

The role of tranexamic acid in prevention of hemorrhage in major spinal surgeries

Afsoun Seddighi, Amir Nikouei, Amir Saeid Seddighi¹, Alireza Zali, Seyed Mahmood Tabatabaei, Fatemeh Yourdkhani, Shoeib Naimian, Iman Razavian

Functional Neurosurgery Research Center of Excellence, ¹Department of Neurosurgery, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Blood loss that necessitates blood transfusion is one of the most frequent complications of major spinal surgeries. This study has been designed to evaluate the efficacy and safety of prophylactic tranexamic acid (TA) in decreasing perioperative blood loss.

Materials and Methods: From January to August 2011, all the patients who needed major spinal surgeries and aged between 18 and 60-year-old were divided into two groups randomly, the experimental group received 10 mg/kg of TA 20 min after inducing the anesthesia as loading dose followed by 0.5 mg/kg/h until skin closure and the control group received equal amounts of normal saline as placebo. Intraoperative blood loss was recorded by estimating blood with the suction tube plus the number of bloody gasses. The amounts compared between the 2 groups and analyzed.

Results: Forty patients were enrolled in this study in the first group intraoperative, the 1st and 2nd postoperative days, the mean blood loss were 574 ml, 80.5 ml, and 669.5 ml while in the second group were 797 ml, 124 ml, and 921.5 ml.

Conclusion: TA seems to be safe and can be considered in spinal surgeries with significant excepted blood loss especially in female patients and instrumental procedures. We suggest further studies on TAs efficacy and safety in larger scales.

Key words: Blood loss, instrumental procedures, spinal surgery, tranexamic acid

Introduction

Spinal surgery can result in significant intraoperative blood loss, which may require a blood transfusion.^[1] Blood transfusions have potential side effects such as alloimmunization and blood transmitted infections (e.g. HIV, cytomegalovirus, and bacterial sepsis). Furthermore, blood transfusion seems to increase the risk of surgical site infection; it may increase the duration of surgery, and cause pulmonary and cerebral edema due to fluid shift and hypovolemic shock.^[2] In addition,

allogeneic blood transfusion costs about 250 USD/blood unit.^[3]

There are multiple pharmacologic approaches and anesthetic techniques recommended to decrease both preoperative and operative blood loss during surgery.^[4-6] Recommended strategies to reduce the blood loss include autologous blood donation before operation,^[7] appropriate positioning of patient, abdominal muscle paralysis to minimize intra-abdominal pressure, epinephrine injection in paraspinal tissues, normovolemic hemodilution,^[8] controlled hypotension,^[9] and antifibrinolytic agents. Antifibrinolytic agents have been effectively used previously in cardiac, orthopedic, and hepatic surgeries.^[10]

The first antifibrinolytic agent was aprotinin but was finally stopped in 2007, due to its reported complications such as renal failure, myocardial infarction (MI), cerebrovascular accidents, and deaths.^[11,12] Although theoretically possible, but data are lacking about the effectiveness of two other antifibrinolytic agents, tranexamic acid (TA), and epsilon-aminocaproic acid in preventing blood loss in preoperative administration.^[13]

TA has been used in nonsurgical situations such as bleedings due to leukemia, ocular bleedings, recurrent hemoptysis and

Access this article online	
Quick Response Code:	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.165791

Address for correspondence:

Prof. Seddighi Amir Saeid, Functional Neurosurgery Research Center of Excellence, Department of Neurosurgery, Shohada Tajrish Hospital, Tajrish Square, Tehran, Iran.
E-mail: eddingtonsierra@hotmail.com

hereditary angioneurotic edema, and cardiac ischemia in recent years.^[14]

TA (trans-4-aminomethyl-cyclohexane-1-carboxylic acid) is a synthetic lysine analog and competitive inhibitor of plasminogen and plasmin. Its half-life with normal renal function is about 80 min. It acts by saturating lysine binding sites on plasminogen and detaching plasminogen of fibrin, which lead to inhibition of fibrinolysis. TA like other antifibrinolytics inhibits the photolytic effect of plasmin.^[14]

The adverse effects of TA include headache, weakness, confusion, blurred color vision, and allergic reactions. The main contraindications are disseminated intravascular coagulation, microscopic hematuria,^[15] subarachnoid hemorrhage, severe renal failure, and hypersensitivity.^[16]

The main concerning point about TA and other antifibrinolytic agents is potentially increased the risk of thrombotic events.^[14]

There are few studies about the role of antifibrinolytic therapy in spinal procedures,^[17,18] especially in our country. In this study, we intend to evaluate the effect of TA in the prevention of hemorrhage in major spinal surgeries.

Materials and Methods

From January to August 2011, all of the patients who were referred to our spine clinic and candidate for major spine surgery were determined.

We considered major spinal surgeries as the following procedures:

1. Laminectomies at two levels or more
2. Any spinal procedure for degenerative problems which lasts more than 2 h
3. Gill's procedures for spondylolisthesis
4. Spinal fusions with or without instrumentation.
 - Our inclusion criteria were: Patients aged 20–70 years who were a candidate for major spinal surgeries, good medical condition, and accepted informed consent to attend the study.
 - Our exclusion criteria were: Patients aged < 20 and more than 70-year-old who had ischemic heart disease, diabetes, hepatic failure, traumatic vertebral fractures, severe renal failure, active intravascular clotting process, recent thromboembolic events, pregnancy, blurred color vision, coagulopathy, alcoholism and consumption of fluoxetine, contraceptives, insulin, and carbamazepine.
 - The recorded data were: age, sex, type of surgery, lab tests including: Complete blood count with differential, blood urea nitrogen (BUN), creatinine (Cr), liver function tests, and coagulative profile. The patients were randomized into 2 groups. The first group received TA, and the second group received normal

saline as a placebo. Neither the surgical team nor the patients were aware of the type of the prescription.

In our study, the first group received 10 mg/kg intravenous TA, 20 min after induction of anesthesia as a loading dose and then 0.5 mg/kg/h, during the operation.

Intraoperative blood loss was estimated by measurement of the blood in the suction tube and weighting the used gauzes. The postoperative bleedings was recorded by measuring the blood in the hemovac drain. We also recorded all the cases who needed a blood transfusion. All the patients with hemoglobin (Hb) lower than 9 mg/dl received the packed cell. If the Hb level was between 7 and 9 mg/dl packed cells were injected only in cases with concurrent hypotension.

In the postoperative period vital signs, neurologic status and coagulative profile were assessed. The diameters of legs were examined daily, and the patients were asked about chest discomfort. After discharge, we followed the patients by regular visits at hospital's clinic, during 1st month after surgery, looking for cases of MI, cerebrovascular accident (CVA), acute tubular necrosis, deep vein thrombosis (DVT), or pulmonary embolism (PE).^[3]

The patient's characteristics, type and duration of surgery, and the intra and postoperative blood loss were recorded as a database using Excel 2010 software, and statistical analysis was performed by Student's *t*-test and Chi-square test, and $P < 0.05$ was considered as significant.

Results

From January to August 2011, all the patients who were referred to our spine clinic and candidate for major spine surgery were determined. According to inclusion criteria, 40 patients were selected. In TA group, mean age was 43.7 years, and in the control group was 49.85, ranged from 28 to 67 years, which were not significantly different ($P = 0.093$). Seven patients (35%) of the TA group and 5 patients (25%) of the placebo group were male, which had not a significant difference ($P = 0.731$). Five patients (25%) of the first group and 4 patients (20%) of the control group have been operated on 3 or more levels, without significant difference ($P = 1.0$) [Tables 1-3].

Ten patients (50%) of first group and 12 patients (60%) of second group had disc herniation, canal stenosis, and spondylolisthesis; and were operated fusion surgery which were not significantly different ($P = 0.751$) [Table 4].

Then total blood loss, blood loss during surgery and after surgery were compared in two groups. In the first group, total blood loss was 669 ml, 574 ml during surgery, and 80.5 ml in the 1st postoperative day while these amounts were 921 ml, 797 and 124, respectively, in the second group.

The intraoperative blood loss ($P = 0.139$) and blood loss of the 1st postoperative day ($P = 0.067$) did not have significant differences, but both had lower mean in TA group. Only one patient in each group had hemorrhage on the 2nd postoperative day, hence we did not compare the blood loss of 2nd day separately and just considered them in total blood loss. The total blood loss in the first group was 669.5 ml, and in the second group was 921.5 ml, which although had lower mean in TA group, had no significant differences. The results were not compared in the patients who had been operated in 3 or more levels due to the limited cases [Table 5].

The average of blood loss at operation ($P = 0.002$), the 1st postoperative day ($P = 0.003$), total blood loss ($P = 0.001$), and the patient's need to blood transfusion ($P = 0.005$) were significantly higher in the patients who had fusion [Table 6].

Data of blood losses in patients with < 3 h of surgery and patients with 3 or more than 3 h of surgery, respectively, are shown in Tables 7 and 8.

The mean of blood transfusion in the first group was 0.40 units of packed cells, and in the second group was 0.45 units

Table 1: Mean and SD of age in TA and placebo group

Group	Number	Mean	SD	P
TA+	20	49.85	12.209	
TA-	20	43.7	10.255	
Total	40	46.775	11.557	0.093

SD – Standard deviation; TA – Tranexamic acid

Table 2: Gender difference of TA and placebo group

Group	Gender		Total
	Female	Male	
TA			
+	13	7	20
-	15	5	20
Total	28	12	40
P			0.731

TA – Tranexamic acid

Table 3: Frequency of patients being operated on <3 or 3 and more levels in TA and placebo group

Group	Levels		Total
	<3	Three or more	
TA			
+	15	5	20
-	16	4	20
Total	31	9	40
P			1

TA – Tranexamic acid

of packed cells, which is lower in the first group, but did not have a statistically significant difference ($P = 0.86$) [Table 9].

Considering the age and number of operated levels as confounding factors, average blood loss was less in TA group. Blood transfusion cases were limited to female patients and the patients with instrumental procedures. Furthermore, TA in the patients who had surgery at 3 levels or more reduced the blood loss. The mean duration of operation in the first group (TA) was 3.3 h, and in the second group (placebo) was 3.5 h [Table 10].

In this study, according to the low number of samples, inclusion and exclusion criteria, none of the patients experienced DVT, PE, CVA, MI, or had rising in BUN or serum Cr more than normal levels and we had no mortality, which is considered as a good feature of this study.

Discussion

Severe bleeding is a common side effect in spinal surgeries. In recent years; a variety of assessment techniques to control

Table 4: Frequency of patients with fusion surgery with pedicular screw in TA and placebo group

Group	Fusion		Total
	Yes	No	
TA			
+	10	10	20
-	12	8	20
Total	22	18	40
P			0.751

TA – Tranexamic acid

Table 5: Mean and SD of blood losses and statistical results between TA and placebo group

Blood Loss	Group	Number	Mean (ml)	SD (ml)	P
Intraoperative blood loss	TA	20	574	377.5	0.139
	Placebo	20	797	543.7	
First day postoperative blood loss	TA	20	80.5	57.9	0.067
	Placebo	20	124	85.4	
Total blood loss	TA	20	669	418.3	0.125
	Placebo	20	921	584.6	

SD – Standard deviation; TA – Tranexamic acid

Table 6: Mean and SD of blood losses and statistical results in patients with and without fusion with pedicular screw between TA and placebo group

Blood Loss	Fusion	Number	Mean (ml)	SD (ml)	P
Intraoperative blood loss	Yes	22	886	502.6	0.002
	No	18	440	302.1	
First day postoperative blood loss	Yes	22	133	79.7	0.003
	No	18	64	49.2	
Total blood loss	Yes	22	1033	527	0.001
	No	18	505	328.9	

SD – Standard deviation; TA – Tranexamic acid

Table 7: Mean and SD of blood losses and statistical results in patients with 3 or <3 h duration of surgery between TA and placebo group

Blood Loss	Group	Number	Mean (ml)	SD (ml)	P
Intraoperative blood loss	TA	14	577	367.4	0.887
	Placebo	10	600	407.5	
First day postoperative blood loss	TA	14	63.5	40.6	0.319
	Placebo	10	83	52.7	
Total blood loss	TA	14	640	396.4	0.806
	Placebo	10	683	428.5	

SD – Standard deviation; TA – Tranexamic acid

Table 8: Mean and SD of blood losses and statistical results in patients with more than 3 h duration of surgery between TA and placebo group

Blood Loss	Group	Number	Mean (ml)	SD (ml)	P
Intraoperative blood loss	TA	6	566	436.6	0.156
	Placebo	10	995	609.3	
First day postoperative blood loss	TA	6	120	76.1	0.341
	Placebo	10	165	94.4	
Total blood loss	TA	6	736	498.6	0.190
	Placebo	10	1160	641.5	

SD – Standard deviation, TA – Tranexamic acid

Table 9: Mean and SD of transfused blood (unit of packed cell) and comparison between TA and placebo group

Packed Cell	TA	Number	Mean	SD	P
Unit of packed cell	+	20	0.40	0.994	0.86
	-	20	0.45	0.825	

SD – Standard deviation; TA – Tranexamic acid

Table 10: Mean and SD of operation's duration in patients with 3 or more levels surgery in TA and placebo group

Group	Number	Mean (h)	SD (h)
TA+	5	3.3	0.8
TA-	4	3.5	1

SD – Standard deviation; TA – Tranexamic acid

and reduce bleeding associated with surgery of the spine has been evaluated. Given the importance of the prevention of severe bleeding during and after the orthopedic surgery and neurosurgery, TA alone or in comparison with other drugs or placebos was evaluated by researchers.^[19] Our finding is compatible with other reported series.^[10,20,21]

In this study, the average of intraoperative, 1st postoperative day, and total blood loss were lower in the TA group, (considering confounding factors including age, gender, number of operated levels, fusion, and duration of operation). According to a limited number of cases and the results of previous similar

studies, the results are considerable although not being statistically significant.

In a study, performed by Hiippala *et al.* reported that TA has been effective in reducing postoperative bleeding and need for blood transfusions in all knee arthroplasty surgery.^[22] In another study by Zufferey *et al.*, TA is effective in reducing the risk of requiring allogeneic erythrocyte transfusion in orthopedic surgery.^[23] Based on the results of Neilipovitz research, reducing the need of blood transfusions by using TA has been noted, and the results are consistent with the output of this study.^[24] Results of a meta-analysis done by Ker *et al.* suggest that strong evidence is available for use of TA and decreased blood transfusion in surgery.^[25] In addition to the effectiveness of TA in reducing blood loss during surgery, decreased transfusion related complications were reported by Elwatidy *et al.* in a prospective placebo-controlled study.^[10]

The patients receiving TA also had less need to blood transfusion, without statistical significance. Blood transfusion cases were limited to female patients and who had undergone fusion surgeries. More need to blood transfusion in female patients might be related to underlying lower levels of Hb. None of the confounding factors, which mentioned above led to a significant difference in the need to blood transfusion. Patients of TA group had passed less under operation significantly, which is important, because of imposed risks of exceeded length of anesthesia ($P = 0.013$).

The patients who had fusion surgeries had lost more blood and the increased need for blood transfusion significantly, which might be related to more expanded dissection of paraspinal muscles and tissues.

About the duration of surgery, the mean operation duration in TA group was significantly lower than the placebo group, which is compatible with other studies,^[26,27] and we had no report of drug-induced complications.

In terms of safety and the incidence of complications, we had no side effects similar to previous studies. No difference in terms of complications between the two groups. Altogether, the results of our study have been compatible with the results of previous researches, both in efficacy and safety.

Conclusion

This study aimed to investigate the effects of TA on major surgeries to reduce bleeding. A prominent feature of our study is that, it is the first study in Iran, and one of the few studies that have been done in this field in the world.

According to safety, inexpensiveness^[28] and efficacy of TA, concluded of this study and in comparison with previous ones, we strongly recommend considering prophylactic administration of TA in patients who candidate for major

spinal surgeries, especially in fusion surgeries and female patients.

Studies on efficacy and safety and dose adjustment of prophylactic TA in patients with renal failure would be beneficial to prevent complications of huge blood loss and worsening of renal function in these patients. Greater, multi-centric, and dose-dependent studies on the efficacy of TA are also suggested and may lead to a defined practical protocol. In this study, TA reduced intraoperative, 1st postoperative day, and total blood loss although one of the confounding factors including age, gender, number of operated levels, length of the operation, and fusion did not have statistically significant difference. This study according to the results of other similar studies and small numbers of our statistical population is considerable.

References

- Hu SS. Blood loss in adult spinal surgery. *Eur Spine J* 2004;13 Suppl 1:S3-5.
- Urban MK, Beckman J, Gordon M, Urquhart B, Boachie-Adjei O. The efficacy of antifibrinolytics in the reduction of blood loss during complex adult reconstructive spine surgery. *Spine (Phila Pa 1976)* 2001;26:1152-6.
- Elgafy H, Bransford RJ, McGuire RA, Dettori JR, Fischer D. Blood loss in major spine surgery: Are there effective measures to decrease massive hemorrhage in major spine fusion surgery? *Spine (Phila Pa 1976)* 2010;35:S47-56.
- Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briët E, *et al.* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: A meta-analysis of clinically relevant endpoints. *Lancet* 1999;354:1940-7.
- Ozler Y, Schlumberger S. Pharmacological approaches to reducing blood loss and transfusions in the surgical patient. *Can J Anaesth* 2006;53:S21-9.
- Weber TP, Grosse Hartlage MA, Van Aken H, Booke M. Anaesthetic strategies to reduce perioperative blood loss in paediatric surgery. *Eur J Anaesthesiol* 2003;20:175-81.
- Singbartl G. Pre-operative autologous blood donation: Clinical parameters and efficacy. *Blood Transfus* 2011;9:10-8.
- Hans P, Collin V, Bonhomme V, Damas F, Born JD, Lamy M. Evaluation of acute normovolemic hemodilution for surgical repair of craniosynostosis. *J Neurosurg Anesthesiol* 2000;12:33-6.
- Rosenblatt MA. Strategies for minimizing the use of allogeneic blood during orthopedic surgery. *Mt Sinai J Med* 2002;69:83-7.
- Elwatidy S, Jamjoom Z, Elgamel E, Zakaria A, Turkistani A, El-Dawlatly A. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: A prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)* 2008;33:2577-80.
- Lien M, Milbrandt EB. A disheartening story: Aprotinin in cardiac surgery. *Crit Care* 2006;10:317.
- Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Aprotinin increases mortality as compared with tranexamic acid in cardiac surgery: A meta-analysis of randomized head-to-head trials. *Interact Cardiovasc Thorac Surg* 2009;9:98-101.
- Wardrop D, Estcourt LJ, Brunskill SJ, Doree C, Trivella M, Stanworth S, *et al.* Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. *Cochrane Database Syst Rev* 2013;7:CD009733.
- Szpalski M, Gunzburg R. Management of haemostasis in spine surgery. *Eur Muskuloskel Rev* 2008;3:53-57.
- Schultz M, van der Lelie H. Microscopic haematuria as a relative contraindication for tranexamic acid. *Br J Haematol* 1995;89:663-4.
- Sweetman SC. *Martindale, the complete drug reference*. 34th ed. London: The Pharmaceutical Press; 2005. p. 918.
- 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.
- Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, *et al.* Efficacy of tranexamic acid in pediatric craniosynostosis surgery: A double-blind, placebo-controlled trial. *Anesthesiology* 2011;114:862-71.
- Gill JB, Chin Y, Levin A, Feng D. The use of antifibrinolytic agents in spine surgery. A meta-analysis. *J Bone Joint Surg Am* 2008;90:2399-407.
- Li ZJ, Fu X, Xing D, Zhang HF, Zang JC, Ma XL. Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. *Eur Spine J* 2013;22:1950-7.
- Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One* 2013;8:e55436.
- Hiipala S, Strid L, Wennerstrand M, Arvela V, Mäntylä S, Ylinen J, *et al.* Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth* 1995;74:534-7.
- Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, *et al.* Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology* 2006;105:1034-46.
- Neilipovitz DT. Tranexamic acid for major spinal surgery. *Eur Spine J* 2004;13 Suppl 1:S62-5.
- Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: Systematic review and cumulative meta-analysis. *BMJ* 2012;344:e3054.
- Zheng F, Cammisa FP Jr, Sandhu HS, Girardi FP, Khan SN. Factors predicting hospital stay, operative time, blood loss, and transfusion in patients undergoing revision posterior lumbar spine decompression, fusion, and segmental instrumentation. *Spine (Phila Pa 1976)* 2002;27:818-24.
- Eldaba AA, Amr YM, Albirmawy OA. Effects of tranexamic acid during endoscopic sinus surgery in children. *Saudi J Anaesth* 2013;7:229-33.
- Guerriero C, Cairns J, Perel P, Shakur H, Roberts I, CRASH 2 Trial Collaborators. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* 2011;6:e18987.

How to cite this article: Seddighi A, Nikouei A, Seddighi AS, Zali A, Tabatabaei SM, Yourdkhani F, *et al.* The role of tranexamic acid in prevention of hemorrhage in major spinal surgeries. *Asian J Neurosurg* 2017;12:501-5.

Source of Support: Nil, **Conflict of Interest:** None declared.