Original Article

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Dentistry Section

Efficacy of Tranexamic Acid in Reducing Blood Loss during Maxillofacial Trauma Surgery–A Pilot Study

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ABSTRACT

Purpose: Tranexamic acid (TXA) is prescribed for short term management of haemorrhage. It is also administered prophylatically in surgeries where blood loss is anticipated. Tranexamic mouth washes are also used in oral surgical procedures for patients with coagulopathies. The purpose of this study was to assess the efficiency of the usage of tranexamic acid on reduction of haemorrhage in maxillo mandibular trauma cases.

Materials and Methods: Twelve consecutive male patients, between the ages 20-40 years, with multiple fractures of the facial bones, were included in this study. Six patients were administered either IV tranexamic acid (10 mg/kg- Group 1) and another six placebo (IV normal saline- Group 2) just before induction of anaesthesia. All patients were operated by the same surgical team, using the same standard techniques and the same anaesthetist and the same drugs were used during the surgery. Hypotension was induced for further reduction of intra operative blood loss. Intra and post-operative blood loss, operation time, transfusion of blood products, pre- and post-operative haemoglobin, number of days of hospitalisation and blood count were recorded for both groups.

Results: Tranexamic acid significantly reduced the volume of blood loss during the surgery when compared with the control group (489.17± 106.7 mL vs 900.83 ± 113.7 mL). Considering the duration of operation and the treatment groups only, the mean total blood loss in the control group was 411.67 mL more than that in the tranexamic acid group. None of the patients of the TXA group required blood transfusion post-operatively. There was no difference in the length of hospital stay between the 2 groups. Two of the patients of the saline group required blood transfusion post-surgery due to significant drop in haemoglobin. The average drop in haemoglobin was 2 ± 1.4 in the tranexamic group and 4 ± 1.09 in the saline group.

Conclusion: Pre-operative intravenous bolus administration of tranexamic acid at 10 mg/kg reduces blood loss compared with placebo during the surgery.

Keywords: Tranexamic acid (TXA), Normal saline (NS), Haemorrhage, Surgery

INTRODUCTION

One of the chief factors that increases the morbidity of trauma management is haemorrhage. Tranexamic acid is an inexpensive, easily used and relatively safe drug. It inhibits plasminogen activation and plasmin [1] thus retards clot disintegration. Therapeutic application of tranexemic acid in trauma for preventing blood loss has been documented since 1960s.The safety and efficacy of prophylactic administration of TXA for reducing blood loss in trauma has been well documented through a recent multi centric randomized trial conducted in more than 20,000 patients [2].

Other haemostatic agents are Aprotinin which is a proteolytic enzyme inhibitor (acts on plasmin) and Etamsylate which acts by correcting abnormal adhesion of platelets.

Since blood loss causes several serious complications, it is compensated emergently by transfusion of blood or its products. However, transfusion of blood and products always carries a risk of inadvertent transmission of infection, antigen-antibody reactions and additional cost all of which can be prevented if blood loss is reduced. Morbidity associated with the delay in compensating the blood loss could also be prevented by pharmaceutically preventing haemorrhage.

TXA is the only drug that can be used safely for reducing blood loss. Infusion of IV TXA to trauma patients within three hours of trauma has successfully saved 372, 315 and 755 life per year 1,000 trauma patients in Tanzania, India and the UK respectively [2].

On comparison, drug induced haemorrhage control is also more economical than blood transfusion. On comparison, the calculated incremental cost per life year gained by infusing TXA in trauma patients is $48, $66 and $64 in Tanzania, India and the UK respectively [2].

During management of maxillofacial injuries, haemostasis is essential to clear the airway also. A retrospective study of 170 patients with 210 maxillofacial fractures reports that blood loss is the most common complication following maxillofacial fractures and their treatment [3]. Though maxillofacial injuries are seldom associated with life-threatening bleeding, there has been a report of an incidence of 10 in 222 cases of the same following maxillary fracture alone [4]. Thaller and Beal also present detailed reports of six patients who have succumbed to haemorrhagic complications or had life-threatening exsanguinations secondary to isolated facial trauma [5]. TXA has also been reported to be successful in reducing haemorrhage in several surgical procedures including craniofacial surgery [6], knee surgery [7], spine surgery [8], prostrate surgeries [9] and the like besides trauma management. TXA oral rinse has been used for preventing excessive haemorrhage for patients with coagulopathies [10-16]. IV TXA has also been proven to be effective in reducing bleeding in healthy adults undergoing third molar surgery [17]. Administration of TXA has also been evaluated and found effective in reducing post-surgical haemorrhage during and after bimaxillary orthognathic surgery [18]. Reports of complications following administration of TXA are uncommon and have not been confirmed by controlled clinical research [19,20]. TXA usage for prevention of excessive haemorrhage, specifically in isolated maxillofacial trauma has not yet been investigated.

The aim of this study was to assess the effect of a single intravenous pre-operative dose of tranexamic acid on blood loss during the treatment of maxillofacial trauma.

MATERIALS AND METHODS

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Male patients, between the age 20-40 years, with pan facial fractures, with normal bleeding, clotting and prothrombin time, with no other medical complications were alone included in the study. This study was approved by the ethics committee of Sree Balaji Dental College and Hospital, Chennai, India. All patients were informed about the study and informed written consent obtained. The study was conducted between November 2009 and October 2011.

Pre-operative Assessment

A blood sample was taken for assessment of haemoglobin (Hb), haematocrit (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), liver function tests (LFT), renal function tests (RFT), random glucose (RG), and grouping. Blood pressure, pulse and respiratory rate were periodically monitored from the time of admission to the time of surgery.

Randomization

Patients were chosen at random, six patients to receive IV TXA 10 mg/kg (Group 1) and another 60.9% normal saline (NS) (Group 2) 15 minutes before surgery. Information regarding the drug administration was maintained by the nursing staff not involved in the study. The information regarding the drug administration was completely blinded to the surgeon, anaesthesiologist and the surgical team till the completion of the study.

Anaesthetic Protocol

No premedication was administered. General anaesthesia was induced by propofol (2-3 mg/kg) with Remifentanil (0.5 µg/kg/min) infusion and maintained using isoflurane. The patient was ventilated adequately and muscle relaxant rocuronium (0.5 mg/kg) used. Patient was intubated and catheterized. Vital signs were monitored, the patient was positioned supine with a 15° head up tilt, and care was taken to avoid obstruction of venous return from the head.

Intraoperative Procedure

One gram of Cefotaxime, and TXA/ NS were given intravenously just before commencement of the surgery. The surgeries were performed by the same surgical team with assistance of post graduate students. The procedures involved exposure of the fractures after adequate pre-surgical aseptic preparations, debridement of the wound, mobilisation and rigid fixation and layered closure. Blood loss was measured intra and post-operatively by calculating the difference in weight between the fluid in suction bottles, blood-soaked gauze, and the irrigation fluid used. All patients received fluid replacement to maintain urine output greater than 0.5 mL/kg/hour. Packed cell (RBC) transfusion was done when the blood loss was greater than one fourth of the blood volume (70 mL/kg for males, 65 mL/kg for females), or the haemoglobin level was less than 8 g/dL. Blood samples were taken at 4, 24, and 48 hours postoperatively for haemoglobin, CBC, PT, and APTT.

Blood loss was calculated as the difference in pre and postoperative haemoglobin and hematocrit values. The following formulae were used assuming the blood volume was normalized at 48 hours postoperatively and the haemoglobin level could be raised by 1 g/dL for every pack of red blood cells transfused:

1. Haemoglobin Loss = Pre-operative Haemoglobin level–48 hours post-operative haemoglobin + Unit of packed RBC transfused x Calculated Blood Loss = Blood Volume × (Haemoglobin Loss/ Pre-operative Haemoglobin)

(Modified from Johansson et al., [18,21]).

2. Red Blood Cell Loss = Blood Volume × (Pre-operative Hematocrit–48 hours postoperative hematocrit) + 320 x Unit of packed red cells transfused x Calculated Blood Loss = Red Blood Cell Loss/((Pre-operative hematocrit + Postoperative hematocrit)/2)

(Adapted from Hurle et al.,[18,22]).

RESULTS

Twelve patients were included in the study, of them 6 received IV TXA (Group 1) and the other 6 received only NS (Group 2). Further statistical analysis using ANCOVA showed that both the operation time and treatment Group ($p < .001$) affected the total blood loss. Tranexamic acid significantly reduced the volume of blood lost due to the surgery when compared with the control group 2 (489.17± 106.7 mL vs. 900.83 ± 113.7 mL). Considering the duration of operation and the treatment Groups only, as the variable, the mean total blood loss in the control Group 2 was 411.67 mL more than that in the tranexamic acid Group 1. None of the TXA group 1 patients required blood transfusion post-operatively. Two of the patients of the saline group 2 required blood transfusion post-surgery due to significant drop in haemoglobin below 8 mg/dL. There was no difference in the length of hospital stay between the 2 groups. The average drop in haemoglobin was 2 ± 1.4 in the tranexamic Group 1 and 4 ± 1.09 in the saline Group 2. No adverse reactions or thromboembolic events were observed. The two patients (saline Group 2) who received transfusions developed fever post-operatively, which was controlled by adequate antipyretics.

DISCUSSION

A randomised controlled trial was conducted in 274 hospitals in 40 countries. This RCT named CRASH-2 assessed the efficacy and safety of TXA by investigating 20,211 adult trauma patients who had or were at a risk of significant haemorrhage. In the trial, the injured patients were randomly separated into two groups within 8 hours of injury. One group received an initial dose of 1g of tranexemic acid and a second dose of 1g as infusion over 8 hrs. The other group received a matching placebo. 110096 patients received tranexemic acid and 10115 received placebo, of these 10,060 and 10,067 (respectively) were analysed. The CRASH-2 randomised control trial established the safety and efficacy of TXA administration for trauma patients. It showed a significant reduction in mortality without any significant increase in thrombo-embolic event [23]. TXA is both safe and effective in reducing the risk of death due to blood loss in trauma cases [24].

Though the safety and the efficacy of the drug have been established, there is no consensus about the dosage and the best time for administration of this drug. The prescribed dosage is 1-1.5 g or 15-25 mg/kg 2-4 times daily. The dosage of TXA advocated ranges from 1gm [25] to 100 mg/kg transfused over 15 minutes with a second infusion of 10 mg/kg/hour transfused until wound closure is achieved [26].

The dose administered in the CRASH RCT was 2 g with 1g as bolus and 1 g as continuous infusion over the next 8 hrs [23,24]. In general surgical conditions and in trauma where life threatening haemorrhages are anticipated, a continuous infusion is advocated. However since maxillofacial procedures are of much shorter time duration, we have employed a single bolus administration, pre-operatively, in order to prevent intraoperative blood loss alone.

One hundred forty eight patients undergoing cardiac surgery with extracorporeal circulation were divided into six groups. One group did not receive TXA. The other five received loading doses before incision ranging from 2.5 to 40 mg/kg and one tenth the loading dose was infused hourly for 12 hours. The quantity of blood collected by test tubes over 12 hours represented blood loss. This prospective, randomised, double blinded study concluded that the group that received prophylactic administration of 10 mg/kg of TXA, followed by continuous infusion of 1 mg/kg per hour, had the least haemorrhage. Larger doses did not provide additional haemostatic benefit [27].

Since TXA has a plasma half-life of 1.9 hours, [28] and our anticipated duration of surgery averaged two hours, a bolus injection of 10 mg/kg weight was chosen as the dosage to

maintain a therapeutically effective concentration between 5 mg/dl. Though 30% of the intravenous dose of 10 mg/kg of TXA was detected in the urine during the first hour after administration and the total excretion rose to 45% after 3 hours, approximately 55% remains in circulation upto 24 hours [29]. Therefore maxillofacial trauma surgery does not require a continuous infusion since post operative haemorrhage is of lesser concern than management of immediate haemorrhage in order to clear the airway.

Our results have shown that two out of six patients who were administered saline had a fall in haemoglobin that required blood replacement while none of the TXA patients (Group 1) needed a transfusion. The average fall in haemoglobin and the volume of blood lost is much lesser in the TXA group 1 than the saline Group 2. This concludes that a single pre-operative dose (10 mg/kg) of tranexamic acid given intravenously immediately before surgery reduced blood loss during trauma surgeries. No thromboembolic incidents, adverse reactions or complications were encountered with the administration of TXA in this study.

TXA does have a few contra indications which include renal impairment, thromboembolic disease, massive haematuria disseminated intravascular coagulation and pregnancy. TXA should be discontinued if colour vision disturbance occurs. Dose of TXA should be reduced if there is gastro intestinal upset (nausea, vomiting, diarrhoea). In about 15% of the population these side effects occur and improve with dose reduction.

CONCLUSION

This inexpensive and safe drug should be incorporated into trauma clinical practice guidelines and treatment protocols. Tranexemic acid usage prior to the commencement of maxillofacial trauma surgery does seem to reduce blood loss. On the basis of this pilot study a double blinded randomised controlled trial can be conducted in a larger population to examine the efficacy of the same further.

REFERENCES

[1] Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid fortrauma patients: a critical review of the literature. *J Trauma*. 2011;71(1Suppl):S9-14. Review.

[2] Guerriero C, Cairns J, Perel P, Shakur H, Roberts I; CRASH 2 trialcollaborators. Cost-effectiveness analysis of administering tranexamic acid tobleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One*. 2011;6(5):e18987.

[3] Mesgarzadeh AH, Shahamfar M, Azar SF, Shahamfar J. Analysis of the pattern of maxillofacial fractures in north western of Iran: A retrospective study. *J EmergTrauma Shock*. 2011;4(1):48-52.

[4] Ardekian L, Samet N, Shoshani Y, Taicher S. Life-threatening bleedingfollowing maxillofacial trauma. *J Craniomaxillofac Surg*. 1993; 21(8):336-8.

[5] Thaller SR, Beal SL. Maxillofacial trauma: a potentially fatal injury. *Ann Plast Surg*. 1991;27(3):281-3.

[6] Maugans TA, Martin D, Taylor J, Salisbury S, Istaphanous G. Comparative analysis of tranexamic Acid use in minimally invasive versus open craniosynostosis procedures. *J Craniofac Surg*. 2011;22(5):1772-8.

[7] Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, Woratanarat P, Chanplakorn P, Wibulpolprasert B, et al. Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial. *Orthop Rev (Pavia)*. 2011;3(2):e12.

[8] Endres S, Heinz M, Wilke A. Efficacy of tranexamic acid in reducing blood loss in posterior lumbar spine surgery for degenerative spinal stenosis with instability: a retrospective case control study. *BMC Surg*. 2011;11(1):29.

[9] Crescenti A, Borghi G, Bignami E, Bertarelli G, Landoni G, CasiraghiGM, et al. Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double blind, randomised, placebo controlled trial. *BMJ*. 2011;343:d5701.

[10] Choi WS, Irwin MG, Samman N. The effect of tranexamic acid on blood lossduringorthognathic surgery: a randomized controlled trial. *J Oral Maxillofac Surg*. 2009;67(1):125-33.

[11] Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: A randomized prospective clinical study. *J Oral Maxillofac Surg*. 2003;61:1432.

[12] Carter G, Goss A. Tranexamic acid mouthwash—A prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg*. 2003;32:504.

[13] Souto JC, Oliver A, Zuazu-Jausoro I, et al. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: A prospective randomized study. *J Oral Maxillofac Surg*. 1996;54:27.

[14] Ramstrom G, Sindet-Pedersen S, Hall G, et al. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. *J Oral Maxillofac Surg*. 1993;51:1211.

[15] Borea G, Montebugnoli L, Capuzzi P, et al. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery (An alternative method to discontinuing anticoagulant therapy). *Oral Surg Oral Med Oral Pathol*. 1993;75:29.

[16] Sindet-Pedersen S, Ramstrom G, Bernvil S, et al. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *N Engl J Med*. 1989;320:840.

[17] Senghore N, Harris M. The effect of tranexamic acid (Cyklokapron) on blood loss after third molar extraction under a day case general anesthetic. *Br Dent J*. 1999;186:634.

[18] Choi WS, Irwin MG, Samman N. The effect of tranexamic acid on blood lossduringorthognathic surgery: a randomized controlled trial. *J Oral Maxillofac Surg*. 2009 Jan;67(1):125-33.

[19] Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs*. 1985;29:236.

[20] Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg*. 1997;84:839.

[21] Johansson T, Engquist M, Pettersson LG, et al. Blood loss after total hip replacement: A prospective randomized study between wound compression and drainage. *J Arthroplasty*. 2005;20:967.

[22] Hurle R, Poma R, Maffezzini M, et al. A simple mathematical approach to calculate blood loss in radical prostatectomy. *Urol Int*. 2004;72:135.

[23] Williams-Johnson JA, McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. *West Indian Med J*. 2010;59(6):612-24.

[24] CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011;343:d3795.

[25] Zellin G, Rasmusson L, Palsson J, et al. Evaluation of hemorrhage depressors on blood loss during orthognathic surgery: A retrospective study. *J Oral Maxillofac Surg*. 2004;62:662.

[26] Sethna NF, Zurakowski D, Brustowicz RM, et al. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. *Anesthesiology*. 2005;102:727.

[27] Horrow JC, Van Riper DF, Strong MD, et al. The dose-response relationship of tranexamic acid. *Anesthesiology*. 1995;82:383.

[28] Eriksson O, Kjellman H, Pilbrant A, et al. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *Eur J Clin Pharmacol*. 1974;7:375.

[29] Pilbrant A, Schannong M, Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol*. 1981;20:65.

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