Original Article

# The Effect of Tranexamic Acid Local Injection on Bleeding during and after Tonsillectomy: A Double-Blind Randomized Placebo-Controlled Trial

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## ABSTRACT

**Background:** Tonsillectomy-related bleeding is one of the most prevalent and potentially fatal complications of this common surgical procedure. We aimed to assess the effect of tranexamic acid (TXA) local injection on bleeding during and after tonsillectomy.

**Methods:** This double-blind, randomized placebo-controlled trial included 20 candidates for tonsillectomy referred to Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, in 2022. The subjects were randomized into two groups. Ten patients received TXA on their left side and the other ten on their right side 10 min before surgery. Placebo was administered to the contralateral side. The primary outcome was the volume of blood loss during tonsillectomy and up to 24 hours post-tonsillectomy. The secondary outcomes were surgeon satisfaction (rated 0-10), hemodynamic complications (patients' heart rate (HR) and mean arterial pressure (MAP) were recorded every 10 min), and rebleeding. The duration of surgery was also noted.

**Results:** The mean age of the patients was 21.35 ± 3.16 years, of whom 8 (30%) were male and 12 (60%) were female. there was no significant difference between groups in terms of HR and MAP at any time point. The median of surgery duration did not differ significantly between the two groups; however, the surgeon satisfaction with the procedure was significantly higher with TXA compared to placebo. None of the patients developed hemodynamic complications, and rebleeding did not occur in any of the subjects.

**Conclusions:** TXA local injection was not superior to placebo in terms of bleeding control during and after tonsillectomy, hemodynamic complications, rebleeding, and surgery duration.

**KEYWORDS**
Hemorrhage; Placebo; Tonsillectomy; Tranexamic acid

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## BACKGROUND

Tonsillectomy is a very common surgical procedure in otolaryngology [1]. One of the most prevalent and potentially fatal complications that may





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develop during or after surgery is tonsillectomy-related bleeding because of the tonsils' abundant blood supply [2, 3]. Between 0.2% and 2.2% of tonsillectomies result in primary bleeding, defined as bleeding within 24 hours following the operation. Secondary bleeding occurs after 24 hours, and its incidence ranges from 0.1% to 3% [4].

To reduce the proportion of patients who require a second operation for post-tonsillectomy bleeding, several alternative techniques have been used with varying degrees of success. Aside from topical epinephrine and thrombin powder, interventions may as well include intravenous fluids, suctioning, direct pressure, and silver nitrate [5].

Tranexamic acid (TXA), a synthetic analogue of the amino acid lysine, has also been introduced for controlling tonsillectomy-related bleeding [6]. By competitively binding to the lysine-binding sites on plasmin and plasminogen, TXA enhances anti-fibrinolysis [7]. Because tonsils have a high concentration of plasminogen activators and low levels of plasminogen inhibitors, it has been suggested that TXA would especially contribute to minimizing tonsillectomy-related bleeding [8].

TXA significantly reduces the intra-operative blood loss volume and post-operative hemorrhage rate in patients who undergo tonsillectomy [6], but TXA was used orally or intravenously in all ten studies included in this meta-analysis. Systemic TXA side effects include gastrointestinal (such as nausea, diarrhea, and cramps) when taken orally, concern for renal toxicity in individuals with impaired kidney function, hypotension after rapid delivery, and seizures at dosages beyond what is considered therapeutic [9]. Therefore, researchers have evaluated other routes of administration. Nebulized TXA treatment for post-tonsillectomy hemorrhage appears to reduce the requirement for surgical bleeding control [10]. On the other hand, topical TXA (gargled or sprayed) did not decrease post-operative bleeding after tonsillectomy [11].

We aimed to assess the effect of TXA local injection on bleeding during and after tonsillectomy.

## MATERIALS AND METHODS

### *Participants and study design*

This double-blind, randomized, placebo-controlled trial included candidates for tonsillectomy referred to Al-Zahra hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from April 03 to August 23, 2022. The inclusion criteria were comparable bilateral tonsil size grading, age 15-45 years, and the American Society of Anesthesiologist (ASA) class I or II. The exclusion criteria were contraindications of TXA administration for any reason such as drug allergy, use of anticoagulants, hematological diseases, including hemolytic conditions, hemoglobinopathies, coagulopathies, and thromboembolic events), and uncontrolled systemic diseases. Moreover, patients for whom electrocauterization was applied intra-operatively to control bleeding were excluded from the study. The sample of 20 in each group was determined to be sufficient for this novel study by the statistician.

The Ethics Committee of Isfahan University of Medical Sciences approved the research: IR.MUI.MED.REC.1400.821 and meets the requirements of the Declaration of Helsinki. The patients gave their verbal and written consent to participate in the study. The trial has also been registered while recruiting at the Iranian Registry of Clinical Trials (IRCT), IRCT20211028052900N2, available at https://www.irct.ir/trial/62462.

First, the general characteristics of the patients, including age and sex, were recorded. In the operating room, all patients were under continuous electrocardiographic, non-invasive blood pressure, pulse oximetry, and capnography monitoring. General anesthesia induction was done by the same anesthesiologist with 2 mcg/kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg atracurium. Then the patients were intubated and underwent mechanical ventilation. Anesthesia maintenance and controlled hypotension were achieved using a 50-ml syringe pump containing propofol at a speed of 100-150 mcg/kg/min and remifentanil at a speed of 0.25-0.5 mcg/kg/min with a target mean arterial pressure (MAP) of 70 mmHg. The surgical technique was cold dissection, and hemostasis was achieved by suturing.

The subjects were randomized into two groups using simple randomization by the Random Allocation software. Ten patients received TXA on their left side and the other ten on their right side 10 min before surgery. Placebo was administered to the contralateral side. A technician uninvolved in the study prepared 2 ml syringes coded 1 and 2, containing 100 mg TXA [12] (company, country) or the same volume of



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distilled water. Therefore, the contents of the syringes were unknown to the surgeon and the investigator responsible for data collection.

The primary outcome was the volume of blood loss during tonsillectomy and up to 24 hours post-tonsillectomy. The intra-operative blood loss was measured based on the volume of blood inside the graduated suction device and the weight difference of blood gases before and after surgery, with every gram weight difference indicating one ml of blood [13]. The post-tonsillectomy blood loss was assessed in the recovery room up to 24 hours after surgery. In case of applying irrigation serum, its volume was subtracted from the volume inside the suction device. The duration of surgery was also noted.

The secondary outcomes were surgeon satisfaction, hemodynamic complications, and rebleeding. The surgeon rated his satisfaction with the procedure from 0 to 10, with "0" indicating complete dissatisfaction and "10" indicating complete satisfaction. As for hemodynamic complications, patients' heart rate (HR) and MAP were recorded every 10 min, and tachycardia, bradycardia, hypotension, and hypertension were noted. Moreover, the measurements taken to control these complications, such as discontinuance of medications for the control of hypotension or the administration of any other drugs, were recorded.

### *Data analysis*

The Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.) was used for data analysis. We used mean (standard deviation [14]) and median (interquartile range [IQR]) to describe continuous variables and frequency and percentage to describe categorical variables. Based on the distribution normality of the continuous variables, the independent t-test or the Mann-Whitney test were used for comparison between groups. P-values <0.05 were regarded as statistically significant.

## RESULTS

Initially, 25 patients (50 tonsils) were evaluated for eligibility, of whom three declined to participate, and two did not meet the inclusion criteria (Fig. 1). The general characteristics of the remaining 20 patients are presented in Table 1. The mean age of the patients was 21.35 ± 3.16 years, of whom 8 (30%) were male and 12 (60%) were female.

The median blood loss volume during and after tonsillectomy was comparable between groups ($P$=0.211) (Table 2). Further, there was no significant difference between groups in terms of HR and MAP at any time point (Table 3). Also, the median of surgery duration did not differ significantly between the two groups ($P$=0.555); however, the surgeon satisfaction with the procedure was significantly higher with TXA compared to placebo ($P$=0.002) (Table 4). None of the patients developed hemodynamic complications. Furthermore, rebleeding did not occur in any.

**Table 1:** General characteristics of the patients

| Variables | Values (n=20) |
|---|---|
| **Age (yr), mean (SD)** | 21.35 (3.16) |
| **Sex, N (%)** | |
| **Male** | 8 (30.0) |
| **Female** | 12 (60.0) |

Abbreviations: N, number; SD, standard deviation.

**Table 2:** Comparison of blood loss volume between groups

| Variable | TXA (n=20) | Placebo (n=20) | *P*-value* |
|---|---|---|---|
| **Blood loss volume (ml), median (IQR)** | 87.50 (40.00; 113.75) | 92.50 (66.25; 130.00) | 0.211 |

Abbreviations: IQR, interquartile range; TXA, tranexamic acid.
*Analyzed by the Mann-Whitney test.



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**Table 3:** Comparison of HR and MAP between groups at different time points

| Variables, mean (SD) | TXA (n=20) | Placebo (n=20) | *P*-value* |
|---|---|---|---|
| **HR (bpm)** | | | |
| **Baseline** | 83.65 (12.58) | 87.10 (11.24) | 0.366 |
| **At 10 min** | 84.85 (13.37) | 87.35 (11.56) | 0.464† |
| **At 20 min** | 89.44 (9.90) [n=9] | 88.08 (13.50) [n=13] | 0.737† |
| **At 30 min** | 89.25 (9.00) [n=4] | 96.20 (13.63) [n=5] | 0.462† |
| **MAP (mmHg)** | | | |
| **Baseline** | 99.05 (17.91) | 96.45 (19.39) | 0.662 |
| **At 10 min** | 98.15 (14.70) | 98.85 (18.40) | 0.895 |
| **At 20 min** | 98.44 (17.60) [n=9] | 99.62 (14.25) [n=13] | 0.865 |
| **At 30 min** | 87.00 (15.94) [n=4] | 100.20 (21.85) [n=5] | 0.221† |

Abbreviations: HR, heart rate; MAP, mean arterial pressure; SD, standard deviation; TXA, tranexamic acid.
*Analyzed by the independent t-test.
†Analyzed by the Mann-Whitney test.

**Table 4:** Comparison of surgeon satisfaction and surgery duration between groups

| Variables, median (IQR) | TXA (n=20) | Placebo (n=20) | *P*-value* |
|---|---|---|---|
| **Surgery duration (min)** | 16.50 (10.00; 25.00) | 20.00 (10.00; 27.50) | 0.555 |
| **Surgeon satisfaction** | 8.00 (6.00; 8.00) | 6.00 (5.00; 7.00) | 0.002 |

Abbreviations: IQR, interquartile range; TXA, tranexamic acid.
*Analyzed by the Mann-Whitney test.

## DISCUSSION

Although TXA is frequently used in many surgical procedures to control blood loss because it is affordable, well-tolerated, and safe, its value when given as local injection to patients undergoing tonsillectomy has not been established. The present study demonstrated that TXA local injection was not superior to placebo for the management of bleeding during and after tonsillectomy. The results of the previous studies regarding the efficacy of TXA for tonsillectomy-related bleeding control have been inconsistent.

Spencer et al. retrospectively reviewed the charts of adult and pediatric patients who underwent tonsillectomy and reported that the requirement for surgical control of post-tonsillectomy hemorrhage reduced when it was treated with TXA [15]. By comparing 15 mg/kg intravenous TXA with controls. The mean blood loss volume during tonsillectomy in the TXA group was considerably lower than controls [16]. On the other hand, compared to an intravenous TXA dose of 5 mg/kg, less bleeding occurred with a 10 mg/kg dose [17]. In addition, in an updated meta-analysis, oral or intravenous TXA significantly reduced intraoperative blood loss and the rate of post-tonsillectomy hemorrhage [6].

Contrarily, 10 mg/kg intravenous TXA did not reduce the bleeding volume in children during adenotonsillectomy [18]. In addition, Soliman et al. reported no effect of 15 mg/kg intravenous TXA in decreasing tonsillectomy-related bleeding in pediatric patients [19]. Similarly, there was no advantage to using TXA to reduce bleeding during pediatric adenotonsillectomy[20]. Moreover, in an earlier systematic review and meta-analysis, TXA did not substantially lower the number of patients who had post-tonsillectomy bleeding [21]. The inconsistent findings of the prior studies can stem from various factors, including the study population, the type of tonsillectomy-related bleeding evaluated (during the procedure, primary, or secondary), the route of administration, the dose of TXA, the control groups, and the study design.

In our study, local TXA injection did not lead to hemodynamic complications, and no rebleeding occurred. The safety of TXA has been confirmed in previous research on various procedures and


[ DOI: 10.61186/wjps.12.3.31 ]

conditions [14, 18, 22-24]. Another finding of the present study was that overall surgeon satisfaction was significantly higher with TXA compared to placebo. Nevertheless, this subjective evaluation cannot be sufficient to promote the use of TXA local injection. The strength of the current study was that the tonsils of every single patient were allocated to receive TXA or placebo; therefore, both groups were similar in terms of sex, age, and ASA class. The are some limitations to the present study. We did not assess bleeding beyond the first 24 hours after surgery, which is defined as secondary bleeding. Moreover, we evaluated the total volume of blood loss during and after tonsillectomy and cannot determine if TXA is effective for either condition separately. Also, since this was a novel study evaluating the effect of TXA local injection, the sample size might have been relatively small, limiting the generalizability of the findings.

## CONCLUSION

TXA local injection was not better than placebo in terms of bleeding management during and after tonsillectomy, hemodynamic complications, rebleeding, and operation length, with the exception of surgeon satisfaction, which was much greater with TXA. Further studies with a larger sample size are required to determine the efficacy of TXA local injection for controlling tonsillectomy-related bleeding, potentially including other arms receiving higher and lower doses of TXA, as well as groups allocated to receive intravenous, oral, or topical TXA.

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## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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