Eur Spine J (2017) 26:2851–2857
DOI 10.1007/s00586-017-5230-4

ORIGINAL ARTICLE

The effectiveness of low-dose and high-dose tranexamic acid in posterior lumbar interbody fusion: a double-blinded, placebo-controlled randomized study

Ki-Tack Kim[1] · Cheung-Kue Kim[1] · Yong-Chan Kim[1] · Hyung-Suk Juh[2] · Hyo-Jong Kim[3] · Hyeon-Soo Kim[4] · Se Jung Hong[1] · Hwee Weng Dennis Hey[5]

Received: 24 March 2017 / Revised: 6 July 2017 / Accepted: 17 July 2017 / Published online: 25 July 2017

Abstract

Purpose Tranexamic acid is a proven drug used for reduction of intraoperative blood loss in spinal surgery. However, optimal dosing considering risk/benefits is not well established owing to the heterogeneity in patient selection and surgical procedures of previous studies. This study aimed to evaluate the effectiveness and safety of various tranexamic acid regimens in reducing perioperative blood loss in single-level posterior lumbar interbody fusion (PLIF).

Methods Patients were randomly grouped into three different interventions: low-dose tranexamic acid (LD), high-dose tranexamic acid (HD), and placebo-controlled (PC) groups. The HD and LD groups received 10 and 5 mg/kg of bolus loading dose and 2 and 1 mg/kg of continuous infusion until 5 h after surgery, respectively. Data on patient demographics and preoperative and 24-h postoperative laboratory values were collected. Outcome parameters include intraoperative blood loss, 24-h postoperative blood loss, and blood loss during removal of the last drain.

Results Seventy-two patients (mean age 63.3 ± 7.6 years) showed similar baseline characteristics. Intraoperatively, blood loss was reduced by the administration of tranexamic acid ($P = 0.04$), contributed predominantly by a difference between the LD and HD groups (123 mL; $P < 0.01$). The 24-h postoperative blood loss was reduced ($P < 0.01$), contributed predominantly by a difference between the PC and LD groups (144 mL; $P = 0.02$). During the removal of the last drain, statistical difference was found between the PC and HD groups (125 mL; $P = 0.00$). No complications or side effects from tranexamic acid use were noted.

Conclusion Tranexamic acid administration for single-level PLIF was effective and safe in reducing perioperative blood loss in a dose-dependent manner. An HD regimen

✉ Cheung-Kue Kim
kchk223@hanmail.net

Ki-Tack Kim
ktkim713@gmail.com

Yong-Chan Kim
yckimspine@gmail.com

Hyung-Suk Juh
97383077@daum.net

Hyo-Jong Kim
nobledoc@nate.com

Hyeon-Soo Kim
hskim0913@gmail.com

Se Jung Hong
superb-hsj@hanmail.net

Hwee Weng Dennis Hey
dennis_hey@nuhs.edu.sg

[1] Department of Orthopedic Surgery, Kyung Hee University Hospital at Gangdong, Seoul, South Korea

[2] Department of Medicine, Graduate School, Kyung Hee University, Seoul, South Korea

[3] Department of Orthopedic Surgery, Park Weon Wook Hospital, Busan, South Korea

[4] Department of Orthopedic Surgery, Samsung Changwon Hospital, Sungkyunkwan University, School of Medicine, Changwon, South Korea

[5] University Orthopaedics, Hand and Reconstructive Microsurgery Cluster (UOHC), National University Health System (NUHS), Singapore, Singapore

comprising 10 mg/kg of bolus loading dose and 2 mg/kg/h of continuous infusion is recommended.
Level of evidence Level 1 study according to Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.

Keywords Tranexamic acid · Posterior lumbar interbody fusion · Perioperative blood loss · Placebo-controlled · Spinal surgery

Introduction

Spinal fusion can be associated with substantial blood loss, which increases postoperative morbidity [1] and prolongs clinical recovery [2]. In such a circumstance, blood transfusion may occasionally be required, albeit its inherent risks [3], to treat symptomatic anemia and facilitate rehabilitation [4]. This could be avoided if adequate hemostasis can be achieved intraoperatively [5]. Another important reason to optimize bleeding control is to reduce the risk of epidural hematoma formation, which can cause neural compression, leading to neurological deficits [6].

Numerous intraoperative methods to control bleeding have been described in the literature [7]. This includes patient positioning [8], deliberate hypotension [9], intra-abdominal pressure control via administration of muscle relaxants [10], infiltration of paraspinal tissues using vasoconstrictors such as epinephrine [6], and intraoperative blood salvage [2]. The use of pharmacological agents to enhance coagulation such as tranexamic acid [11], a synthetic lysine analogue of *trans*-4-aminomethyl-cyclohexane-1-carboxylic acid, has already been extensively employed owing to its proven benefits in reducing perioperative blood loss and the need for blood transfusion [12, 13]. However, studies investigating the use of tranexamic acid in posterior spinal fusion are heterogeneous [14, 15] and are unable to recommend distinct dosing guidelines for use in specific conditions and surgical procedures.

Moreover, the timing for administering tranexamic acid during induction is crucial. This drug has been shown to reach peak plasma concentration 5 min after bolus injection and 60 min after surgery infusion [16]. Its approximate half-life is 80–120 min [17]. Therefore, the primary objective of our study is to analyze the effectiveness and dose requirements of tranexamic acid in reducing perioperative blood loss in single-level posterior lumbar interbody fusion (PLIF) administered 5 min before knife-to-skin. The secondary objective of this study is to identify possible side effects following administration of low- and high-dose tranexamic acid regimens.

Materials and methods

Study design

This is a double-blinded, placebo-controlled randomized study conducted in a single institution from January 2014 to April 2015. Power analysis was performed using an arbitrarily defined, clinically significant difference of 50 mL of blood loss among study groups. To achieve a statistical power of 80% while accepting a false-positive rate of 0.05%, 70 patients were deemed necessary to identify differences in blood loss among study groups. Ethics approval was obtained from the institutional review board before the commencement of this study.

Patient population

This study included patients who had symptomatic lumbar spinal stenosis with borderline to grade 1 spondylolisthesis, based on magnetic resonance imaging findings and flexion–extension stress X-rays. All patients underwent an unsuccessful course of physiotherapy and hence were clinically indicated for PLIF (Table 1). They were recruited from the spine outpatient clinic by a single surgeon after consenting to surgery. Patients with previous spinal surgery, previous or current bleeding or coagulation issues, established renal or hepatic diseases, or contraindication to antifibrinolytic agents were excluded from the study.

Methods

All patients underwent clinical assessment and preoperative workup. Demographic data collected include age, sex, and body mass index (BMI). Laboratory investigations performed include hemoglobin (Hb), hematocrit (Hct), fibrinogen, prothrombin time/activated partial thromboplastin time (PT/APTT), aspartate aminotransferase/alanine transaminase (AST/ALT), and blood urea nitrogen-to-creatinine (BUN/Cr). These investigations were performed preoperatively and repeated 24 h after surgery. Venous thromboembolism (VTE), as a lower limb complication, is evaluated using ultrasonography 1 day before and 1 week after surgery.

Tranexamic acid (Shin Poong Pharm Co., Seoul, South Korea) was the interventional drug used in this study. All patients were computer-randomized into three groups: the low-dose tranexamic acid treatment group (LD), the high-dose tranexamic acid treatment group (HD), and the placebo-control group (PC). Randomization results were concealed until the day of surgery, when only the anesthetist was informed. Because the anesthetist would be

Table 1 Univariate comparison of baseline characteristics in each group

	PC	LD	HD	*P* value
Demographics				
Age	65.2 ± 7.0	63.3 ± 7.6	61.0 ± 9.0	0.19
Gender (M/F)	15/9	8/16	12/12	0.13
Body mass index	25.1 ± 3.2	25.2 ± 2.9	25.9 ± 3.2	0.71
Laboratory investigations				
Hemoglobin (g/dL)	13.2 ± 1.5	13.3 ± 1.6	13.1 ± 1.1	0.89
Hematocrit (%)	39.4 ± 4.7	39.7 ± 4.8	37.3 ± 4.1	0.14
Fibrinogen (mg/dL)	254.5 ± 44	261.8 ± 55.8	285.2 ± 65.7	0.07
PT (s)	12.9 ± 0.3	12.7 ± 0.7	13.1 ± 0.6	0.10
APTT (s)	35.0 ± 3.4	34.6 ± 3.2	31.5 ± 2.9	0.16
AST (U/L)	22.4 ± 5.3	22.6 ± 5.4	25.3 ± 5.5	0.12
ALT (U/L)	19.0 ± 7.9	20.4 ± 8.9	22.0 ± 8.0	0.47
BUN (mg/dL)	16.1 ± 4.1	15.8 ± 4.6	15.2 ± 6.3	0.81
Cr (mg/dL)	0.7 ± 0.0	0.7 ± 0.1	0.7 ± 0.1	0.67

All values are displayed as means with standard deviations. Gender is displayed as a ratio of male/female

CG placebo-controlled group, *LD* low-dose group, *HD* high-dose group, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *AST* aspartate transaminase, *ALT* alanine transaminase, *BUN* blood urea nitrogen, *Cr* creatinine

aware of clinical information such as underlying disease and hemorrhagic tendency of all study subjects in advance and prepare for any unexpected accidents. TXA injection was performed by an anesthetist. The surgeon was blinded to the results of the randomization during the entire patient management process.

Each group received a bolus of 100 mL normal saline (0.9%) at induction followed by infusion of crystalloids based on intraoperative requirements until 5 h after surgery. The patients in the HD group received 10 mg/kg of tranexamic acid as a bolus in 100 mL of normal saline (0.9%) followed by an infusion at a rate of 2 mg/kg/h until 5 h after surgery. The patients in the LD group received a bolus dose of 5 mg/kg of tranexamic acid followed by an infusion at a rate of 1 mg/kg/h in a similar manner. The PC group received 100 mL normal saline (0.9%) without tranexamic acid followed by crystalloid infusion. All bolus tranexamic acid doses were delivered 5 min before knife-to-skin, followed by the continuous infusion protocol.

The primary outcome measure was the amount of intraoperative and postoperative blood loss. Postoperative blood loss was assessed 24 h after surgery and during the removal of the final drain.

Intraoperative blood loss was assessed by a qualified scrub nurse using an electronic scale that can measure down to 0.01 g of weight. The information obtained came from two sources: (1) the weight of blood-soaked gauze and towels after subtracting their dry weight and (2) the total volume of fluids in the suction canisters after subtracting the volume of the irrigation fluids that have been used. Postoperative blood loss was measured by another qualified staff nurse both at the 24-h time point and during the removal of the final drain.

Surgical technique and postoperative regimen

All the operations were performed by a single surgeon with more than 20 years of experience in PLIF. Patients were positioned prone on a Wilson frame for the surgery. A standard midline incision of 10 cm was made followed by paravertebral muscle dissection using monopolar diathermy at 40 Hz to the base of the transverse processes for the insertion of pedicle screws (Perfix; U&I Corporation, Gyeonggi-do, South Korea).

Four pedicle screws were inserted using freehand technique. Their placement was assessed using image intensifier only after all screws have been inserted. Routine bilateral decompression of lateral recesses and both neuroforamina were performed for all patients. This was followed by annulotomy, discectomy, and preparation of endplates. Sentinel bone grafting was performed. Two PEEK cages (Neo IC; U&I Corporation) filled with morcelized, local bone autografts were then inserted into the intervertebral disc space under intervertebral distraction. This was followed by final compression of the intervertebral space using connecting rods on screw heads. Hemostasis was achieved throughout each operation using a combination of bipolar diathermy, oxidized regenerated cellulose (Surgicel; Johnson & Johnson Medical Korea Ltd, Seoul, South Korea), and gelatin sponge (Cutanplast sponge; Mascia Brunelli, Milan, Italy). Layered wound

closure was finally performed after the insertion of two negative-pressure drains into the deep tissues.

Postoperatively, patients were advised to stay in bed until all drains had been removed. The criterion for drain removal was hemoserous discharge of less than 50 mL/day, which occurred either on the third or fourth postoperative day in all our patients. No patient received chemoprophylaxis against VTE during or after surgery. Nonsteroidal anti-inflammatory medications and anticoagulants were discontinued in all patients at least 24 h before surgery and restarted no earlier than the removal of the last drain.

Statistical analysis

Data were collected on Microsoft Excel Spreadsheet 2011 (version 14.0, 32-bit; Microsoft Corp., Redmond, WA, USA) and analyzed using Statistical Package for the Social Sciences (SPSS) (version 23.0; IBM Corp., Armonk, NY, USA). Categorical data were represented as percentages, and continuous data were represented as means with standard deviations. $P < 0.05$ was considered statistically significant based on initial power analysis.

Baseline characteristics comprising patient demographics and laboratory investigations were compared across the three groups using one-way analysis of variance. The differences in outcomes (intraoperative blood loss, postoperative blood loss at 24 h after surgery, blood loss during final drain removal, and overall blood loss) among the LD, HD, and PC groups were compared using the same statistical test. Laboratory investigations obtained before and after surgery were also statistically compared.

Results

This study included 72 patients (35 men and 37 women) with a mean age of 63.3 ± 7.6 years and a mean BMI of 25.3 ± 3.0. There was no statistical difference in baseline parameters among the three groups in terms of age, sex, BMI, or laboratory findings (Table 1). In terms of fusion levels, eight patients had surgery at L3–4, 38 at L4–5, and 26 patients at L5–S1.

The duration of surgery was similar among the three groups ($P = 0.91$). Nevertheless, significant differences in blood loss were found intraoperatively, within 24 h postoperatively, during the removal of the last drain, and overall.

Intraoperatively, blood loss was significantly reduced with tranexamic acid administration ($P = 0.04$). This was predominantly contributed by a difference in blood loss between the LD and HD groups (mean difference, 123 mL; $P < 0.01$) (Table 2).

The 24-h postoperative blood loss was also reduced with tranexamic acid use ($P < 0.01$). This marked decrease in blood loss was found between the PC and LD groups (mean difference, 144 mL; $P = 0.02$). No significant difference in blood loss was found between the LD and HD groups ($P = 0.08$).

Blood loss during the removal of the last drain was also reduced with tranexamic acid use, but did not reach statistical significance ($P = 0.9$). However, statistical difference was found between the PC and HD groups (mean difference, 125 mL; $P = 0.00$) and borderline statistical difference between the LD and HD groups (mean difference, 97 mL; $P = 0.05$) (Table 2).

There were no statistically significant differences between preoperative and 24-h postoperative Hb, Hct, fibrinogen, PT/APTT, AST/ALT, and BUN/Cr values (Table 3). No major complications resulting from surgery were noted in any of the patients. In particular, no patients had dural tear, wound infection, epidural hematoma formation, systemic reaction, liver and renal failure, or cardiopulmonary complications. Furthermore, none of the patients developed symptoms as a result of side effects from tranexamic acid such as a headache, nausea, vomiting, and diarrhea. No patient required blood transfusion during or after surgery.

Two patients in the PC group were found to have subclinical intramuscular deep vein thromboembolism in the lower limbs 1 week postoperatively.

Discussion

Surgery results in a transient activation of the fibrinolysis cascade, which accounts for increased perioperative blood loss [18]. Tranexamic acid prevents fibrinolysis by (1) blocking the lysine-binding site of plasminogen, which binds to fibrin; (2) inhibiting the activation of plasminogen by the plasminogen activator [19], and (3) displacing plasminogen from the fibrin surface [20, 21]. It is, therefore, crucial to administer tranexamic acid in a timely fashion before the activation of the fibrinolysis cascade. As the half-life of tranexamic acid is approximately 80–120 min and the drug reaches peak plasma concentration 5 min after bolus administration and 60 min after commencement of infusion [22], our study was designed to ensure strict administration of tranexamic acid in a controlled manner: bolus injection 5 min before knife-to-skin, followed by a continuous infusion protocol. In addition, to allow simultaneous evaluation of tranexamic acid use as well as its varying dose-dependent effects, this study was designed to enable a 3-way comparison among a placebo-controlled group, a low-dose group, and a high-dose group.

Table 2 Univariate analysis of operative time and perioperative blood loss

	CC	LD	HD	Anova *P* value	CG vs. LD	CG vs. HD	LD vs. HD
Operative time (min)	157 ± 25	159 ± 26	155 ± 26	0.91	0.86	0.80	0.68
Intraoperative blood loss (mL)	542 ± 333	508 ± 269	385 ± 139	0.04	0.74	0.03	0.03
24-h postoperative blood loss (mL)	541 ± 28	397 ± 25	384 ± 33	0.03	0.02	0.04	0.08
Last drain removal blood loss (mL)	274 ± 50	247 ± 49	149 ± 18	0.09	0.09	0.02	0.04
Total blood loss (mL)	1356 ± 516	1151 ± 473	934 ± 293	0.03	0.18	0.02	0.03

All values are displayed as means with standard deviations

CG placebo-controlled group, *LD* low-dose group, *HD* high-dose group

Table 3 Differences in preoperative and 24-h postoperative laboratory results

	CG	LD	HD	Anova *P* value	CG vs. LD	CG vs. HD	LD vs. HD
Hemoglobin (g/dL)	1.7 ± 0.2	1.6 ± 0.5	1.3 ± 0.6	0.66	0.67	0.75	0.87
Hematocrit (%)	5.8 ± 2.3	4.9 ± 3.0	2.3 ± 1.6	0.49	0.27	0.15	0.11
Fibrinogen (mg/dL)	9.8 ± 4.1	14.0 ± 6.9	16.6 ± 7.4	0.67	0.10	0.08	0.13
PT (s)	0.9 ± 1.0	0.2 ± 0.4	0.6 ± 0.3	0.84	0.12	0.24	0.19
APTT (s)	3.2 ± 1.9	3.9 ± 1.6	3.7 ± 1.0	0.29	0.43	0.65	0.57
AST (U/L)	6.1 ± 3.5	5.9 ± 2.2	8.5 ± 3.2	0.32	0.16	0.27	0.31
ALT (U/L)	5.7 ± 2.0	3.5 ± 1.3	2.2 ± 0.6	0.83	0.45	0.58	0.37
BUN (mg/dL)	0.6 ± 0.1	1.6 ± 0.8	1.4 ± 0.4	0.63	0.82	0.74	0.84
Cr (mg/dL)	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.80	0.61	0.70	0.54

All values are displayed as means with standard deviations

CG control group, *LD* low-dose group, *HD* high-dose group, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *AST* aspartate transaminase, *ALT* alanine transaminase, *BUN* blood urea nitrogen, *Cr* creatinine

The effectiveness of tranexamic acid in reducing perioperative blood loss has been shown in numerous randomized, controlled studies [7]. Its superiority over other antifibrinolytics such as aprotinin and epsilon-aminocaproic acid has also been shown in systemic reviews [5]. However, the evidence on optimal doses of tranexamic acid for spine surgeries remains weak owing to the heterogeneity of study cohorts and the lack of strict study protocols evaluating the use of tranexamic acid. Only few studies considered specific spine conditions and surgical procedures [14, 23]. Furthermore, only one study performed a 3-way comparison of placebo and groups with different dose regimens [24]. Many existing studies did not control for the timing of tranexamic acid administration, which was highlighted earlier to be extremely crucial [19]. For a common surgical procedure such as single-level PLIF, extremely high doses of tranexamic acid may not be required for risk/benefit purposes. As such, a protocol of 10 and 5 mg/kg of bolus loading dose and 2 and 1 mg/kg of continuous infusion in the HD and LD groups, respectively, was deemed sufficient, as evaluated in this study.

This study presents a well-randomized cohort with similar baseline parameters among groups. Surgery was performed by a single, blinded, experienced surgeon using a standardized technique. This can also be shown by the comparable operative duration (Table 1). The method of assessing blood loss was robust, as it involves objective intraoperative and postoperative measurements performed by one nurse for patients in all groups. Although measurements could include serous body fluids [25] and are incapable of determining insensible losses [26], they represent the best effort to determine blood loss. As comparisons are made across patients in different groups, this would not have resulted in systematic bias.

Across the three groups, a trend showing a reduction in overall blood loss both intraoperatively and postoperatively with tranexamic acid use could be observed from the PC group, to the LD group, and to the HD group. Overall blood loss was reduced by 15.2 and 31.1% in the LD and HD groups, respectively. In fact, intraoperative blood loss in the HD group was remarkably low, 385 ± 139 mL, such that additional benefits would be unlikely even if the dose of tranexamic acid is further

increased. This represents 157 mL (29%) of blood loss reduction comparing the HD and PC groups ($P = 0.03$) and 123 mL (24.2%) of blood loss reduction comparing the HD and LD groups ($P < 0.01$). Therefore, it is in the authors' opinion that the study's HD regimen of 10 mg/kg of bolus loading dose and 2 mg/kg of continuous infusion is sufficient in minimizing intraoperative blood loss for single-level PLIF. Several studies have proven that higher doses of tranexamic acid (up to 100 mg/kg bolus and 4 mg/kg infusion delivered as long as 12 h) [27, 28] give a greater benefit in terms of blood loss, but they were unable to agree on the ideal dose regimen for specific procedures. Furthermore, those studies are limited by the heterogeneity of their study population and type of surgical procedure.

Postoperative blood loss showed a similar trend, with reduced blood loss observed in the LD (26.6%) and HD (29%) groups. However, stronger significance was found between the LD and PC groups at 24 h after surgery ($P = 0.02$) and between the LD and HD groups during removal of the last drain ($P = 0.05$). The greater ability of tranexamic acid to reduce blood loss when comparing the LD and PC groups at 24 h after surgery could be related to the drug's effectiveness in controlling bleeding via fibrinolysis inhibition, which, at this phase, results from the slow oozing of blood from tissue surfaces [29]. The HD regimen does not seem to confer additional advantage, which may be due to the "ceiling effect" [30]. This is shown by the minimal reduction in blood loss between the LD and HD groups (13 mL; $P = 0.08$).

Beyond 24 h after surgery, tranexamic acid would have been substantially washed out from the blood circulation [31]. This is supported by the lack of significant differences in blood loss reduction between the PC and LD groups ($P = 0.09$). The borderline statistical significance between the LD and HD groups ($P = 0.05$) could be related to residual doses of tranexamic acid in view of higher doses administered or its unknown lingering effects [32]. Future studies should evaluate the clinical effects of tranexamic acid over longer periods.

VTE is a major concern related to the use of tranexamic acid [27]. Despite numerous studies investigating the effects of high-dose tranexamic acid, evidence showing its association with VTE is lacking [7]. Systemic reviews have so far shown more cases of VTE occurring in control groups, suggesting a paradoxical effect of tranexamic acid [33]. In our study, there were two subclinical cases of VTE in the control group, which did not require treatment. This interesting finding should prompt further studies looking specifically at both the possible "protective" and "deleterious" effects of tranexamic acid with regard to VTE. The absence of complications and side effects from tranexamic acid use further supports the use of tranexamic acid at a bolus loading dose of 10 and 2 mg/kg of continuous infusion, per our HD regimen.

This study examines the effectiveness and safety of tranexamic acid in single-level PLIF using a large, well-controlled, single-surgeon series. Although it may be argued that this procedure is a relatively small operation that does not involve much intraoperative blood loss (i.e., only a small margin of benefit could be obtained from the study), the advantage of reducing perioperative blood loss in patients who have lower baseline Hb levels or are physiologically challenged remains promising, as the margin of benefit is magnified. Future studies should continue to evaluate the effects of various tranexamic acid dosages on specific spinal conditions and specific spinal surgeries.

Conclusions

Tranexamic acid was effective in reducing intraoperative and postoperative blood loss in a dose-dependent manner for single-level PLIF. Remarkable results were observed with the HD regimen (10 mg/kg bolus and 2 mg/kg infusion up to 5 h after surgery), but additional benefits are unlikely with higher doses of tranexamic acid. No side effects were observed, suggesting its safety. This study recommends the routine use of tranexamic acid at the aforementioned dosages.

Compliance with ethical standards

Conflict of interest Cheung Kue-Kim, Ki-Tack Kim, Yong-chan Kim, Hyung-Suk Juh, Hyo-jong Kim, Hyeon-Soo Kim, Se jung Hong, and Hwee Weng Dennis Hey declare that they have no conflict of interest.

Ethics approval Ethics approval was obtained from the institutional review board before the commencement of this study. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Funding No funds were received in support of this work.

References

1. Hu SS (2004) Blood loss in adult spinal surgery. Eur Spine J 13:3–5
2. Yuan QM, Zhao ZH, Xu BS (2017) Efficacy and safety of tranexamic acid in reducing blood loss in scoliosis surgery: a systematic review and meta-analysis. Eur Spine J 26(1):131–139. doi:10.1007/s00586-016-4899-0
3. Tsutsumimoto T, Shimogata M, Ohta H et al (2011) Tranexamic acid reduces perioperative blood loss in cervical laminoplasty. Spine (Phila Pa 1976) 36:1913–1918
4. Tse EYW (2011) Reducing perioperative blood loss and allogeneic blood transfusion inpatient undergoing major spine surgery. J Bone Jt Surg Am 93:1268–1277

5. Gill JB, Chin Y, Levin A et al (2008) The use of antifibrinolytic agents in spine surgery: a meta-analysis. J Bone Jt Surg Am 90:2399–2407
6. Sokolowski MJ, Garvey TA, Perl J II et al (2008) Prospective study of postoperative lumbar epidural hematoma: incidence and risk factors. Spine 33:108–113
7. Yang B, Li H, Wang D et al (2013) Systemic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. PLoS One 8(2):e55436
8. Cardone D, Klein AA (2009) Perioperative blood conservation. Eur J Anaesthesiol 26:722–729
9. Farrokhi MR, Kazemi AP, Eftekharian HR et al (2011) Efficacy of prophylactic low dose of tranexamic acid in spinal fixation surgery: a randomized clinical trial. J Neurosurg Anesthesiol 23:290–296
10. Lemaire R (2008) Strategies for blood management in orthopaedic and trauma surgery. J Bone Jt Surg Br 90(9):1128–1136
11. Colomina MJ, Koo M, Basora M et al (2017) Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial. Br J Anaesth 118(3):380–390. doi:10.1093/bja/aew434
12. Cheriyan T, Maier SP, Bianco K et al (2015) Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J 15(4):752–761
13. Neilipovitz DT, Murto K, Hall L et al (2001) A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. Anesth Analg 93:82–87
14. 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 107:1479–1496
15. Raksakietisak M, Sathitkarnmanee B, Srisaen P et al (2015) Two doses of tranexamic acid reduce blood transfusion in complex spine surgery. Spine 40:E1257–E1263
16. Pilbrant A, Schannong M, Vessman J (1981) Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol 20(1):65–72
17. Sethna NF, Zurakowski D, Brustowicz RM et al (2005) Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. Anesthesiology 102:727–732
18. Benoni G, Fredin HA (1996) Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomized, double-blind study of 86 patients. J Bone Jt Surg Br 78(3):434–440
19. 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 Jt Surg Br 83(5):702–705
20. Shi H, Ou Y, Jiang D, Quan Z et al (2017) Tranexamic acid reduces perioperative blood loss of posterior lumbar surgery for stenosis or spondylolisthesis: a randomized trial. Medicine (Baltimore) 96(1):e5718. doi:10.1097/MD.0000000000005718
21. Mannucci PM (1998) Hemostatic drugs. N Engl J Med 339:245–253
22. Li ZJ, Fu X, Xing D et al (2013) Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. Eur Spine J 22:1950–1957
23. Elwatody S, Jamjoom Z, Elgamal E et al (2008) Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery. Spine 33(24):2577–2580
24. Wang Q, Liu J, Fan R et al (2013) Tranexamic acid reduces postoperative blood loss of degenerative lumbar instability with stenosis in posterior approach lumbar surgery: a randomized controlled trial. Eur Spine J 22:2035–2038
25. Holte K, Kehlet H (2002) Compensatory fluid administration for preoperative dehydration—does it improve outcome? Acta Anaesthesiol Scand 46(9):1089–1093
26. Perel P, Roberts I (2007) Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 4:CD000567
27. Porte RJ, Leebeek FW (2002) Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. Drugs 62:2193–2211
28. Neilipovitz DT (2004) Tranexamic acid for major spinal surgery, review article. Eur Spine J 139(suppl 1):S62–S65
29. Abou Diwan C, Sniecinski RM, Szlam F et al (2011) Plasma and cerebral spinal fluid tranexamic acid quantitation in cardiopulmonary bypass patients. J Chromatogr B Analyt Technol Biomed Life Sci 879(78):533–536
30. Yamasaki S, Masuhara K, Fuji T (2001) Tranexamic acid reduces postoperative blood loss in cement less total hip arthroplasty. J Bone Jt Surg Am 87(4):766–770
31. Huang Cheng YML (2011) Tranexamic acid for the elderly with multi segmental spinal stenosis perioperative blood loss and the safety assessment of the impact. Chin J Postgrad Med 10:17–22
32. Ker K, Prieto-Merino D, Roberts I (2013) Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. Br J Surg 100:1271–1279
33. Zufferey P, Merquiol F, Laporte S et al (2006) Do antifibrinolytics reduce allogeneic blood transfusion in orthopaedic surgery? Anesthesiology 105:1034–1046