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Review

Effects of Tranexamic Acid on Intraoperative Bleeding and Surgical Field Visualization During Middle Ear Surgery: A Narrative Review

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Tranexamic acid is an antifibrinolytic agent widely used in several surgical procedures to reduce intraoperative bleeding. Intraoperative bleeding is a crucial problem for the ear surgeon, as it prevents good visualization of the surgical field. The aim of this work was to analyze the relevant literature about the use of tranexamic acid in ear surgery. A literature search was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, across 3 databases (Medline, Cochrane, and Google Scholar), with the terms "tranexamic acid," and "ear," and "surgery." Three prospective, randomized, and double-blind clinical trials met the inclusion criteria. Studies were not able to be pooled because of heterogeneity in material, methods of delivery and evaluation, and procedures used. Despite these limitations, all 3 papers found a significant reduction in intraoperative bleeding, allowing a better visualization of the operating field. Despite the scarcity of published trials, tranexamic acid is safe and seems to be useful in reducing intraoperative bleeding in ear surgery, thus improving operative field visualization.

KEYWORDS: Ear, surgery, tranexamic acid

INTRODUCTION

Intraoperative bleeding is a major concern during middle ear surgery, with a direct impact on surgical technique, accuracy, and safety.

During the last few years, endoscopic ear surgery has gained in interest for more and more otologists, with indications for endoscopic procedures rising. While waiting for routine technical improvements such as a robotized endoscope holder, one of the main limitations of endoscopic ear procedures is the so-called 1-hand surgery, which is particularly bothersome in cases of intraoperative bleeding.

Besides usual maneuvers to reduce intraoperative blood flow, such as Trendelenburg position, intraoperative controlled hypotension, external auditory canal (EAC) infiltration with diluted epinephrine, cotton balls soaked with adrenaline, electrocautery, and surgical field wash-out with peroxide hydrogen,[1,2] tranexamic acid (TXA) could be an additional measure in contributing to a bloodless surgical bed.

Tranexamic acid has hemostatic properties, and a systematic review pooling randomized articles from different surgical specialties showed that patients receiving TXA needed less transfusion (by 30%) than control cases.[3]

The purpose of this narrative review is to analyze the clinical interest of TXA for middle ear surgical procedures.

MATERIAL AND METHODS

This review was performed in agreement with the PRISMA 2020 statement.[4] A dedicated PICOS (Population: subjects undergoing ear surgery, Intervention: utilization of TXA, Comparator: TXA group compared to normal saline or epinephrine

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group, Outcomes: reduction of intraoperative bleeding and improvement of operative field, impact on surgery outcome, side effects as primary outcomes, change in intraoperative blood pressure (BP) and heart rate, and impact on surgery and recovery times were secondary endpoints, Study design: prospective randomized clinical trials) question was designed. The focused questions of this review were:

(1) Is tranexamic acid a useful drug for minimizing intraoperative bleeding and enhancing access to the surgical site during middle ear surgery?
(2) Are the outcomes of middle ear procedures impacted by the use of tranexamic acid?
(3) Are there any side effects when using tranexamic acid in middle ear surgery?

The literature search was conducted by 2 independent senior authors (DA and MD) using PubMed, Cochrane Central Register of Controlled Trials, and Google Scholar. Combinations of 3 keywords were used: "tranexamic acid" AND "ear" AND "surgery." The request was done on March 22, 2023, with no time limitation.

Titles and abstracts of articles were screened for eligibility. In cases of no or not enough precise abstracts, the full article was read. The reference sections of the eligible articles were hand-screened for possible electronically missed studies.

Criteria for inclusion in this review were: prospective randomized and double-blind clinical trials; patients undergoing ear surgery; at least 10 participants per group; a test group having received IV or topical intraoperative TXA; comparison with a control group having received either a placebo or another hemostatic drug. Articles such as retrospective studies, case reports, viewpoints, or non-English language were excluded.

The authors performed the data extraction individually, considering the following information to answer the focused questions outlined for the review: study period, drug administration, demographics, gender distribution, surgical procedures, and main outcomes.

The authors cross-checked all the extracted data. In cases of disagreement, a debate was held between the 4 authors (DA, MM, MD, and VP) until consensus was reached.

RESULTS

As shown in Figure 1, 16 studies were gathered for full reading. Of these 16 studies, 13 were further excluded since they did not meet inclusion criteria. Eventually, 3 studies were kept for the review.

Table 1 shows the general characteristics of the 3 included studies.[5-7] All of them were double-blind, placebo-controlled, randomized trials written in English between 2019 and 2020. They included a number of participants of 50, 69, and 60, respectively, with a mean age between 28.5 and 33.5 years. The male/female ratio was between 1 and 1.4.

The 3 studies used different inclusion criteria: Das et al[5] included patients undergoing endoscopic ear procedures (27 endoscopic tympanoplasties, 6 endoscopic mastoidectomies, 11 endoscopic ossiculoplasties, and 6 endoscopic stapedotomies), while Ziaei et al[6] included only microscopic mastoidectomies and Hamed and Hamed[7] only exploratory tympanotomies.

All studies compared test and control groups. Participants in the test cohort received tranexamic acid in different formulations and doses: patients from study 1[5] received a slow intravenous (IV) tranexamic acid (TXA) bolus (10 mg/kg) half an hour before the start of surgery, followed by an infusion (5 mg/kg/hour); participants in study 2[6] received IV TXA (10 mg/kg) at the beginning of surgeries; and in study 3[7] a topical solution of TXA 1000 mg in 200 mL normal saline (0.9%) was used to rinse the surgical field and soak with gauzes for local compression. The control group received placebo (the same volumes of IV normal saline) in the case of the first 2 studies[5,6] and topical epinephrine (1 mg diluted in 200 mL normal saline) for rinsing and local compression in the third study.[7]

A homogenous distribution in terms of demographic characteristics was found between the test and control groups in the 3 studies (P-value > .05) (Table 2).

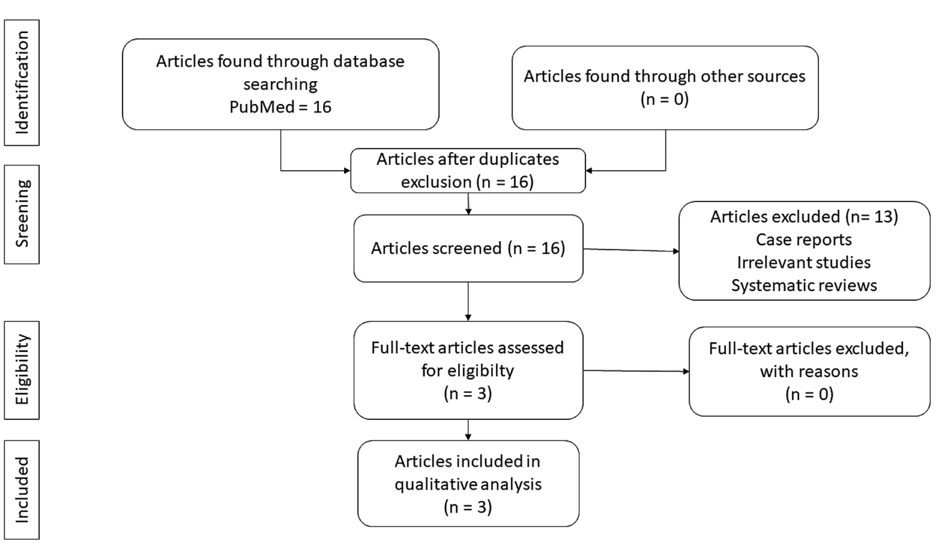

Figure 1. Study inclusion flowchart.

Table 1. General Characteristics of the Included Studies

Authors (Year)	Study Design	Sample Size (N)	Age (Mean (Range), Years)	Male/Female Ratio	Surgical Procedures (TXA vs. C)	Study Groups: N	Study Outcome
Das et al (2019)	Double-blind RCT	50	28.5 (18-50)	29/21	Endoscopic tympanoplasty 14 vs. 13 Endoscopic mastoidectomy 3 vs. 3 Endoscopic ossiculoplasty 5 vs. 6 Endoscopic stapedotomy 3 vs. 3	Group 1 (IV TXA): 25 Group 2 (placebo): 25	1) Das & Mitra EES BS; (2) surgical time; (3) mean BP; (4) Heart rate
Ziaei et al (2020)	Double-blind RCT	69	33 (NA)	38/31	Mastoidectomy 34 vs. 35	Group 1 (IV TXA): 34 Group 2 (placebo): 35	(1) Bleeding volume; (2) surgical time; (3) recovery time; (4) systolic BP; (5) diastolic BP; (6) mean BP; (7) heart rate
Hamed et al (2020)	Double-blind RCT	60	33.5 (NA)	30/30	Exploratory tympanotomy 30 vs. 30	Group 1 (topical TXA): 30 Group 2 (epinephrine): 30	(1) Boezaart BS; (2) bleeding volume; (3) surgical time; (4) recovery time; (5) mean BP; (6) heart rate; (7) adverse events

BP, Bleeding pressure; BS, bleeding score; C, control; EES, endoscopic ear surgery; NA, not available; RCT, randomized controlled trial; TXA, tranexamic acid.

The follow-up period was not specified in any cases.

Table 2 reports the surgical outcome in the selected studies. Two studies evaluated intraoperative bleeding and operative field visualization, even though they used 2 different scores. Das et al[5] used the Das and Mitra endoscopic ear surgery bleeding and field visibility score, which was separately analyzed at 2 different surgical times during EAC and middle ear dissections. Hamed et al[7] assessed the bleeding with the Boezaart score[8] every 15 minutes, starting once the targeted surgical area was reached. The intraoperative ear bleeding scores are summarized in Table 3.

Das et al[5] demonstrated a significantly lower Das & Mitra bleeding score for the patients receiving tranexamic acid when compared to those receiving placebo (normal saline) for the EAC ($P = .03752$), but not for the middle ear ($P = .123$) (Table 2). Using the Boezaart bleeding score, Hamed et al found statistically significant lower records in the TXA group compared to the epinephrine group throughout the entire procedure duration (15 min: $P < .01$; 30 min: $P < .0001$; 45 min: $P < .0001$; 60 min: $P < .001$) (Table 2).

Bleeding volume was assessed by 2 studies. Ziaei et al[6] evaluated the total bleeding volume at the end of the procedure, while Hamed et al[7] measured it every 15 minutes throughout the intervention. In the latter study, the "suction chamber" method was employed in order to assess the exact bleeding volume amongst the volumes of normal saline used intraoperatively, applying the following formula: Quantity of blood (mL) = (mass of used + fresh gauze − the weight of all sponges before surgery)/1.05.

Both the authors[6,7] found significantly smaller bleeding volumes in the TXA group when compared to placebo ($P = .001$) or topical epinephrine ($P < .0001$ at 15, 30, 45, and 60 minutes).

All the selected studies evaluated the surgical time (in minutes), and 2 evaluated the recovery time (in minutes). No statistically significant differences were found between the 2 groups ($P > .005$).

None of the studies explored the impact of the use of TXA on the outcomes of middle ear surgeries.

As shown in Table 1, the 3 selected studies included an assessment of BP and heart rate. However, the comparison between TXA and control groups was carried out using different approaches in the 3 studies:[5-7] Ziaei et al and Hamed et al compared the single measurements recorded at 15-minute intervals and at 5-minute (till 50 minutes) or 10-minute intervals (from 50 minutes until the end of the surgery), respectively, while Das et al compared the mean values throughout the surgical procedures, calculated as the average of the measurements recorded at 30-minute intervals. Besides, while Das et al and Hamed et al only presented data concerning mean BP, Ziaei et al also considered systolic and diastolic BP.

Intravenous administration of TXA was found by Ziaei et al to be associated with lower systolic, diastolic, and mean intraoperative BPs if compared to IV normal saline administration, particularly from minute 30 after the beginning of surgery,[6] in contrast to Das et al's findings.[5] Topical use of TXA was also demonstrated to be associated with lower values of mean BP compared to epinephrine, particularly at intervals between minutes 20 and 45 of surgery ($P < .05$).

No significant variation of heart rate was found in the considered studies between TXA and control groups ($P > .05$).

Only one of the 3 studies[7] specified the absence of adverse events.

The analysis of the included studies shows that the use of IV or topical TXA can significantly reduce the bleeding volume and ameliorate the surgical field visibility despite not reducing surgical and recovery times. Besides, steady levels of BP and the absence of recorded side effects imply the safety of its utilization.

A quantitative data assessment was not feasible because of the wide variability of the inclusion criteria and evaluation parameters for the 3 studies.

Table 2. Results of the Included Studies

Authors (Year)	Age (Mean ± SD, Years) (TXA vs. C)	Male/Female Ratio (TXA vs. C)	Bleeding Score (Median (Range)) (TXA vs. C)	Bleeding Volume (Mean ± SD, mL) (TXA vs. C)	Surgical Time (Mean ± SD, Minutes) (TXA vs. C)	Recovery Time (Mean ± SD, Minutes) (TXA vs. C)	Systolic Blood Pressure (Mean ± SD, mmHg) (TXA vs. C)	Diastolic Blood Pressure (Mean ± SD, mmHg) (TXA vs. C)	Mean Blood Pressure (Mean ± SD, mmHg) (TXA vs. C)	Heart Rate (Mean ± SD, bpm) (TXA vs. C)	Adverse Events
Das et al (2019)	28.96 ± 16.9 vs. 28.06 ± 6.8	15/10 vs. 14/11	EAC: 2 (1-4) vs. 2 (2-5) * ME: 2 (0-5) vs. 2'1-5)	NA	116.94 ± 2.89 vs. 117.4 ± 3.09	NA	NA	NA	85.32 ± 0.7 vs. 86.8 ± 2.4	89.36 ± 0.707 vs. 89.56 ± 2.64	NA
Ziaei et al (2020)	32.87 ± 7.9 vs. 33.20 ± 6.25	20/14 vs. 18/17	NA	60.2 ± 17.5 vs. 90.4 ± 26.4 *	161.3 ± 16.6 vs. 157.0 ± 14.9	47.8 ± 6.6 vs. 44.8 ± 8.1	0 min: 117.7 ± 6.6 vs. 119.1 ± 6.3 15 min: 117.4 ± 6.2 vs. 117.5 ± 6.0 30 min: 115.5 ± 5.8 vs. 116.8 ± 5.4 45 min: 111.2 ± 5.4 vs. 113.3 ± 5.0* 60 min: 110.5 ± 4.7 vs. 112.5 ± 4.9* 75 min: 108.4 ± 4.0 vs. 110.8 ± 4.6* 90 min: 106.9 ± 3.5 vs. 110.4 ± 4.4* 105 min: 106.3 ± 3.1 vs. 109.6 ± 3.9* 120 min: 104.9 ± 2.9 vs. 108.2 ± 3.8*	0 min: 77.8 ± 8.8 vs. 79.6 ± 8.1 15 min: 76.2 ± 8.4 vs. 78.3 ± 7.5 30 min: 73.5 ± 7.9 vs. 77.5 ± 6.4* 45 min: 71.2 ± 6.5 vs. 77.0 ± 6.0* 60 min: 68.5 ± 5.4 vs. 75.6 ± 5.6* 75 min: 66.4 ± 5.0 vs. 74.2 ± 5.3* 90 min: 65.3 ± 4.3 vs. 73.2 ± 5.0* 105 min: 65.0 ± 3.5 vs. 72.0 ± 4.8* 120 min: 63.1 ± 2.6 vs. 71.2 ± 4.2*	0 min: 93.1 ± 6.4 vs. 94.2 ± 5.6 15 min: 89.8 ± 6.1 vs. 92.4 ± 5.2 30 min: 87.0 ± 5.3 vs. 91.0 ± 4.7* 45 min: 85.2 ± 5.0 vs. 88.8 ± 4.7* 60 min: 82.5 ± 4.7 vs. 88.2 ± 4.4* 75 min: 80.3 ± 4.0 vs. 87.0 ± 4.1* 90 min: 79.6 ± 3.2 vs. 86.5 ± 4.0* 105 min: 77.0 ± 2.6 vs. 84.7 ± 3.9* 120 min: 75.2 ± 2.4 vs. 83.1 ± 3.7*	0 min: 74.2 ± 5.1 vs. 75.0 ± 4.5 15 min: 71.4 ± 7.2 vs. 77.5 ± 5.6 30 min: 74.3 ± 6.9 vs. 77.8 ± 4.0 45 min: 72.4 ± 5.8 vs. 75.1 ± 5.7 60 min: 74.1 ± 6.4 vs. 74.2 ± 6.2 75 min: 73.2 ± 7.2 vs. 73.8 ± 5.4 90 min: 73.4 ± 5.0 vs. 74.2 ± 4.8 105 min: 73.7 ± 6.2 vs. 72.9 ± 5.2 120 min: 73.9 ± 4.5 vs. 75.3 ± 5.2	NA
Hamed et al (2020)	32 ± 9.7 vs. 35 ± 10.9	14/16 vs. 16/14	15 min: 2.03 ± 0.41 vs. 2.33 ± 0.47 * 30 min: 1.93 ± 0.45 vs. 2.67 ± 0.47 * 45 min: 1.73 ± 0.52 vs. 2.40 ± 0.49 * 60 min: 1.73 ± 0.45 vs. 2.03 ± 0.18 *	15 min: 9.03 ± 5.30 vs. 12.87 ± 4.55 * 30 min: 7.77 ± 4.45 vs. 16.4 ± 4.48 * 45 min: 5.30 ± 2.89 vs. 13.3 ± 4.08 * 60 min: 6.7 ± 4.36 vs. 11.07 ± 3.33 *	90.3 ± 16.7 vs. 93.3 ± 13.5	9.9 ± 3.2 vs. 10 ± 2.0	NA	NA	Lower measurements in group TXA compared to group C at the period of 20-45 minutes of monitoring*	Lower measurements in group TXA compared to group C starting at 10 minutes	None

C, control; EAC, external auditory canal; min, minutes; TXA, tranexamic acid.

Table 3. Bleeding Scores Used in the Selected Studies

	Grade	Bleeding	Description	Field Visibility
Das & Mitra	**0**	None	Suctioning not required	Excellent
	1	Minimal	Suctioning rarely required	Very good
	2	Slight	Intermittent suctioning required	Good
	3	Moderate	Adrenaline-soaked cotton balls + intermittent suctioning	Fair
	4	Moderately severe	Adrenaline-soaked cotton balls + suction instrument required to maintain visibility	Poor
	5	Severe	Procedure converted to microscopic approach or abandoned	Endoscopic visualization not possible
Boezaart	**0**	None	Cadaveric conditions	-
	1	Slight	No suctioning required	-
	2	Slight	Occasional suctioning required	-
	3	Slight	Frequent suctioning required	Bleeding threatens surgical field a few seconds after suction is removed
	4	Moderate	Frequent suctioning required	Bleeding threatens surgical field directly after suction is removed
	5	Severe	Constant suctioning required; bleeding appears faster than can be removed by suction	Surgical field severely threatened and surgery usually not possible

DISCUSSION

One of the major concerns in ear surgery, and particularly endoscopic ear surgery, is the intraoperative bleeding, which can significantly affect the surgical field visibility and, consequently, have an impact on the risk of injury and on the surgical outcome. Several techniques are currently in use in ear surgery to achieve intraoperative hemostasis, including injection of vasoconstricting agents like diluted epinephrine in the EAC skin, topical application of epinephrine[9] or hydrogen peroxide, cautery, bone wax, or diamond burr drilling for mastoid bone bleeding.[1] Besides, some anesthesiologic procedures can be applied, such as controlled hypotension[10] and reverse Trendelenburg position.[11] However, such measures may be significantly time-consuming and affect the patient's hemodynamic parameters (epinephrine) or cerebral oxygenation (reverse Trendelenburg position).[12] Local anesthesia causes less intraoperative bleeding than general anesthesia, which nevertheless remains the most frequently used method of anesthesia for middle ear surgeries.[13] Hence, the constant need for an adequate surgical visibility and comfort while minimizing risks for the patient has led to the development of different modern hemostatic topical agents, such as absorbable gelatine sponges, fibrin sealants, thrombin/gelatine preparations, microfibrillar collagen, or oxidized regenerated cellulose.[1,2] At the same time, interest in a traditional hemostatic agent such as tranexamic acid has recently re-emerged, particularly since 1-hand endoscopic ear surgery has gained in popularity.

Tranexamic acid is a synthetic lysine-analog antifibrinolytic agent that inhibits fibrinolysis and thus improves clot stability by blocking its breakdown.[14] This inexpensive therapy has been used in a wide variety of surgical specialties, including cardiac surgery, trauma, orthopedic surgery, liver surgery, solid organ transplantation, obstetrics, gynecology, and neurosurgery.[15] Several systematic reviews and metanalysis[3,15,16] have demonstrated the strong effects of TXA on the reduction of blood loss and transfusion but with divergent results in terms of its effects on thromboembolic events and mortality.

While little has been published in otosurgery, more studies have dealt with TXA in other ENT subspecialties. In a systematic review of TXA effects in tonsillectomy, the authors concluded that TXA reduced blood loss intraoperatively but did not change the rate of postoperative hemorrhage.[17] Interest of TXA in head and neck surgery is controversial, with studies showing no effects on intraoperative blood loss, while other authors found a significant reduction in postoperative bleeding.[18-21] In rhinology and sinus surgery, several papers have pointed out the benefits of using TXA.[22-29]

Several limitations could hamper the conclusions of this review. One of the major limitations was the poor number of included studies and patients. Significant heterogeneity was found amongst the 3 selected trials in terms of TXA administration modalities and doses as well as for the placebo or drug administered to the control group. The types of surgical procedures varied significantly, too. In addition, different bleeding scores were used, and their assessment, together with the evaluation of hemodynamic parameters, was carried out at different time intervals in the different trials. Also, the modality of estimation of the bleeding volume was well defined by Hamed et al[7] but not by Ziaei et al.[6] This relevant heterogeneity precluded us from realizing a quantitative analysis. Furthermore, only 1 of the 3 trials specifies the absence of side effects. In fact, the effect of TXA on thromboembolic events and mortality cannot be adequately assessed by such small trials. But TXA safety was already demonstrated in other larger series, systematic reviews, or meta-analyses in a wide range of surgical settings, reporting very rare side effects.[16,30,31]

This work aimed to pool and analyze studies focused on the effects of tranexamic acid on intraoperative bleeding during middle ear surgery by following recommendations for reporting a scientific review. The scarcity of reported studies and, even more, the heterogeneity of the 3 selected publications made it unavailable to achieve a solid systematic review but made it possible to complete an interesting narrative review.

Despite all these limitations, we found that TXA can significantly reduce the intraoperative bleeding and improve the surgical field visibility, particularly during the EAC dissection. However, data in our possession does not reveal a real benefit in terms of reduction of the surgical time, reduction of intraoperative accidents, or improvement of postoperative outcome. Besides, significantly lower values of BP were recorded when TXA was used. If this finding could be easily understandable when compared to topical epinephrine,[7,32,33] we could not find a consistent explanation for the comparison with placebo.[6]

Further studies may be necessary in order to confirm the utility of TXA in ear surgery by setting more homogenous recruitment parameters and assessment methods. The use of a validated bleeding score for ear surgery could be necessary; at present, the Boezaart score has been validated only for sinus surgery and adapted to ear surgery,[8] while the Das & Mitra[5] score has not undergone a proper validation process; to our knowledge, the only validated score is the Modena bleeding score.[34] Besides, a more objective assessment of bleeding could be made using laser-Doppler flowmetry for the measurement of the middle ear blood flow,[10] but the need for that measurement device is clearly a restricting factor in multicentric large prospective studies. It would be interesting if major international otological societies collaborate to develop and validate a universal ear surgery bleeding score.

CONCLUSION

Tranexamix acid, an inexpensive therapy, has already shown its effectiveness and safety in several fields of surgery. Despite its limitations, mainly due to the scarcity of trials and heterogeneity of applied material and methods in published series, our narrative review indicates that the use of perioperative TXA, by both systemic or topical administration, may be useful in reducing the intraoperative bleeding and improving the visibility of the surgical field during ear surgery, with only little influence on hemodynamics. Thus, this review could encourage either further studies on the interest of TXA or a wider use of TXA in otosurgery.

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