



## Original Article

# Tranexamic Acid - Evaluation of its use in Decreasing Blood Loss and Transfusion in Knee Arthroplasty

Author

**Dr Ratnam Raoji**

Associate Professor, Department of Anaesthesiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India

Correspondence Author

**Dr Ratnam Raoji**

Associate Professor, Department of Anaesthesiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India

## Abstract

**Background:** *Peri-operative bleeding is one of the major indication for allogenic blood transfusion. To reduce Post-operative blood loss, a number of antifibrinolytic agents like tranexamic acid have been used, which act by competitive inhibition of plasminogen.*

**Aims and Objectives:** *To assess the role of tranexamic acid in reducing blood loss and transfusion in patients undergoing knee arthroplasty.*

**Materials and Methods:** *A prospective randomized study was conducted on 60 patients who underwent bicondylar cemented knee arthroplasty. All the patients were randomly allocated in to two groups, Group A (n=30): receiving TXA 10 mg/Kg, 30 minutes before the release of tourniquet followed by an inflation of 1 mg/Kg/hour for 12 hours, whereas group B (n=30) did not received any treatment for prevention of blood loss. During surgery, blood loss was assessed, the contents of drain were measured and recorded and the number of units of blood transfused during the perioperative period and five days postoperatively was recorded and any complications were also documented.*

**Results:** *The intraoperative blood loss was similar in both the groups, whereas there was a statistical difference between both the groups in respect to post intraoperative blood loss and total blood loss. 40% controls required blood transfusion compared to only 20% TA patients required blood transfusion i.e. 50% reduction in requirement.*

**Conclusion:** *Tranexamic acid can be safely advocated for knee arthroplasty as an effective strategy to reduce perioperative blood loss and it minimizes the need for blood transfusion.*

**Keywords:** *Blood transfusion, Fibrin, Knee Arthroplasty, Plasminogen, Tranexamic acid.*

## Introduction

Surgery as a stress condition affects the body's coagulation system in several manners, a hyper adrenergic state, tissue injury causes release of tissue plasminogen activator (t-PA) leads to hyper

fibrinolysis.<sup>1,2</sup> Bleeding and hemodilution with crystalloids secondarily leads to consumption of coagulation factors, platelets and physiologic anticoagulants. All these conditions leads to increase in bleeding during surgeries. Blood loss

during surgeries depends surgical on non- surgical factors. Surgical factors include surgical skill and experiences as well as degree of invasion of procedures. Non surgical factors include haemostatic system, vascular abnormalities (connective tissue disorders), arterial and venous blood pressures etc.<sup>3</sup>

Bleeding can be hazardous as inadequate oxygen delivery can lead to multiple organ dysfunction and death. It can lead to increase in length of hospital stay, reoperations, prolonged operation time, necessitate transfusion to restore blood loss and increase cost. Transfusion of blood helps restore circulatory volume and improves oxygen carrying capacity, also having limitations and potentially negative consequences that should be considered. Transfusions are associated with risks of mismatched blood, allergic reactions, transmission of infections, and acute lung injury can have potentially adverse immune consequences and end organ effects.<sup>4,5</sup>

In general peri-operative bleeding and the need for blood transfusion is correlated with increased cost, morbidity and mortality. In the management of blood loss the available evidence-based blood conservation techniques includes<sup>2,5</sup>

1. Drugs that increase pre-operative blood volume (eg. erythropoietin) or decrease post-operative bleeding (eg. antifibrinolytes).
2. Devices that conserve blood (eg. intraoperative blood salvage and blood sparing interventions).
3. Autologous predonation
4. Institution specific blood transfusion algorithms supplemented with point of care testing.
5. A multimodality approach to blood conservation combining all the above

Antifibrinolytic agents includes tranexamic acid (TXA) and ε Amino Caproic Acid (EACA), which acts by competitive inhibition of plasminogen. TXA has been found to be 6-10 times more potent in vitro than EACA.<sup>6-8</sup>

## Materials and Methods

**Study Area:** After ethical committee approval, this study was conducted in Prathima Institute of Medical Sciences. This is a prospective, randomized controlled study.

### Inclusion Criteria

ASAI, II patients who underwent bicondylar cemented knee arthroplasty

### Exclusion Criteria:

- i. Known allergic to TXA and any other systemic complication
- ii. Pre-operation hepatic or renal dysfunction
- iii. Serious cardiac or respiratory diseases
- iv. High abnormal prothrombin time or activated partial thromboplastin time
- v. Congenital or acquired coagulopathy
- vi. History of thromboembolic disease and
- vii. Any malignant disease

A total of 60 patients were recruited in the study. Informed consent was obtained from each patient.

### Anaesthetic Details

All patients underwent a pre anaesthetic check up and were premedicated with oral tablet Alprazolam 0.25 mg before night and tablet omeprazole 20 mg in the morning of surgery. Patients were monitored with 5 lead electrocardiography (ECG), pulse oxymetry and tidal carbondioxide, temperature and non-invasive blood pressure. Patients were anaesthetised using sub-arachnoid block with 0.5% hyperbaric bupivacine An end welling epidural catheter was placed for postoperative pain relief. The extremity to be operated was drained of blood by elevation and tourniquet was inflated to a pressure of 150 mm Hg which is above systolic BP.

All the patients were randomly allocated in to two groups, Group A (n=30): receiving TXA 10 mg/Kg, 30 minutes before the release of tourniquet followed by an inflation of 1 mg/Kg/hour for 12 hours, whereas group B (n=30) did not receive any treatment for prevention of blood loss. A haemoglobin level of less than 8gm/dl was considered as transfusion trigger

except in patients who could have poor tolerance to these levels because of associated conditions such as myocardial ischemia, chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented with signs, symptoms, or both of hypoxia, such as tachycardia, dyspnoea, or syncope. The transfusion trigger was placed at less than 10gm/dl for these patients. During surgery and postoperative period measured blood losses was replaced with ringers lactate in 3:1 ratio and or Tetra Hydroxyl ethyl starch (THES) in 1:1 ratio until Hb concentration fall below the transfusion trigger point. Thereafter patients received allogenic packed red blood cells.

During surgery, blood loss was assessed by measuring the weight change of surgical swabs (by digital weighing scale) and the volume in suction reservoir. In the recovery room and in postoperative ward, the contents of drain were measured and recorded. The number of units of blood transfused during the perioperative period and five days postoperatively was recorded and any complications were documented.

#### Post operative follow up

After surgery, patients were shifted to post anaesthetic care unit. Post operative pain was managed with 0.125% bupivacaine with fentanyl 2 µg/ml infusion at 4-6 ml/hr. Haemoglobin

concentration and haematocrit were measured 24 hours postoperatively. Drains were removed after 24 hours. Pneumatic compression devices (PCD) were used for all patients for prevention of deep venous thrombosis (DVT) and all of them were screened clinically for DVT regularly until discharge.

#### Statistical Analysis

Data were expressed as mean±SD and analyzed by software SPSS Version 20 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY: USA). Chi-square test and independent two sample 't'-test for unpaired samples were used. A P value < 0.05 was considered as significant.

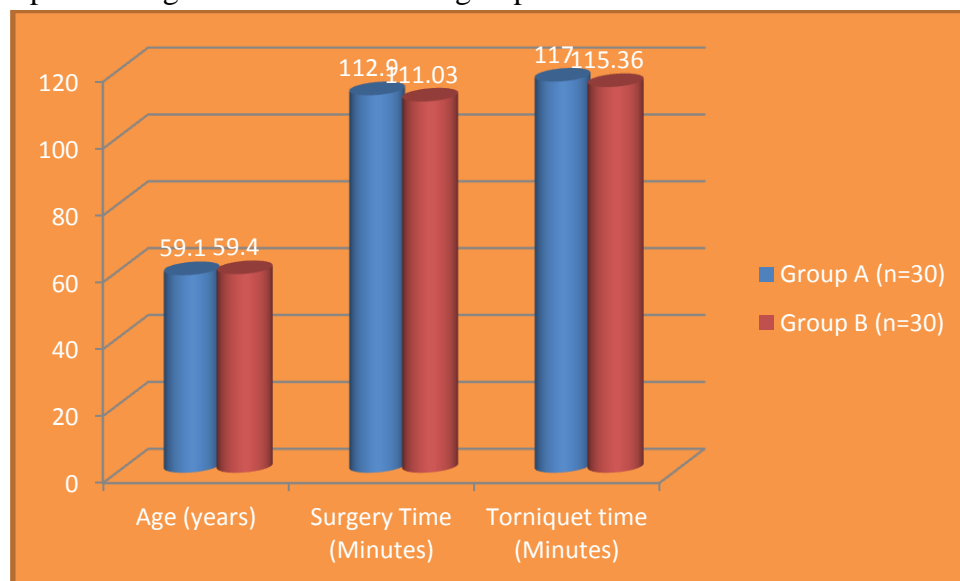
#### Results

Confounding variables like age, sex, surgical time, and previous surgery on same site, were comparable in both the groups and there was no statistically significant difference between them. Average age in group A and B was 59.1 and 59.4 years respectively (Table 1 and Graph 1).

**Table 1:** Variables in both the groups

Parameter	Group A (n=30)	Group B (n=30)
Age (years)	59.1 ± 9.7	59.4 ± 7.74
Gender (Male/Female)	8/22	7/23
Surgery Time (Minutes)	112.9 ± 10.7	111.03 ± 14.73
Torniquet time (Minutes)	117 ± 11.29	115.36 ± 15.47

**Graph 1:** Bar Graph showing variables in both the groups



**Blood Loss**

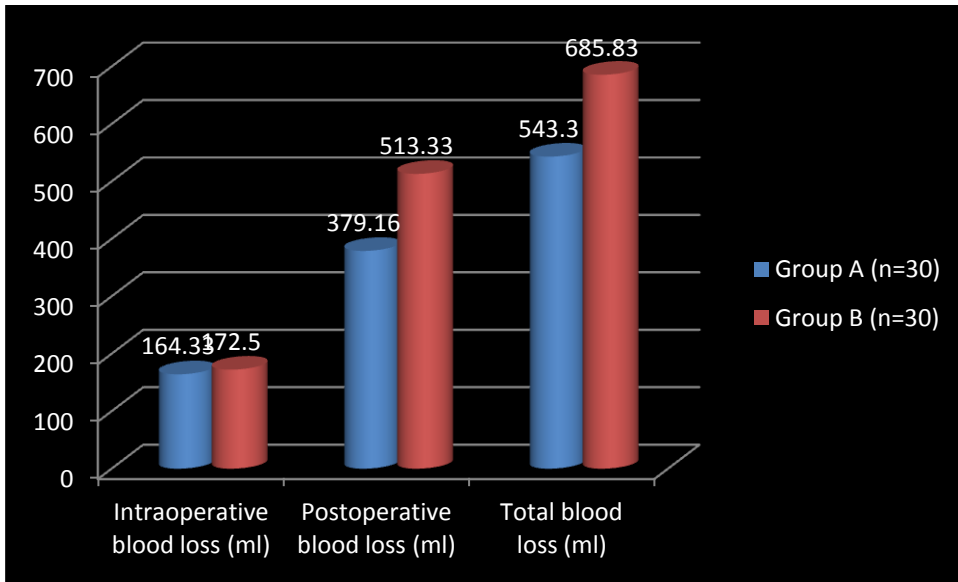
The intraoperative blood loss was similar in both the groups and there was no statistical difference between both the groups, whereas there was a statistical difference between both the groups in respect to post intraoperative blood loss and total

blood loss. A greater fall in Hb postoperatively was seen in control group than TXA group, the difference being statistically insignificant. Fall in haematocrit among the groups was statistically insignificant (Table 2; Graph 2 and Graph 3).

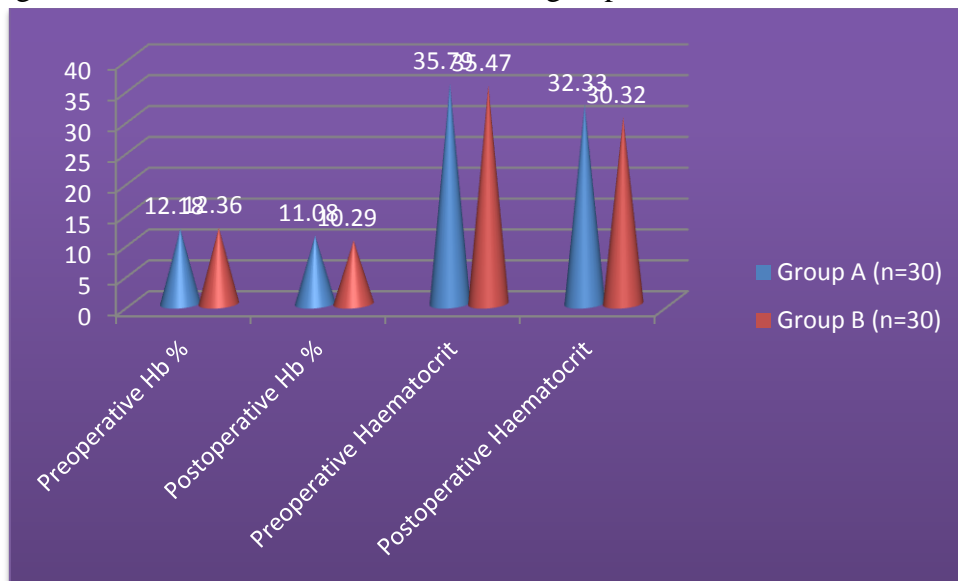
**Table 2:** Parameters of Blood loss

Parameter	Group A (n=30)	Group B (n=30)	P value
Intraoperative blood loss (ml)	164.33 ± 62.09	172.5 ± 77.64	0.664
Postoperative blood loss (ml)	379.16 ± 174	513.33 ± 143.89	0.00088
Total blood loss (ml)	543.3 ± 184.85	685.83 ± 176.74	0.00259
Preoperative Hb %	12.18 ± 1.79	12.36 ± 1.33	0.658
Postoperative Hb %	11.08 ± 1.69	10.29 ± 1.34	0.100
Preoperative Haematocrit	35.79 ± 5.51	35.47 ± 5.91	0.858
Postoperative Haematocrit	32.33 ± 4.20	30.32 ± 3.87	0.357

**Graph 2:** Bar graph showing Parameters of Blood loss



**Graph 3:** Haemoglobin and Haematocrit values in both the groups



### Blood Transfusion Requirements

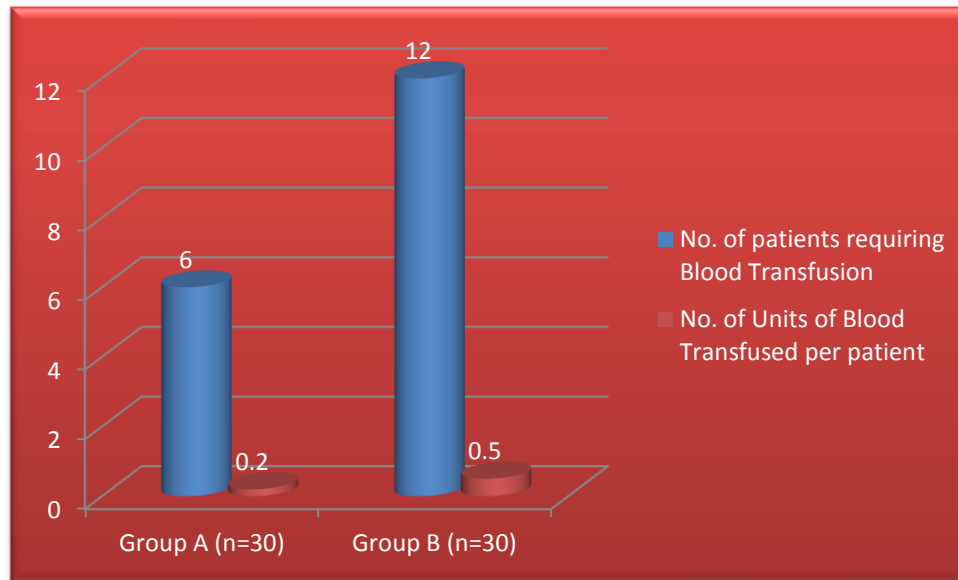
40% controls required blood transfusion compared to only 20% TA patients required blood

**Table 3:** Number of patients requiring Blood transfusion

Parameter	Group A (n=30)	Group B (n=30)
No. of patients requiring Blood Transfusion	6	12
No. of Units of Blood Transfused per patient	0.2	0.5

transfusion i.e. 50% reduction in requirement (Table 3 and Graph 4).

**Graph 4:** Number of patients requiring Blood transfusion



### Discussion

Peri-operative bleeding is one of the major indication for allogenic blood transfusion (whole blood or packed red cells from an unrelated donor). Public concern regarding the safety of transfused blood has prompted a reconsideration of the role of blood transfusion. To reduce Post-operative blood loss a number of pharmacological agents have been used, these include the antifibrinolytic agents like TXA and EACA.<sup>8,9</sup>

TXA and EACA are synthetic lysine analogues that act as effective inhibitors of fibrinolysis. TXA and EACA act principally by blocking the lysine binding sites on plasminogen molecule, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis. TXA is about ten times more potent than EACA and binds much more strongly to both the strong and weak sites of the plasminogen molecule than EACA.<sup>8-10</sup>

Arthroplasty accounts for nearly 40% of blood transfusions in orthopedic patients. Perioperative antifibrinolytic therapy is recommended as part of

a comprehensive blood management strategy. The use of a pneumatic tourniquet ensures a dry surgical field and minimal intraoperative bleeding, but it augments fibrinolysis stimulated by surgical trauma. This activation of the antifibrinolytic system might lead to high postoperative blood loss and this could be more significant in patients undergoing bilateral Total Knee Arthroplasty (TKA) in a single stage. The increased requirement of blood transfusions predisposes these patients to high postoperative morbidities. The use of antifibrinolytic agents is based on the fact that surgical trauma besides promoting clot formation by activating the intrinsic and extrinsic coagulation cascades also leads to concomitant activation of plasminogen inducing a state of hyper fibrinolysis accelerating clot degeneration and increasing surgical site bleeding.<sup>5-8</sup>

EACA and P-Aminomethyl Benzoic Acid (PAMBA) and TXA are synthetic antifibrinolytic aminoacids. On a molar basis TXA is at least seven times more potent than EACA and twice as

potent as PAMBA. All three compounds are readily absorbed from gastrointestinal tract and excreted in active form in the urine. The plasma half life of TXA is 80 minutes.<sup>6-8</sup> The main indications of TXA are prevention of excessive bleeding after tonsillectomy, prostate surgery and IUD induced menorrhagia. TXA penetrates very well in to major joints producing a concentration similar to serum concentration.<sup>8</sup>

With trauma or surgery, damage occurs to the endothelium of blood vessels that results in the exposure of collagen and release of tissue factors. These tissue factors and exposed collagen will activate the intrinsic and extrinsic coagulation cascades and allow for the formation of thrombin and creation of clot with the assistance of platelets. This in turn will allow the blood to clot and prevent excessive blood loss. Plasminogen which is a zymogen that is made in liver and released in to the blood stream, binds to blood clots and cell surfaces. It is converted to its active form plasmin via enzymes such as tissue Plasminogen activator (tPA), Urokinase Plasminogen activator (uPA), Kallikrein and factor XII (Hageman factor). Plasmin in turn cleaves the fibrin clots in to fibrin degradation products (FDP), allowing clots to dissolve. Therefore TXA is a synthetic analogue of aminoacid lysine that reversibly occupies lysine binding sites on plasminogen preventing its binding to the surface of fibrin and activation, resulting in inhibition of fibrinolysis. Thus TXA allows mature fibrin clots to be maintained and coagulation.<sup>10-12</sup>

The structure of TXA is composed of  $C_8H_{15}NO_2$ . At room temperature TXA has a solid form, but is freely soluble in water. After ingestion or injected intravenously, it has a short half life of about 2-3 hours, and is rapidly excreted via kidneys. In adults, TXA is typically administered with a loading dose of 10mg/Kg, followed by infusion of 1mg/Kg/hr. The values were primarily based on studies of antifibrinolytic uses during cardiac surgeries. A recent cochrane review showed that TXA does not significantly increase the risk of

stroke, MI, DVT, pulmonary embolism (PE) and renal failure. Multiple studies and systemic reviews have shown that Iv injection of TXA in TKA does not increase the risk of DVT or PE. With various multivariate statistics in some studies, the authors unanimously found that preoperative anaemia and perioperative ABT were both independent risk factors for postoperative mortality, ischemia and infections.<sup>4-6</sup>

Despite encouraging observations regarding safety of TXA use, repeated administration of an antifibrinolytic drug in elderly patients undergoing surgeries which promotes a hyper coaguable state and who often are with co morbidity putting them with increased risk of DVT (diabetes, obesity, cardiovascular disease) still raises concern. In order to address this issue studies to establish the safety and effectiveness of topical TXA administration have been conducted.<sup>6,7</sup>

In this study we have probed a modern therapy amid at decreasing haemorrhage induced by surgical trauma. We have investigated the effect of a bolus dose of TXA just before deflation of tourniquet, followed by infusion for 12 hours on blood loss and blood transfusion required in total knee joint arthroplasty. From previous studies we found that factors such as cemented or uncemented arthroplasty, method of surgery, type of anaesthesia, surgeon preferences could all influence blood loss. In designing our study we tried to control these factors as much as possible. We included surgeries in which only cemented arthroplasty was done. All patients were anaesthetised using a subarachnoid block with indwelling epidural catheter for postoperative analgesia. Only one team of surgeons performed all the surgeries.<sup>8-11</sup>

Literature reports that blood transfusion is needed in about 39% of the patients undergoing TKA. In our study, 40 % of patients from control group and 20% from TXA group required blood transfusion. Overall 60% less blood was needed in the study group.

Regarding dosage length of TXA treatment, studies revealed that 10 mg/Kg/hr followed by

infusion of 1 mg/Kg/hr was the minimum dosage needed to obtain the desired antihemorrhagic effect. Larger doses provide no additional savings in blood loss whereas smaller doses carry decreased haemostatic efficacy. It has been postulated that application of a pneumatic tourniquet and (consequent tissue hypoxia) increases tissue plasminogen activator secretions from the vascular endothelium. As a result there is increased fibrinolytic activity and because excessive fibrinolysis increases bleeding, postoperative bleeding may be attributed to fibrin dissolution. TXA inhibits fibrinolysis by saturating lysine binding sites on plasminogen molecule. As a result plasminogen is displaced from the fibrin surface. Because plasmin controls fibrin degradation, TXA is a potent inhibitor of fibrinolysis.<sup>10-12</sup>

We hypothesise that the postoperative bleeding associated with TKA is secondarily to extensive tourniquet induced fibrinolysis in the operative time. As shown in numerous studies, the fibrinolytic response after trauma is biphasic with an increased activity during the first hours followed by a shut down that peaks at about 24 hours. The dose regimen which we used maintains a constant therapeutic plasma concentration of TXA for constant fibrinolytic inhibition until it starts shutting down. Clinical screening for DVT was regularly done until discharge. None of the patients any signs of DVT. This may be due to the fact that fibrinolytic activity in vein walls is not affected by TXA.

### Conclusion

TXA at a dose of 10mg/Kg IV, before deflation of tourniquet followed by 1mg/Kg/hr for 12 hours can be safely advocated for knee arthroplasty as an effective strategy to reduce perioperative blood loss and thus minimizing the need for blood transfusion.

### References

1. Keating EM. Preoperative Evaluation and Methods to Reduce Blood Use in

Orthopedic Surgery. *Anesthesiology Clinics* 2005;23 (2):305-313.

2. Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs*. 2002;62(15):2193-211.
3. Sculco TP. Global blood management in orthopaedic surgery. *Clin Orthop Relat Res*. 1998 Dec;(357):43-9.
4. Zimmerman LH. Causes and consequences of critical bleeding and mechanisms of blood coagulation. *Pharmacotherapy*. 2007 Sep;27(9 Pt 2):45S-56S.
5. Benoni G1, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br*. 1996 May;78(3):434-40.
6. Okamoto S, Sato S, Takada Y, Okamoto U. An Active Stereo-Isomer (Trans-Form) Of Amcha And Its Antifibrinolytic (Antiplasminic) Action In Vitro And In Vivo. *Keio J Med*. 1964 Dec;13:177-85.
7. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs*. 1999 Jun;57(6):1005-32.
8. Mannucci PM1, Levi M. Prevention and treatment of major blood loss. *N Engl J Med*. 2007 May 31;356(22):2301-11.
9. Jansen AJ, Andreica S, Claeys M, D'Haese J, Camu F, Jochmans K. Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. *Br J Anaesth*. 1999 Oct;83(4):596-601.
10. Ponnusamy KE, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. *J Bone Joint Surg Am*. 2014 Nov 5;96(21):1836-44.
11. Mannucci PM. Hemostatic drugs. *N Engl J Med*. 1998 Jul 23;339(4):245-53.
12. Johnson DJ, Johnson CC, Goobie SM, Nami N, Wetzler JA, Sponseller

PD, Frank SM. High-dose Versus Low-dose Tranexamic Acid to Reduce Transfusion Requirements in Pediatric Scoliosis Surgery. J Pediatr Orthop. 2017 Dec;37(8):e552-e557.