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Clinical Investigation

CLINICAL INVESTIGATION

Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial

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Abstract

Background. Perioperative tranexamic acid (TXA) use can reduce bleeding and transfusion requirements in several types of surgery, but level I evidence proving its effectiveness in major spine surgery is lacking. This study was designed to investigate the hypothesis that TXA reduces perioperative blood loss and transfusion requirements in patients undergoing major spine procedures.

Methods. We conducted a multicentre, prospective, randomized double-blind clinical trial, comparing TXA with placebo in posterior instrumented spine surgery. Efficacy was determined based on the total number of blood units transfused and the perioperative blood loss. Other variables such as the characteristics of surgery, length of hospital stay, and complications were also analysed.

Results. Ninety-five patients undergoing posterior instrumented spine surgery (fusion of >3 segments) were enrolled and randomized: 44 received TXA (TXA group) and 51 received placebo (controls). The groups were comparable for duration of surgery, number of levels fused, and length of hospitalization. Transfusion was not required in 48% of subjects receiving TXA compared with 33% of controls ($P = 0.05$). Mean number of blood units transfused was 0.85 in the TXA group and 1.42 with placebo ($P = 0.06$). TXA resulted in a significant decrease in intraoperative bleeding ($P = 0.01$) and total bleeding ($P = 0.01$) relative to placebo. The incidence of adverse events was similar in the two groups.

Conclusions. TXA did not significantly reduce transfusion requirements, but significantly reduced perioperative blood loss in adults undergoing major spinal surgery.

Clinical trial registration. NCT01136590.

Key words: tranexamic acid; ~~major spine surgery; multicentre randomized control trial; blood loss; transfusion requirements~~

Major surgery of the spine is associated with considerable blood loss during the perioperative period, making transfusion a frequent requirement.[1] Because of an increasing awareness of the risks associated with this practice (e.g. infection, immunomodulation, graft-host rejection), it has become a priority to reduce the number of transfusions. Thus, various strategies have been developed to help maintain red blood cell mass, as encompassed within the concept *patient blood management*.[2 3]

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Editor's key points

- Intraoperative tranexamic acid reduces blood loss and transfusion in certain conditions, but its efficacy in major spine surgery is unclear.
- In a multicentre study in Spain, subjects treated with intraoperative tranexamic acid had less bleeding than control subjects.
- Further studies are required to establish optimal dosing and safety.

Since the introduction of tranexamic acid (TXA) to clinical practice in the 1960s,[4] evidence from numerous prospective randomized studies and meta-analyses has verified its effectiveness in reducing perioperative and traumatic bleeding, and lowering transfusion requirements in cardiac, obstetric, and urologic surgery.[5] In orthopaedic surgery, TXA has proved effective in total knee and hip replacement procedures in placebo-controlled trials.[6–8]

The efficacy of TXA has also been assessed in spine surgery. Initial data supporting its effectiveness were from retrospective case series or heterogeneous cohort studies.[9–15] Subsequently, various prospective clinical trials analysed the performance of TXA in adolescents[16–18] and adults[19–24] undergoing several types of surgery of varying complexity, with divergent results. The first meta-analysis on TXA use in spine surgery, published in 2008,[25] did not offer a clearly favourable recommendation because of the poor methodological quality of the studies included. The drug was being used in off-label conditions because spine surgery was not one of the labelled indications listed in the product insert.[26 27] More recent meta-analyses[28–32] suggested the need for additional studies with larger patient samples because of the considerable heterogeneity of available studies regarding the type of surgery, the drug dose and administration regimen used.

We believe that TXA efficacy can best be tested against a placebo in prospective randomized clinical trials in patients older than 18 yr undergoing spine surgeries, with a high probability of requiring a blood transfusion, and using a drug dose and transfusion trigger in accordance with expert consensus criteria.[33 34]The safety profile of the drug should also be investigated, as there is little available information on this aspect.[4] In light of the current lack of consensus regarding the efficacy of TXA use in major spine surgery and the scarcity of related safety information, we designed the present study based on the hypothesis that TXA reduces intraoperative and postoperative blood loss and transfusion requirements relative to a placebo in patients undergoing major spine procedures, while presenting an acceptable safety profile.

Methods

Trial design

This is a multicentre, prospective, randomized, double-blind clinical trial performed in four hospitals in Spain, approved by the Ethics and Clinical Research Committees of the participating centres, and registered in ClinicalTrials.gov (NCT01136590).

Participants

Inclusion criteria: Patients >18 yr of both sexes with an ASA anaesthesia risk of I to III and BMI of $<35\,kg\,m^{-2}$ undergoing complex spine surgery and providing informed consent to participate in the study.

Exclusion criteria: History of allergy or hypersensitivity to TXA, current treatment with drugs that interfere with coagulation (oral anticoagulant or antiplatelet agents), a clinical history of frequent bleeding, baseline plasma creatinine $>1.5\,mg\,dL^{-1}$, platelet count $<150\,10^9$ Litre^{-1}, prothrombin time (PT) $<60\%$ and activated partial thromboplastin time (APTT) $>38s$, history of any thromboembolic episode before surgery, or a family history of thromboembolism. In addition, we excluded patients who chose not to participate in the study, those with an infectious, neoplastic, or traumatic spinal condition as the reason for surgery, and patients for whom an anterior and posterior surgical approach had been planned, either sequentially or on the same day.

Characteristics of the surgery

The patients included were undergoing instrumented surgery involving the thoracic and/or lumbar spine (between T1 and S1) by a posterior midline approach. The characteristics of the surgical intervention were agreed on by consensus among the participating surgeons and included exposure of the posterior vertebral arches, decompression, posterior release, posterior spinal osteotomy (Schwab types 1-6[35]), posterior and posterolateral fusion techniques, posterior lumbar interbody fusion (PLIF) or transforaminal lumbar interbody fusion (TLIF), and instrumentation with pedicle screws, wires or hooks of at least four vertebrae (three intervertebral segments). Participants had the following diagnoses: multisegmental degenerative disc disease, multisegmental lumbar canal stenosis, degenerative scoliosis, idiopathic scoliosis, or abnormal sagittal alignment (degenerative lumbar kyphosis, post-traumatic kyphosis). Subfascial and subcutaneous suction drains were placed at completion of surgery and were maintained for 48 h postoperatively.

Centres

All four participating centres are tertiary teaching hospitals, and the types of surgery proposed for the study are commonly carried out in their normal practice. The number of patients from each centre evaluated and included in the study, and the number of participating professionals in each centre are reported in the Appendix.

Randomization and blinding

Patient eligibility for inclusion was decided at the preoperative assessment visit, informed consent was signed, and patients were randomized to receive tranexamic acid (TXA group) or a saline solution (PLACEBO, control group). Randomization was stratified by centres. A random number list was electronically generated, with blocks of four, six, and eight patients. Enrolment was started in September, 2010 and completed in May, 2014.

The study had a double-blind design with products masked and coded so that the anaesthetist and other participants were unaware of which product each patient was receiving. Patients withdrawn from the study were included in the analysis (intention to treat analysis).

Treatment groups

TXA group: An i.v. infusion of 10 mg kg^{-1} of TXA (Amchafibrin® 500 mg; Rottapharm S.L., 5-mL vials) was administered for 20 min before the surgical incision, followed by perfusion of 2 mg kg h^{-1} up to surgical wound closure at completion of surgery.

PLACEBO group: Saline solution placebo was administered according to the same infusion pattern and timing as in the TXA arm.

All solutions were prepared in identical 5-mL vials (100 mg ml^{-1}). The anaesthetists, operating team, and study investigators were unaware of the treatment assigned to each patient.

Evaluation periods

The study visits were scheduled as follows: a screening visit (which included laboratory results) within one month before surgery; day one (day of surgery), a visit before and after the surgical procedure; day two (day after surgery); day three (second day after surgery); and at hospital discharge or on day seven to record observations relevant to the study and the results of laboratory testing. At the follow-up visit 6 (2) weeks after the surgical procedure), laboratory results and observations related to treatment safety were recorded.

The laboratory tests included a complete haemogram with platelet count, PT, INR, APTT, fibrinogen, ferritin, and transferrin saturation index (TSAT), and serum glucose, creatinine, AST, and ALT concentrations. On day one, blood was collected before and after the surgical procedure. On the remaining days, blood was collected in the morning. Hb concentration and haematocrit were determined on the day of surgery and before transfusion of any blood component.

Preoperative administration of i.v. iron or erythropoietin to optimise the haemoglobin concentrations was recorded. All centres used the same protocol for this purpose, as described.[36]

Outcomes

The primary outcome measure was the total number of transfusion units required during the intraoperative and postoperative period up to postoperative day seven. To evaluate the total transfusion requirements of each group, we determined the total number of autologous units (autologous blood predonation and intraoperative cell saver [ICS] blood) and allogeneic blood units administered. We also calculated the percentage of patients in each group who received any type of transfusion during surgery and up to day seven after surgery or hospital discharge, and the number of units given per patient and by each participating centre. We analysed whether the transfusion was autologous (autologous blood predonation and ICS) or allogeneic, taking into account that the transfusion trigger was the same for both types, and whether the patient received FFP, platelets, or other blood products. In addition, we calculated the total dose of TXA patients received in the TXA group.

The secondary outcome measures included intraoperative blood loss and total blood loss. The total blood loss was the sum of the intraoperative and postoperative values, measured as described in the section "Transfusion requirements and blood loss" (see Appendix).

Because perioperative bleeding is related to certain characteristics of the surgery, such as duration of the procedure and the number of fused spinal segments, the following ratios were calculated: intraoperative blood loss/number of fused levels, total blood loss/number of fused levels, intraoperative blood loss per min of surgery, and intraoperative blood loss/weight of patient.

In addition, the intraoperative blood loss was calculated relative to the total blood volume, and the total blood loss relative to the total blood volume. This latter percentage enabled us to categorize blood loss associated with this type of surgery (considered to have a high bleeding risk), which was assumed to be greater than 30% of total blood volume. In addition, we analysed variables related to the medical results during the intraoperative period and postoperative period (up to hospital discharge), including duration of hospitalization, duration of the surgical procedure, and duration of the postoperative recovery room stay.

Safety variables

Adverse events occurring in the intraoperative period, immediate postoperative period and up to 6 (2) weeks after the procedure were recorded. We collected specific adverse events that might be related to TXA treatment, including incidence of clinical VTE, impaired renal function (plasma creatinine increase $>$ 20% of baseline level), liver function changes relative to baseline, and neurological complications, such as seizures and vision abnormalities. Adverse events apparently unrelated to use of the drug were also recorded.

Sections including description of the anaesthesia technique, transfusion requirements and blood loss, and venous thromboembolism prophylaxis are described in the Appendix.

Statistical analysis

The sample size was calculated assuming a clinically relevant difference of 1 unit of packed RBCs with a standard deviation (SD) of 2 (effect size, 0.5).[15] To have a statistical power of 80% to detect differences at a two-tailed significance level of 5%, 64 subjects per group would be needed.

In the data analysis, descriptive results are expressed as mean (SD) for continuous variables with an approximately normal distribution or as the median (interquartile range) otherwise. Categorical values are presented as frequency and percentage. Simple comparisons of continuous data between groups were carried out with the Student's *t*-test or Mann-Whitney *U*-test, depending on whether the distribution was normal or non-normal, respectively. Categorical variables were compared using the Fisher exact test.

Multivariate analysis was performed to test whether differences between TXA and placebo groups persisted after accounting for effects of other covariates. A mixed effects model regression analysis was used. Independent variables included were the treatment group, participating centre (as the random effect to preserve the stratified design), age, BMI, number of levels instrumented, use or not of decompression, surgical time and volume per h of crystalloids/colloids administered. Total number of packed red blood cell blood units, intraoperative blood loss (IBL), total blood loss (TBL), IBL/total blood volume (TBV) ratio and TBL/TBV ratio were separately included as dependent variables. Perioperative and total blood loss data were fitted to a lognormal distribution. The number of units transfused was analysed using the same model, but assuming a negative binomial distribution. The results for each group and the differences between groups were expressed as the geometric mean with the 95% confidence interval. A P-value $<$ 0.05 was

considered statistically significant. All statistical analyses were carried out using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

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In total, 166 patients were evaluated during the period of September 2010 to May 2014; 95 met inclusion criteria and completed the study (Fig. 1). Forty-four subjects (29 women, mean age 59 yr) received TXA, and 51 (38 women, mean age 50 yr) received placebo. Subject characteristics, type of surgery and baseline laboratory parameters are summarized in Table 1. There were no significant differences between the two groups with the exception of age ($P = 0.01$) and BMI ($P = 0.03$), which were higher in the TXA group. No significant differences were found in the number of segments fused, number of decompressions, osteotomies or levels, total duration of surgery, or any of the baseline or postoperative laboratory parameters studied.

To optimize haemoglobin concentrations preoperatively, 10 (44%) subjects in the TXA group and 14 (45%) control subjects received i.v. iron ($P = 1.00$). In addition, three TXA subjects (6.8%) and two (3.9%) controls were given erythropoietin ($P = 0.65$).

The total dose of TXA treated subjects was 21 mg kg^{-1} (SD 3.5, median 20).

Outcomes

Packed RBC transfusion was not required in 48% of subjects in the TXA group compared with 33% of those receiving placebo (Fig. 2). The mean number of units transfused was 0.85 in the TXA and 1.42 in the control groups ($P = 0.06$, Table 2 and Fig. 2). 57% of the TXA group and 45% of the placebo controls did not receive any allogeneic transfusion (Table 3).

The allogeneic transfusion rate was 41% in the TXA group compared with 56% in the control group (Tables 2 and 3).The distribution of the number of units required in each group is shown in Fig. 2. Of note, the percentage of subjects needing two units was 27% (14) in the control group and 6% (3) in the TXA group.

We were able to recover and reinfuse at least 200 mL of packed RBCs (equivalent to one unit of packed RBCs, included in the calculation of total units transfused in Fig. 2) in 17 (36%) of subjects in the TXA group and in 21 (41%) of control subjects ($P = 0.15$) (Table 3).

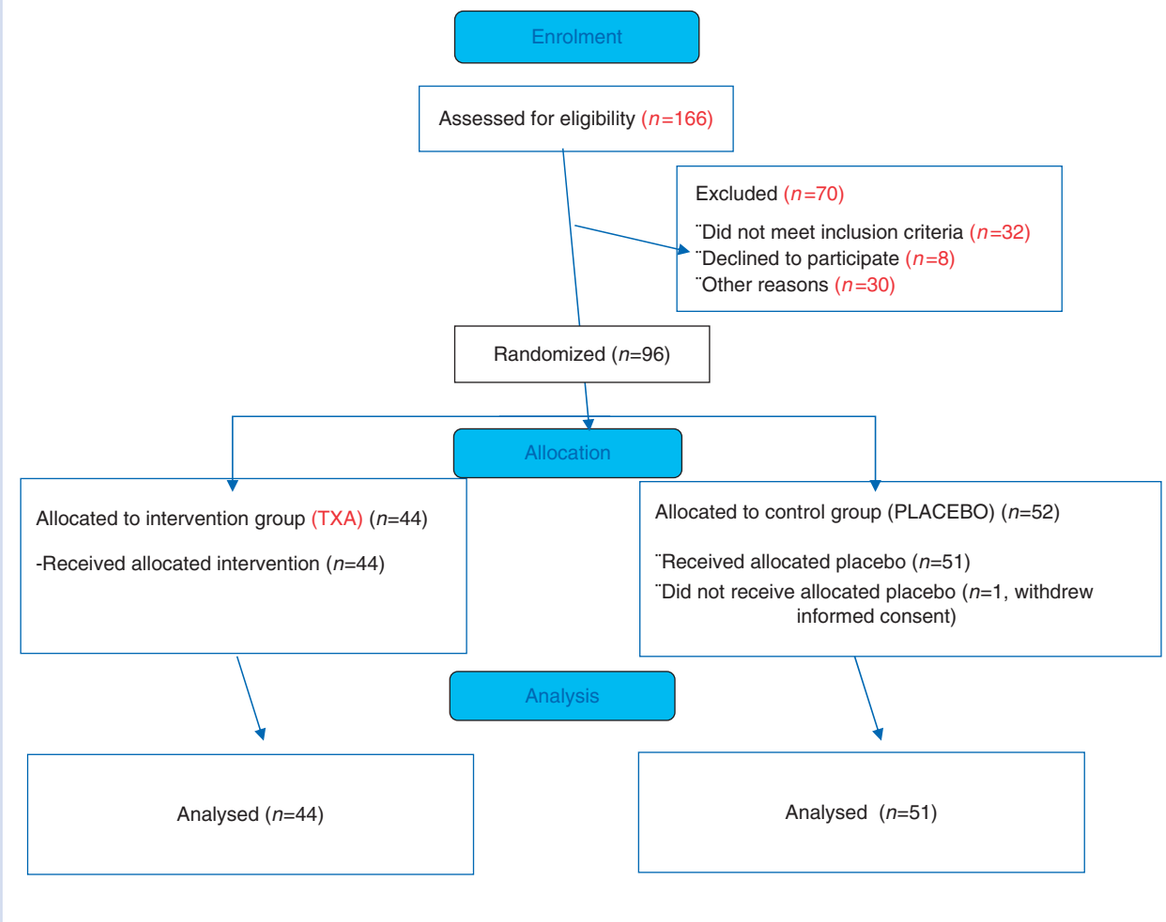

Fig 1 Flow chart of patient progress through the study.

Table 1 Subject characteristics, baseline laboratory parameters, surgery characteristics, and postoperative laboratory parameters at completion of surgery in the study population. Values are presented as the [a]mean (SD), [b]median (Q1-Q3), or number (%). ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; EPO, erythropoietin; PLACEBO, control group receiving placebo; TSI, transferrin saturation index; TXA, group receiving tranexamic acid

Groups		TXA (n=44)	PLACEBO (n=51)	P
Patient characteristics	Age, yr[a]	59.2 (20–75)	50.8 (18–75)	0.01
	Sex, female, n (%)	29 (65.9)	38 (73.1)	0.50
	Weight, kg[b]	72.0 (48.5–97.3)	67.7 (44.0–101.0)	0.10
	Height, m[a]	1.61 (0.08)	1.62 (0.08)	0.73
	BMI[a]	27.6 (3.9)	25.8 (4.4)	0.03
Baseline laboratory parameters	Haemoglobin, g dL^{-1} [a]	14.1 (1.3)	13.9 (1.3)	0.43
	Haematocrit, %[a]	41.5 (3.4)	41.6 (3.6)	0.98
	Platelets, x10^9 L^{-1} [a]	252 (61)	241 (44)	0.32
	Prothrombin time(INR)[a]	1.00 (0.09)	1.01 (0.07)	0.82
	APTT (INR)[a]	0.97 (0.07)	0.99 (0.10)	0.49
	Fibrinogen, g L^{-1} [a]	3.27 (0.83)	3.30 (0.86)	0.91
	Glucose, mg dL^{-1} [a]	101 (33)	96 (21)	0.34
	Creatinine, mg dL^{-1} [a]	0.79 (0.15)	0.78 (0.19)	0.84
	AST, IU L^{-1} [a]	22.5 (8.0)	22.8 (7.2)	0.87
	ALT, IU L^{-1} [a]	19.8 (9.2)	21.9 (17.7)	0.54
	Ferritin, ng mL^{-1} [a]	57.4 (51.7)	74.1 (71.3)	0.41
	TSI, %[a]	30.7 (13.7)	34.0 (12.4)	0.45
	I.V. iron treatment, n (%)	10 (43.4)	14 (45.1)	1.000
	EPO, n (%)	3 (6.8)	2 (3.9)	0.66
Surgery characteristics	Levels fused[b]	5.5 (4–9)	6 (3–11)	0.85
	Decompression, and osteotomies, n (%)	29 (69.1)	35 (70.0)	1.00
	Duration surgery, min[b]	297 (247–390)	300 (250–395)	0.75
	Recovery room stay, h[b]	20.0 (6.7-23.2)	20.1 (8.3–39.8)	0.41
	Admittance to discharge, days[b]	10 (8–14)	11 (8–16)	0.44
	Autologous blood predonation, n (%)	4 (9.1)	6 (11.8)	0.75
	Intraoperative cell salvage, n(%)	16 (36.3)	21 (41.1)	0.63
	Intraoperative total crystalloids + colloids, mL[b]	3750 (2500–5050)	3400 (2200–5100)	0.62
	Intraoperative total crystalloids + colloids, mL kg^{-1} [b]	57.5 (34.9–69.1)	52.8 (31.7–83.8)	0.97
Postoperative laboratory parameters (24 h)	Haemoglobin, g dL^{-1} [a]	10.0 (1.3)	9.6 (1.3)	0.17
	Haematocrit, %[a]	29.9 (4.0)	28.9 (4.2)	0.27
	Platelets, x 10^9 L^{-1} [a]	179 (47)	162 (48)	0.09
	Prothrombin time (INR)[a]	1.19 (0.16)	1.25 (0.28)	0.28
	APTT (INR)[a]	1.01 (0.11)	1.02 (0.13)	0.65
	Fibrinogen, g L^{-1} [a]	3.55 (1.05)	4.31 (1.83)	0.23

The total number of units transfused per centre is shown in the Appendix. A significantly higher number of units was administered in the centre promoting the study, where the largest number of subjects were enrolled (see Appendix). In the remaining centres, there were no significant differences in the number of transfusion units administered.

Compared with placebo, treatment with TXA resulted in lower intraoperative blood loss (940 mL *vs* 1280 mL, $P=0.01$) and total blood loss (1700 mL *vs* 2100 mL, $P=0.01$) (Table 2).

The percentage of total blood loss relative to the total blood volume was greater than 30% in both groups (and in some procedures greater than 50%), an indication that the surgery undertaken involved a high risk of transfusion. Perioperative blood loss was significantly lower in subjects receiving TXA than in control subjects (Table 2).

None of the subjects receiving TXA required administration of FFP, platelets, or other blood components. In the control group, three patients needed FFP and five needed platelets.

The calculation of blood loss indices in both groups was intended to reflect the blood loss pattern in relation to use of the drug and complexity of surgery (number of levels fused and duration of the procedure). TXA use resulted in a significant reduction in intraoperative and total blood loss per fusion level and per operative min (Table 4).

On multivariate analysis, the participating centre, age, BMI, and number of instrumented levels showed no relationship to blood loss or transfusion requirements, whereas TXA administration, duration of surgery and volume per h of crystalloids/colloids administered had an influence on these variables ($P<0.001$).

There were no significant differences between groups with regard to the length of hospitalization (Table 1).

Safety variables

There were no adverse effects in 21 (48%) subjects in the TXA group and in 20 (39%) control subjects, with no significant differences. Two thrombotic complications (one PE, one DVT) were seen in the TXA group (4.5%), with only one such event in the placebo group (one PE, 1.9%), with no significant differences. In all subjects, intermittent pneumatic compression was applied from the start of surgery to the start of ambulation. None of the

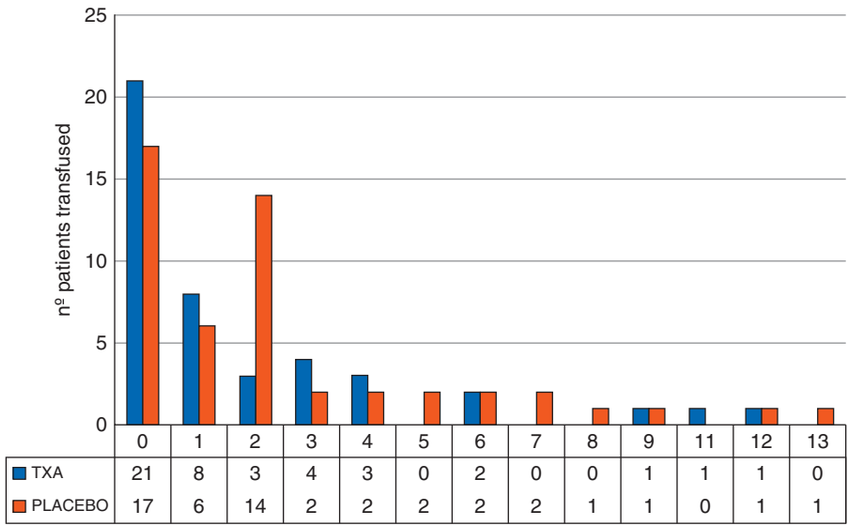

Fig 2 Total packed red blood cell units administered by treatment group. TXA, group receiving tranexamic acid; PLACEBO, control group receiving placebo.

Table 2 Transfusion requirements and perioperative blood loss. IBL, intraoperative blood loss; PLACEBO, control group receiving placebo; PRBC, packed red blood cells; TBL, total blood loss; TBV, total blood volume; TXA, group receiving tranexamic acid. Results are expressed as geometric means (95% CI)

Group	TXA (n=44)	PLACEBO (n=51)	Difference	P
IBL,mL	945 (826–1081)	1277 (1123–1452)	−333 (−586, −121)	0.01
TBL (IBL + drains), mL	1695 (1499–1916)	2112 (1878–2375)	−417 (−796, −96)	0.01
Total number. PRBC units transfused	0.85 (0.54–1.33)	1.42 (0.97–2.08)	−0.57 (−1.59, 0.02)	0.06
IBL/TBV, %	20.7 (18.0–23.9)	28.7 (25.0–32.8)	−8.0 (−13.9, −3.0)	0.01
TBL/TBV,%	37.1 (32.7–42.2)	47.4 (41.9–53.6)	−10.3 (−19.2, −2.7)	0.01

Table 3 Types of transfusion in individual subjects in each group. TXA, group receiving tranexamic acid; PLACEBO, control group receiving placebo

Type of PRBC	TXA (n=44)	PLACEBO (n=51)	P
No Transfusion n (%)	21 (47.73)	17 (33.33)	0.15
Autologous blood predonation n (%)	4 (9.09)	6 (11.76)	0.67
Autologous + allogeneic n (%)	6 (13.64)	10 (19.61)	0.44
Allogeneic transfusion n (%)	13 (29.55)	18 (35.29)	0.55

subjects who developed a thrombotic complication had a significant history of these events. The TXA subject who experienced a PE had onset of chest pain with no haemodynamic repercussions. CT angiography was performed, which confirmed the clinically suspected diagnosis. Doppler ultrasound study of the lower limbs was negative. The subject received standard anticoagulant treatment and had a favourable clinical course. The TXA subject who experienced DVT had a central venous line by peripheral access through the cephalic vein in the right arm, which had been in place since the day of surgery. Seven days later he was diagnosed with thrombophlebitis in this region, which resolved with antibiotics and thromboprophylaxis. In the control subject with PE, symptoms developed at 48 h postoperatively, diagnosis was confirmed with CT angiography, and Doppler ultrasound of the lower limbs was negative. Anticoagulant treatment was given for six months with a favourable clinical course.

Impaired renal function occurred in two TXA subjects, was mild and did not require treatment. Of note, liver function parameters were elevated in 44% of controls *vs* 25% of TXA subjects, and there was one patient (1.9%) of cholecystitis in the control group that required surgery. Over the follow-up period, there were no cardiac or cerebral ischaemic events or vision disturbances. No subjects experienced seizures or neurological disturbances.

Table 4 Calculated indices related to blood loss and surgical conditions. IBL,intraoperative blood loss; PLACEBO, controls receiving placebo; TBL, total blood loss; TXA, patients receiving tranexamic acid

Groups	TXA(n=44)		PLACEBO (n=51)		Dif. mean	P
		Mean	SD	Mean		
SD						
IBL per fused level, mL	204	145	299	272	95	0.04
TBL per fused level, mL	327	171	434	305	107	0.04
IBL per min surgery, mL	3.71	2.02	5.14	3.61	1.43	0.02
IBL per kg body weight, mL	18.3	13.5	28.5	25.2	10.2	0.08

Discussion

This multicentre, randomized clinical trial included 95 patients undergoing major instrumented posterior spine surgery. Perioperative use of TXA with a mean total dose of 20 mg kg^{-1} did not reduce significantly transfusion requirements compared with placebo. In addition, TXA-treated subjects had significantly lower intraoperative and total blood loss. Multivariate analysis showed that the effect of TXA on blood loss was independent of other significant covariates, such as operative time and surgical complexity. The incidence and severity of adverse events was similar in the two groups. Thus, this trial provides reliable evidence that TXA administration at the dosing regimen used reduces blood loss but not transfusion requirements, in patients undergoing major spine surgery.

Our findings are consistent with those reported by some other authors investigating TXA use. Wong and colleagues[22] included patients undergoing surgical treatment of degenerative lumbosacral disease, 30% of whom underwent surgery of only one or two vertebral segments. The authors reported a significant reduction in intraoperative blood loss relative to patients receiving placebo, but no differences in allogeneic blood transfusion rates. We believe that TXA should be used in surgeries associated with a risk of major bleeding (at least 30% of the total estimated blood volume). Its use in surgeries involving only one or two vertebral segments is debatable, until the safety profile of the drug in this patient population is better delineated.[4] The same reasoning would apply to TXA use in cervical surgery. Elwatidy and colleagues[19] and Tsutsumimoto and colleagues[20] failed to demonstrate efficacy of TXA in cervical procedures, which is not surprising considering that patients with intraoperative bleeding volumes of less than 100 mL were included. Our results show that the larger the number of levels fused and the longer the duration of surgery, the more effective was TXA administration, coinciding with the findings of Peters and colleagues.[24] These results support our study design, in which only surgeries involving three or more fusion levels were included and the total estimated blood loss was > 30% of total blood volume.

The transfusion trigger used in related studies may have had an impact on the main outcome measures. In the present study, the Hb trigger used was ≤ 8 g dL^{-1}.

This Hb concentration was applied for each unit of blood administered to minimize bias, and was the same for autologous and allogeneic blood. If Hb concentration differed from this value before transfusion, the investigator had to justify transfusion in that particular patient. In a randomized clinical trial including patients undergoing fusion of more than three levels for degenerative lumbar spine disease, Farrokhi and colleagues[21] did not observe a significant reduction in intraoperative bleeding or transfusion requirements. However, the authors set the transfusion trigger at Hb < 10 g dL^{-1}, a value that many consider excessively high.[33 34 39] In our study, the allogeneic transfusion rate was 41% in subjects receiving TXA *vs* 56% in the control group. This rate seems much higher compared with other studies.[29–31] Reasons contributing to this high rate of transfusion include surgeries with blood loss exceeding 37% of total blood volume and non-compliance with the study protocol as a result of the clinical condition of the patient requiring transfusion without prior Hb determination.

The appropriate total dose of TXA has not been definitively established. We used an initial bolus of 10 mg kg^{-1}, followed by continuous infusion at 2 mg kg h^{-1}; that is, a total dose of around ~20 mg kg^{-1}. With the use of this lower-dose[32] regimen, there was a considerable reduction in the transfusion needs and allogeneic transfusion rate in the TXA-treated group (Table 2). The efficacy of this dosing regimen in spine surgery had not been investigated previously.

In a recent study examining a retrospective series of paediatric patients undergoing corrective spine surgery, Xie and colleagues[40] reported efficacy and safety with an initial TXA dose of 100 mg kg^{-1} (10-fold higher than the doses used to date) followed by continuous infusion of 10 mg kg h^{-1}, with no mention of the total dose given. This evidence does not suffice to consider increasing the total TXA dose in major spine surgery.[32] A recent study recommended high-dose TXA (total maximum dose, 100 mg kg^{-1}) for certain cardiothoracic procedures in patients older than 50 yr,[4] but the recommendation has not been extended to include spine surgery.

Up to now, there are no studies comparing different doses of TXA in orthopaedic surgery or other procedures.[5] Favourable results have been reported for both high[17 41] and lower doses, such as that used in our study. The ideal therapeutic effect of TXA consists in obtaining adequate antifibrinolysis to decrease operative bleeding without major side-effects. At one extreme of this goal is the insufficient dose that does not reduce bleeding and at the other extreme, an excessive dose that could favour a prothrombotic state.[4 42] A major problem in TXA management is that we have no biological parameters to enable monitoring of the effective cut-off for the necessary fibrinolysis produced by TXA administration. Until reliable methods to monitor the effect of TXA become available, it will be difficult to determine the appropriate dosing regimen for this drug. TXA pharmacokinetics should also be taken into consideration in future investigations.

One of the greatest concerns regarding the use of TXA and other antifibrinolytic drugs is their potential to increase the risk of thrombotic events. In our study, two subjects in the TXA group and one control subject had a thrombotic complication, although the difference was not statistically significant. In contrast to aprotinin,[43 44] TXA use has not been associated with a higher risk of death or arteriovenous thrombotic events compared with placebo, in orthopaedic surgery or other procedures.[45] Nonetheless, because available clinical trials as a whole include a small number of TXA-treated patients, some doubt persists regarding the safety of TXA.[46–48] The European Society of Anaesthesiology guidelines[39] recommend TXA administration in total hip and knee arthroplasty and in spine surgery. However, these recommendations are accompanied by the suggestion to individually evaluate the risk-benefits of the treatment in women, patients with a history of VTE, and individuals older than 60 yr.

Among the other adverse events evaluated in our study, mildly impaired renal function with no clinical repercussions occurred in two subjects in the TXA group. The product insert recommends adjusting the dose according to renal function because TXA is mainly eliminated by urinary excretion.[27] Our subjects had normal renal function at baseline and mild impairment was detected. This side-effect has not been described previously. Other reported adverse events, such as convulsions[49] or vision disturbances were not seen in our series. Nonetheless, to properly evaluate the safety of TXA in major spine surgery, additional prospective placebo-controlled studies including appropriate numbers of subjects are needed.

The incidence of VTE should be carefully evaluated and include not only DVT and PE, but also stroke, myocardial infarction, and death. Furthermore the follow-up period should extend beyond the hospitalization period, as some of these complications can appear at a later time point. In contrast to the limited follow-up in other studies, ours had a minimum follow-up of six weeks after surgery, and one patient with VTE was recorded at follow-up. Considering the low incidence of these complications (<3%), at least 5000 patients per treatment arm (TXA vs placebo) would be needed to detect a difference of 1%. To date, all the related reviews concluded that there are too many limiting factors to establish firm recommendations regarding the safety of TXA in spine surgery.[28–31 50]

Our study has some limitations. The most important is related to sample size. Based on previous results from our working group[15] we had to enrol at least 128 subjects to achieve statistical significance in the reduction of at least one transfusion unit with TXA use. However, because of time constraints in the funding for the study, we were unable to reach this number of subjects. Nonetheless, the 95 subjects ultimately randomized for the trial is the largest number among existing prospective studies having the same objective, it is the only multicentre study to date carried out with TXA in complex spine surgery, and some significant findings were obtained. In addition, we made every attempt to minimize the risk of bias by controlling factors that would have an influence on the variable *transfusion*, including the preoperative Hb concentration, total amount of autologous blood transfused, fluid replacement therapy and colloids administered, transfusion protocol for each unit of packed RBCs, and evaluation of blood loss adjusted according to BMI and total estimated blood volume.

Another important limitation is the finding of supranormal values of Hb at 24 h after surgery. This indicates non-adherence to the study protocol in a group of subjects estimated to be about 15%. This can be explained by certain haemodynamic and/or metabolic conditions, and above all, clinical conditions that led to transfusion, especially the second unit of packed RBCs.

Another potential limitation was that the study included patients undergoing "major (posterior instrumented) spine surgery", which might be debatable. Our intention was to include surgery carrying a significant risk of blood transfusion in order to have a homogeneous population. At least three vertebral segments (four vertebrae) were to be included in fusions, and in all patients, instrumented fusions were planned. Ultimately, the study included fusions of three to 11 segments, which indicates a certain heterogeneity of the sample. We enrolled patients undergoing fusion alone, and those in whom decompression was carried out. According to the Schwab posterior osteotomy classification,[35] the magnitude of posterior release and corrective manoeuvres ranged from simple flavectomy (type 1) to vertebral column resection by posterior approach (type 6). These procedures are associated with major intraoperative bleeding,[51] and therefore seemed to be a particularly interesting area of study. Nonetheless, we recognize that the sample was somewhat heterogeneous, as shown by the wide range of intraoperative bleeding (700 mL-1500 mL) recorded.

Conclusions

Intraoperative TXA administration at a mean dose of 20 mg kg^{-1} of body weight resulted in a significant reduction in intraoperative and total blood loss, but no significant reduction in blood transfusion in the TXA group compared with placebo, in patients undergoing posterior instrumented spine surgery. The rate of thromboembolic complications in the TXA group (4.5%) was similar to that observed in patients receiving placebo. Further studies are needed to find the optimal TXA dose, with attention to the pharmacokinetics of this drug.

Authors' contributions

Study design/planning: M.J.C., M.K., M.B., J.B.
Study conduct: M.J.C., M.K., M.B., J.P., L.M., J.B.
Data analysis: M.J.C., M.K., M.B.
Writing paper: M.J.C., M.K., M.B.
Revising paper: all authors

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Declaration of interest

None declared.

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Number of participating patients and professionals in each centre. TXA, group receiving tranexamic acid; PLACEBO, control group receiving placebo

Centre	Anaesthetists	Surgeons	N° of patients assessed	N° patients randomized to treatment	TXA	PLACEBO
Hospital Universitari Vall d'Hebron Barcelona	5	2	79	40	19	21
Hospital Clínic, Barcelona	2	1	24	14	6	8
Hospital UniversitariBellvitge, Barcelona	3	2	39	29	13	16
Hospital de Getafe, Madrid	1	2	24	13	6	7

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Number of PRBC units transfused at the four participating centres. PLACEBO, control group receiving placebo; PRBC, packed red blood cells; TXA, group receiving tranexamic acid. 95LL; lower limit of 95% confidence interval; 95UL; upper limit of 95% confidence interval

Centre	PRBC TXA	PRBC PLACEBO	Dif PRBC PLACEBO - TXA	Dif PLACEBO – TXA95LL	Dif PLACEBO– TXA95UL	P
Hospital Universitari Vall d'Hebron Barcelona	1.25	4.11	2.86	0.67	7.56	0.003
Hospital Clínic, Barcelona	0.06	0.11	0.05	−0.05	2.30	0.654
Hospital UniversitariBellvitge, Barcelona	0.75	0.55	−0.20	−0.64	2.06	0.694
Hospital de Getafe, Madrid	1.70	3.41	1.70	−0.77	10.73	0.253

Specific characteristics of the anaesthesia technique

All patients underwent general anaesthesia with propofol, fentanyl, and midazolam, with rocuronium bromide or cisatracurium as a neuromuscular blocking agent. Maintenance anaesthesia consisted of continuous fentanyl perfusion, rocuronium bromide or cisatracurium, and desflurane or propofol as a hypnotic agent. The target parameters for maintenance anaesthesia during the intraoperative period were as follows: oesophageal temperature >35°C, mean arterial pressure 55 to 70 mm Hg (monitored invasively) and Pa_{CO_2} 34 to 40 mm Hg (monitored by arterial blood gas measurement).

Fluid therapy consisted of continuous infusion of crystalloids (Ringer lactate or Ringer acetate) at 4 ml Kg^{-1} h^{-1} up to completion of the procedure. Colloid administration (hydroxyethyl starch 6% [130/0.4]) was indicated when blood loss exceeded 10% of the patient's total estimated blood volume. The maximum dose allowed was 20 ml kg^{-1}over 24 h (including the time since the start of the procedure) to avoid uncontrolledhaemodilution and achieve a crystalloid: colloid replacement ratio of 3:1.

All patients were monitored in the recovery room for at least 24 h after completion of surgery and were followed by the same surgical/anaesthesia team up to the time of hospital discharge.

Transfusion requirements and blood loss

Intraoperative haemoglobin (Hb) concentration was monitored in each patient at a frequency depending on the individual blood loss and always before administration of each unit of blood or blood products. According to the established protocol, the Hb transfusion trigger used to indicate administration of packed RBCs was $\leq$8 g dL^{-1}. If the Hb concentration differed from this value at transfusion, the investigator had to provide the reasons why transfusion had been performed. This value was applied to indicate both autologous and allogeneic transfusion, and for each unit administered. Intraoperative cell salvage (ICS) was allowed, and the red blood cell (RBC) content was reinfused when the amount recovered was greater than 200 mL (red cell mass comparable with that of one unit of allogeneic packed RBCs). This condition was established as a transfusion criterion to unify the transfusion practice in all centres and to prevent this variable from becoming a confounder in the analysis of transfusion requirements. We also allowed autologous blood predonation to save on allogeneic blood transfusion, when this option was available at the centre and the Ethics Committee approved its use. The autologous blood units administered were recorded and analysed within the transfusion requirements.

Intraoperative blood loss was assessed by measuring the amount collected by aspiration and by weighing the surgical gauze compresses using a digital scale (identical in each centre). Blood loss from the floor, surgical gowns, and surgical drapes was not included.

In patients undergoing surgery with use of an ICS system, the estimated total blood loss from the system (ICS) was calculated using the following formula: *Total blood loss (ml): (Final volume accumulated in the reservoir of the system) – (Total volume of anticoagulant, saline, heparin) – (Total irrigation fluid used intraoperatively) + (Total blood recovered)*.

Postoperative blood loss was recorded as the blood volume collected through the suction drains at 48 h (the same for all patients). The sum of intraoperative and postoperative loss was the total blood loss (TBL).

Haemostasis was monitored by measuring the PT, APTT, INR concentration, fibrinogen concentration, and platelet count at the study evaluation time points.

Administration of fresh frozen plasma (FFP) as primary treatment for hypo-fibrinogenemia was indicated on INR concentrations (patient's PT ratio relative to the laboratory reference value) of >1.5 or fibrinogen <0.5 g l^{-1}. If platelet count was < 80 10^9 L^{-1} during surgery and the patient showed active bleeding, platelet concentrate was used.

Venous thromboembolism prophylaxis

Patients received antithrombotic prophylaxis according to the institutional guidelines and protocols of each participating centre, and the individual risk estimated by the investigator. The study protocol included evaluation of the probability that a patient would experience venous thromboembolism (VTE) using the Wells clinical prediction guide for deep venous thrombosis (DVT)[36] and pulmonary embolism (PE)[36] or the Geneva criteria for PE.[37] In patients with a high probability of developing VTE, the laboratory request included D-dimer determination. If the value obtained for this parameter was less than 500 ng mL^{-1}, the diagnosis of DVT could be reliably ruled out. If D-dimer values were higher and a diagnosis of VTE was plausible on clinical grounds, high-resolution computed tomography (HRCT) study was requested. In addition, compression ultrasonography or ascending phlebography could be performed to confirm the presence VTE in patients with clinical signs of VTE and a previous D-dimer determination. Clinically and radiologically confirmed DVT or PE were considered severe adverse events.

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