Eur Spine J (2013) 22:2035–2038
DOI 10.1007/s00586-013-2836-z

ORIGINAL ARTICLE

Tranexamic acid reduces postoperative blood loss of degenerative lumbar instability with stenosis in posterior approach lumbar surgery: a randomized controlled trial

Qi Wang · Jun Liu · Rong Fan · Yu Chen · Hailong Yu · Yan Bi · Zhengzhe Hua · Meihui Piao · Mingming Guo · Weijian Ren · Liangbi Xiang

Received: 5 April 2012 / Revised: 23 February 2013 / Accepted: 8 May 2013 / Published online: 29 May 2013

Abstract
Study design This study is randomized controlled trial.
Purpose To evaluate the effect of tranexamic acid (TXA) on reducing postoperative blood loss in posterior approach lumbar surgery for degenerative lumbar instability with stenosis.
Methods Sixty patients with degenerative lumbar instability with stenosis were randomized into TXA and control groups, receiving 15 mg/kg body weight of TXA or placebo (0.9 % Sodium chloride solution) intravenously, respectively, before the skin incision was made. The operation of pedicle screw system fixation was performed for all patients, and then selective laminectomy and posterior lumbar interbody fusion (PLIF) were carried out. Intraoperative and postoperative blood loss were compared between the two groups. And the complication of TXA was also investigated.
Results There were no statistically significant differences between the TXA and control groups in terms of age, sex, body mass index, and operation time. There was no significantly difference in intraoperative blood loss between the two groups. However, in the TXA group, postoperative blood loss was significantly lower than that in the control group (13.0 %). Especially, postoperative blood loss during the first 12 h was reduced by 29.9 % as compared to the control group. There were no thromboembolic events or other complications occurred in either group.
Conclusions Preoperative single-dose TXA can significantly reduce postoperative blood loss in posterior approach lumbar surgery, and there were no significant side effects.

Keywords Tranexamic acid · Postoperative · Blood loss · Degenerative lumbar disease · Randomized controlled trial

J. Liu and R. Fan are Co-first authors.

Q. Wang · J. Liu · Y. Chen · H. Yu · Y. Bi · Z. Hua · M. Piao · M. Guo · W. Ren · L. Xiang (✉)
Department of Orthopedics, The General Hospital of Shenyang Military Area Command, No. 83, Wenhua Road, Shenyang 110840, China
e-mail: xiangliangbi1963@sina.com

Q. Wang
e-mail: wangqi_orth@126.com

J. Liu
e-mail: ven15@163.com

R. Fan
Department of Pharmacy, The General Hospital of Shenyang Military Area Command, No. 83, Wenhua Road, Shenyang 110840, China

Introduction

The degenerative lumbar instability with stenosis is a common disease of the elderly, which often requires surgery. However, the surgery often needs a long-segment fixation, canal decompression and interbody fusion, thus much longer operative time and much more blood loss are inevitable. Excessive blood loss may increase the risk of infection, hematoma formation within the spinal canal, and also allogeneic blood transfusion, which may result in immunologic reactions or viral transmission [1–4]. Therefore, how to control postoperative blood loss is one of the urgent problems focused [5, 6]. Tranexamic acid (TXA), a synthetic antifibrinolytic drug, is widely used to reduce perioperative blood loss in clinical surgery [1, 6–17]. Most of previous studies had poor reliability due to the differences of age, diagnosis and surgical approach. The 60 patients eligible for this study, who were same in diagnosis, surgical approach, and individual conditions, were scheduled to undergo a prospective randomized controlled to

evaluate the effectiveness of TXA in reducing postoperative blood loss in spinal surgery.

Patients and methods

Patient population

Sixty patients (39 males and 21 females), with an average age of 64.7 years (range, 60–78 years), were enrolled in the study from June 2008 to December 2010. All the patients suffering from degenerative lumbar instability with stenosis diagnosed according to the Panjabi and White's methods [18] (a difference of 11° or greater from the angle of either adjacent interspace, or an anterior posterior or lateral distance of 3.5 mm or greater is suggestive of clinical instability) failed in conservative treatment and required surgical procedures with L2–S1 pedicle screw fixation, L4/5 and L5/S1 laminectomy, interbody fusion with cages (PLIF), and also intertransverse autologous bone and β-TCP graft. Patients with chronic renal failure, cirrhosis of the liver, serious cardiac disease, allergy to TXA, thromboembolic disease, bleeding disorders, hyper coagulation status, disseminated intravascular coagulation, and those who were receiving antiplatelet and/or anticoagulant drugs at the time of the study were excluded. Nonsteroidal anti-inflammatory medication was withdrawn at least 24 h before surgery [11, 19].

Study design

The patients were randomized by medical record number, that is, odd numbers (TXA group, $n = 30$) and even numbers (control group, $n = 30$), and received either a dose of 15 mg/kg body weight of TXA mixed in 100 ml saline or a placebo (an equal dose of saline only) intravenously over 15 min before the skin incision was made [12].

Surgical technique

All the operations were performed by the same four surgeons with prone position under general anesthesia. After the back fascia in line with the midline skin incision was longitudinally divided, the paravertebral muscles were dissected from the spinous processes and lamina, and the facet joints of L1–S1 were exposed. Ten pedicle screws were implanted successively, then two connecting rods were installed. After resection of the L4, L5 laminae and removal of the L4/5 and L5/S1 disc, a CAGE filled with autogenous bone granules was obliquely placed into L4/5 and L5/S1 intervertebral space, respectively. Radiography was taken to confirm the pedicle screws and CAGEs in good position. Then the incision was rinsed, hemostasis was accomplished, a negative pressure drainage was placed, and a layer-to-layer suture was carried out to close the wound. The drainage was pulled out routinely after 48 h. Anticoagulants were not used until the drainage was pulled out.

Evaluation

Intra and postoperative blood loss for each patient were measured by a nurse who was blinded to the patient groups. Intraoperative blood loss was estimated by weighing surgical sponges and measuring the volume of blood collected by suction canisters. The weight of irrigation fluids added to the surgical field and the sponge weight were then subtracted from this value. Postoperative blood loss was measured from the volume of blood accumulated in the drainage bags. Postoperative drainage volume for 12 and 48 h were calculated, respectively. Total blood loss was calculated as the sum of intra and postoperative blood loss.

Statistical strategies

Statistical differences between the randomized groups were compared using the χ^2 or Fisher exact test for categorical variables and Student *t*-test (equal variance groups with parametric data), Welch *t*-test (unequal variance groups with parametric data), or the Mann–Whitney *U* test (non-parametric data) for continuous variables appropriately. Furthermore, the Kruskal–Wallis test was used to analyze the differences in intraoperative blood loss among the surgeons. A value of $P < 0.05$ was considered statistically significant.

Results

In TXA group, 11 patients had spondylolisthesis (8 in L5/S1, 3 in L4/5), and 4 had lateral listhesis (all in L4/5), while in control group, 8 patients had spondylolisthesis (6 in L5/S1, 2 in L4/5), and 5 had lateral listhesis (all in L4/5) ($P < 0.05$). There were no statistical differences in parameters of age, sex, body mass index, or diagnosis between the two groups (Table 1). The preoperative hemoglobin (Hb) level, hematocrit (Hct) level, bleeding time, prothrombin time, activated partial thromboplastin time, and platelet count were not significantly different between the groups (Table 2).

There were no significant differences in the operation duration (194.5 ± 20.1 min vs. 187.5 ± 22.2 min, $P = 0.30$) and the intraoperative blood loss during operation (731.5 ± 81.5 ml vs 688 ± 64.7 ml, $P = 0.06$) between the control group and the TXA group. The TXA group had significantly less postoperative blood loss during

Table 1 Common data of patients in each group

	Control group ($n = 30$)	TXA group ($n = 30$)	P value
Age (years)	62.0 ± 4.6	63.1 ± 4.0	0.34
Gender (female/male)	12/18	14/16	0.60
BMI	22.2 ± 1.9	21.7 ± 1.9	0.31

Table 2 Preoperative hematologic data

	Control group ($n = 30$)	TXA group ($n = 30$)	P value
Hemoglobin (g/dL)	14.1 ± 0.5	13.7 ± 1.1	0.09
Hematocrit (%)	41.5 ± 1.3	42.1 ± 1.8	0.18
Bleeding time (min)	2.7 ± 0.2	2.6 ± 0.3	0.80
PT (s)	11.6 ± 0.7	11.9 ± 0.6	0.11
APTT (s)	26.1 ± 0.9	25.8 ± 1.1	0.21
Platelet count (10^9/L)	22.9 ± 2.5	23.3 ± 2.3	0.55

Table 3 Intraoperative and postoperative blood loss

	Control group ($n = 30$)	TXA group ($n = 30$)	P value
Operation time (min)	194.3 ± 17.4	185.0 ± 20.3	0.06
Intraoperative blood loss (ml)	723.7 ± 70.2	695.3 ± 62.6	0.10
Postoperative 12 h blood loss (ml)	364.0 ± 39.6	255.3 ± 23.0	0.00
Total blood loss	1260.7 ± 99.4	1096.3 ± 85.0	0.00

the first 12 h (29.9 %) and 48 h (13.0 %) as compared to the control group ($P < 0.01$) (Table 3).

There were no serious complications such as cerebrospinal fluid leakage, infection, epidural hematoma, liver and kidney failure and cardiopulmonary complications. The side effects of TXA were also not observed such as deep vein thrombosis, pulmonary embolism, allergic reactions, headache, nausea, vomiting, diarrhea, etc.

Discussion

Transient increase in fibrinolysis during surgery and contribution of enhanced of fibrinolysis to perioperative blood loss in spinal surgery have been observed [7, 20]. Fibrinolytic activation is a cascade process. TXA blocks the lysine-binding site of plasminogen to fibrin and inhibits the activation of plasminogen by the plasminogen activator, thereby retarding fibrinolysis [8]. TXA should be used before fibrinolysis is activated, the administration timing of which is critical [10, 11]. In this study, we evaluated the effects of a single bolus dose of TXA, and injected intravenously 15 min before surgery. The TXA group demonstrated a 13.0 % decrease in total blood loss, indicating that the drug has significant role in the postoperative period to reduce blood loss. The results of this study showed that blood loss in the TXA group was less than that in the control group, especially at the first 12 h after surgery (29.9 %). The half-life of TXA is reported to be 2 h, the effective plasma concentration of which is 1 μg/ml. Once the intravenous infusion is 15 mg/kg, it will last for about 16 h above effective plasma concentration, that is to say, TXA can keep most effective during the first 16 h after the administration [21, 22]. In this study, TXA was administered 15 min before operation, which went through 3 h, and the results showed that the TXA group blood loss was reduced mainly in the first 12 h after operation. The concentration of TXA has dropped below the effective plasma concentration in the next 36 h, but the blood loss was still less than that in the control group, suggesting that TXA may have subsequent effects. Although the postoperative blood loss in TXA group was less than that in the control group during 12 to 48 h, there was much blood loss. Whether TXA can be intravenously infused repeatedly in order to further reduce postoperative bleeding and whether the additional dose of TXA will increase its side effects are still to be further studied.

Theoretically, the use of TXA may potentially increase the risk of thrombosis. However, many studies have confirmed that the use of TXA did not increase the risk of thrombotic complications [6, 9, 16]. There were no clinical symptoms or signs of thrombosis in this study. In addition, we had not found other side effects of TXA, which suggests that the single dose of TXA in posterior lumbar surgery is safe.

Although Elwatidy et al. [23] reported on the antihemorrhagic effect of TXA in spinal surgery in 2008, whose study was a well-designed randomized controlled trial; however, the patient population was heterogeneous. The age of the patients at the time of surgery ranged from 4 to 86 years, and patients underwent various types of surgical procedures such as anterior cervical surgery, lumbar spinal decompression with or without spinal fixation, excision of a spinal tumor, etc. Because perioperative blood loss is influenced by diagnosis, the age of the patient at the time of surgery, and the type of surgical procedure including the level of decompression and the use of spinal instrumentation, Elwatidy's results are not reliable enough. However, in our study there was uniformity in the diagnosis and operative procedures between the study groups; therefore, the results are more convincible.

In short, the study groups have shown that preoperative single-dose TXA can effectively reduce postoperative

blood loss in posterior approach lumbar surgery, and there are no significant side effects.

Conflict of interest None of the authors having conflict of interests.

References

1. Lemaire R (2008) Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg Br 90(9): 1128–1136
2. Yonenobu K, Hosono N, Iwasaki M et al (1991) Neurologic complications of surgery for cervical compression myelopathy. Spine 16(11):1277–1282
3. Kebaish KM, Awad JN (2004) Spinal epidural hematoma causing acute cauda equina syndrome. Neurosurg Focus 16(6):e1
4. Sokolowski MJ, Garvey TA, Perl J II et al (2008) Prospective study of postoperative lumbar epidural hematoma: incidence and risk factors. Spine 33(1):108–113
5. Hu SS (2004) Blood loss in adult spinal surgery. Eur Spine J 13(Suppl 1):3–5
6. Mannucci PM, Levi M (2007) Prevention and treatment of major blood loss. N Engl J Med 356(22):2301–2311
7. Neilipovitz DT (2004) Tranexamic acid for major spinal surgery. Eur Spine J 13(Suppl 1):62–65
8. Mannucci PM (1998) Hemostatic drugs. N Engl J Med 339(4): 245–253
9. Henry DA, Carless PA, Moxey AJ et al (2007) Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev; 4:CD001886
10. Benoni G, Fredin H (1996) 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 78(4):434–440
11. Tanaka N, Sakahashi H, Sato E et al (2001) Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br 83(5):702–705
12. Johansson T, Pettersson LG, Lisander B (2005) Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double blind study in 100 patients. Acta Orthop 76(3):314–319
13. Yamasaki S, Masuhara K, Fuji T (2005) Tranexamic acid reduces postoperative blood loss in cement less total hip arthroplasty. J Bone Joint Surg Am 87(4):766–770
14. Neilipovitz DT, Murto K, Hall L et al (2001) A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. Anesth Analg 93(1):82–87
15. Sethna NF, Zurakowski D, Brustowicz RM et al (2005) Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. Anesthesiology 102(4):727–732
16. Gill JB, Chin Y, Levin A et al (2008) The use of antifibrinolytic agents in spine surgery. A meta-analysis. J Bone Joint Surg Am 90(11):2399–2407
17. Wong J, El Beheiry H, Rampersaud YR et al (2008) Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesth Analg 107(5):1479–1486
18. Panjabi MM, White AA 3rd (1980) Basic biomechanics of the spine. Neurosurgery 7(1):76–93
19. Douketis JD, Berger PB, Dunn AS et al (2008) The perioperative management of antithrombotic therapy: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest 133(Suppl 6):299S–339S
20. Griffiths NJ (1979) Factors affecting the fibrinolytic response to surgery. Ann R Coll Surg Engl 61(1):12–16
21. Pilbrant A, Schannong M, Vessman J (1981) Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol 20(1):65–72
22. Tsutsumimoto T, Shimogata M, Ohta H et al (2011) Tranexamic acid reduces perioperative blood loss in cervical laminoplasty: a prospective randomized study. Spine (Phila Pa 1976); 36(23): 1913–8
23. Elwatidy S, Jamjoom Z, Elgamal E et al (2008) Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine 33(24):2577–2580