Evaluation of local tranexamic acid on septoplastic surgery quality

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PII: S1748-6815(21)00097-8
DOI: https://doi.org/10.1016/j.bjps.2021.03.008
Reference: PRAS 7075

To appear in: *Journal of Plastic, Reconstructive & Aesthetic Surgery*

Received date: 25 April 2020
Accepted date: 11 March 2021

Please cite this article as: Ebrahim Hazrati MD , Behzad Kazemi Haki BSc , Alireza Masnour-Ghanaei MD , Ali Soleimanlo MD , Mohammadreza Rafiei MD , Evaluation of local tranexamic acid on septoplastic surgery quality, *Journal of Plastic, Reconstructive & Aesthetic Surgery* (2021), doi: https://doi.org/10.1016/j.bjps.2021.03.008

Running Title:

Local tranexamic acid in septoplastic surgery

Title

Evaluation of local tranexamic acid on septoplastic surgery quality

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Abstract

Background: Even the small amount of bleeding during nose surgery can impair the surgeon's vision, prolonged the duration of operation and affected on surgery quality therefore, various techniques have been proposed to control the bleeding. The aim of this study was to compare the efficacy of local use of tranexamic acid in the dry field of surgery.

Method: This Randomized, double-blinded, controlled trial conducted in Operating room of Imam Reza Hospital, Tehran, Iran, from January 10, 2016, to February 8, 2017. sixty patients with age range of 20 to 60 years and the ASA physical status classes I candidates to septoplasty enrolled. Patients were randomized through white and black cards to receive either syringes. 30 patients in intervention group received lidocaine + adrenaline + tranexamic acid and 30 patients in control group received lidocaine + adrenaline.

Bleeding volume measured by accumulated in the suction chamber and nasopharyngeal pack, and hemodynamic variations were measured. Surgeon's satisfaction scores and suitability of operation field, were obtained from the surgeon by respectively Likert scale and Boezaart grading scale.

Results: The intervention group had a higher score of surgeon satisfaction [4.1 vs 3.16 in control group (P= 0.001)] and fewer hemodynamic variations. The mean bleeding volume in the intervention was 187.23 ± 54.61 mL and in the control group was 341.22 ± 49.17 mL (P=0.001). The mean Boezaart score (suitability of operation field) in the intervention group was 1.8 (score range: 1-3) and in the control group was 2.53 (score range: 2-4) and it was statically significant (P= 0.001).

Conclusion: The local use of tranexamic acid + lidocaine + adrenaline is associated with reduced bleeding, greater surgeon satisfaction, reduces the need for Karpol injection, and caused hemodynamic stability.

Keywords: Tranexamic acid - SeptoPlasty - Bleeding – Antifibrinolysis

Key Messages: Local application of tranexamic acid without imposing intravenous side effects can help improve the field of surgery.

Introduction

Septoplasty is a surgical procedure used to correct congenital or traumatic abnormalities of the nose. Tranexamic acid is a synthetic derivative of lysine amino acid whose antifibrinolytic effects are due to its irreversible binding to lysine binding sites on plasminogen molecules (1). Hemorrhage during septoplasty is important because even a small amount of hemorrhage can impair the surgeon's vision and lead to an increased risk of surgical complications and prolonged bleeding time and incomplete surgical operation (2).

There are various techniques to improve the surgeon's field of vision, including controlled hypotension, cauterization, packing, and the use of topical vasoconstrictors, cauterization leads to tissue damage and delayed bleeding on the other hand, topical vasoconstrictors may cause hemodynamic instability, especially in patients with a history of hypertension or ischemic heart disease, deliberated hypotension exposed patient to greater doses of anesthetic drugs and more side effects, in general, none of the above methods can provide desired surgical field(3).

The use of TXA (tranexamic acid) as an intravenous infusion for endoscopic sinus surgery has already been established (3). The use of tranexamic acid on bleeding in patients undergoing cardiac surgery and major orthopedic surgery and liver transplant and prostatic surgery has been proved (1, 4). Tranexamic acid has been used in dentistry as a mouthwash prior to tooth extraction (5). Although the intravenous infusion of TXA can significantly reduce postoperative blood loss, the associated risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) makes its use controversial (6, 7). Complications of CNS depression, hypersensitivity reactions, color vision, and vision loss, seizures and thromboembolic events, and ureteral obstruction are due to intravenous tranexamic acid injection (8).

Koster and colleagues observed that in patients undergoing cardiovascular bypass surgery, the rate of seizures due to tranexamic acid administration was doubled, with a higher incidence of embolic and hypoglycemic events (9). The optimal route and method of administration of TXA are yet to be determined (10, 11).

Given the benefits of using this drug for reducing intraoperative hemorrhage, along with the possible side effects of intravenous injection, as a new approach, we aimed to evaluate the efficacy of topical administration in a double-blind placebo-controlled trial while eliminating the possibility of complications of intravenous injection.

METHODS:

Study design:

After being approved by the Research and Ethics Committee of the AJA University of Medical Sciences and Iranian Registry of Clinical Trials (IRCTID: IRCT201604145536N6), and received written informed consent from all individuals involved in the trial, this randomized double-blind prospective study was conducted among 60 patients (30 patients in each group) aimed to evaluate the local tranexamic acid effects on the septoplastic surgery field under general anesthesia in Imam Reza Hospital, Tehran, Iran, from January 10, 2016, to February 8, 2017. Based on the similar study and considering the power (probability) test 80% and confidence interval 95% (α =0.05 β= %10), The sample size 30 patient in each group was determined.

Blinding:

In this study, blinding performed in a double-blinded method. the researcher, manager, anesthesiologists, surgeons, nurses, and the data analyzer were kept blind. Medications were prepared by other nurses who were totally unaware of the nature of the study. The coding was done randomly by the supervisor of the design, and the project manager, the patient, and the analyst of the results of the codes did not know anything about codes.

Patients were divided into two groups (intervention and control groups) according to the random black and white card, and the surgeon, surgical and anesthesia technologist and anesthesiologist did not know which patient belonged to which group. A person, who gave the drugs, was also blind to the content of the syringe. Two trained personnel collected all data separately to increase the accuracy of data collection.

Subjects and setting:

All patients were visited by anesthesiologist the day before the surgery. Inclusion criteria were candidates for elective septoplastic surgery with the age range of 20 to 60 years and the American Society of Anesthesiologists (ASA) physical status classes I.
Exclusion criteria include the patient's refusal to participate, people with ASA class III, II, and IV, any history of bleeding disorder, history of thromboembolism, low platelets, and impaired coagulation tests.

In the operating room, standard pulse oximetry monitor, capnographic monitoring, noninvasive blood pressure (SBP and DBP) measurement system and an electrocardiogram were attached. And baseline of heart rate, respiratory rate, SPO2, and ECG were noted. After insertion of an 18-cm venous catheter on the arm, all patients received oxygen at 5 L/min and they were placed in the supine position.

Intervention design:

After ensuring accurate patient identification, the same induction of anesthesia (2mg midazolam, 3µg/ kg fentanyl, 2mg/kg propofol, 0.5mg/kg atracurium, and 0.1mg/kg

morphine) and same anesthesia maintenance conducted in both groups (isoflurane with MAC 1.2, O2 3 L/min, N2O 3L/min). Remifentanil with dose 0.01µg/kg (for controlled hypotension) to reduce the amount of intraoperative hemorrhage, infused in both groups. All Vital parameters including HR, NIBP, RR, and SPO2were measured and recorded in the checklist every 5 min for the first 60 min. The duration of surgery was recorded.

In the control group (group A) patients received the syringe contained lidocaine + adrenaline 1:100000. (manufactured by Caspian Tamin Pharmaceutical Company in Rasht-Iran).

In intervention group (group B) patients received the syringe contained lidocaine + adrenaline 1:100000 + tranexamic acid 100 mg (manufactured by Caspian Tamin Pharmaceutical Company in Rasht-Iran).

Administration in both groups was similar and injected as local in the field of surgery by the surgeon. Solutions in both groups were used when the surgical site did not have a good vision and was bloody.

Outcomes and measurements:

The primary outcomes that measured in this study were the quality of the surgical site by using Boezaart grading scale (12) and blood loss that measured by Visual Guide for determining blood loss (13). The secondary outcomes of interest included the duration of surgery, times of Karpol injection and hemodynamic variations.

Bleeding in both groups were carefully calculated by using blood accumulated in the suction chamber after subtracting the volume of irrigation fluid used for washing and measurement of nasopharyngeal pack weight and converting the blood weight into ml (1 gr = 1cc).
And all blood gauzes absorber 4×4 inch that used in the duration of surgery in each patient was collected and measured by Visual Guide for determining blood loss and full wet gauze considered 12 mL. Fig. 1.

Surgeon satisfaction was measured by 5-item Likert scale, where 1 = poor and 5 = excellent. Suitability of operation field, were obtained from the surgeon by Boezaart grading scale. Table 1 (12).

Statistical analysis

In this study, to investigate qualitative variables such as gender, the Chi-square test was used, and for quantitative variables in two groups, an independent t-test was used for normal data and for non-normal data the Man-Whitney test was used. The normality of data was tested using the Kolmogorov-Smirnov test. P-Value less than 0.05 were considered as significant. Statistical analysis was carried out by utilizing SPSS version 20 (IBM corporation, Chicago, IL).

Results

There was no statistically significant difference between the two groups in terms of (demographic variables) gender, age, weight and it shows that the distribution of the studied variables is normal in the target population. ($p>0.05$)(Table 2).

The mean arterial pressure and heart rate variations in the fifth minute were not statistically significant between the two groups ($p>0.05$) and it's due to delays in drug systemic absorption. But at other times of the study period, this difference was significant ($p<0.05$) (Fig 2 and 3).

The two groups were significantly different in terms of surgeon satisfaction and suitability of surgical field variables. The intervention group had a higher score of surgeon satisfaction [4.1 vs 3.16 in control group (P= 0.001)]. Also the mean Boezaart score (suitability of operation field) in the intervention group was 1.8 (score range: 1-3) and in the control group was 2.53 (score range: 2-4) and it was statically significant (P= 0.001).
(Table 3).

The times of needing adrenaline lidocaine injection (known as Karpol), for hemostasis controlling in the intervention group (syringe B contained adrenaline-infused lidocaine 1 in 100000 and 100 mg tranexamic acid) was fewer than the control group ((syringe A contained adrenaline-infused lidocaine 1 per 100000) and this difference was significant ($p = 0.011$). and the mean bleeding volume in the intervention was 187.23 ± 54.61 mL and in the control group was 341.22 ± 49.17 mL and this difference was significant (P=0.001). (Table 4). Also the duration of surgery in the intervention group was lesser than control group [44.21 ± 4.61 minutes vs 56.17 ± 2.82 minutes (P= 0.002)] (Table 4).

Discussion

There is no doubt about the hemostatic effect of TXA (12).Some studies and meta-analyses have suggested that TXA reduces blood loss without increasing the risk of DVT and PE (15). However, there are also opposing reports (16). Intravenous drip is the most commonly used method at present. Other drug delivery methods include intramuscular injection, oral administration, and intra-articular injection (17).

Studies have shown that only a small portion of intravenous TXA solution reaches the target tissue (18). In view of the high coagulation state of the whole body and the serious consequences of thrombosis complications, local application is a better choice. Compared with intravenous drip, the systemic TXA plasma concentration after topical administration is 70% lower while the hemostasis effect is similar (19). In terms of overall impact, if the effect is the same, local application is more advantageous than systemic application (20).

We addressed the comparison of two different drug combinations to improve the quality of the septoplasty surgery field. In this study, the target population was the patients undergoing septoplastic surgery. One group (group A) received adrenaline-infused lidocaine and another group (group B) received adrenaline-infused lidocaine and tranexamic acid. To assess the efficacy of these combinations we measured the hemodynamics variables including heart rate (HR) and mean arterial pressure (MAP) and the suitability of the operation field and surgeon's satisfaction as outcomes.

In our study differences in hemodynamic changes, such as heart rate and mean arterial pressure, which was fewer in the group receiving local tranexamine acid than in the other group, indicate a significant reduction in bleeding volume in the TXA group this finding is consistent with Dr. Lee's study in which topical application of TXA in knee surgery caused less bleeding than intravenous injection (21). The reason for decreased of HR and MAP in the intervention group versus the control group is reduced times of Karpol injection in intra-operative, because the surgeons apply the prepared syringes (known as Karpol in both groups), just for hemostasis controlling. And it is obvious any type injection of adrenaline + lidocaine (known as Karpol), raised the heart rate and mean arterial pressure, and when the consumption of this drug mixture decreased, the HR and MAP will be normalized and not raised. And also due to the using this drug mixture in both groups as a local injection in the field of surgery, it will be taken a few minutes to absorb the drug and reveal the pharmacodynamics effects such as tachycardia and raised MAP, for this reason, and reduced the needing of Karpol consumption and the times of using it in the intervention group the hemodynamic stability (HR and MAP) was better than the control group after 5 minutes and generally. Because our study illustrates that the combination of TXA with Karpol reduced the times of needing it in septoplasty surgery for hemostasis.

We have shown that following local administration of tranexamine, by reducing the amount of bleeding during surgery, the field of surgery is drier and, as a result, the surgeon's vision is better and more satisfied. This finding consistent with the Hankerson MJ study in which the use of topical TXA for nasal bleeding had more satisfaction with the medical staff (22).

The times of needing intra-operative injections of Karpol, blood loss, and the duration of surgery was lesser in the intervention group and these findings were consistent with Rafael A Couto study their study showed that local infiltration of TXA with the local anesthetic prior to a facelift appears to decrease bleeding, operative time, and postoperative facelift drainage output (23).

To justify this we can say that the TXA acts directly on the microvasculature and clot stabilization, thus reducing local bleeding (24, 25).

Conclusions

In this study, the local application of tranexamic acid in septoplastic surgery results in reduced bleeding, greater surgeon satisfaction, reduces the need for Karpol injection, less blood loss, shorter surgery time, and caused hemodynamic stability compared with those in the control group without other general complications.

Acknowledgments

The authors would like to thank the personnel of the Imam Reza Hospital operating room personnel of AJA University of medical sciences because of their kind cooperation in data collection process.

Financial support and sponsorship

None

Conflict:

There are no conflicts of interest

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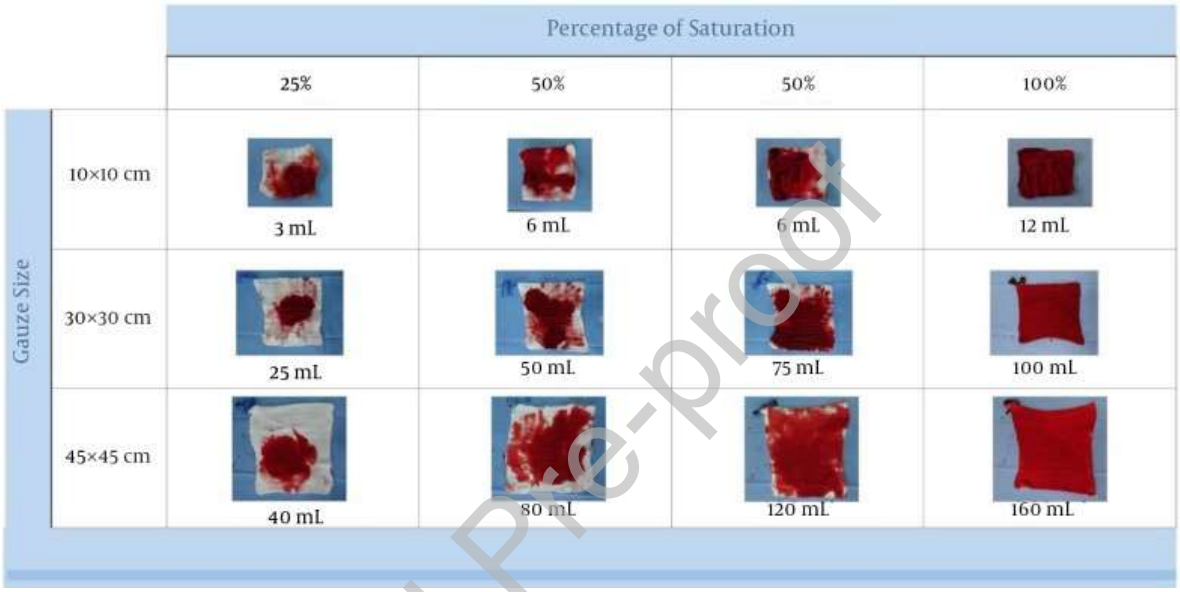
Fig. 1: Visual Guide for determining blood loss (13).



Visual Guide for Determining Blood Loss for Three Different Sizes of Gauze

Table 1: Boezaart et al. grading scale for scoring of surgical field bleeding (12**)**

Score	Assessment
0	No bleeding
1	Slight bleeding: no suctioning required
2	Slight bleeding: occasional suctioning required
3	Slight bleeding: frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed
4	Moderate bleeding: frequent suctioning required. 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

Table 2. Demographic characteristics of participants

Variables	Group A	Group B	P-value
Gender (M/F)	12/18	12/18	1.000*
Age (year)	57.99±.5667	58±.5643	0.752**
Weight (kg)	58 ± 6.8	57. 5 ±5.7	1.000**

* Chi-square test ** independent T-Student test
Group A: adrenaline-infused lidocaine
Group B: adrenaline-infused lidocaine and tranexamic acid

Table 3.Suitability of operation field and Surgeon's satisfaction				
Variables		Group A (control group)	Group B (intervention group)	P-value
Suitability of operation field (Boezaart grading score)	Score 1	0	11	0.001
	Score 2	17	14	
	Score 3	10	5	
	Score 4	3	0	
	Mean score	2.53	1.8	
Surgeon's satisfaction (Likert score)	Score 1	2	0	0.001
	Score 2	7	0	
	Score 3	9	7	
	Score 4	8	13	
	Score 5	4	10	
	Mean score	3.16	4.1	

* Mann-Whitney- U Test
Surgeon satisfaction was measured by Likert scale.
Group A: adrenaline-infused lidocaine
Group B: adrenaline-infused lidocaine and tranexamic acid
The intervention group had a higher score of surgeon satisfaction [4.1 vs 3.16 in control group (P= 0.001)]. Also the mean Boezaart score in the intervention group was lower than control group [1.8 vs 2.53] and it was statically significant (P= 0.001).

Table 4. Duration of surgery and intra-operative injections of Karpol				
Variables		Group A (control group)	Group B (intervention group)	P-value
Duration of surgery (minute)		56.17±2.82	44.21±4.61	0.002
Mean Blood Loss (ml)		341.22 ± 49.17	187.23 ± 54.61	0.001
intra-operative injections of Karpol	once	2 (patients)	2(patients)	0.001
	twice	7(patients)	0(patients)	
	3 times	4(patients)	2(patients)	
	4 times	2(patients)	0(patients)	

Group A: adrenaline-infused lidocaine
Group B: adrenaline-infused lidocaine and tranexamic acid
The times of needing Karpol in the intervention group was fewer than the control group and this difference was significant (p = 0.011). The mean bleeding volume in the intervention was lesser than in the control group (P=0.001). Also the duration of surgery in the intervention group was lesser than control group (P= 0.002).

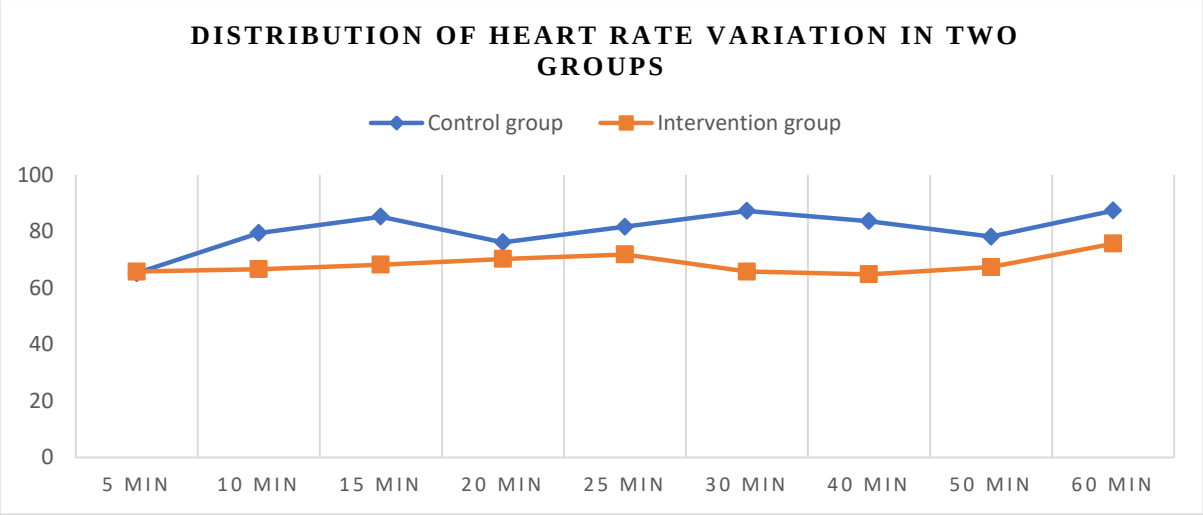


Fig.2: Distribution of Heart rate variation in two groups.
* T-test
Group A: adrenaline-infused lidocaine
Group B: adrenaline-infused lidocaine and tranexamic acid
The mean arterial pressure and heart rate variations in the fifth minute were not statistically significant between the two groups ($p>0.05$) But in other times of the study period, this difference was significant ($p<0.05$).

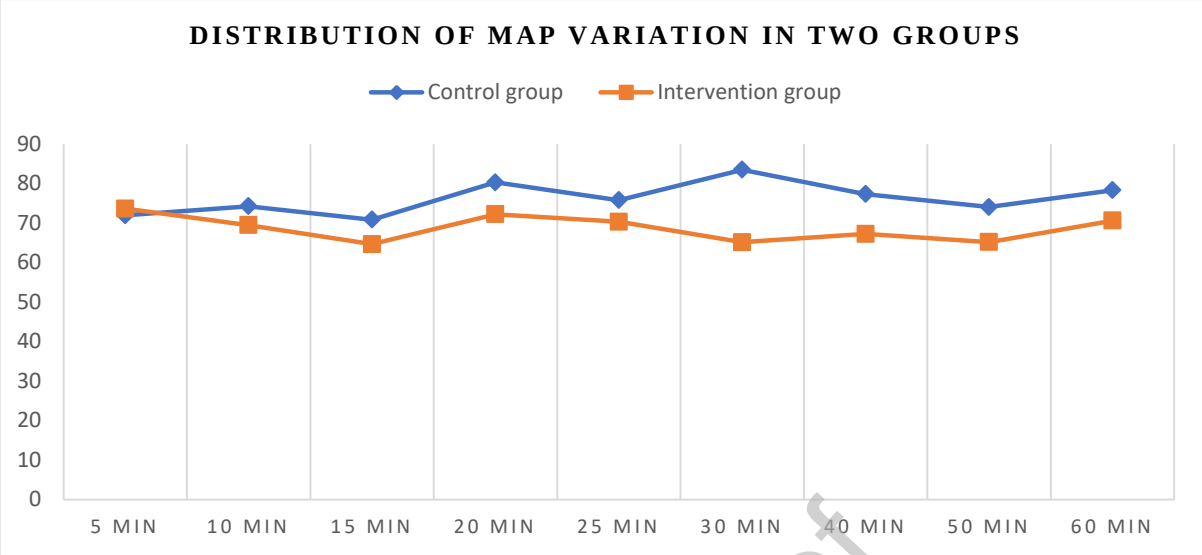


Fig.3: Distribution of Mean Atrial Pressure variation in two groups.
Control group (Group A): adrenaline-infused lidocaine
Intervention group (Group B): adrenaline-infused lidocaine and tranexamic acid