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Efficacy and Safety of Prophylactic Large Dose of Tranexamic Acid in Spine Surgery

A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

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Study Design. This is a double blind randomized placebo controlled study, after obtaining approval of ethics committee in the hospital and informed written consent, 64 patients were randomized equally into 2 groups (tranexamic acid (TA) and placebo).

Objective. To evaluate efficacy and safety of large doses of TA on blood loss during spinal operations.

Summary of Background Data. Blood loss associated with spinal operations is a common potential cause of morbidity and often requires blood transfusion which subject patients to the known risks of blood transfusion including transmission of diseases. TA is used routinely to reduce bleeding in cardiac, orthopaedic, and hepatic surgery, however, its use in neurosurgery is uncommon and only few studies reported the use of antifibrinolytic drugs in spine surgery.

Methods. Sixty-four consecutive patients undergoing spinal surgery with expected significant blood loss at King Khalid University Hospital between June 2005 and December 2006 were randomly assigned to 2 groups, TA and placebo. Shortly after the induction of anesthesia, patients received either TA or placebo as a loading dose of 2 g (for adults) or 30 mg/kg (for children), followed immediately by continuous infusion of 100 mg/h (for adults) or 1 mg/kg/h (for children) during surgery and for 5 hours after the operation. Outcome measures included total (*i.e.,* intraoperative and postoperative) blood loss, amount of blood transfusion, as well as postoperative hemoglobin, and hematocrite levels. The data were analyzed by means of Statistical Package for the Social Science Version 12.0. The results were presented as mean ± SD. Independent Student *t* test was used to compare the 2 groups and differences were considered significant if the *P*-value was <0.05.

Results. There were 39 males and 25 females, ranging in age from 4 to 86 years with a mean of 51 and median of 56 years. Eighteen patients had multilevel anterior cervical discectomies with or without internal fixation, 22 patients had decompressive surgery (12 laminectomies and 10 intersegmental decompressions) for multisegment spinal stenosis, 15 patients had laminectomy with posterior spinal fixation, and remaining 9 patients had laminectomy and excision of spinal tumor. Statistical analysis showed no significant differences between the 2 study groups with regard to age, sex, weight, preoperative hemoglobin, and hematocrite levels, type of surgery, as well as operative time. In contrast, patients who received TA had 49% reduction of blood loss ($P < 0.007$) and required 80% less blood transfusion ($P < 0.008$) than patients who received placebo. The hospital stay was shorter in the TA group, but it did not achieve statistical significance. There were no complications related to the use of large doses of TA in this study.

Conclusions. Prophylactic use of large doses of TA provides an effective, safe, and cheap method for reducing blood loss during and after spinal operations. Hence, TAmay help in reducing not only transfusion related complications but also operative expenses. Considering the limited number of patients in this study, our results need, however, to be validated on a larger number of patients, probably in a multicenter study.

Key words: spinal surgery, spinal fixation, laminectomy, blood loss, blood transfusion, tranexamic acid, antifibrinolytic drugs, randomized trials. **Spine 2008;33: 2577–2580**

Surgical procedures are inevitably associated with bleeding, the amount of blood loss vary widely between different surgical operations and depends on surgical as well as non surgical factors. Spinal operations that entail spinal instrumentation are particularly associated with excess blood loss. Different techniques are applied for blood conservation including preoperative autologous donation, proper positioning of the patient, muscle paralysis to minimize intra-abdominal pressure, infiltration of paraspinal tissues with epinephrine, intraoperative blood salvage, deliberate controlled hypotensive anesthesia, and use of antifibrinolytic agents.[1–4] Antifibrinolytic agents have been routinely used during cardiac, orthopaedic, and hepatic surgery with positive effect on blood loss without apparent increase in the risk of postoperative complications, most notably there is no increased risk of venous thromboembolism.[5–8] Tranexamic acid (trans-4-aminomethyl-cyclohexane-1-carboxylic acid) (TA), synthetic lysine analogue, is a competitive inhibitor of plasmin and plasminogen; its half life is approximately 80 minutes provided there is normal renal function.[9,10] It produces its effect *via* complex interactions with plasminogen and displaces plasminogen from the fibrin surface (saturates the lysine binding sites of human plasminogen, displacing plasminogen from the fibrin

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surface) which results in inhibition of fibrinolysis. In addition, TA inhibits the proteolytic activity of plasmin and, as other antifibrinolytic agents, crosses the blood-brain barrier and counteracts the increased fibrinolytic activity of cerebrospinal fluid.[10] The side effects of TA includes headache, numbness or weakness, confusion, disturbed color vision, or allergic reactions, and contraindications to its use includes; active intravascular clotting process, acquired defective color vision, subarachnoid hemorrhage, and hypersensitivity.[1,4,10]

The aim of this study is to evaluate the efficacy of a large dose of TA in reducing blood loss and its safety during spinal operations.

■ Materials and Methods

This study was conducted as a research project funded by the CMRC at King Khalid University Hospital during the period from June 2005 to December 2006. After obtaining approval of the ethics committee in the hospital and informed written consent, patients were randomized (using odd and even numbers) into 2 equal groups that received either TA or placebo. Identical medicine bags for TA and placebo were prepared and coded by the pharmacy staff who did not know patients. Both anesthetist and surgeon were unaware of the content of the bag. At the end of the study the code was disclosed for statistical analysis.

Inclusion and Exclusion Criteria

All patients undergoing spinal operations with expectant significant blood loss were included in the study. Cases of microdiscectomy, and patients on anticoagulation therapy or with coagulopathy, have previous thrombo-embolic events, renal impairment, hepatic disease, as well as patients known to have contraindications to antifibrinolytic treatment were excluded from the study.

Drug Dose

The drug was given as a loading dose administered over 20 minutes after induction of anesthesia (2 g in 100 mL in case of adults or 30 mg/kg for children), followed immediately by maintenance dose (1 g in 100 mL infusion at a rate of 100 mg/h for adults, or 1 mg/kg/h in case of children) during surgery and continued for 5 hours after operation. The placebo bag contained 100 mL normal (0.9%) saline and was externally indistinguishable from the TA bag.

Anesthetic Technique

All patients were premedicated with lorazepam 1 to 2 mg orally (Vallergan 50 mg orally was used in case of children) 1 hour before going to theater. Induction of anesthesia was carried out using intravenous drugs (propofol 3 to 4 mg/kg, fentanyl 1 μg/kg, and atracurium 0.5 mg/kg as muscle relaxant) and maintained with inhalation of 1 MAC sevoflurane in a mixture of air and 50% oxygen. Atracurium and fentanyl were given during procedure when required. Patients were monitored as routine and the mean arterial blood pressure was maintained above 60 mm Hg during surgery. Blood was transfused during surgery if hemoglobin levels dropped (below 9g/L, or hematocrite <27%) with a decreasing trend.

The amount of blood loss during surgery was accurately calculated by measuring blood collected by drain and suction canisters, weighing the swabs, and subtracting all irrigation fluids used during surgery. After surgery, blood in the drains was accurately calculated and recorded. Blood, packed red blood cells, and its substitutes which were transfused during and after surgery were documented.

The patient's data sheet recorded the demographic data, patient's weight, past medical history, comorbid conditions, current medications, current surgical diagnosis, operation to be performed, preoperative laboratory work up including complete blood count, clotting profile, renal, and liver function tests. It also included accurate calculation of blood loss during and after surgery. Preoperative, intraoperative, and postoperative hemoglobin (HB) and hematocrite (HCT) values were documented, as well as the amount of blood and blood products transfused during and after surgery.

Data were analyzed using Statistical Package for the Social Science Version 12.0, independent Student *t* test was used to compare the 2 groups, results were presented as mean ± SD, and differences were considered significant if *P*-value was <0.05.

■ Results

The study included 64 patients who were distributed equally between both groups (the placebo and TA). There were 39 (61%) males and 25 (39%) females, the age ranged from 4 to 86 years; mean age was 51 years and median age was 56 years (49.75 ± 21.04 for placebo and 51.56 ± 19.08 years for TA group). Patient's weight was 69.63 ± 19.29 for placebo and 72.48 ± 13.81 Kg for TA group. All Surgeries were done by the first 3 senior authors, first surgeon did 22 operation (11 in each group), the second surgeon did 28 operations (13 in TA and 15 in placebo groups), and the third surgeon did 14 operations (8 in TA and 6 in placebo groups). The difference in operative time, amount of blood loss, and amount of transfusion between the 3 surgeons was insignificant, (*P*-value 0.694).

The duration of surgery was 195.69 ± 74.08 minutes for placebo and 178.48 ± 72.04 minutes for TA group. Preoperative HB and HCT values were more or less the same in both groups (Table 1). Eighteen patients had multiple level anterior cervical discectomy with or without fixation (10 in the TA and 8 for placebo groups), 37 patients had spinal decompression for multisegment spinal stenosis (18 patients in TA and 19 in placebo group), 15 of them had, in addition, spinal fixation. Nine patients had laminectomy and excision of spinal tumor (4 in TA and 5 in the placebo group) (Table 2).

Table 1. Comparison of Variables Between the Two Groups

Mean	TA Group	Placebo Group	*P*
Age	51.56 ± 19.08	49.75 ± 21.04	0.5
Gender			0.3
Male	21	18	
Female	11	14	
Weight	72.48 ± 13.81	69.63 ± 17.29	0.3
Preoperative haemoglobin	13.37 ± 1.58	13.42 ± 1.31	0.87
Preoperative haematocrite	39.73 ± 5.23	39.19 ± 3.97	0.64
Duration of surgery (min)	178.48 ± 72.04	195.69 ± 74.08	0.09
Hospital stay	8.45 ± 5.79	10.69 ± 8.27	0.21

Table 2. Comparison of Surgical Procedures in Both Groups

Procedure	TA Group	Placebo Group	Total
Multiple levels ACD ± fixation	10	8	18
Laminectomy and discectomy (more than 1 level)	6	6	12
Laminectomy with pedicle screw fixation	9	6	15
Inter segmental decompression (2 levels or more)	3	7	10
Laminectomy and excision of spinal tumor	4	5	9
Total	32	32	64

ACD indicates anterior cervical discectomy.

Blood loss during surgery from patients in TA group was almost half the amount lost from patients in Placebo group (49% reduction), 311.25 ± 412.49 cc *versus* 584.69 ± 797.30 cc, ($P < 0.05$). The blood and fluids collected from wound drains was much less in case of TA than in placebo groups, 97.94 ± 136.28 cc *versus* 215.31 ± 276.04 cc, ($P < 05$). Total blood loss for patients in TA group was 406.13 ± 495.31 cc *versus* 800.00 ± 1034.25 cc for placebo group, ($P < 0.05$). Consequently the amount of blood transfusion was 80% less in TA than in placebo group, 93.75 ± 267.53 cc *versus* 531.25 ± 1275.94 cc, ($P < 0.05$). The total number of blood units given to patients in TA group was 6 U compared with 34 U transfused to patients in the placebo group. There was also significant difference in the postoperative HB and HCT values for patients in both groups, 12.39 ± 1.28 g/dL *versus* 11.35 ± 1.57, and 35.98 ± 3.59 *versus* 32.79 ± 4.41g/dL, respectively. There was a trend of shorter hospital stay for patients in TA than those in placebo group, 8.45 ± 5.79 *versus* 10.69 ± 8.27 days ($P > 0.05$) (Table 3).

The follow-up period ranged from 12 month to 3 years. It is expected that thromboembolic complications related to TA will occur during hospital stay or within the first 3 month after surgery; none was reported in patient files (during hospital stay nor in the 3 month visit after surgery). In our study, the use of large doses of TA during spine surgery was not associated with complications, no patient reported disturbed color vision, weakness, and no recorded cases of confusion or allergic reactions after surgery.

Table 3. Blood Loss and Transfusion Requirements in Both Groups

Mean	TA Group	Placebo Group	*P*
Blood loss during surgery	311.25 ± 412.49	584.69 ± 797.30	0.03
Blood in wound drains	97.94 ± 136.28	215.31 ± 276.04	0.004
Total blood loss	406.13 ± 495.31	800.00 ± 1034.25	0.007
Amount of transfusion	93.75 ± 267.53	531.25 ± 1275.94	0.008
Postoperative hemoglobin	12.39 ± 1.28	11.35 ± 1.57	0.006
Postoperative haematocrite	35.98 ± 3.59	32.79 ± 4.41	0.003
Patients received blood	4	12	0.021
Total No. blood units transfused	6	34*	0.025

*One patient received 14 U blood.

■ Discussion

The use of pharmacological therapies to reduce blood loss and blood transfusions in surgery is restricted to a few drugs: aprotinin (Trasylol), TA(cyklocapron), aminocaproic acid, desmopressin, and recombinant factor VIIa).[1,3] A recent systematic review of randomized controlled trials (RCT)s of antifibrinolytic agents in elective surgical patients identified 211 RCTs that recruited 20,781 participants.[11] It has concluded that antifibrinolytic drugs provided worthwhile reductions in blood loss and the need for allogeneic red cell transfusion. Based on the results of RCTs, the efficacy of these drugs did not seem to be offset by serious adverse effects. In most circumstances, the lysine analogues (TA and EACA) were probably as effective as aprotinin and were cheaper; the evidence was stronger for TA than for aminocaproic acid.[11] Few studies have investigated the use of TA for pediatric and adult patients undergoing spinal surgery.[12–15]

In the present study, 64 patients were randomly assigned to large dose of TA and placebo groups (32 patients in each group), both groups were more or less similar in the mean age, body weight, preoperative HB and HCT values, operative time, and the type of surgical procedure. Contributing factors that could alter blood loss were monitored during the study (coagulation profile, standardized anesthetic technique, and mean arterial blood pressure). The results have shown significant difference in both groups, blood loss during surgery was reduced by 48% with the use of TA (*P*-value 0.03). The amount of blood and fluids collected from wound drains was less by 55% in patients who received TA, (*P*-value 0.004), and the total amount of blood loss was less by 49% in the TA group, (*P*-value 0.007). Consequently, the amount of blood transfusion to patients in TA group was 80% less than in placebo group (*P*-value 0.008). There was also significant difference in the postoperative HB and HCT values of patients in both groups (*P*-value 0.006 and 0.003, respectively). Large dose of TA was well tolerated by patients included in our study and there were no hemodynamic disturbances, apparent thromboembolic complications, or other drug complications associated with its use, such as disturbed color vision, numbness or weakness, confusion, or allergic reactions.

Dose regimens of TAvary widely in the literature, loading doses range from 2.5 mg/kg to 100 mg/kg and maintenance doses from 0.25 mg/kg to 4 mg/kg/h delivered over time periods of 1 to 12 hours.[16] In our study, we used a relatively large dose of TA, loading dose (2 g in 100 mL in case of adults or 30 mg/kg for children), and a maintenance dose (1 g in 100 mL infusion at a rate of 100

mg/h for adults, or 1 mg/kg/h in case of children). With this dose, adequate hemostasis (49% reduction of blood loss) and 80% reduction of transfusion requirements was achieved. Sethna *et al*[15] randomized 44 pediatric patients undergoing scoliosis surgery to a larger dose of TA (100 mg/kg bolus dose given before skin incision followed by infusion of 10 mg/kg/h during surgery), in the TA group blood loss was reduced by 41% compared with placebo.

Recent reports on the use of antifibrinolytics (Aprotinin) in spine surgery had shown significant reduction of blood loss, Urban *et al*[17] randomized 60 patients undergoing major spine surgery to 2 different antifibrinolytic drugs (EACA, Aprotinin, or placebo). They found that both drugs reduced total blood loss and transfusion requirements; however, only aprotinin reached significant levels. Cole *et al*[18] assessed the efficacy of aprotinin to reduce blood loss and transfusion requirement in 44 children and adolescents undergoing posterior spinal fusion, they reported significant reduction in blood loss and transfusion requirements in their group of children who are at increased risk of bleeding.

Aprotinin is an expensive drug (half dose regime costs about $1000) and its use might be associated with anaphylactic reaction, on the other hand, TA is a very cheap drug and large dose regimen, as used in our study, cost only few US dollars.[19] In addition, most reports concluded that TA is a safe drug and its use was not associated with complications and the efficacy of the drugs does not seem to be offset by serious adverse effects.[1,2,7,8,11–13,19–22]

■ Conclusion

Prophylactic use of large dose of TA provides an effective, safe, and cheap method for reduction of blood loss during and after spinal operations. Hence TA may help in reducing not only transfusion related complications but also operative expenses. Considering the limited number of patients in this study, our results need, however, to be validated on a larger number of patients.

■ Key Points

- Use of tranexamic acid in spine surgery is safe and effective.
- It has reduced blood loss by 49% ($P < 0.007$).
- It has reduced blood transfusion by 80% ($P < 0.008$).

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References

1. Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. *Lancet* 2003;361:161–9.
2. Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. *Semin Hematol* 2004;41:55–64.
3. Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002;62:2193–211.
4. Zheng F, Cammisa FP Jr, Sandhu HS, et al. Factors predicting hospital stay, operative time, blood loss, and transfusion in patients undergoing revision posterior lumbar spine decompression, fusion and segmental instrumentation. *Spine* 2002;27:818–24.
5. Maddali MM, Rajakumar MC. Tranexamic Acid and primary coronary artery bypass surgery: a prospective study. *Asian Cardiovasc Thorac Ann* 2007;15:313–9.
6. Caglar GS, Tasci Y, Kayikcioglu F, et al. Intravenous tranexamic acid use in myomecomy: a prospective randomized double-blind placebo controlled study. *Eur J Obstet Gynecol Reprod Biol* 2008;137:227–31.
7. Johansson T, Pettersson LG, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. *Acta Orthop* 2005;76:314–9.
8. Dalmau A, Sabaté A, Acosta F, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000;91:29–34.
9. Fiechhtner BK, Nuttall GA, Johnson ME, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anaesth Analg* 2001;92:1131–6.
10. Longstaff C. Studies on the mechanisms of action of aprotinin and tranexamic acid as plasmin inhibitors and antifibrinolytic agents. *Blood Coagul Fibrinolysis* 1994;5:537–42.
11. Horrow JC, Van Riper DF, Strong MD, et al. The dose-response relationship of tranexamic acid. *Anesthesiology* 1995;82:383–92.
12. Henry DA, Charless PA, Moxey AJ et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007;4:CD 001886.
13. Wong J, El-Behairy H, Suntheralingam Y, et al. Tranexamic acid reduces blood loos and transfusion in adult patients having spinal fusion surgery. *Can J Anaesth* 2006;53:6385.
14. Neilipovitz DT, Murto K, Hall L, et al. A Randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. *Anesth Analg* 2001;93:82–7.
15. Sethna NF, Zurakowski D, Bustowicz RM, et al. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. *Anesthiology* 2005;102:727–32.
16. Neilipovitz DT. Tranexamic acid for major spinal surgery, review article. *Eur Spine J* 2004;13(suppl 1):S62–5.
17. Urban MK, Beckman J, Gordon M, et al. The Efficacy of Antifibrinolytics in reduction of blood loss during complex adult reconstructive spine surgery. *Spine* 2001;26:1152–7.
18. Cole JW, Murray DJ, Sinder RJ, et al. Aprotinin reduces blood loss during spinal surgery in children. *Spine* 2003;28:2482–5.
19. Bennett-Guerrero E, Sorohan JG, Gurevich ML, et al. Cost-benefit and efficacy of aprotinin compared with epsilon-aminocaproic acid in patients having repeated cardiac operations: a randomized, blinded clinical trial. *Anesthiology* 1997;87:1373–80.
20. Prentice CR. Basis of antifibrinolytic therapy, review article. *J Clin Pathol Supp* 1980;14:35–40.
21. Dell R, de Ruiter J, Levine M, et al. Does tranexamic acid decrease blood loss in children undergoing posterior spinal fusion for idiopathic scoliosis? *Can J Anaesth* 1999;46:A56.
22. Lentschener C, Cottin P, Bouaziz H, et al. Reduction of blood loss and transfusion requirements by aprotinin in posterior lumbar spine fusion. *Anaesth Analg* 1999;89:590–7.