Effect of topical and systemic tranexamic acid on bleeding and quality of surgical field during ear exploration surgery: a double-blind, randomised clinical trial

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Background
The surgical field during microscopic ear surgery is small and needs specific anesthetic considerations to improve the surgical field quality and control the bleeding during ear surgery, as little amount of bleeding can impair the quality of the surgical field and the surgical outcome. This can be achieved by different methods, which carry specific risks, such as hypotensive anesthesia, and use of local vasoconstrictors, which are associated with cardiac and hemodynamic risks. The objective of this study was to assess the effect of tranexamic acid (TXA) topically and systemically on bleeding and quality of surgical field during ear exploration surgery.

Materials and methods
A total of 90 patients undergoing ear exploration surgery were randomly divided into three group. Group A included 30 patients who received systemic TXA in a dose of 10–15 mg intravenous over 30 min, followed by infusion in a dose of 1 mg/kg/h throughout surgery. Group B included 30 patients who received topical TXA in dilution of 1 g diluted in 200 ml saline for surgical wash and soaking the used gauze for compression on the bleeding site. Group C included 30 patients who received diluted adrenaline 1 mg diluted in 200 ml saline used for surgical wash and soaking gauze used for compression of the bleeding site, and this was considered as a control group. Assessment parameters included intraoperative blood loss, quality of surgical field using Boezaart grading with 0–5 scores, hemodynamics and perioperative adverse effects.

Results
There were no significant differences between groups in the demographic and clinical characteristics regarding age, sex, weight, and height and in anesthesia time, surgical time or time of recovery.
The quality of the surgical field was better in group B than groups A and C. The intraoperative bleeding was significantly reduced in group B more than groups A and C, and postoperative nausea, vomiting and blurring of vision were more in group A than the other groups.

Conclusion
Topical application of TXA has a more significant effect on reducing bleeding and improving the quality of the surgical field during ear exploration surgery with nonsignificant adverse effects.

Keywords:
Ear exploration surgery, surgical field quality, topical application, tranexamic acid

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Introduction

Bleeding during ear surgery is still a challenge for surgeons and anesthesiologists. Although extensive blood loss is rare during ear surgery; however, establishing a favorite surgical field is often difficult. The reason is that even slight bleeding may distort the view of the field and increase the occurrence of complications, including deafness, longer duration of surgery, or even inconclusive surgery.

Techniques such as bipolar diathermy, packing, topical vasoconstrictors, and induced hypotension have been used to improve the surgical field in ear exploration surgery. However, some complications are associated with these methods. For example, induced hypotension is an anesthetic technique that is used in various types of operations to reduce intraoperative bleeding and to provide a clear operative field. It has been found to be beneficial in neurosurgery, plastic surgery, major orthopedic procedures, head and neck surgery, radical cancer operations, and procedures on the middle ear [1,2]. Induced hypotension exposes patients to

more anesthetic drugs and their associated adverse effects, diathermy can cause local tissue damage and subsequent bleeding, and topical vasoconstrictors can cause hemodynamic instability, especially in patients with a history of hypertension or ischemic heart disease.

Tranexamic acid (TXA) is an antifibrinolytic agent that blocks lysine-binding sites on plasminogen, thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin [3].

Some studies have reported the efficacy of topical and oral forms of TXA in achieving hemostasis and improving the surgical field in nasal surgery including functional endoscopic sinus surgery (FESS) [4,5].

Materials and methods

This prospective, randomised, double-blind study was conducted in Assiut University Hospital after approval from the Medical Ethics Committee, faculty of medicine, Assiut University, Assiut, Egypt. Trial registration was prospectively undertaken in ClinicalTrials.gov (ID: NCT03112135). A written informed consent was obtained from the participants before participation in the study. All collected data were confidential and were used for scientific research only. A total of 90 patients aged more than 20 and less than 60 years, with American Society of Anesthesiology II and III, hemoglobin level greater than 10 mg/dl, and standard coagulation profile (international normalized ratio and prothrombin time) were scheduled for ear exploration surgery under general anesthesia. Patients with a history suggestive of drug allergy, bleeding disorder, psychiatric illness, chronic renal failure, used heparin 48 h before surgery, color blindness, cardiac stent, cirrhosis, or pregnant were excluded from the study.

Based on computerized generated randomization tables, patients were randomly assigned into three groups of 30 patients each.

Group A: systemically administered tranexamic acid

A total of 30 patients received systemic TXA in a dose of 10 mg/kg intravenously over 30 min, followed by infusion in a dose of 1 mg/kg/h throughout surgery. Overall, 200 ml of normal saline 0.9% was used for surgical wash and soaking the used gauze for compression on the bleeding site.

Group B: topically administered tranexamic acid

A total of 30 patients received topical TXA in a dilution of 1 g diluted in 200 ml normal saline 0.9% for surgical wash and soaking the used gauze for compression on the bleeding site.

Group C: control group

A total of 30 patients received diluted adrenaline 1 mg diluted in 200 ml normal saline 0.9% used for surgical wash and soaking dressing used for compression of the bleeding site, and this was considered as a control group.

Anesthesia

All patients were premedicated with intravenous midazolam (20–40 μg/kg) 30 min before surgery. After establishing standard monitoring procedures (ECG, SPO_2, end-tidal CO_2, and non-invasive blood pressure (NIBP)), general anesthesia was induced with fentanyl (3 μg/kg) combined with propofol (1–2 mg/kg) and lidocaine (1 mg/kg). Endotracheal intubation was performed after achieving muscle relaxation with atracurium (0.5 mg/kg). Mechanical ventilation was instituted to maintain eucapnia. Anesthesia was maintained using isoflurane (1–2%) and propofol infusion (1.5–4.5 mg/kg) to keep mean arterial blood pressure (BP) 60–70 mm/Hg. A maintenance dose of atracurium was repeated every 20 min. Lactated ringer solution was infused to maintain euvolemia. All patients were kept in the reverse Trendelenburg position with the head up 30°. The quality of surgical field was based on Boezaart grading, with a higher score meaning more blood loss [6,7] (Table 1).

Assessments

Health care personnel provided direct patient care, and patients were blinded to the patient's group assignment. The trial was planned such that neither the doctors (the investigator and the surgeon) nor the patients were aware of the group allocation and drug received, as the study drugs were prepared by an anesthesiologist not involved in patient monitoring or in data collection.

(1) Demographic and clinical data: the data on patient's age, sex, weight, height, type of surgery,

Table 1 Boezaart grading for categorizing the quality of the surgical field

Grade	Description
0	No bleeding (cadaveric conditions)
1	Slight bleeding: no suctioning required
2	Slight bleeding: occasional suctioning required
3	Slight bleeding: frequent suctioning required, and bleeding threatens surgical field a few seconds after suction is removed
4	Moderate bleeding: frequent suctioning required and bleeding threatens surgical field directly after suction is removed
5	Severe bleeding: constant suctioning required; bleeding appears faster than can be removed by suction; surgical field severely threatened and surgery usually not possible

and the American Society of Anesthesiology physical status were collected.

(2) Intraoperative vital signs: systolic BP, diastolic BP, mean BP, HR, arterial oxygen saturation, and end-tidal CO_2 were measured; all of them were taken every 5 min. The quality of the surgical field at 15, 30, 45, and 60 min after the start of surgery was assessed using Boezaart grading, with 0–5 scores. Moreover, the amount of blood loss at 15, 30, 45, and 60 min after the start of operation was estimated using a scale after reducing the amount of normal saline used for washing blood accumulated in the suction and weighting the gauze and converting the blood weight into ml. This was estimated using the following [6]:

$$\text{The quantity of blood (ml)} = \frac{\left(\begin{array}{l}\text{weight of used materials + unused materials}\\ \text{–the weight of all materials before surgery}\end{array}\right)}{1.05}$$

(3) Postoperative assessment parameters: postoperative assessment parameters included evaluation of the potential adverse effects of the TXA such as (a) nausea, (b) vomiting, and (c) impaired color vision 24 h after surgery.

Statistical analysis

A power analysis estimated that a sample size of 30 patients in each group would have an 80% power at the 0.05 level of significance to detect a statistically significant difference between groups.

The Shapiro–Wilk tests assessed the distribution of baseline variables. Continuous data were reported as mean ± SD and were analyzed using an independent sample *t*-test or analysis of variance for multiple comparisons with the least significant difference test for post-hoc analysis. Categorical data were reported as percentages and were analyzed using the χ^2-test or Fisher exact test as appropriate. Nonparametric data such as Boezaart score were analyzed using the Mann–Whitney *U*-test. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, Illinois, USA).

Results

Quality of surgical field

Boezart score was significantly higher in group C compared with group A at 30, 45, and 60 min. Moreover, there were statistically significant differences in group C compared with group B at 15, 30, 45, and 60 min, whereas there was a statistically significant difference between group A and group B only at 15 min, as shown in Table 2 and Fig. 1.

Total amount of blood loss during surgery

When comparing the total amount of blood loss between the study groups, there were statistically significant differences between group B and group C and between group A and group B but not between groups A and C at 15 min, whereas there was a statistically significant difference between the different groups at times 30, 45, and 60 min, as shown in Table 3 and Fig. 2.

Complications

There was a higher rate of complication in group A in comparison with groups B and C, with a statistically significant difference, as shown in Table 4 and Fig. 3.

Discussion

In this study, the administration of topical TXA 1 g diluted in 200 ml saline for surgical wash and soaking the used gauze for compression on the bleeding site resulted in a significantly lower intraoperative bleeding volume compared with systemic TXA in a dose of 10 mg/kg intravenously over 30 min, followed by infusion in a dose of 1 mg/kg/h throughout the duration of surgery, and the third group that received adrenaline 1 mg diluted in 200 ml saline used for surgical wash and soaking gauze used for compression of the bleeding site. Moreover, there was a significant

Table 2 Comparison of Boezaart score in the study groups

Items	GA and GC	GB and GC	GA and GB
At 15 ms	*P*=0.804 (NS)	*P*<0.01*	*P*<0.01*
At 30 ms	*P*<0.000***	*P*<0.000***	*P*=0.162 (NS)
At 45 ms	*P*<0.000***	*P*<0.000***	*P*=0.095 (NS)
At 60 ms	*P*<0.04*	*P*<0.001**	*P*=0.098 (NS)

**P* value of less than 0.05, ***P* value of less than 0.01, ****P* value of less than 0.001. GA, group A; GB, group B; GC, group C.

Table 3 Comparison of total bleeding in study groups

Items	GA and GC	GB and GC	GA and GB
At 15 ms	*P*=0.305n.s	*P*<0.003**	*P*<0.04*
At 30 ms	*P*<0.000***	*P*<0.000***	*P*<0.01*
At 45 ms	*P*<0.001**	*P*<0.000***	*P*<0.002**
At 60 ms	*P*<0.002**	*P*<0.000***	*P*<0.000***

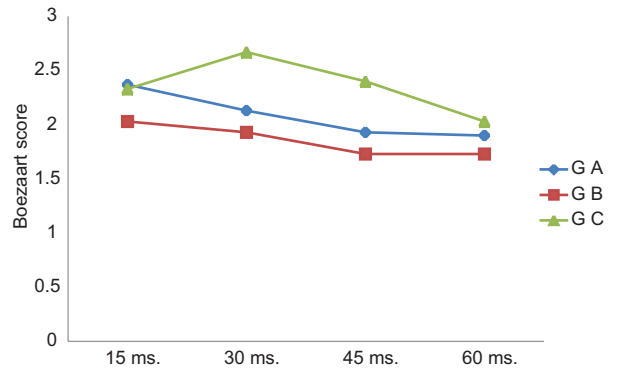
**P* value of less than 0.05, ***P* value of less than 0.01, ****P* value of less than 0.001. GA, group A; GB, group B; GC, group C.

Table 4 Complication in study groups

Items	Group A (*n*=30) [*n* (%)]	Group B (*n*=30) [*n* (%)]	Group C (*n*=30) [*n* (%)]	*P*
Nausea	9 (30.0)	0	0	*P*<0.000***
Vomiting	5 (16.67)	0	0	*P*<0.001**
Blurred vision	3 (10.0)	0	0	*P*<0.002**

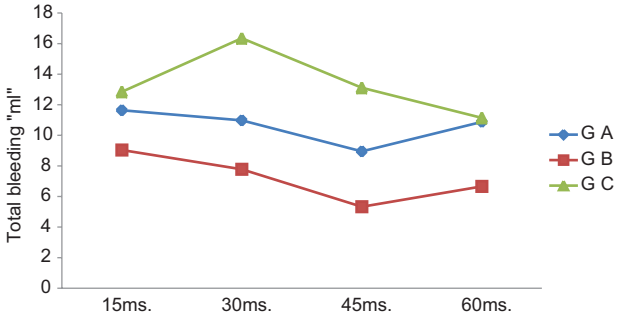
**P* value of less than 0.05, ***P* value of less than 0.01, ****P* value of less than 0.001.

Figure 1



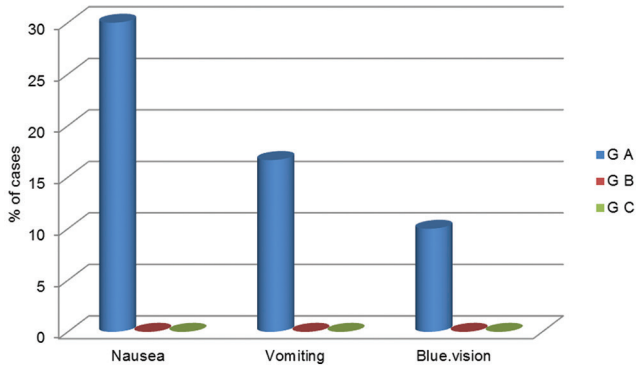
Boezaart score in study groups. GA, group A; GB, group B; GC, group C.

Figure 2



Total bleeding (ml) in study groups. GA, group A; GB, group B; GC, group C.

Figure 3



Complication in study groups. GA, group A; GB, group B; GC, group C.

improvement in the quality of surgical field in group B than group A than group C by using Boezaart score.

Previous studies proved that TXA is effective when administered via the topical and intravenous route [3,8–10].

Our finding was consistent with a study by Shehata *et al.*[11] in 2012, which evaluated 25 patients who received TXA 1000 mg diluted in 200 ml of normal saline used for packing and irrigation during surgery, 25 patients who received hot saline, and 25 patients who received normal saline was used for packing and irrigation during operation and showed the potency of local TXA and local hot saline in making a bloodless surgical field during FESS in comparison with the normal saline [11].

Moreover, Jabalameli and Zakeri [12], conducted a clinical trial on 56 patients who were prepared for FESS to assess the effects of topical TXA on improving surgical field and hemostasis. In this trial, 26 patients received topical TXA, and 30 patients received placebo. According to the results of this study, the amount of bleeding in the TXA group was less than the placebo group. They concluded that topical application of TXA could reduce intraoperative bleeding in FESS [12].

Moreover, Alimian and Mohseni[9] approved that intravenous TXA in a dose of 10 mg/kg, in comparison with sterile water 0.1 ml/kg (placebo group) as a bolus dose, immediately after induction of anesthesia effectively decreases bleeding and improves the quality of surgical field during FESS.

Nuhi *et al.*[13] approved that administration of intravenous TXA 15 mg/kg on 100 patients scheduled for FESS in comparison with 70 patients received placebo resulted in a significantly lower intraoperative bleeding volume compared with the placebo group.

Athanasiadis *et al.*[4], evaluated 30 patients undergoing FESS who were separated into three groups (2.5 g aminocaproic acid, 100 mg TXA, or 1 g TXA sprayed on one side of the nose and saline on the other). No significant bleeding reduction was observed in the aminocaproic acid group. The results of both TXA groups revealed significant improvement in the surgical environment. The application of 1-g TXA was more effective compared with application of a 100 mg dose. The method of TXA administration was different from our study, with Athanasiadis *et al.*[4] adopting a spraying technique compared with the washing protocol used in our study.

In line with our experience, periarticular TXA is more effective than intravenous TXA in reducing postoperative blood loss and less decrease in hemoglobin concentrations according to Pinsornsak *et al.* [14].

Moreover, the use of intravenous TXA in elective posterior thoracic or lumbar instrumented spinal fusion surgery and revision knee replacement surgery resulted in significant reduction in the estimated and calculated total amount of perioperative blood loss, the transfusion rate, and hemoglobin drop [15,16].

In contrast with our results, Langille *et al.*[17] in 2013 evaluated 28 patients prepared for FESS. In the saline group, patients received normal saline intravenously, and the intervention group received TXA diluted in normal saline intravenously. In this study, the rate of bleeding and Wormald grading was recorded. The results showed that administration of intravenous TXA had no significant effect on decreasing blood loss and improving the surgical field during FESS. The difference in results between this study and our study may be the small sample size of this study and that all patients underwent decongestion of the nasal mucosa, initially with oxymetazoline and subsequently with nasal pledgets soaked in 1:1000 epinephrine. A bilateral intranasal injection was performed in the region of the sphenopalatine artery with 1% lidocaine with 1: 100 000 epinephrine [17].

Moreover, Soni *et al.*[18] demonstrated that topical TXA is equally effective as intravenous regimen in reducing blood loss during TKA, and Kaewpradub *et al.*[19] demonstrated that the use of TXA in an irrigant fluid during orthognathic surgery did not significantly decrease intraoperative blood loss compared with a placebo group (normal saline only). A possible explanation for such difference among reported studies is differences in doses and different routes of administration as well as the difference in the type of surgery.

The most common early postoperative adverse effects of TXA are nausea, vomiting and thrombotic events [8].

Our study revealed a higher percentage of complication in group A than groups B and C, with significant difference ($P < 0.000$), with rates of nausea and vomiting of 30 and 16%, respectively, in group A.

Similarly, Alimian and Mohseni [9], used intravenous TXA in a dose of 10 mg/kg in comparison with sterile water 0.1 ml/kg (placebo group) as a bolus dose immediately after induction of anesthesia and reported less than 15% nausea and vomiting in their study.

In addition, Nuhi *et al.* [13], evaluated the effects of intravenous TXA and placebo on 100 patients and 70 patients, respectively, as well as the potential adverse effects and revealed rates of nausea and vomiting of 7% and 12% in the TXA and placebo groups, respectively, with no significant difference between the two groups.

We also reported that three patients of group A complaining of postoperative blurring of vision which was mild and resolved spontaneously after a few hours. This result was consistent with Schultz and van der Lelie [20], who demonstrated a blurring of vision as an adverse effect of TXA. Moreover, Lukes *et al.* [21], described the safety of TXA in women with heavy menstrual bleeding, where the women received 1.3 g TXA orally three times daily for up to 5 days per menstrual cycle for a total of nine menstrual cycles, and found that approximately 4% of patients (10 out of 260) reported ophthalmic adverse effects during the study in the form of blurring of vision and an increase in intraocular pressure.

Conclusion

This study demonstrated the topical application of TXA is a safe alternative to systemic administration of TXA and the topical application of the local vasoconstrictors. It has better surgical field quality with a lesser amount of blood loss during microscopic ear surgeries.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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