Research Article

Effect of Intravenous Tranexamic Acid on Blood Loss and Quality of Surgical Field in Orhoganthic Surgery

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Abstract
Objective: The aim of this prospective randomized double blinded study was to evaluate the effect of intravenous tranexamic acid on the volume of intra-operative blood loss, quality of surgical field, duration of operation, satisfaction of the surgeon, incidence of blood transfusion, and side effects of tranexamic acid. **Methods:** Thirty four patients ASA I or II aged between 18 and 50 years scheduled for orthoganthic surgery were included in the study. They received nitroglycerin infusion for mild hypotension during surgery and they were randomly divided into two groups each one was seventeen patients, the 1st group received pre-operative bolus dose 10mg/kg of tranexamic acid followed by 1mg/kg/hr tranexamic acid which was diluted in normal saline while the 2nd group received the same infusion of plain normal saline. Intra-operative blood loss volume, quality of surgical field, satisfaction of the surgeon, duration of surgery, post-operative hemoglobin, incidence of blood transfusion, and side effects of tranexamic acid were recorded. **Results:** Volume of intra-operative blood loss was significantly lower than that of control group, quality of surgical field as evaluated by the surgeon was more favorable in tranexamic acid, satisfaction of the surgeons was significantly higher in tranexamic acid, and incidence of blood transfusion was less in tranexamic acid group than that of control group. **Conclusion:** Intravenous administration of tranexamic acid 10mg/kg followed by intravenous infusion of 1 mg/kg/hr could decrease volume of intr-operative blood loss, decrease incidence of blood transfusion rate, improve quality of surgical field, improve satisfaction of the surgeons, and shorten operative time without side effects in orthoganthic surgeries.
Key words: Tranexamic acid, Orthoganthic surgery, Blood transfusion

Introduction
Orthoganthic surgery is a well-established technique for correction of dentofacial deformities to maintain oral function and facial symmetry but it is usually associated with significant bleeding and blood loss which reported in many studies to be up to 1.5 liter, and this may requires blood transfusion to replace the lost blood volume[(1)]. This significant bleeding is caused by the extensive vascularity of maxillofacial region and it leads to impaired vision of the surgeon who needs frequent suctioning of the blood with subsequent prolongation of the operative time which in turn increases the blood loss and incidence of blood transfusion[(2)]. Different methods have been used to decrease the intra-operative bleeding such as elevation of the head, deliberate hypotension, and infiltration with local vasoconstrictors. These methods don't ensure favorable surgical field with no bleeding and they have many side effects as impaired tissue perfusion with deliberate hypotension use and hemodynamic instability with vasoconstrictors use [(3)].

Activation of fibrinolytic system during and after the orthoganthic surgery by various mechanisms such as surgical trauma, blood loss, consumption of coagulation factors, hypothermia, and acidosis leads to increased bleeding form surgical site[(4)].

Tranexamic acid (4-aminoethyl cyclo-hexane carboxylic acid) which is a synthetic lysine derivative and has antifibrinolytic activity by inhibiting plasminogen conversion into plasmin with subsequent stabilization of fibrin mesh and prevention

of its dissolution which results in reduction of bleeding and blood loss [5].

It has been investigated in different surgeries such as orthopedic[6] cardio-thoracic surgeries[7], and spine surgery [8] to decrease intra-operative blood loss.

The use of tranexamic acid is not completely safe as large doses of tranexamic acid is associated with several side effects such as nausea, vomiting, dizziness, blurred vision, hypotension, seizures, and thromboemolic events[9].

It was hypothesized that systemic tranex-amic acid could decrease intra-operative blood loss, and improve quality of surgical field in orthoganthic surgery. This prospective randomized blinded study was designed to evaluate the effect of intravenous tranexamic acid on the volume of intra-operative blood loss (primary outcome), quality of surgical field, duration of operation, satisfaction of the surgeon, incidence of blood transfusion, and side effects of tranexamic acid (secondary outcomes).

Methods

After obtaining approval from the medical ethics committee of faculty of medicine in El-Minia unversity and informed written consent from all patients, this randomized comparative study was conducted in El-Minia university hospital in the period from June 2012 to December 2014. Thirty four patients who were of ASA physical status I or II, aged from 18 to 50 years, scheduled for orthoganthic surgery to correct orofacial deformity were included in the study. Patients who refused to participate, who had a history of hypersensitivity to the studied drugs, patients with uncontrolled hypertension, renal or hepatic dysfunction, coagulopathy or on anticoagulant therapy, deep venous thrombosis, peripheral vascular disease, and patients with suspected difficult intubation were excluded from the study.

The study was prospectively assigned in a double-blinded manner (the anesthetist who injected the drugs and recorded the parameters, the surgeon, and the patient didn't know the type of the drugs given). Patients were randomly allocated into two equal groups of seventeen patients in each using a computer-generated randomization chart. The allocation ratio was 1:1. The identification card was placed in opaque envelop to hide the group. The first group received 10 mg/kg tranexamic acid (TXA) in 100 ml normal saline 0.9% followed by infusion of 1mg/kg/hr (500mg TXA diluted in 500 ml of saline so each 1 ml contained 1 mg TXA) while the second group received the same volume of normal saline 0.9% the two solutions were colorless so the blindness was maintained.

When the patient entered the operation room, 18 guage cannula was inserted in the non dominant hand; standard monitoring (electrocardiogram ECG, mean blood pressure MBP, oxygen saturation SPO2) were applied to the patient. Pre-oxygenation with 100 % oxygen through the face mask for three minutes then induction of anesthesia was done by 2mg/kg propofol with 2ml lidocaine 2% in the same syringe and atracucrium 0.5 mg/kg followed by mask ventilation with sevoflurane 2% till adequate relaxation then nasal endotracheal tube of suitable size was inserted and fixed with a stitch in the nares. Maintenance of anesthesia was done by isoflurane 1.2 % in 100% oxygen and atracurium 0.25mg/kg with controlled ventilation to maintain normocapnia. Mild deliberate hypotension was produced by nitroglycerine 0.5-5 µg/kg/min to maintain mean blood pressure between 60 and 70 mmHg.

Lactated ringer's solution was used to replace fluid deficit and fluid maintenance. Blood loss was replaced by colloid till hemoglobin level reached 9 g/dl. At the end of surgery stop nitroglycerine infusion, stop inhalational anesthetics, reversal of neuromuscular block with neostigmine 0.05 mg/kg plus atropine 0.01 mg/kg. When the patient had adequate tidal volume, respiratory rate, and when airway reflexes returned extubation was done with good suctioning of the nasopharynx. Patient was transported to the post anesthesia care unit (PACU) where he was observed until full consciousness, acceptable blood pressure, and heart rate.

The following parameters were assessed:

- Intra-operative Blood loss, which calculated as follow: the total volume of bloody fluid in suction jar – volume of irrigating fluids used plus the number of used gauze pads and cotton swabs (calculated as it contained 5ml mildly soaked and it contained 15 ml if completely soaked) .Volume of blood loss was calculated and recorded.
- Pre-operative hemoglobin concentration, then 24 hours post operative hemoglobin concentration.
- Hemodynamic parameters: Heart rate (beat/min) and mean blood pressure (mmHg) were recorded before induction, after intubation, every 15 minutes till the recovery.
- Quality of surgical field was assessed by Fromme's ordinal scale[10] where 0= bloodless field 1= minima bleeding without nuisance 2=mild bleeding 3= moderate bleeding, slightly impairs dissection 4= severe bleeding marked impairment of dissection 5= massive bleeding cannot perform dissection.
- Duration of the surgery (skin incision till the end) and duration of anesthesia (from induction to recovery).
- Surgeon satisfaction was assessed at the end of surgery by the surgeon according to Likert scale in which not satisfied =1 slightly satisfied =2 moderately satisfied = 3 very satisfied =4 extremely satisfied =5.
- The incidence of side effects of tranexamic acid such as nausea, vomiting, pruritus, fever, vascular events.
- Incidence of blood transfusion (patient was indicated for transfusion if hemoglobin concentration reached 9 g/dl)

Statistical analysis

The study, the number of patients required in each group was determined after a power calculation according to data obtained from pilot study. Pilot study reported a mean blood loss volume of 440 ml & SD of 55.1 with the use of TXA group, and reported a mean blood loss volume of 550 ml & SD of 98.7 within control group. A sample size of 15 patients in each group was determined to provide 95% power for two-tail 't' test at the level of 5% significance using G Power 3.1 9.2 software with 10 % dropout ratio, the number increased to 17 patients in each group.

Statistical analysis was done using IBM SPSS version 20.0 (SPSS Inc, Chicago, USA) Parametric results were expressed as mean ± SD while categorical results were expressed as number and percentage.
Student's t- test was used to compare the numerical data between the two groups. Chi-square test was used for categorical data. All the tests were two tailed. *P* vale < 0.05 considered significant.

Results

Thirty four Patients were eligible for the study; all of them continued the study the analysis fig (1). There was no significant difference between the two groups as regards the demographic data or the site of surgery table (1). Tranexamic acid (TXA) group showed significant short duration of the operation and anesthesia in comparison to the control group table (1). As regards the volume of intra-operative blood loss it was 450 ± 55.1 ml in TXA group which was significantly lower than the control group in which it was 614 ± 98.7 ml table (2). There was no significant difference between the two groups a regards the pre-operative hemoglobin concentration. As regards the 24 hour post-operative hemoglobin concentration, it was higher in the TXA but the difference was not statistically significant table (2). Number of patients needed blood transfusion was 4 patients in the control group while only one patient needed transfusion in TXA group without significant difference between the two groups table (2). As regards the quality of surgical field which was assessed by the surgeon it was more favorable conditions in the TXA group than the control group and this difference was statistically significant at all study times table (3). Satisfaction of the surgeon was significantly better in TXA group in comparison to the control group table (4). There was no significant difference between the two groups as regards the heart rate table (5) or the blood pressure table (6). There was no side effects related to the TXA was noticed in the patients during the study period.

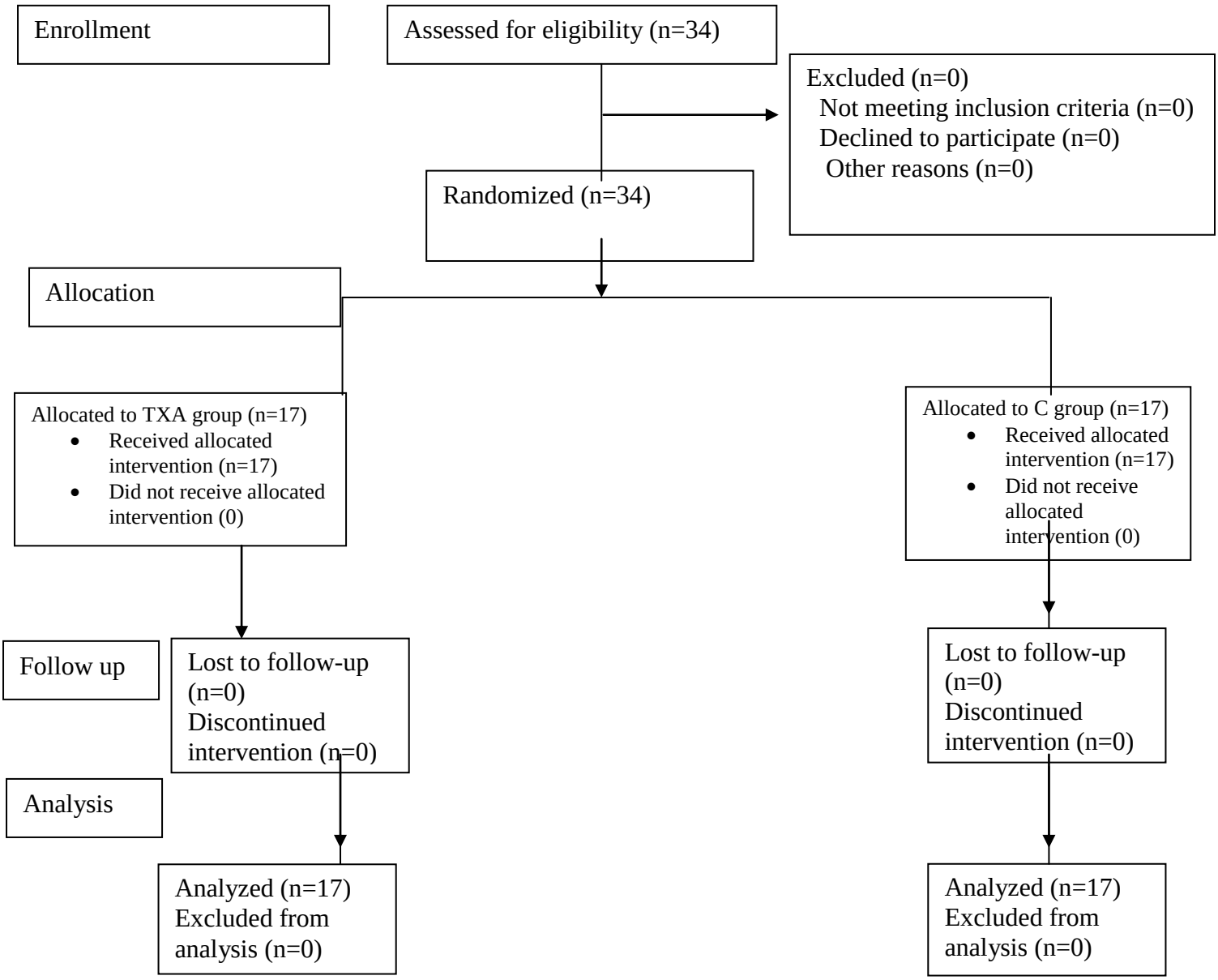

Figure (1): Flow chart in the study.

Table (1): Demographic data, duration of surgery and anesthesia.

Item	Tranexamic acid group TXA (n=17)	Control group (n=17)	P value
Age (years)	30 ± 5.4	31.4 ± 5.0	0.439
Sex **Male** **Female**	 9 8	 11 6	0.486
Weight (Kg)	73.4 ±7.01	74.1± 6.6	0.766
site of surgery **maxillary** **mandibular**	 10 7	 9 8	0.730
Duration of surgery(min)	242.5±54.4	291.7 ± 71.6	0.031*
Duration of anesthesia(min)	264.5±51.2	310 ± 67.4	0.034*

Results are expressed as mean ± SD. Categorical results are expressed as number and percentage. *P* value <0.05 considered significant.

Table (2): Intra-operative blood loss, pre operative and post operative hemoglobin.

Item	Tranexamic acid TXA (N=17)	Control group (n=17)	P value
Intra-operative Blood loss volume (ml)	450 ±55.1	614 ±98.7	<0.001*
Pre-operative Hb (g/dl)	12.3 ± 1.73	12.6 ± 1.5	0.593
24 hours Post-operative Hb (g/dl)	10.1 ± 1.3	9.2 ± 1.4	0.061
Need for transfusion	1 patient	4 patients	0.146

Data are expressed as mean ± SD. Patients need transfusion are expressed as number.
P value <0.05 considered significant.

Table (3): quality of surgical field.

Item	Tranexamic acid TXA (n=17)	Control group (n=17)	P value
30 minutes	2.8 ± 0.3	3.2 ± 0.7	0.038*
60 minutes	2.0 ± 0.2	3.0 ± 0.66	<0.001*
90 minutes	1.8 ±0.23	3.1 ± 0.65	<0.001*
120 minutes	1.8 ± 0.17	3.1 ± 0.54	<0.001*
150 minutes	1.8 ± 0.15	3.0 ± 0.48	<0.001*
180 minutes	1.6 ± 0.16	2.7 ± 0.42	<0.001*

Data are expressed as mean ± SD. *P* value <0.05 considered significant.

Table (4): Satisfaction of surgeon (Likert scale).

Item	Tranexamic acid TXA (n=17)	Control group (n=17)	P value
30 minutes	3.8 ± 0.78	2.7 ± 1.3	0.005*
60 minutes	4.0 ± 0.61	3.0 ± 0.54	<0.001*
90 minutes	4.3 ± 0.5	3.1 ± 0.61	<0.001*
120 minutes	4.1 ± 0.45	2.8 ± 0.34	<0.001*
150 minutes	4.2 ± 0.6	3.0 ± 0.25	<0.001*
180 minutes	4.0 ± 0.65	3.3 ± 0.4	0.001*

Data are expressed as mean ± SD. *P* value <0.05 considered significant.

Table (5): Heart rate (beat/min) changes during operation.

Item	Tranexamic acid TXA (n=17)	Control group (n=17)	P value
Pre-operative	87.3 ± 8.1	88.1 ± 7.2	0.763
After induction	95.4 ± 6.6	96.2 ± 7.8	0.749
30 minutes	80 ± 7.1	84.1 ± 6.8	0.095
60 minutes	77.2 ± 9.4	75.6 ± 7.0	0.577
90 minutes	73.4 ± 8.6	75.4 ± 6.9	0.460
120 minutes	74.2 ± 7.6	75.0 ± 6.7	0.627
150 minutes	67.7 ± 6.1	66.9 ± 7.1	0.729
180 minutes	66.8 ± 6.2	66 ± 5.8	0.7

Data are expressed as mean ± SD. *P* value <0.05 considered significant.

Table (6): Mean blood pressure (mmHg) changes during operation.

Item	Tranexamic acid TXA (n=17)	Control group (n=17)	P value
Pre-operative	75 ± 8.1	76.3 ± 7.6	0.633
After induction	81.4 ± 6.7	83 ± 8.1	0.535
30 minutes	73.6 ± 5.2	72.7 ±6.4	0.656
60 minutes	64.4 ± 4.9	65 ± 4.7	0.718
90 minutes	63.6 ± 5.3	64.1 ± 5.2	0.783
120 minutes	64.3 ± 5	64.2 ± 4.6	0.952
150 minutes	62.6 ± 4.9	62.3 ±4.6	0.855
180 minutes	63 ± 5.1	62.4 ± 5.2	0.836

Data are expressed as mean ± SD. *P* value <0.05 considered significant.

Discussion

This prospective randomized blinded study was designed to evaluate the effect of systemic tranexamic acid (TXA) on the volume of blood loss, and quality of surgical field in patients scheduled for orthoganthic surgery, and it found that intravenous tranexamic acid decreased intra-operative blood loss, decreased the incidence of blood transfusion, decreased the duration of surgery, improved quality of surgical field and satisfaction of the surgeons without side effects.

Orthoganthic surgeries are associated with excessive fibrinolysis caused by plasminogen activator released by oral and nasal mucosa during maxillofacial surgery which results in significant blood loss and high incidence of blood transfusion which may reach up to 30 % of patients [(11)].

The dose of tranexamic acid which was 10 mg/kg loading dose followed by 1mg/kg infusion was chosen within the range of previous studies and considering the long duration of the surgery in comparison to the short duration of action of tranexamic acid (2 hours), continuous infusion was chosen as the method of tranexamic acid administration.

These results coincided with the results of Choi et al.,[(12)] in their randomized controlled study to evaluate the effect of tranexamic acid as intravenous bolus dose of 20 mg/kg on the volume of blood loss, and duration of surgery in seventy three

patients scheduled for bimaxillary osteotomy and they found that tranexamic acid significantly decreased the volume of intra-operative blood loss by 30% during bimaxillary osteotomy.

Also Song et al.,[13] in their meta-analysis of four randomized controlled trials which were published until 2012 and included 183 patients, concluded that intravenous tranexamic acid could significantly decrease the intra-operative blood loss in orthoganthic surgery but it could not affect postoperative hemoglobin and hematocrit level.

Sankar et al.,[14] in their prospective randomized, double blinded study on 50 patients scheduled for orthoganthic surgeries to evaluate the efficacy of 10 mg /kg bolus tranexamic acid followed by 1 mg/kg continuous infusion on intra-operative blood loss, quality of surgical field, duration of surgery, and transfusion requirements, they found that tranexamic acid could decrease the volume of intra-oerative blood loss and improve quality of surgical field but without significant difference on the incidence of blood transfusion rate or the duration of surgery which could be explained by the slow dissection with dry field and rapid brisk dissection when there was uncontrolled bleeding to control it.

Christabel et al.,[15] in their triple randomized blinded clinical trial on 49 patients scheduled for Le Fort osteotomy to evaluate the efficacy of tranexamic acid in conjunction with hypotensive anesthesia on volume of blood loss found that bolus dose of intravenous tranexamic acid 10 mg/kg in combination with hypotensive anesthesia could decrease volume of blood loss, decrease incidence of blood transfusion, improved quality of surgical field, and decreased the operation time.

The current study found that TXA could improve quality of surgical field, and could increase satisfaction of surgeons, these results coincided with the results of Alimian and Mohesni [16] in their study on 84 patients scheduled for sinus surgery to evaluate the effect of intravenous TXA on quality of surgical field and volume of blood loss and they found that TXA could improve surgical field during sinus surgery. Abbasi et al.,[17] in their study to compare between two doses of bolus intravenous tarnexamic acid 5mg/kg and15 mg/kg found that TXA was effective in improving quality of surgical field, satisfaction of surgeon, decreased intra-operative bleeding, decreased duration of surgery without serious side effects.

The current study found that TXA could limit the descent in post-operative hemoglobin level which coincided with the results of Vijay et al.,[18] in their study on forty five patients scheduled for surgery for major hip and femoral fractures in which they gave the patients a bolus dose of 500 mg TXA followed by intravenous infusion and they found that TXA could decrease volume of postoperative blood loss, limited the descent of hemoglobin level, and decreased the incidence of blood transfusion.

As regards the incidence of side effects the present study showed that use of TXA is not associated with serious side effects, this coincided with different studies which examined the hemostatic effects of TXA in different surgical procedures and they found that the use of TXA was not associated with serious side effects [19].
On the other hand Zufferey et al.,[20] showed three folds increase in the risk of vascular events with the use of tranexamic acid during surgeries for hip fracures but this could be explained by the nature of orthopedic surgery which is associated with high incidence of fat embolism and the long standing recumbence of patients with fractures.
Limitations:

This study was limited by the surgical team members with different skills and duration of experience who participated in the different parts of the surgery under supervision of the main surgeon, and different sites of orthoganthic surgery from mandibular, maxillary or bimaxillary which participate in different volumes of bleeding.

Conclusion

This study concluded that intravenous administration of tranexamic acid 10mg/kg followed by intravenous infusion of 1 mg/kg/hr could decrease volume of intra-operative blood loss, decrease incidence of blood transfusion rate, improve quality of surgical field, improve satisfaction of the surgeons, and shorten operative time without side effects in orthoganthic surgeries.

Conflict of interest: The authors decaled no conflict of interest. The fund of this research was from the university budget.

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