Tranexamic Acid Reduces Perioperative Blood Loss in Adult Patients Having Spinal Fusion Surgery

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BACKGROUND: Spinal reconstructive surgery in adults can be associated with significant blood loss, often requiring allogeneic blood transfusion. The objective of this randomized, prospective, double-blind, multicenter study was to evaluate the efficacy of tranexamic acid (TXA) in reducing perioperative blood loss and transfusion in adult patients having elective posterior thoracic/lumbar instrumented spinal fusion surgery.

METHODS: One hundred fifty-one adult patients were randomized to receive either a bolus of 10 mg/kg IV of TXA after induction followed by a maintenance infusion of 1 mg/kg/hr of TXA, or an equivalent volume of placebo (normal saline). The primary outcome was the total perioperative estimated and calculated blood loss intraoperatively and 24 h postoperatively. Secondary outcomes were incidence of allogeneic blood exposure, and duration of hospital stay.

RESULTS: Four patients were withdrawn for identifiable surgical bleeding, therefore 147 patients were included in the analysis. The total estimated and calculated perioperative blood loss was approximately 25% and 30% lower in patients given TXA versus placebo (1592 ± 1315 mL vs 2138 ± 1607 mL, $P = 0.026$; 3079 ± 2558 vs 4363 ± 3030, $P = 0.017$), respectively. There was no difference in the amounts of blood products transfused, and length of stay between the two groups. TXA, surgical duration, and number of vertebrae fused were independent factors related to perioperative blood loss. Predictors for the need for allogeneic red blood cell transfusion were ASA classification, surgical duration and number of levels fused.

CONCLUSIONS: TXA significantly reduced the estimated and calculated total amount of perioperative blood loss in adult patients having elective posterior thoracic/lumbar instrumented spinal fusion surgery.

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Spinal reconstructive surgery in adults may be associated with significant perioperative blood loss often requiring allogeneic blood transfusion.[1–3] Despite current blood-conservation interventions, many patients still require blood transfusion with the associated risks and costs. Concern about the risks of transmission of infectious diseases, increased postoperative infection,[4] and immune modulation effects[5] of allogeneic blood have led to the investigation of various antifibrinolytic drugs for reducing bleeding during major spine surgery.

Tranexamic acid (TXA) is a synthetic antifibrinolytic drug that prevents the breakdown of fibrin, thereby stabilizing blood clots and reducing blood loss in conditions that promote fibrinolysis. In the pediatric population, two prospective studies found that TXA reduced perioperative blood loss,[6] and reduced the total amount of blood transfused in patients having scoliosis surgery.[7] However, the blood-conservation effect is still uncertain in adult spine surgery.[8–10]

Therefore, the objective of this prospective, randomized, double-blind, placebo controlled multicenter study was to evaluate the effect of TXA on perioperative blood loss and transfusion of blood products in adult patients undergoing posterior thoracic or lumbar instrumented spinal fusion surgery.

METHODS

After obtaining Research Ethics Board approval from the three participating centers in Toronto, Canada (University Health Network, St. Michael's Hospital, and Trillium Health Center), informed consent was obtained from all participants. One hundred fifty-one adult patients (age ≥18 yr) undergoing elective posterior thoracic/lumbar instrumented spinal fusions were enrolled in the study. Exclusion criteria were patients with a history of allergy to TXA, acquired disturbances of color vision, spine tumor, intradural pathology, ankylosing spondylitis, preoperative anemia, i.e., hemoglobin

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<11 g/dL in females; hemoglobin <12 g/dL in males, refusal of blood products i.e., Jehovah's witnesses, coagulopathy, preoperative anticoagulant therapy, fibrinolytic disorders requiring intraoperative antifibrinolytic treatment, preoperative platelet count <150,000/mm^3, International Normalized Ratio (INR) >1.4, prolonged partial thromboplastin time (PTT) (>1.4 × normal), a history of thromboembolic disease, pregnancy, significant co-morbidities i.e., severe ischemic heart disease New York Heart Association Class III–IV, previous myocardial infarct (MI), severe pulmonary disease, i.e., forced expiratory volume in 1 min <50% normal, chronic renal failure, hepatic failure. If intraoperative surgical complications such as uncontrollable surgical bleeding from broken vertebral laminae, or dural tears, etc. occurred, the patients were excluded from the study.

By protocol at the participating institutions, preoperative erythropoietin 40,000 to 80,000 IU was offered to all patients with a hemoglobin <13 g/dL and autologous blood donation of 2 U was allowed 2 to 3 weeks before the proposed surgery. Patients who were receiving preoperative acetylsalicylic acid, antiplatelet drugs, or nonselective cyclooxgenase inhibitors were advised to discontinue these medications 7 to 14 d before the scheduled surgery.

Patients were randomized to receive either TXA or placebo (normal saline). To account for different surgical practices (case mix and surgical techniques) of each spine surgeon, a stratified randomization for surgeon was used. In addition, as the number of levels fused is a factor influencing blood loss, a stratified randomization for the number of levels of vertebrae fused (1–2 levels, 3–5 levels, >5 levels) was used. Random numbers were computer-generated and the randomization schedule was kept inaccessible throughout the study period. Patient assignments were placed into sequentially numbered opaque sealed envelopes. A research pharmacist, not involved with care of the patient, prepared the placebo and treatment medications that were identical in appearance. The research personnel, anesthesiologists, surgeons, and operating room staff were blinded to the randomization.

Patients in the TXA group received a bolus of 10 mg/kg IV of TXA after anesthetic induction before the surgical incision. A maintenance infusion of 1 mg/kg/hr of TXA was continued until skin closure. Patients in the control group were given a bolus of an equivalent volume of placebo (normal saline) and a maintenance placebo infusion until skin closure.

In addition to standard monitoring, an arterial line and/or central venous catheter were inserted as indicated. All patients had a standard general anesthetic consisting of propofol; an opioid i.e., fentanyl, remifentanil or morphine; rocuronium; and a volatile anesthetic, i.e., sevoflurane or desflurane with or without nitrous oxide. Minute ventilation was titrated to maintain normocarbia. Mild induced hypotension, i.e., mean arterial blood pressure (MAP) ~20% below preoperative MAP was induced with the volatile anesthetic or remifentanil for a minimum MAP of 65 mm Hg until spinal manipulation, at which time the MAP was returned to the baseline pressure, or at any time requested by the surgeon.

All patients were positioned prone on a Jackson table with the abdomen free. A forced-air warming blanket was used to maintain normothermia and the esophageal temperature was monitored in all patients.

The Cell-saver (Cobe Brat 2, Cobe Cardiovascular, CO) was used when requested by the surgeon and scavenged red blood cells (RBCs) were returned to the patient. The cell saver equipment used in this study processes suctioned blood from the surgical field when the latter reaches a certain threshold volume, i.e., ~ 800 mL given that the preoperative hemoglobin of the patient was within normal limits. Therefore, not every patient in whom the cell saver was used may have been given scavenged RBCs. Maintenance fluid requirements and third-space losses were replaced with balanced crystalloid solutions and pentastarch (Pentaspan, Bristol-Myers Squibb, Montreal, Canada), maximum of 25 mL/kg/24 h.

Intraoperative blood loss was measured by adding the volume of blood in the suction bottles, the cell saver and the weight of sponges. All fluids added to the surgical field intraoperatively were quantified and deducted from the measured blood loss. Postoperative blood loss was measured from wound drainage of the surgical drain for the first 24 h. The calculated blood loss was determined using the formulas from Mercuriali and Inghilleri.[11] The guidelines for transfusion of packed RBCs was to give 1 U at a time to maintain a hemoglobin concentration >7 g/dL, or at a higher hemoglobin concentration if continuing blood loss was occurring or signs or symptoms of anemia developed.[12] The criteria for transfusing fresh frozen plasma (FFP) was INR>1.5, or PTT ≥1.5 × normal baseline with continuing bleeding.[12] The criteria for transfusing platelets (5 U at a time) were a platelet count <50,000/mm^3, with continuing bleeding.[12] If the anesthesiologist/surgeon considered it clinically unsafe to withhold transfusion of RBC, FFP or platelets before laboratory confirmation of anemia, coagulopathy, or thrombocytopenia, blood products were given.

The primary outcome was the total estimated and calculated perioperative blood loss occurring intraoperatively and 24 h postoperatively. Secondary outcomes were the incidence of allogeneic blood exposure, including RBCs, and coagulation components i.e., FFP, and platelets administered during the hospitalization, lowest hemoglobin concentration, and duration of hospital stay.

Patients were assessed daily for any clinical symptoms of deep vein thrombosis (DVT) and if suspected, venous Doppler ultrasonography was performed to confirm the diagnosis. All patients at one center received postoperative DVT prophylaxis with Tinzaparin on the evening after the day of surgery as per

Table 1. Demographics and Baseline Characteristics

	Tranexamic acid ($n = 73$)	Placebo ($n = 74$)	*P*
Age (yr)	56.8 ± 16.2	50.0 ± 16.2	0.011
Gender (female/male)	52/21	48/26	0.408
Height (cm)	162.3 ± 12.5	165.2 ± 10.2	0.132
Weight (kg)	72.9 ± 17.2	73.9 ± 16.1	0.717
ASA status: I/II/III	5/43/24	14/35/24	0.166
No. (%) of patients with osteotomy	13 of 73 (17%)	17 of 74 (22%)	0.437
No. (%) of patients with revision	19 of 73 (26%)	24 of 74 (32%)	0.393
No. of levels	4.7 ± 4.6	4.8 ± 4.3	0.910
Level groups: I/II/III	35/17/21	32/19/23	0.848
No. (%) of patients predonated	39 of 73 (53%)	45 of 74 (60%)	0.366
No. of units predonated	1.0 ± 0.9	1.1 ± 0.9	0.499
No. (%) of patients given erythropoietin	20 of 73 (27%)	25 of 74 (33%)	0.401
Amount of erythropoietin given (IU)	64760 ± 34000	79130 ± 36420	0.185

Values are presented as mean ± SD (standard deviation) or proportion (%). Distribution of the number of patients among the 3 centers: Toronto Western Hospital: 107 St. Michaels's Hospital: 17, Trillium Health Center: 23.

standard practice at that institution. The incidence of thromboembolic events was tracked for 3 months after surgery by contacting patients.

The albumin, ionized calcium, fibrinogen, D-dimers, PTT, prothrombin time (PT), and INR were measured preoperatively and on postoperative day one. Hemoglobin was measured preoperatively, and at multiple times postoperatively (day 1–3).

Statistical Analysis

Demographics, laboratory variables, blood loss, transfusion requirements, rate of complications, and the length of hospital stay were compared between the TXA and placebo groups with the two-sample Student's *t*-test for mean values and the Pearson χ^2 test for proportions. For each laboratory test, percentage of change from the preoperative value was calculated using the formula: %change = (postoperative value-preoperative value/preoperative value) × 100 as shown in Table 3. The independent two-sample Student's *t*-test was used to compare the preoperative and postoperative laboratory tests and the percentage of change between the placebo and TXA group. Continuous variables were expressed as mean ± SD. The number of patients receiving blood transfusion was reported as proportion and percentage. A per-protocol analysis was used to compare the two groups. Two-sided tests were used to determine the *P* value. A *P* value <0.05 indicated statistical significance.

Multiple linear regression analysis was performed to elucidate predictors of the perioperative blood loss. Logistic linear regression was also used to identify independent variables related to the need for allogeneic RBC transfusion. The independent variables included in the analyses were demographic characteristics (age, gender, body weight, ASA classification, number of levels fused, revision surgery), preoperative factors (INR, PTT, hemoglobin, ionized calcium, fibrinogen) and intraoperative factors (treatment with TXA, spinal osteotomy, surgical duration). All statistical analyses were performed with SPSS statistical software (version 14.0, SPSS, Chicago, IL). A *P* value <0.05 indicated statistical significance.

The sample size calculation for this trial was based on a previous study in our institution* where the mean blood loss for 154 patients having spinal fusion was 1713 ± 1680 mL. Hence, the total sample size required to demonstrate a 30% reduction in perioperative blood loss, i.e., ~500 mL in the treatment group is 150 patients assuming a type I [*alpha*] error of 0.05 (two-tailed) and a statistical power of 0.8.

RESULTS

One hundred fifty-one patients were recruited from three hospitals. All patients had thoracic, thoracolumbar or lumbar spinal decompression and instrumented fusion. Four patients (3 females and 1 male) were subsequently withdrawn due to excessive and initially uncontrollable surgical bleeding from broken vertebral laminae, dural tears or severe sinusoidal epidural bleeding. Therefore, 147 patients, 100 females and 47 males, aged 18 to 82 years, were included in the study. Seventy-three patients were enrolled in the TXA group and 74 patients in the placebo group. Patients in the placebo group were slightly younger than the TXA group patients, otherwise, patient demographics, intraoperative characteristics, number of fused vertebral levels, frequency of revision surgery and incidence of spinal osteotomies did not differ between the groups (Table 1). There was no difference in the MAC equivalents administered and doses of propofol, IV narcotics or muscle relaxants between the two groups. The extent and duration of induced hypotension were similar in both groups (Table 2).

The amount of estimated and calculated perioperative blood loss was significantly less in the TXA versus placebo group 1592 ± 1315 mL vs 2138 ± 1607 mL, $P = 0.026$; 3079 ± 2558 vs 4363 ± 3030, $P = 0.017$, respectively. The total perioperative blood loss was

*Karkouti K, Rampersaud YR, McCluskey S, Evans L, Ghannam MM, Mahomed NN. Blood conservation in elective spine surgery. Can J Anaesth 2002;49:A12.

Table 2. Perioperative Outcomes

	Tranexamic acid (n = 73)	Placebo (n = 74)	P
Surgery time (min)	276.9 ± 115.3	278.2 ± 111.8	0.943
Intraoperative lowest MAP (mm Hg)	64.0 ± 8.5	63.4 ± 10.2	0.755
Duration of intraoperative hypotension (min)	136 ± 61	129 ± 74	0.563
Intraoperative lowest temperature (°C)	34.6 ± 1.1	34.3 ± 1.3	0.209
End of surgery temperature (°C)	35.6 ± 0.9	35.4 ± 1.2	0.464
Length of hospital stay (d)	9.19 ± 5.48	8.47 ± 4.12	0.378
Crystalloid (mL)	4219 ± 1686	4758 ± 1967	0.131
Pentaspan (mL)	707 ± 251	777 ± 298	0.314
No. of patients with cell saver collected (%)	65 of 73 (89%)	66 of 74 (89%)	0.980
Perioperative EBL (mL)	1592 ± 1315	2138 ± 1607	0.026
Calculated perioperative blood loss (mL)	3079 ± 2558	4363 ± 3030	0.017
Calculated perioperative RBC loss (mL)	1078 ± 895	1527 ± 1060	0.017
Intraoperative EBL (mL)	1203 ± 1060	1600 ± 1301	0.044
Postoperative EBL (mL)	536 ± 471	737 ± 524	0.039
Perioperative blood transfusion			
No. (%) of patients given pRBC	23 of 73 (31%)	30 of 74 (40%)	0.254
Total amount of pRBC transfused	266 ± 541	406 ± 649	0.159
No. (%) of patients given AWB	24 of 73 (32%)	27 of 74 (36%)	0.646
Total amount of AWB transfused	222 ± 343	315 ± 672	0.296
No. (%) of patients given cell saver blood	33 of 73 (45%)	47 of 74 (63%)	0.026
Total amount of cell saver blood transfused	218 ± 347	334 ± 450	0.083
No. (%) of patients given FFP	5 of 73 (7%)	9 of 74 (12%)	0.273
No. (%) of patients given platelets	2 of 73 (3%)	2 of 74 (3%)	0.989
Intraoperative blood transfusion			
No. (%) of patients given pRBC	14 of 73 (19%)	17 of 74 (23%)	0.573
Total amount of pRBC transfused	169 ± 486	208 ± 436	0.614
No. (%) of patients given AWB	18 of 73 (25%)	21 of 74 (28%)	0.609
Total amount of AWB transfused	150 ± 278	249 ± 656	0.239
No. (%) of patients given cell saver blood	33 of 73 (45%)	46 of 74 (62%)	0.039
Total amount of cell saver blood transfused	210 ± 343	323 ± 443	0.086
No. (%) of patients given FFP	4 of 73 (5%)	7 of 74 (9%)	0.359
No. (%) of patients given platelets	2 of 73 (3%)	2 of 74 (3%)	0.989
Postoperative blood transfusion			
No. (%) of patients given pRBC	11 of 73 (15%)	21 of 74 (28%)	**0.**051
Total amount of pRBC transfused	97 ± 239	198 ± 384	0.057
No. (%) of patients given AWB	10 of 73 (13%)	10 of 74 (13%)	0.974
Total amount of AWB transfused	72 ± 200	66 ± 198.2	0.854
No. (%) of patients given cell saver blood	2 of 73 (3%)	3 of 74 (4%)	0.660
Total amount of cell saver blood transfused	8 ± 49	11 ± 64	0.731
No. (%) of patients given FFP			
No. (%) of patients given platelets	0	0	NA

Values are mean ± SD or proportion (%).

MAP = mean arterial blood pressure; EBL= estimated blood loss; AWB = autologous whole blood; pRBC = packed red blood cells; FFP = fresh frozen plasma.

approximately 25% to 30% less in patients given TXA compared to those receiving placebo (Table 2). The incidence of blood product transfusion during the perioperative period did not differ between the TXA and placebo groups (Table 2). However, there was a trend towards less frequent and smaller amounts of RBC transfusion in the TXA compared to placebo group (Table 2). The incidence of cell saver use was similar between the two groups (Table 2). However, the frequency of transfusion of cell saver blood and the amount of transfused cell saver blood was significantly less in the TXA group during surgery (Table 2). In addition, the TXA group had a higher postoperative hemoglobin compared with the placebo group (Table 3).

Preoperative hematological and coagulation profiles were also comparable between the two groups (Table 3). Postoperative fibrinolysis, as assessed by the intergroup comparison of D-dimer levels, was significantly increased in both groups. However, TXA therapy attenuated the increase in postoperative fibrinolytic activity (Table 3). The postoperative coagulation profile for patients, including PT, INR and platelet counts as well as fibrinogen levels, were similar between the TXA and placebo group and were not significantly different from preoperative values (Table 3). There was a significant reduction in serum albumin after surgery in both study groups compared with baseline but the reduction was significantly larger in the placebo group (Table 3).

The length of hospital stay was similar between the TXA and the placebo group (Table 2). There were two patients with postoperative medical complications, one in each group. In the TXA group, one patient developed an asymptomatic non-Q MI 6 days after surgery

Table 3. Hematological and Coagulation Test Results

Lab tests	Tranexamic acid ($n = 73$)	Placebo ($n = 74$)	P
Hgb (g/dL)			
Preoperative	13.5 ± 1.5	13.5 ± 1.6	0.879
Postoperative (lowest)	9.4 ± 1.4	8.9 ± 1.3	0.033
% of change (↓)	31.1 ± 14.2	34.5 ± 13.7	0.154
Fibrinogen (g/L)			
Preoperative	2.8 ± 0.78	2.7 ± 0.62	0.292
Postoperative	3.1 ± 1.2	3.3 ± 1.3	0.605
% of change (↑)	4.6 ± 64.3	11.6 ± 58.4	0.502
d-dimer (μg/mL)			
Preoperative	0.56 ± 0.63	0.68 ± 0.93	0.368
Postoperative	1.5 ± 1.1	1.9 ± 1.4	0.043
% of change (↑)	251.2 ± 419.5	388.1 ± 595.3	0.117
PT (s)			
Preoperative	14.0 ± 1.4	14.3 ± 2.1	0.387
Postoperative	16.0 ± 1.8	16.2 ± 1.8	0.445
% of change (↑)	11.9 ± 9.4	12.5 ± 16.30	0.782
INR (s)			
Preoperative	1.0 ± 0.1	1.0 ± 0.1	0.831
Postoperative	1.2 ± 0.2	1.2 ± 0.2	0.530
% of change (↑)	19.0 ± 22.5	21.8 ± 18.8	0.437
PTT (s)			
Preoperative	34.4 ± 4.5	35.5 ± 5.2	0.177
Postoperative	34.4 ± 5.2	36.6 ± 6.8	0.034
% of change (↑)	0.4 ± 13.5	3.5 ± 14.9	0.193
Ionized Ca^{2+} (mmol/L)			
Preoperative	1.1 ± 0.05	1.1 ± 0.06	0.779
Postoperative	0.99 ± 0.14	1.0 ± 0.10	0.063
% of change (↓)	11.3 ± 12.4	6.1 ± 9.6	0.014
Serum albumin (g/L)			
Preoperative	31.9 ± 4.1	32.7 ± 3.7	0.206
Postoperative	27.3 ± 4.1	24.7 ± 4.5	0.001
% of change (↓)	12.1 ± 19.1	24.1±14.2	0.000

Values are mean± standard deviation.

(↓) = decrease; (↑) = increase; Independent-sample Student's t test (two-sided) was used for analyzing the data.

Hgb = hemoglobin; PT = prothrombin time; INR = International Normalized Ratio; PH = partial thromboplastin time.

diagnosed by increased cardiac enzymes. The patient completely recovered and was discharged home. One patient in the placebo group who had received preoperative erythropoietin had a DVT despite DVT prophylaxis that was confirmed with Doppler ultrasonography. Both patients were included in the analysis.

Multiple linear regression analysis was performed to identify the independent factors that are linearly related to the extent of perioperative blood loss in all patients included in the study. Factors that were not significantly related to perioperative blood loss were: age, gender, weight, ASA classification, revision of fusion, preoperative PT, INR, PTT, preoperative hemoglobin, preoperative fibrinogen, preoperative erythropoietin administration, preoperative autologous blood donation and spinal osteotomy. The regression was a good fit (R^2 adjusted = 0.6) and the overall relationship was significant ($P < 0.0005$). This indicates that the model can explain 60% of the variance in the total perioperative blood loss. The model is only 60% predictive because of the presence of other factors that were not measured in this study, i.e., osteoporosis and bony abnormalities. According to the regression model prediction, the administration of TXA compared to placebo decreased the estimated perioperative blood loss by 580 mL as indicated by the unstandardized regression coefficient for the TXA treatment variable (Table 4). Additionally, with other variables held constant, the perioperative blood loss was positively related to the surgical duration in minutes, and increasing number of vertebrae fused (Table 4).

The logistic regression model predicted that the shorter the surgery, the lower the number of levels fused and the lower ASA classification, the less likely it is that a patient will need allogeneic RBC transfusion (Table 5). However, the odds of a patient treated with

Table 4. Results of Multiple Linear Regression Analysis for Factors Significantly Related to Amount of Perioperative Blood Loss in mL ($n = 131$)[a]

Variables	Unstandardized coefficients (B)	se	Standardized coefficients (β)	95% CI for B	t	P
Intercept	−691.5	1079.50				
Tranexamic acid treatment[b]	−580.13	186.39	−0.193	−949.29 to −210.97	3.11	0.002
Surgical duration (min)	5.94	0.89	0.45	4.18 to 7.71	6.67	0.0005
Number of levels fused[c]						
1–2 levels vs >5 levels	−1440.63	258.70	−0.48	−1953.03 to −928.23	5.57	0.0005
3–5 levels vs >5 levels	−1042.98	274.70	−0.30	−1587.07 to −498.90	3.80	0.0005

B is the regression coefficient, i.e., the weight by which the independent factor affects the dependent variable.

β is a partial correlation coefficient, i.e., a measure of the relationship between an independent variable and a dependent variable with the influence of the other independent variables held constant. $\beta = B \times$ [SD of independent variable/SD of dependent variable].

t-value indicates the statistical significance of the B coefficient. $t = B$/standard error (se).

Intercept is the predicted value of the dependent variable when each of the independent variables are equal to zero.

SE is the standard error of B or the intercept.

[a] Factors that were not significantly related to perioperative blood loss are not shown in the table. These factors were: age, gender, weight, ASA classification, revision of fusion, preoperative prothrombin time (PT), International Normalized Ratio (INR), prolonged partial thromboplastin time (PTT), preoperative hemoglobin, preoperative fibrinogen, preoperative erythropoietin administration, preoperative autologous blood donation and spinal osteotomy.

[b] Indicates a binary variable coded into tranexamic acid treatment = 1 and placebo treatment = 0. The placebo group was considered the reference group.

[c] The number of levels fused was considered a categorical variable coded into 3 categories (1–2 levels fused, 3–5 levels fused and >5 levels fused). The >5 levels fused category was considered the reference group during the analysis process.

Table 5. Results of Logistic Regression Analysis for Predictors of the Need for Perioperative Allogeneic Packed Red Blood Cell Transfusion ($n = 131$)[a]

Variables	Coefficients (B)	se	P	Odds ratio	95% CI for odds ratio
Tranexamic acid treatment[b]	−0.847	0.468	0.068	0.429	0.171–1.065
Surgical duration (min)	0.005	0.003	0.039	1.005	1–1.010
Number of levels fused[c]					
1–2 levels vs >5 levels	−1.78	0.630	0.005	0.169	0.049–0.580
3–5 levels vs >5 levels	1.836	0.693	0.008	0.159	0.041–0.620
ASA I vs ASA III[d]	−2.52	1.201	0.036	0.08	0.008–0.846
Constant[e]	1.033	2.683	0.700	2.810	

B is the regression coefficient for a independent variable that indicates how one unit change in the independent variable changes the natural logarithm of the odds ratio of the outcome, i.e., dependent variable.

se is the standard error of *B* or the constant.

[a] Other factors that were not significantly related to the amount of perioperative blood transfusion are not shown in the table. These factors were: age, gender, weight, ASA II, revision of fusion, preoperative International Normalized Ratio (INR), preoperative prolonged partial thromboplastin time (PTT), preoperative hemoglobin, preoperative fibrinogen, preoperative erythropoietin administration, preoperative autologous blood donation and spinal osteotomy.

[b] Indicates a binary variable coded into tranexamic acid treatment = 1 and placebo treatment = 0. The placebo group was considered the reference group. This factor is not statistically significant but kept in the table for comparison with Table 4.

[c] Indicates the number of levels fused coded as a categorical variable into 3 categories (1–2 levels fused, 3–5 levels fused and >5 levels fused). The 3–5 levels fused category was considered as the reference group during the analysis process.

[d] ASA classification was considered a categorical variable that included only three categories (ASA I, ASA II, ASA III). The ASA III category was considered the reference group during the analysis process. It is noted that none of the patients were ASA IV.

[e] Indicates the constant of the logistic regression equation. Because it was not statistically significant, it can be omitted from the equation.

TXA to receive allogeneic blood transfusion were not different from a patient treated with placebo ($P = 0.068$; Table 5). The factors that were not significantly related to the need for perioperative blood transfusion were: age, gender, weight, ASA II, revision of fusion, preoperative INR, preoperative PTT, preoperative hemoglobin, preoperative fibrinogen, preoperative erythropoietin administration, preoperative autologous blood donation and spinal osteotomy.

DISCUSSION

In this study, the administration of TXA significantly reduced the total perioperative blood loss in adult patients having elective posterior thoracic/lumbar instrumented spinal fusion surgery. The total estimated and calculated perioperative blood loss was approximately 25% and 30% less in patients given TXA compared to those receiving placebo with a mean difference of approximately 500 or 1200 mL, respectively. The administration of TXA did not reduce the incidence of allogeneic blood products transfused; nonetheless, there was a trend towards reduced amount of RBC transfusion in the TXA group. The patients in the TXA group also had higher postoperative hemoglobin levels than the placebo group.

Our findings of reduced blood loss, but not transfusion requirements, are consistent with a previous randomized trial in pediatric patients having scoliosis surgery.[6] The dose of TXA used in the current study was the dose recommended for noncardiac surgery.[13] This dose is consistent with another study of pediatric patients having scoliosis surgery[7] and similar to a study in 22 adult patients having spine surgery.[10] The optimal dose regimen in adult patients having spine surgery has not been determined in randomized controlled trials.[8] The dose of TXA used in Sethna et al.'s study of pediatric patients was much larger compared with our study, i.e., 100 mg/kg bolus, followed by an infusion of 10 mg/kg/h. We used the lower dose because our patient population included adult patients who may have had a higher incidence of associated co-morbid medical conditions placing them at increased risk of adverse effects of TXA. Future dose-ranging studies are necessary to determine the dose-dependent effects of TXA in spine surgery.

Recently, concern about the safety of the perioperative use of antifibrinolytic drugs, has been raised[14–15] particularly since the Food and Drug Administration requested the manufacturer of aprotinin (Trasylol®) to suspend marketing of aprotinin in early November 2007 based on results from the interim analyses of the BART study (Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population). There are insufficient data to evaluate the safety of TXA for spine surgery, as previous studies are small. However, a recent meta-analysis of 18 trials of TXA versus placebo in cardiac surgery[16] and a Cochrane review[17] did not find an increase in mortality, stroke or MI. In our study, one patient in the TXA group developed an asymptomatic non-Q MI 6 d after surgery.

The etiology of perioperative bleeding during spine reconstructive surgery is multifactorial.[18–19] The exposed bony surfaces are not amenable to standard hemostatic maneuvers used during soft tissue surgery and bleeding can continue after the wound is closed.[2,3] TXA can decrease this type of bleeding by attenuating the enhanced fibrinolytic activity that has been shown to occur in major spine surgery.[20] We found that TXA did attenuate the increase in D-dimers compared to placebo, indicating the presence of an antifibrinolytic effect. The mechanism of such as antifibrinolytic effect of TXA is mediated by the blockade of lysine binding sites on plasminogen molecules, thereby inhibiting the

interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Thus plasmin is unable to bind to and degrade fibrin, leading to a decrease in clot dissolution as well as an increase in thrombus formation and thrombus weight.[21]

Other blood-conservation interventions (cell saver, preoperative erythropoietin, preoperative autologous donation, acute normovolumic hemodilution) are important components of the multimodal blood-conservation strategies used to reduce perioperative bleeding and possibly blood transfusion. However, these interventions do not reduce the amount of blood shed from the surgical wound. A disadvantage of these approaches is the use of substantial amounts of crystalloids, colloids and salvaged or autologous blood to replace excessive bleeding. Our results showed a larger reduction in the serum albumin concentration in the placebo compared with the TXA group, suggesting the occurrence of more blood loss and greater fluid replacement to maintain intravascular volume in the placebo group. This may lead to a dilutional coagulopathy[22] as well as acute anemia which, by itself, can produce platelet dysfunction manifested by an increase in bleeding time.[23]

Our results are consistent with previous reports indicating that surgical duration,[24–26] and number of levels decompressed were independent factors in predicting larger amounts of intraoperative blood loss; and higher ASA classification was an independent factor for blood transfusion during posterior spinal instrumented fusion.[1,27–29] In contrast to previous studies,[1,25] we did not find preoperative hemoglobin concentration, or age[26,28] to be an independent predictor of either perioperative blood loss or the need for blood transfusion. The reason for this contrast may be that patients with preoperative anemia were excluded from our study though they were included in the previously published reports.[25]

One of the limitations of this study is that it is not powered to examine the assumption that TXA can decrease the amount or incidence of RBC transfusion. This will require a multicenter trial with a larger sample size. Our goal was to demonstrate the efficacy of the pharmacodynamic action of TXA on reducing perioperative blood loss. Nevertheless, we noted a trend toward less allogeneic RBC transfusion during the perioperative period in the TXA group, and a higher postoperative hemoglobin in the treatment group. This study was a single-dose randomized, controlled trial and was not designed to show dose-dependent efficacy of TXA.

In conclusion, the administration of TXA reduced the total estimated and calculated perioperative blood loss by approximately 25% and 30%, respectively, in patients given TXA versus those given placebo. However, there was no difference in the amount of perioperative blood products transfused. Large comparative trials are needed to further assess the relative efficacy and safety of TXA for spinal fusion surgery and dose-response studies should be performed.

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