mean ± SD: TXA = 0.7 ± 0.9 vs placebo = 1.5 ± 1.1
Sallam 2019, article[65]	43 (86)	Open hysterectomy	20 mg/ml, 50 ml irrigation, 50 ml intraabdominally	50 + 50 ml saline as placebo	Total blood loss (ml) TXA 395 ± 118 vs placebo 609 ± 119, $p < 0.001$	Transfusion need (n): TXA = 2 vs placebo = 4
Shady 2018, article[66]	35 (70)	Open myomectomy	20 mg/ml, 100 ml, soaked gauze for 5 minutes	100 ml saline as placebo	Total blood loss (ml) TXA = 684 ± 215 vs placebo = 1080 ± 126, $p < 0.001$	Transfusion need (n): TXA = 7 vs placebo = 19
Pourfakhr 2016, article[63]	186 total	Prostatectomy	100 mg/ml, 5ml, topical irrigation after resection	5 ml saline as placebo	Total blood loss (ml) TXA = 340 ± 152 vs placebo 515 ± SD not given, $p = 0.01$	Transfusion need (n): TXA = 0 vs placebo = 5

TXA, tranexamic acid; SD, standard deviation.
*Values are mean unless otherwise stated.
†Values (*n*) are number of patients unless otherwise stated.

lidocaine significantly reduced the dressing blood stain–to–wound size ratio by 28 percent compared to lidocaine diluted with saline.[61] Sagiv et al.[60] 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.[64] 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[65] and Shady et al.[66] combined irrigation and an intraabdominal bolus using 20 mg/ml tranexamic acid, whereas in open myomectomy, Shady et al.[66] 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.[63] 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,[67,69] percutaneous nephrolithotomy,[68] and hysteroscopic myomectomy[70] by 24 to 38 percent.

The visibility of the surgical field influences both operative result and safety. In nephrolithotomy, Bansal and Arora[68] 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.[70] 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 TUMESCENCE

Intraarticular tranexamic acid combined with adrenaline has shown superiority to tranexamic acid alone in reducing blood loss in joint arthroplasties.[79]

Namazi first suggested adding tranexamic acid to tumescence solution both for hair transplantation[80] and liposuction.[81] Fernau[24] 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,

Table 4. Randomized Controlled Trials on Local Use of Tranexamic Acid in Soft-Tissue Surgery: Inner Organs, Minimally Invasive Procedures

Reference, Year, Publication Type	TXA Group (total sample size)	Procedure	Concentration of TXA, Volume, Mode of Administration	Comparator	Bleeding*	Postoperative Hemorrhagic Incidence/Intervention/ Transfusion†
Abdullah 2012, conference abstract[67]	52 total	TURP	0.5 mg/ml in irrigation fluid	Standard irrigation fluid	Drop in Hb (g/dl) on first and second POD; TXA 0.87 and 0.31 vs placebo 0.98 and 0.95	Not assessed
Rani 2018, article[69]	30 (60)	TURP	0.2 mg/ml in irrigation fluid	Standard irrigation fluid	Intraoperative blood loss (ml) TXA = 145 ± 13 vs placebo 198 ± 18, $p < 0.01$ Drop in Hb (g/dl) TXA = 0.81 ± 0.40 vs. placebo = 1.46 ± 0.37, $p < 0.01$	No transfusions in either group
Bansal 2017, article[68]	200 (400)	Percutaneous nephrolithotomy	1 mg/ml in irrigation fluid	Distilled water as placebo in irrigation fluid	Total blood loss (ml) TXA = 155 ± 47 vs placebo 213 ± 68, $p < 0.001$	Transfusion need (n): TXA = 10 vs placebo = 25. Need of angioembolization (n): TXA = 1 vs placebo = 8
Rasheedy 2019, article[70]	40 (80)	Hysteroscopic myomectomy	1 mg/ml in distention fluid	Glycine as placebo in distention fluid	Drop in Hb after 24 h (g/dl) TXA = 1.11 ± 0.58 vs placebo = 1.46 ± 0.61, $p = 0.001$	Excessive perioperative bleeding reported by surgeon (n): TXA = 1 vs placebo = 9. Good surgical view (n): TXA = 23 vs placebo = 8

TXA, tranexamic acid; TURP, transurethral prostatectomy; Hb, hemoglobin; POD, postoperative day.
*Values are mean ± SD unless otherwise stated.
†Values (*n*) are number of patients unless otherwise stated.

Schroeder and Langsdon[82] 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.,[83] Nayak and Linkov,[25] and Kochuba et al.[84] 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.[85] have reported adding tranexamic acid to the local anesthetic solution in addition to using intravaneous tranexamic acid. Randomized controlled trials on the use of tranexamic acid in rhinoplasty generally address systemic administration.[20,22]

In the four randomized controlled trials by our group and Zilinsky's group[31,58,60,61] (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,[25] 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,[86,87] studies assessing infiltration are few and find less effect.[88,89]

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.[90]

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.[16–18] Tissue concentration after intravenous

Table 5. Randomized Controlled Trials on Local use of Tranexamic Acid in Orthognathic and Endoscopic Sinus Surgery

Reference, Year, and Publication Type	TXA Group (total sample size), n	Procedure	TXA Concentration, Volume, Mode of Administration	Comparator	Bleeding*	Postoperative Hemorrhagic Incidence/Intervention/Transfusion*
Jabalameli 2006, brief report[74]	26 (56)	Endoscopic sinus surgery	50 mg/ml, 20 ml of bolus instillation	20 ml saline as placebo	Intraoperative bleeding (ml) TXA = 174 ± 11 vs placebo 229 ± 24, $p < 0.05$	Surgical visual field score according to Boezaart (0–5): TXA = 2.31 ± 0.20 vs placebo 2.53 ± 0.15, $p < 0.05$
Athanasiadis 2007, article[71]	20 (40)	Bilateral endoscopic sinus surgery	Paired case/control. Investigation of two different concentrations. 100 mg/ml, 10 ml (n = 10) and 10 mg/ml, 10 ml (n = 10) topical irrigation after resection	10 ml saline as placebo	Operating site assessed as bleeding the least by surgeon (n): TXA = 16 vs placebo = 4, $p = 0.007$	None in either group
Kaewpradub 2011, article[76]	20 (40)	Orthognathic surgery	0.5 mg/ml in irrigation fluid	Standard irrigation solution	Intraoperative bleeding (ml) TXA = 833 ± 316 vs comparator 918 ± 424, $p = 0.47$	Transfusion need (units of transfused blood): TXA = 0.15 ± 0.36 vs comparator = 0.25 ± 0.55, $p = 0.50$
Jahanshahi 2014, article[75]	30 (60)	Endoscopic sinus surgery	50 mg/ml in combination with adrenaline 5 mg/ml, soaked pledgets applied for 10 minutes before surgery	5 mg/ml adrenaline solution as comparator	Blood loss from initiation until 45 minutes (ml) TXA = 100 ± 53 vs placebo 170 ± 46, $p = 0.001$	Surgical visual field score according to Boezaart (0–5): grading significantly lower in TXA group up to 30 minutes ($p = 0.003$) but not at 45 minutes ($p = 0.163$)
Shehata 2014, article[77]	25 (50)	Endoscopic sinus surgery	50 mg/ml, 20 ml, for packing and irrigation during surgery	20 ml saline as placebo	Intraoperative blood loss (ml) TXA = 214 ± 77 vs placebo = 273 ± 178, $p < 0.01$	Surgical visual field score according to Boezaart (0–5): TXA = 1.92 ± 0.64 vs placebo 2.64 ± 0.7, $p < 0.01$
Eftekharian 2015, article[73]	28 (56)	Orthognatic surgery	1 mg/ml in irrigation fluid	Standard irrigation fluid	Intraoperative blood loss (ml) TXA = 575 ± 287 vs comparator 818 ± 262, $p < 0.05$	No transfusion needs in either group. Postoperative bleeding not measured
Barandaranfar 2017, article[72]	30 (60)	Endoscopic sinus surgery	5 mg/ml in first 400 ml of irrigation fluid	Standard irrigation fluid	Intraoperative blood loss (ml) TXA = 236 vs comparator = 234 (SD not given), $p = 0.31$	Surgical visual field according to Boezaart (0–5): TXA = 2.73 vs comparator 3.0 (SD not given) $p = 0.305$

TXA, tranexamic acid; SD, standard deviation.
*Values are mean ± SD unless otherwise stated.

administration quickly matches that of plasma,[44,52] 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 timepoints,[91–94] and peak plasma concentrations have therefore been largely unknown. In a pharmacokinetic study in patients undergoing abdominoplasties,[95] 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[94] 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[96] and after a 3-g dose without drain clamping.[97]

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,[99–102] 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[56,107,108] 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[114] 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

ACKNOWLEDGMENTS

The authors thank Sindre Andre Pedersen at the Library Section for Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, for extensive assistance with the literature searches.

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

Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg.* 2011;91:944–982.
3. Heyns M, Knight P, Steve AK, Yeung JK. A single preoperative dose of tranexamic acid reduces perioperative blood loss: A meta-analysis. *Ann Surg.* 2021;273:75–81.
4. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: Systematic review and cumulative meta-analysis. *BMJ.* 2012;344:e3054.
5. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): An international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:2105–2116.
6. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *The Cochrane Database of Systematic Reviews* 2011(3):Cd001886.
7. 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.
8. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet* 2010;376:23–32.
9. Gerstein NS, Kelly SP, Brierley JK. Yet another tranexamic acid-related thrombotic complication. *J Cardiothorac Vasc Anesth.* 2016;30:e21–e22.
10. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of post-traumatic venous thromboembolism. *J Trauma Acute Care Surg.* 2019;86:20–27.
11. The HALT-IT Trial Collaborators. 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.
12. Takagi H, Ando T, Umemoto T; All-Literature Investigation of Cardiovascular Evidence (ALICE) Group. Seizures associated with tranexamic acid for cardiac surgery: A meta-analysis of randomized and non-randomized studies. *J Cardiovasc Surg (Torino)* 2017;58:633–641.
13. Bhatia N, Sen I, Kumari K, Kumar P, Bharti N. Impact of single dose intravenous tranexamic acid on peri-operative blood transfusion requirements in burn patients: A prospective, randomized trial. *Egyptian Journal of Anaesthesia* 2017;33:251–255.
14. Jennes S, Degrave E, Despiegeleer X, Grenez O. Effect of tranexamic acid on blood loss in burn surgery: A preiminary study. *The Journal of Burn Care & Rehabilitation* 2003;24:s59.
15. Walsh K, Nikkhah D, Dheansa B. What is the evidence for tranexamic acid in burns? *Burns* 2014;40:1055–1057.
16. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *The Cochrane Database of Systematic Reviews* 2013;7:Cd010562.
17. Montroy J, Hutton B, Moodley P, et al. The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis. *Transfusion Medicine Reviews* 2018;32:165–178.
18. Teoh WY, Tan TG, Ng KT, et al. Prophylactic topical tranexamic acid versus placebo in surgical patients: A systematic review and meta-analysis. *Ann Surg.* 2020;273:676–683.
19. Brown S, Yao A, Taub PJ. Antifibrinolytic agents in plastic surgery: Current practices and ruture directions. *Plast Reconstr Surg.* 2018;141:937e–949e.
20. McGuire C, Nurmsoo S, Samargandi OA, Bezuhly M. Role of tranexamic acid in reducing intraoperative blood loss and postoperative edema and ecchymosis in primary elective rhinoplasty: A systematic review and meta-analysis. *JAMA Facial Plast Surg.* 2019;21:191–198.
21. Murphy GR, Glass GE, Jain A. The efficacy and safety of tranexamic acid in cranio-maxillofacial and plastic surgery. *J Craniofac Surg.* 2016;27:374–379.
22. Ping WD, Zhao QM, Sun HF, Lu HS, Li F. Role of tranexamic acid in nasal surgery: A systemic review and meta-analysis of randomized control trial. *Medicine (Baltimore)* 2019;98:e15202.
23. Butz DR, Geldner PD. The use of tranexamic acid in rhytidectomy patients. *Plast Reconstr Surg Glob Open* 2016;4:e716.
24. Fernau J. Commentary on: Local infiltration of tranexamic acid with local anesthetic reduces intraoperative facelift bleeding: A preliminary report. *Aesthet Surg J.* 2020;40:594–596.
25. Nayak LM, Linkov G. The role of tranexamic acid in plastic surgery: Review and technical considerations. *Plast Reconstr Surg.* 2018;142:423e.
26. Rohrich RJ, Cho MJ. The role of tranexamic acid in plastic surgery: Review and technical considerations. *Plast Reconstr Surg.* 2018;141:507–515.
27. Wokes JET, Erdmann MWH, McLean NR. The role of tranexamic acid in aesthetic plastic surgery: A survey of the British Association of Aesthetic Plastic Surgeons. *Aesthet Surg J.* 2021;41:244–249.
28. Oliver JD, DeLoughery EP, Gupta N, et al. Local pro- and anti-coagulation therapy in the plastic surgical patient: A literature review of the evidence and clinical applications. *Medicina (Kaunas)* 2019;55:208.
29. Eftekharian H, Vahedi R, Karagah T, Tabrizi 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.
30. Kaewpradub P, Apipan 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.
31. 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.
32. Astrup T, Permin PM. Fibrinolysis in the animal organism. *Nature* 1947;159:681.
33. Lu H, Soria C, Li H, et al. Role of active center and lysine binding sites of plasmin in plasmin-induced platelet activation and disaggregation. *Thromb Haemost.* 1991;65:67–72.
34. Miles LA, Parmer RJ. Plasminogen receptors: The first quarter century. *Semin Thromb Hemost.* 2013;39:329–337.
35. Law RH, Abu-Ssaydeh D, Whisstock JC. New insights into the structure and function of the plasminogen/plasmin system. *Curr Opin Struct Biol.* 2013;23:836–841.
36. Law RHP, Wu G, Leung EWW, et al. X-ray crystal structure of plasmin with tranexamic acid-derived active site inhibitors. *Blood Adv.* 2017;1:766–771.
37. Pluskota E, Soloviev DA, Plow EF. Convergence of the adhesive and fibrinolytic systems: Recognition of urokinase by integrin alpha Mbeta 2 as well as by the urokinase receptor regulates cell adhesion and migration. *Blood* 2003;101:1582–1590.
38. Dunn CJ, Goa KL. Tranexamic acid: A review of its use in surgery and other indications. *Drugs* 1999;57:1005–1032.
39. Wu G, Mazzitelli BA, Quek AJ, et al. Tranexamic acid is an active site inhibitor of urokinase plasminogen activator. *Blood Adv.* 2019;3:729–733.
40. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest.* 2012;122:4654–4666.

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.* 2002;301:168–173.
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, Nilsoon 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, Pilbrant A, Schannong 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, Memtsoudis SG. Tranexamic acid administration during total joint arthroplasty surgery is not associated with an increased risk of perioperative seizures: A national database analysis. *Reg Anesth Pain Med.* 2020;45:505–508.
47. Dowd NP, Karski JM, Cheng DC, et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. *Anesthesiology* 2002;97:390–399.
48. Fergusson DA, Hébert PC, Mazer CD, 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. Guo J, Gao X, Ma Y, et al. Different dose regimes and administration methods of tranexamic acid in cardiac surgery: A meta-analysis of randomized trials. *BMC Anesthesiol.* 2019;19:129.
50. Goobie SM, Staffa SJ, Meara JG, et al. High-dose versus low-dose tranexamic acid for paediatric craniosynostosis surgery: A double-blind randomised controlled non-inferiority trial. *Br J Anaesth.* 2020;125:336–345.
51. Shi J, Zhou C, Liu S, et al. Outcome impact of different tranexamic acid regimens in cardiac surgery with cardiopulmonary bypass (OPTIMAL): Rationale, design, and study protocol of a multicenter randomized controlled trial. *Am Heart J.* 2020;222:147–156.
52. Ahlberg A, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. *Acta Orthop Scand.* 1976;47:486–488.
53. Abou-Diwan C, Sniecinski RM, Szlam F, et al. Plasma and cerebral spinal fluid tranexamic acid quantitation in cardiopulmonary bypass patients. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011;879:553–556.
54. Reust DL, Reeves ST, Abernathy JH 3rd, et al. Temporally and regionally disparate differences in plasmin activity by tranexamic acid. *Anesth Analg.* 2010;110:694–701.
55. Sharma H, Arora S, Bhatia N, Rattan V, Sethi S. Tranexamic acid is associated with improved operative field in orthognathic surgery. *J Oral Maxillofac Surg.* 2020;78:1509–1517.
56. 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.
57. Albirmawy OA, Saafan ME, Shehata EM, Basuni AS, Eldaba AA. Topical application of tranexamic acid after adenoidectomy: A double-blind, prospective, randomized, controlled study. *Int J Pediatr Otorhinolaryngol.* 2013;77:1139–1142.
58. 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.
59. Parisi Q, Messano L, Santamaria M, Alessandrini F. Pocket irrigation with tranexamic acid reduces the risk of hematoma formation in patients on anticoagulant therapy submitted to pacemaker/defibrillator surgery. *Europace.* 2013;15:ii71.
60. 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.
61. 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.
62. 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.
63. Pourfakhr P, Gatavi E, Gooran S, et al. Local administration of tranexamic acid during prostatectomy surgery: Effects on reducing the amount of bleeding. *Nephrourol Mon.* 2016;8:e40409.
64. Sabry MM, Sallam AA, Elgebaly 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.
65. Sallam HF, Shady NW. Reducing blood loss during abdominal hysterectomy with intravenous versus topical tranexamic acid: A double-blind randomized controlled trial. *J Obstet Gynaecol India* 2019;69:173–179.
66. 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.
67. Abdullah A, Javed A. Does topical tranexamic acid reduce post-turp hematuria: A double blind randomized control trial. *Urology* 2012;187:2022.
68. 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;35:1233–1240.
69. Rani R, Mittal S, Choubey SK, Pipara G. Use of tranexemic acid as a topical agent to reduce bleeding during TURP: A novel technique! *Int J Sci Res.* 2018;7:66–68.
70. Rasheedy R, Makled A, Abou-Gamrah A, Giuma H. Intrauterine 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.
71. Athanasiadis T, Beule AG, Wormald PJ. Effects of topical antifibrinolytics in endoscopic sinus surgery: A pilot randomized controlled trial. *Am J Rhinol.* 2007;21:737–742.
72. Baradaranfar MH, Dadgarnia 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.
73. Eftekharian H, Vahedi R, Karagah T, Tabrizi 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.
74. Jabalameli M, Zakeri K. Evaluation of topical tranexamic acid on intraoperative bleeding in endoscopic sinus surgery. *Iranian Journal of Medical Sciences* 2006;31:221–223.
75. 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. *PLoS One* 2014;9:e104477.
76. Kaewpradub P, Apipan 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.
77. 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;30:327–331.
78. Amal Das 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/central/CN-01415759/full. Accessed January 28, 2022.
79. 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.
80. 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.
81. Namazi MR. Practice pearl: Using 'Namazi solution' for decreasing the formation of bruises in liposuction. *J Cutan Aesthet Surg.* 2014;7:69–70.
82. Schroeder RJ 2nd, Langsdon PR. Effect of local tranexamic acid on hemostasis in rhytidectomy. *Facial Plast Surg Aesthet Med.* 2020;22:195–199.
83. 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.
84. Kochuba AL, Coombs DM, Kwiecien GJ, 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. .
85. Brown S, Brown T, Tessone A. Role of tranexamic acid in rhinoplasty. *Plast Reconstr Surg Glob Open* 2019;7:12.
86. 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.
87. 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.
88. 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.
89. 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.
90. Cho MJ, Rohrich RJ. The role of tranexamic acid in plastic surgery: Review and technical considerations. *Plast Reconstr Surg.* 2018;142:424e.
91. De Bonis M, Cavaliere F, Alessandrini 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.
92. Krohn CD, Sorensen R, Lange JE, Riise R, Bjornsen S, Brosstad F. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. *The European Journal of Surgery Supplement: = Acta Chirurgical Supplement* 2003;588:57–61.
93. Nadeau R, Howard J, Ralley F, Somerville L, Naudie D. Systemic absorption of intravenous and topical traneamic acid in primary total hip arthroplasty *Orthopaedic Proceedings* 2016;98-B:56.
94. 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.
95. 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.
96. 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.
97. 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.
98. Lecker I, Wang DS, Kaneshwaran K, Mazer CD, Orser BA. High concentrations of tranexamic acid inhibit ionotropic glutamate receptors. *Anesthesiology* 2017;127:89–97.
99. McLean M, McCall K, Smith IDM, et al. Tranexamic acid toxicity in human periarticular tissues. *Bone Joint Res.* 2019;8:11–18.
100. 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.
101. Sitek P, Wysocka-Wycisk A, Kępski F, Król D, Bursig H, Dyląg S. PRP-fibrinogen gel-like chondrocyte carrier stabilized by TXA-preliminary study. *Cell Tissue Bank* 2013;14:133–140.
102. 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.
103. Bergenholtz A, Gustafson GT, Hänström L. The effect of antifibrinolytic agents on would healing in vitro. *Experientia* 1977;33:254–256.
104. 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.* 2003;72:734–746.
105. Furst 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.
106. 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.
107. 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.
108. 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, Lyahovetsky 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 ÖT, 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, Yilmaz 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.