

Efficacy of tranexamic acid on blood loss during bimaxillary osteotomy: A randomized double blind clinical trial

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ABSTRACT

Background: Tranexamic acid has been used to reduce bleeding and the subsequent need for blood transfusion in many surgeries. Because orthognathic surgery can be associated with significant bleeding, this study evaluated the efficacy of prophylactic intravenous (IV) tranexamic acid on blood loss during bimaxillary osteotomy. **Methods:** Thirty-two consecutive patients, scheduled for elective bimaxillary osteotomy, were included in the study and 16 were randomly assigned to each group. They received tranexamic acid (20 mg/kg) or equal volume of placebo (normal saline) intravenously just before induction of anesthesia. Intraoperative blood loss, pre and post operative hemoglobin (Hb) and hematocrit (Hct) concentration, duration of surgery, hospital stay time, and rate of blood transfusion were recorded for each patient. **Results:** Intraoperative blood loss in the tranexamic group and control group were 585.9 and 790 mL respectively ($P=0.008$). Postoperative Hb concentration at the 6th hour was greater in the tranexamic group ($P=0.008$). There was no significant difference in the Hct concentration between the study groups. There was no significant difference in blood transfusion rate, hospital stay time and duration of surgery between the study groups. **Conclusion:** Preoperative IV administration of tranexamic acid reduces the amount of blood loss during bimaxillary osteotomy.

Key words: Bimaxillary osteotomy, blood loss, hemoglobuin, hematocrit tranexamic acid

INTRODUCTION

The orofacial region is very vascular and significant blood loss can occur and a subsequent need for blood transfusion is often encountered. The major sources of bleeding in maxillofacial surgery including Le Fort I and sagittal split osteotomies are the descending palatine and inferior alveolar arteries respectively. Although bleeding from these arteries is usually controllable, there may be significant blood loss in long time maxillofacial surgeries.

Several approaches have been used to reduce intraoperative blood loss, including: Hypotensive anesthesia which can

reduces perfusion of vital organs especially in patients with altered baseline auto regulatory mechanisms (hypertension) or those likely to be particularly vulnerable (eg, diabetes, coronary artery disease, stroke, and chronic renal failure).^[1,2]

The alternate approaches are administration of antifibrinolytic agents such as aprotinin, aminocaproic acid and tranexamic acid perioperatively to stabilize the multiple micro clots that form within the surgical wound.^[3,4]

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

Lysine exerts its antifibrinolytic effect by competitively inhibiting the activation of plasminogen thereby reducing the conversion of plasminogen to plasmin. It can also directly inhibit plasmin activity.

Adverse effects of tranexamic acid including nausea, diarrhea and occasional orthostatic events, are uncommon. Isolated cases of thromboembolism after the use of

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tranexamic acid have been reported; however, these observations have not been confirmed by the results of controlled clinical studies.^[5]

Tranexamic acid has been used in neuro, orthopedic, cardiac, spine and maxillofacial surgeries and has reduced the amount of blood loss and subsequent need for blood transfusion.^[6-11]

The most common application of topical tranexamic acid in oral and maxillofacial surgery is in patients with congenital or acquired coagulation disorders.^[12,13]

Despite of mentioned studies, in a study by Kaewpradub *et al.* on 40 patients, tranexamic acid in an irrigant fluid did not significantly decrease intraoperative blood loss compared with the placebo during orthognathic surgery.^[13]

The aim of this study is to evaluate the efficacy of preoperative IV tranexamic acid on intraoperative blood loss during bimaxillary surgeries.

METHODS

This randomized double blind clinical trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences from August 2010 to January 2011. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki.

Ethics

Ethical approval for this study was provided by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Islamic Republic of IRAN, protocol number 220, on April 20, 2010.

All American Society of Anesthesiologists (ASA) Class I patients between 18 and 40 years of age scheduled for bimaxillary osteotomy at Dr. Shariati Hospital between August 2010 to January 2011 were consecutively recruited to the study after written informed consent. Exclusion criteria were patients with uncontrolled systemic diseases, anticoagulant consumption, simultaneous temporomandibular joint (TMJ) surgery or rhinoplasty, concomitant craniofacial surgery, bone disease (eg, fibrous dysplasia), or massive autogenous graft. Randomization was by means of computer-generated codes. Sealed envelopes containing the information of the randomization allocation were prepared and kept by the staff not involved in the study. The specific envelope was transferred to a specific member of the anesthesia team not involved in the study before the induction of anesthesia. The study drug was prepared by this member and was transferred to the anesthetist for administration after induction of anesthesia. The envelope was sealed again and kept in the patient's folder until the end of the study period. All members of the surgical team, nursing staff, and the anesthetist were unaware of the allocation. Subject enrollment and allocation is summarized in a CONSORT flow diagram [Figure 1].

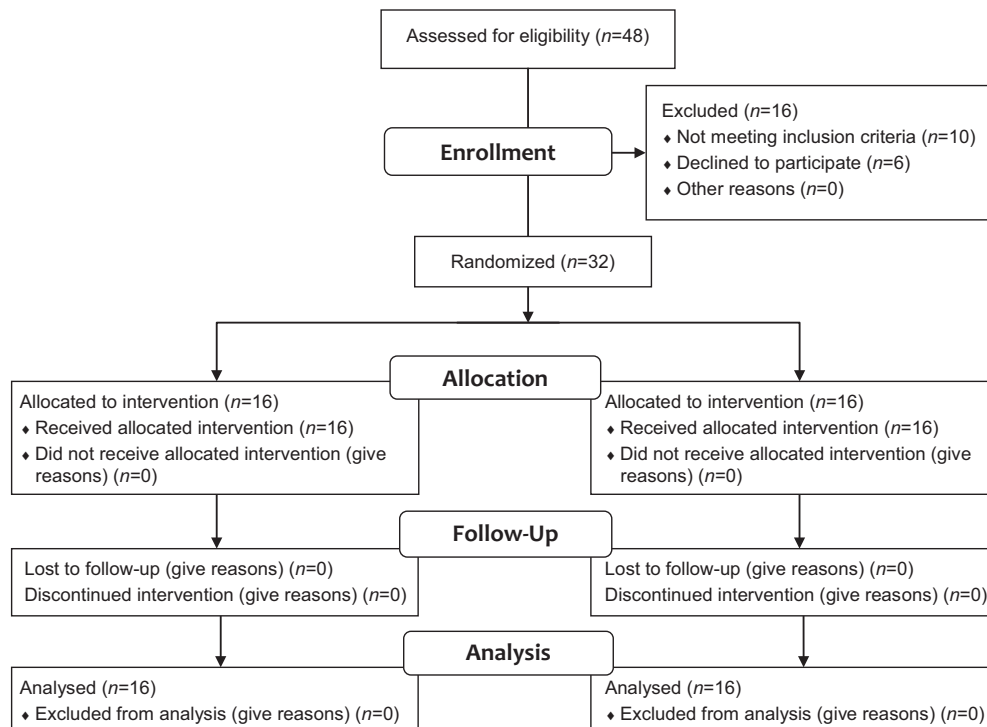


Figure 1: CONSORT flow diagram

IV infusion of normal saline 4 ml/kg/h was started 1 h before patients, were transferred to the operating room. Standard monitoring including electrocardiogram, arterial blood pressure, arterial oxygen saturation, core temperature, and end-tidal carbon dioxide were used throughout the operation.

Patients were premedicated with 1 mg of modazolam and 3 µg/kg of fentanyl intravenously.

Anesthesia was induced with 5 mg/kg of thiopental sodium intravenously. Patients were nasotracheally intubated after IV administration of 0.5 mg/kg atracurium and 1 mg/kg lidocaine. Anesthesia was maintained with 1%–2% isoflurane and 50% nitrous oxide in oxygen. Arterial blood pressure was monitored continuously via radial catheter and was kept 20% below the patient's mean arterial pressure (mild hypotension) by changing isoflurane concentration and infusion of 0.15-0.5 µg/kg/h remifentanyl. Intraoperative fluid therapy was obtained with 0.9% saline or lactated Ringer's solution 4ml/kg/h and blood loss was replaced with three fold saline in order to maintain the urine output more than 0.5 ml/kg/h. When 15% of the estimated blood volume (EBV) was lost, hydroxyethyl starch (Voluven; Fresenius Kabi Pharmaceutical, Bad Homburg, Germany) was given on a matching basis (milliliter for milliliter) or according to the vital signs (pulse and blood pressure) and urine output of more than 0.5 ml/kg/h.

The surgeon injected 20 mL saline containing 1/200,000 epinephrine into the surgical field a few minutes before the incisions. Surgeons and the technique of surgery were all the same for patients and consisted of Le Fort I osteotomy of the maxilla and bilateral sagittal split osteotomy of the mandible followed by internal fixation.

During the surgery, the amount of blood loss was meticulously measured as follows:

1. The amount of irrigation solution used during the surgical procedure was detracted from the total amount of fluid accumulated in portable suction device
2. The average weight of standard 20-cm gauze was detracted from the mean weight of completely blood-soaked gauze and the total amount of 7 mL blood was considered for each blood-soaked gauze
3. The sum of blood accumulated in suction device and surgical gauze was measured and considered as the estimated blood loss (EBL).

In patients undergoing concomitant genioplasty, the total amount of blood loss during this procedure was recorded and detracted from the total blood loss.

Hemoglobin (Hb) and hematocrit (Hct) concentrations

were checked at 1th and 6th hours after operation to control the patient's status and verify the need for blood transfusion. Any complications related to tranexamic acid injection, blood transfusion rate, length of hospital stay, and surgery time were also recorded.

Statistical analysis

According to the previous studies, the blood loss of bimaxillary osteotomy was within a range of 600 mL to 2,000 mL, with a mean of 1,000 mL and a standard deviation (SD) of 350 mL, and the use of tranexamic acid was associated with a reduction of intraoperative blood loss by 30%.^[11]

A power analysis using these assumptions showed that 16 patients per group was sufficient to detect a 30% difference in the intraoperative blood loss, assuming a power of 85% and a significance level of 5%. Normality of distribution was tested by Kolmogorov Smirnov test. Data were analyzed by SPSS version 11.5 (SPSS, Chicago, IL, USA). Independent sample *t*-test and Chi-squared tests were used for comparing demographic data. Repeated measures of analysis of variance (ANOVA) (within subject and between subject) was used for comparing mean Hb and Hct concentration.

RESULTS

Demographic data, duration of surgery and hospital stay time were not statistically different between the study groups [Table 1].

Twenty-eight patients (87.5%) underwent bimaxillary orthognathic surgery and the same procedure plus genioplasty was performed on the remaining 4 patients [Table 2].

Intraoperative blood loss in the tranexamic group and control group were 585.9ml and 790ml respectively ($P=0.008$) [Figure 2].

In the txa group, preoperative mean Hb concentration was 14.11 g/dl which was decreased to 11.56 g/dl at 1th and 11.8 g/dl at 6th hour after operation respectively. In the control group, the preoperative mean Hb concentration

Table 1: Comparing demographic data, duration of surgery and hospital stay time between the study groups

Variable	Group T	Group S
Sex (M/F)	6/10	7/9
Age (years)	22.8±12.8	23.9±12.2
Weight (kg)	62.6±18.9	61.8±19.3
Operating time (minutes)	211±25	210±31
Hospital stay duration (days)	3.0	2.8

Data are presented as mean±SD, $P>0.05$, SD = Standard deviation

was 13.78 g/dl which was reduced to 10.68 g/dl at 1st and 10.84 g/dl at 6th hour after operation respectively (repeated measures ANOVA, within subject, $P>0.05$) [Figure 3].

In the txa group, preoperative mean Hct concentration was 41.46%, which was decreased to 34.03% at the 1th and 34.93% at the 6th hour after operation respectively. In the control group, the preoperative mean Hct concentration was 40.67% which was reduced to 32.06% at first and 33% at sixth hour after operation respectively (repeated measures ANOVA, within subject, $P>0.05$) [Figure 4].

There was a statistical difference in the mean Hb concentration at 6th hour after operation between the study groups (repeated measures ANOVA, between subject, $P=0.02$) [Figure 3].

There was no significant difference in postoperative Hct concentration between the study groups (repeated measures ANOVA, between subjects, $P>0.05$).

Only 1 patient in the control group received packed red blood cell. Although there was a statistical difference in the blood loss between both the groups but there was no difference in the blood transfusion rate because the Hb concentrations were higher than 10 g/dl. Hospital stay time and duration of surgery were not statistically different between the study groups. No complications related to tranexamic acid injection were recorded.

DISCUSSION

Tranexamic acid has been used to reduce blood loss and the subsequent need for transfusion in neuro, orthopedic, spinal, and cardiac surgery.^[6-10]

Orthognathic surgery can be associated with significant bleeding and strategies have been used to reduce the amount of bleeding during this type of surgeries including: Antifibrinolytic agents, moist pressure dressings, diluted hydrogen peroxide, microfibrillar collagen, topical

Table 2: Comparing surgical treatment plan between the study and control groups

	Study group	Control group	Total (%)
Mandible			
Set back	11	12	23 (71.8)
Advancement	1	2	3 (9.4)
Osteotomy	3	3	6 (18.8)
Maxilla			
Advancement	12	11	23 (71.8)
Set back	0	1	1 (3.1)
Impaction	4	4	8 (25)

(n=16)

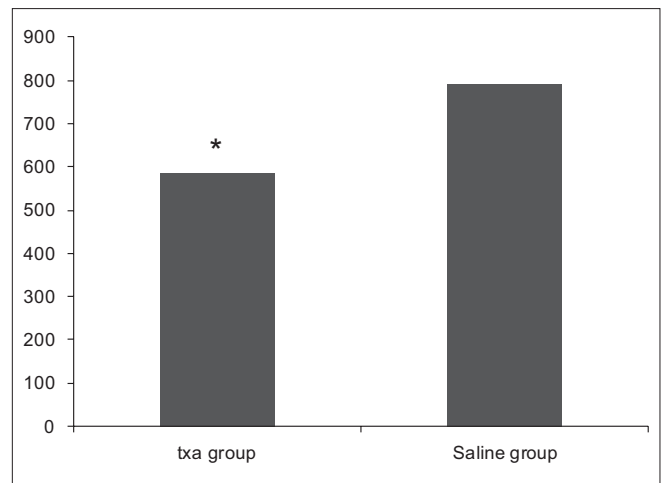


Figure 2: Comparison of blood loss (mL) between the tranexamic acid group (txa) and saline group (control). * $P=0.008$

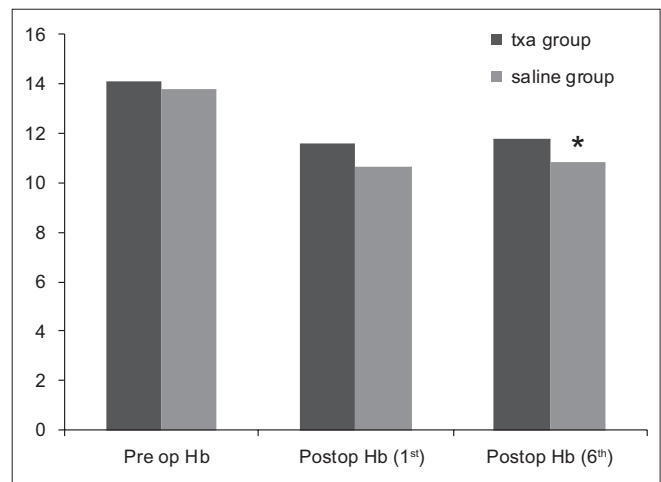


Figure 3: Comparison of pre and postoperative Hb concentration (at 1st and 6th hour) between the tranexamic acid group (txa) and saline group (control). Preop Hb: Preoperative hemoglobin concentration. Post-Op Hb: Postoperative hemoglobin concentration. * $P=0.02$

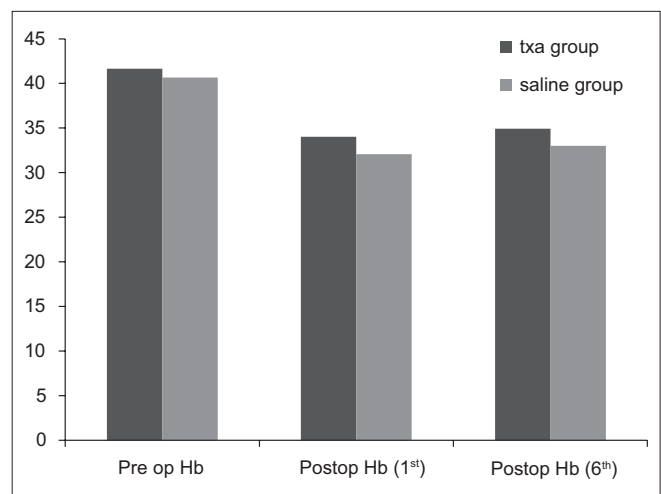


Figure 4: Comparison of preoperative and postoperative Hct concentration (at 1st and 6th hour) between the tranexamic acid group (txa) and saline group (control), $P>0.05$

solutions containing thrombin, patient's positioning (reverse Trendelenburg), vasoconstrictors, and hypotensive anesthesia.^[11]

In a study by Choi *et al.* the effect of tranexamic acid on blood loss during orthognathic surgery was evaluated. They found that the total blood loss and intraoperative bleeding was reduced significantly in the txa group compared with control group.^[11]

We did not calculate postoperative oozing (concealed blood loss). It is not easy to measure the amount of oozing precisely because:

1. Application of suction systems, such as hemovac In oral and maxillofacial surgeries, as a result of confined surgical field and intraoral incisions, is not practical
2. The variation of salivary secretion in different patients may interfere with reliable measurement of intraoral oozing
3. A significant proportion of oozing after orthognathic surgeries is post pharyngeal which can be easily swallowed by patients and is concealed.

In another study by Kaewpradub *et al.*,^[13] 0.05% tranexamic acid in normal saline solution or normal saline as placebo was used as an irrigant fluid during orthognathic surgery on 40 patients and intraoperative blood loss was evaluated. They found no difference in blood loss during bimaxillary surgery in the txa group compared with the control group.

This finding was different from our study because they used 0.05% tranexamic acid in normal saline for tissue irrigation. This concentration was approximately equal to 5 fold of that in which 15 to 25 mg/kg tranexamic acid was administered intravenously.

Application of tranexamic acid has reduced the amount of blood loss during surgeries that have been conducted in other fields; these findings were also correlated to our study.^[6-11]

There is no strong evidence for risk of thromboembolism associated with the use of tranexamic acid. However, it should be used with caution in patients with risk for thrombosis (eg, history of a thromboembolic event or a family history of thromboembolic disease). Because tranexamic acid is excreted in the urine, dose reduction may also be required in patients with renal insufficiency.

In conclusion, this study showed that the preoperative IV administration of tranexamic acid significantly reduced intra operative bleeding in bimaxillary surgery.

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