European Spine Journal (2020) 29:3044–3050
https://doi.org/10.1007/s00586-020-06572-8

ORIGINAL ARTICLE

Efficacy of topical versus intravenous tranexamic acid in spinal deformity

Karen A. Weissmann[1,2] · Virginie Lafage[3] · Carlos Barrios Pitaque[1] · Renaud Lafage[4] · Francoise M. Descazeaux[5]

Received: 18 February 2020 / Revised: 13 August 2020 / Accepted: 16 August 2020 / Published online: 31 August 2020

Abstract

Purpose To compare topical tranexamic acid versus intravenous tranexamic acid in reducing intra- and postoperative blood loss and transfusion rate in deformity patients.

Materials and method We performed a retrospective cohort study with posterior fusion deformity patients, between 2009 and 2016. Patients were categorized in 4 groups: "No TXA" ($n=35$) if the wound was packed with saline soaked sponges, "IV TXA" ($n=37$) the patient received 20 mg/kg bolus at the beginning of the surgery followed by continuous infusion of 1 mg/kg/hr until closure, "Topical TXA" ($n=23$) the wound was packed with sponges soaked in 6 g of TXA diluted in a 3 L saline solution, or "Combined TXA" ($n=86$) the patient received both IV and topical TXA. The primary outcomes were total, intra- and postoperative blood loss, surgical time, postoperative Ht/Hb, transfusion rates, and duration of drain insertion.

Results A total of 181 patients were analyzed (78.6% *F*, 15.08 yo). No differences were found in total and intraoperative blood loss, surgical time, postoperative Ht/Ht, and transfusion rates. "Combined TXA" group had significantly less postoperative bleeding than "no TXA" group ($p=0.022$). IV TXA patients (with o/without topical TXA) removed drains one day earlier than the no TXA group ($p=0.002$). There were no complications related to the use of tranexamic acid.

Conclusion There is significant decrease in postoperative bleeding in pediatric deformity patients with combined topical and IV tranexamic acid.

Keywords Tranexamic acid · Scoliosis · Topical

Introduction

Despite all the recent advances in deformity surgery, blood management remains a major issue. Excessive blood loss increases complications, hospital stays, and costs [1].

Excessive bleeding affects patients intraoperatively [2] and impacts the recovery process, it can lead to an extended length of stay, nausea, and unnecessary allogeneic transfusions with increased risk of infection [3], and it also involves extra strain for the family in procuring blood and increased costs.

On a very high level, there are two ways to mitigate the issue of blood loss [4]: replace or save blood. Replacing blood involves autotransfusions, cell saver, or allotransfusions [3]; all of these are potentially associated with complications, increase procedures, and cost. Saving blood includes two types of interventions: hemodynamic and chemical/biological. The first consists in hemodilution, controlled hypotension, epidural block, and vasoconstrictor drugs [4]. Chemical/biological interventions are diverse and include: 1) use of erythropoietin (a time-consuming and costly solution, useful in patients refusing allotransfusion), 2) sealing the origin of bleeding with bonewax or thrombin-gelatin hemostatic matrix, or 3) use of systemic or topical chemicals that intervene on the coagulation chain. Within this last set of interventions, aprotinin [5] and epsilon aminocaproic acid [6, 7] (EACA) demonstrated excellent results in spine

✉ Karen A. Weissmann
kweissmann@mail.ucv.es; kweissmannm@uchile.cl

1 Escuela de Doctorado, Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain

2 Departamento de Ortopedia y Traumatología, Area Sur., Universidad de Chile, Gran Avenida Jose Miguel Carrera 3100, San Miguel, Santiago, Chile

3 Department of Surgery, Hospital for Special Surgery, New York, NY, US

4 Department of Orthopedic Surgery, Hospital for Special Surgery, New York, NY, US

5 Hospital Exequiel Gonzalez Cortés, Santiago, Chile

surgery but were discontinued due to the risk of deep venous thrombosis, pulmonary embolus, myocardial ischemia, bradycardia, renal failure, or allergies [8].

In this context tranexamic acid (TXA) is a competitive synthetic analog to lysine that reversibly binds to lysine receptor sites in plasminogen, thus preventing the conversion from plasminogen to plasmin and preventing fibrin degradation; it does not affect platelet count, it prevents platelet asthenia [9], and it does not decrease coagulation parameters such as activated partial thromboplastin time or prothrombin times. It has shown promising results during surgical procedures in patients with hematological disorders [5] and spine surgery [10, 11] when used intravenously (IV), but some complications have been described [12], such as venous thrombose, seizures, pulmonary embolism, myocardial infarction, strokes, and blood–brain barrier[5]penetration, which is a concern in children. There is a growing interest in administering TXA in a topical fashion, with positive results reported in dental procedures, epistaxis [2], and intraarticular in hip and knee procedures [13, 14]. In spine surgery, only two level-1 RCTs with topical tranexamic acid have been published; in one, the wound was washed with a topical TXA diluted in saline before closure; in the other, topical TXA was sprayed after laminectomy. Both reported a significant reduction in drain output [2]. Topical TXA has shown to achieve sufficient plasmatic levels to inhibit plasminogen at lower doses and with less complications [9]

The objective of the current study was to investigate if topical TXA was a viable and safe alternative to IV TXA in the setting of deformity surgery. More specifically, this study aimed to compare the efficacy of topical TXA versus intravenous TXA in reducing intraoperative and postoperative blood loss, and the need for transfusion.

Material and method

This is a retrospective cohort study with deformity patients from one academic pediatric hospital (ethics committee approval, 3/2018), the surgeries were performed by one of five surgeons from the same team, and the anesthesiologist rotated in a scheduled by shift system.

Study subjects

Patients were recruited between 2009 and 2016. Records from this period were recovered from the hospital database. Inclusion criteria were patients less 25 years old who underwent deformity surgery. Exclusion criteria were patients with revision surgery, growing system, anterior approach, hematological or hepatic conditions. Patients with dural tears were not excluded from this study.

Anesthesiology preparation

Total intravenous anesthesia (TIVA) was employed to permit continuous evoked potentials (MEP and SSEP). All patients received prophylactic antibiotic with cefazolin 50 mg/kg/dose or clindamycin in patients allergic to B-lactamic (10 mg/kg/dose). Hemodilution or cell saver was not used in this series of patients.

Surgical procedure

A posterior approach was performed in all patients while maintaining a medial blood pressure between 55 and 75 mmHg. Bleeding was controlled with saline or tranexamic soaked sponges.

All patients were instrumented with screws and rods. Medial blood pressure was increased to over 85 mmHg during the reduction maneuvers and during the immediate 24 h. Grafting was done with osteoconductors and local bone obtained after decortication. Wound closure was conducted in four stages: deep fascial plane, subcutaneous, subdermal, and either intradermic suture or staples. Drains were placed deep and superficial when an osteotomy was performed and only superficial when the spinal canal was intact. Suction drains were removed when drainage was less than 50 mL/day. Surgical time was measured from skin incision to dressing.

The criteria for transfusion were based on the blood transfusion protocols from our hospital [15]. All patients received antibiotics until the drainage was removed (cefazolin or clindamycin). Patients were monitored during at least 24 h in a pediatric intensive or intermediate care unit.

Subjects categorization

Patients were categorized in four groups according to the way TXA was used during their surgery:

- No tranexamic acid (No TXA): The wound was packed with gauzes soaked in saline.
- IV tranexamic acid (IV TXA): TXA IV dose of 20 mg/kg in bolus and then a continuous infusion of 1 mg/kg/hr until skin closure. The bolus was injected at the time of the incision.
- Topical tranexamic acid (topical TXA): 6 g of TXA diluted in a 3L saline solution. The gauzes for packing were soaked in this solution; if solution remained after the surgery it was irrigated directly into the wound. If more irrigation was needed it was performed with pure saline.

- Topical and IV tranexamic acid (topical + IV TXA): This group received both interventions with the previously described doses.

Outcomes

Intraoperative bleeding was determined by measuring the amount of blood collected in the suction canister and subtracting the amount of irrigation saline used, including the one in the sponges for packing. These were crushed to remove all liquid and weighted along with compresses used during surgery. The drain debit was measured every 12 h and recorded in the patient's chart. In the first 24 h, the drain was left with negative pressure and posteriorly at free fall. The total blood loss was defined as the sum of the intraoperative bleeding and the total drain output.

Additionally, we reported the preoperative and postoperative hematocrit and hemoglobin, the number of levels instrumented and average bleeding per level, surgical time, surgeon in charge, scoliosis etiology as adolescent idiopathic scoliosis (AIS) or neuromuscular scoliosis (NMS), number of days the drain was left in place, intraoperative or postoperative transfusions, and the presence of complications.

Statistical analysis

After describing the entire cohort in term of demographic and surgical metrics using mean and standard deviation or median and percentile, association between operative time and fusion length with blood information was conducted using Pearson's correlations. Patients were stratified by type of blood management protocol, and surgical outcomes, especially intraoperative blood loss, postoperative blood loss, and total blood loss, were compared using either an ANOVA or a Kruskal–Wallis test, when appropriate. This analysis was conducted for the entire cohort was well as by fusion length group (less than 6 level fused, 6–12 level fused, more than 6 level fused). Complication rates were reported and compared between TXA groups. Finally, a sub-analysis by type of deformity (NMS versus AIS) and by surgeon was conducted. Statistical analysis was performed using SPSS 20.0 (IBM, Chicago, IL, USA), and $p < 0.05$ was considered statistically significant.

Results

Demographics

A total of 181 patients were included in the analysis; 78.6% were female, with a mean age of 15.08 years (8–25 years). There were 35 patients in the No TXA group, 37 in the IV TXA group, 23 in the topical TXA, and 86 in the IV + topical TXA group (Table 1). Primary diagnosis was significantly different in the four groups as there were no neuromuscular cases in the topical TXA group.

The total blood loss overall was 1,390 ± 886 mL, median 1235 mL (25th 758.5–75th 1836.5 mL) with mean intraoperative bleeding of 1043 ± 749.06 mL, median 800 mL (25th 500–75th 1475 mL), and a mean drain output of 352 ± 352 mL, median 253 mL (25th 93.5–75th 498.25 mL). Mean preoperative Ht for this series was 40.01% with 13.34 grs/dL of hemoglobin, postoperative 27.21% Ht and 9.21 grs/dL Hb.

Correlation analysis between surgical metrics and estimated blood loss

There was a positive correlation between surgical time and number of instrumented levels ($p = 0.000$, $r = 0.359$), intraoperative bleeding ($p = 0.000$, $r = 0.494$), intraoperative transfusions ($p = 0.000$, $r = 0.438$), postoperative Ht/Hb ($p = 0.000$, $r = 0.367$), postoperative bleeding ($p = 0.028$, $r = 0.163$), number of days with drain ($p = 0.041$, $r = 0.155$), and total bleeding ($p = 0.000$, $r = 0.484$). There was no correlation between operative time and number of complications.

A total of 2003 levels were instrumented, with a medial of 11 levels (25th 9 to 75th 13 levels) per patient, and a total bleeding per level of 126.32 mL; of this 94.9 mL were intraoperative bleeding, and 32.02 mL were postoperative

Table 1 Mean demographic data for the four groups

	No TXA ($n = 35$)	IV TXA ($n = 37$)	Topical TXA ($n = 23$)	IV and topical TXA ($n = 86$)	p value
Sex male/female	6/29	4/33	7/16	21/65	0.281
Age	14.71 ± 2.21	14.59 ± 2.07	14.70 ± 3.71	15.57 ± 2.91	0.608
Diagnosis NMS/AIS*	30/5	5/32	23/0	30/56	**0.000**
Pre op Ht	39.86	39.21	39.33	40.55	0.693
Pre op Hb	13.21	13.19	12.47	13.66	0.052

Bold: Statistically significant ($p < 0.005$)

**AIS* adolescent idiopathic scoliosis *NMS* neuromuscular scoliosis

bleeding. The number of instrumented levels significantly correlated with the amount of intraoperative bleeding ($r=0.237$), with intra- and postoperative transfusions ($r=0.353$ and 0.209), postoperative Ht/Hb ($r=0.226$ and 0.221), postoperative bleeding ($r=0.269$), total bleeding ($r=0.316$), drain days ($r=0.228$), and number of complications ($r=0.283$) (all $p<0.005$). IV TXA had significantly more levels fused (12.67 ± 3.84) than the no TXA and the topical + IV TXA groups (resp 10.56 ± 2.25 levels and 10.22 ± 3.12 levels, $p<0.001$).

Group analysis

No significant differences were found in total blood loss, intraoperative blood loss, surgical time, postoperative Ht/Hb, intraoperative and postoperative transfusion rates. Deeper analysis demonstrated that topical + IV TXA group had significantly less postoperative bleeding than the control/no TXA group (295 ± 321 mL vs. 480 ± 447 mL, $p=0.022$) (Table 2).

The operative time ranged from 80 to 400 min with a mean of 218.39 ± 74.64 ($p=0.199$). On average, the drains were used during 3.23 days (25th 2 days and 75th 4 days, with a maximum of 11 days); patients who received IV TXA (with or without topical TXA) had their drain taken out one day earlier than the no TXA group ($p=0.002$). In an effort to control for the number of levels fused, a sub-analysis based on the distribution of levels fused was conducted. It demonstrated that postoperative bleeding ($p=0.051$) and drain day usage ($p=0.006$) were still significantly different in the IV and topic TXA groups; for the 6–12 level group, which was the biggest group in the cohort, the rest of the parameters were not significant.(Table 3)

Rate of complication for the entire cohort was 17.7% with a total of 32 complications, of which 8.8% were major complications (Table 4). The rate of complications for the neuromuscular group was 44% and 3.17% for the adolescent idiopathic scoliosis group. When compared by TXA group, there was no significant difference in complication rate based on TXA usage ($p=0.376$). No complications associated with the use of tranexamic acid were found in this series.

Table 3 ANOVA analysis for the four groups by percentile of the number of instrumented levels

Levels	0–6	6–12	12–18
Intra-op bleeding (mL)	0.932	0.159	0.603
Intra-op transfusion (*U*)	0.063	0.115	0.081
Post-op transfusion (*U*)	–	0.474	0.856
Post-op Ht (%)	0.091	0.787	0.527
Post-op Hb (grs/dl)	0.093	0.426	0.467
Drain days	0.314	**0.006**	0.155
Post-op bleeding (mL)	0.113	**0.051**	0.441
Total bleeding (mL)	0.756	0.165	0.581
Complications	0.682	0.774	0.632

Bold: Statistically significant ($p<0.005$)

Sub-analysis by diagnosis and surgeon

The analysis by diagnosis (Table 5) demonstrated that NMS had significantly more postoperative transfusions ($p=0.015$) and higher postoperative Ht/Hb ($p=0.005$ and <0.001). For patients with neuromuscular scoliosis, there was no significant difference by TXA groups in postoperative bleeding or the number of days the drain was left in place. On the other hand, for AIS patients, the total drain debit ($p=0.010$) and drain days ($p=0.002$) were significantly lower in the topical + IV TXA group than for the other three groups.

The analysis by surgeons (Table 6) demonstrated that Surgeon #5 performed 50% of all the AIS surgeries, and 100% of the NMS surgeries. The ANOVA analysis by surgeon revealed that surgeon #5 had a faster OR time ($p<0.001$), less intraoperative bleeding ($p<0.001$), less postoperative

Table 2 Comparative outcomes for patients treated with tranexamic acid

	No TXA ($n=35$)	IV TXA ($n=37$)	Topical TXA ($n=23$)	IV and topical TXA ($n=86$)	*p* value
No. of levels fused	10.56 ± 2.25	12.67 ± 3.84	11.96 ± 2.22	10.22 ± 3.12	**0.001**
Surgical time (min)	239.44 ± 62.43	210.56 ± 81.48	200.00 ± 83.3	217.78 ± 73.19	0.199
Drain days	4.0 ± 1.87	3.00 ± 0.74	3.45 ± 1.50	2.94 ± 1.22	**0.002**
Intraoperative bleeding (mL)	1130.89 ± 607.52	984.44 ± 796.35	811.08 ± 403.91	1093.72 ± 843.21	0.348
Postoperative bleeding (mL)	480.58 ± 447.61	372.57 ± 345.84	350.39 ± 262.55	295.13 ± 321.18	**0.022**
Total bleeding (mL)	1611.47 ± 764.35	1357.08 ± 893.45	1161.48 ± 510.96	1388.84 ± 988.62	0.262
Intraoperative transfusion (*U*)	1.14 ± 0.96	1.16 ± 1.21	0.61 ± 0.89	0.85 ± 1.01	0.112
Postoperative transfusion (*U*)	0.139 ± 42	0.30 ± 0.74	0.44 ± 0.84	0.259 ± 0.66	0.410
Post-op Ht (%)	26.9 ± 3.85	27.49 ± 5.25	28.00 ± 5.14	27.01 ± 5.16	0.806
Post-op Hb (grs/dL)	8.87 ± 1.27	9.53 ± 1.87	9.52 ± 1.86	9.13 ± 1.74	0.330

Bold: Statistically significant ($p<0.005$)

Table 4 Complications

Complication	Percentage (%)
Superficial infection	3.13
Deep infection	4.7
Occipital pressure sore	1.6
Bilateral pneumonia	4.7
Minor pneumothorax/atelectasis	4.7
Varicella	1.6
Intraoperative screw pullout repositioned during same surgery	1.6
Unidentified fever for 2 days	4.7
Incidental durotomy	3.13
Hypovolemic shock	4.7
Tongue biting	1.6
Post-op convulsions	3.13
Paraparesis (complete recovery 3 weeks)	1.6
Postoperative paralytic ileum	1.6
Late complications	
Proximal screw pullout due to PJK	3.13
Pedicle fracture due to traumatic accident	1.6
Nonunion	3.13

bleeding ($p = 0.047$), less total bleeding ($p < 0.001$), less intraoperative transfusions ($p < 0.001$), higher postoperative Ht/Hb ($p = 0.018$ and 0.004), and less complication rates ($p = 0.011$). There was no significant difference across the surgeons in terms of postoperative transfusions ($p = 0.455$) or drain duration ($p = 0.656$). We then isolated the data for surgeon number #5 with a total of 126 patients (64 NMS and 60 AIS), multivariate analysis showed that the topical + IV TXA group maintained a lower number of drain days ($p = 0.029$) in the 6–12 number of instrumented levels group. There were no other significant differences.

Discussion

Patients, with spinal deformity, frequently have multiple reasons for intraoperative bleeding; the use of multiple interventions all contributes to avoiding transfusions in these patients.

In this context, IV TXA is a well-documented tool [2, 11, 16] in pediatric deformity patients. This study identified three main predictors of increased bleeding in pediatric deformity surgery: number of instrumented levels, total surgical time, and the surgeon performing the surgery. Age, sex, and diagnosis did not influence bleeding, although transfusion rate was higher and postoperative Hb/Ht were lower in the neuromuscular group. The use of IV tranexamic acid with topical TXA decreased the number of drain days and postoperative bleeding.

The competitive mechanism of actions of TXA should be effective when applied in topical fashion as it avoids fibrin degradation. When administered IV, the half-life is reached within 80 min and peak plasma concentration is 1 h after injection [17]. It has high tissue penetration and absorbance as a one-time IV administration of 10 mg/kg allows for 80%

Table 5 Intraoperative and postoperative blood loss according to scoliosis type

	AIS	NMS	*p* value
Intraoperative bleeding (mL)	1099.30 ± 785.96	938.89 ± 668.016	0.151
Postoperative bleeding (mL)	323.84 ± 330.28	405.36 ± 387.47	0.137
Total blood loss (mL)	1423.14 ± 866.35	1423.21 ± 866.35	0.498
Intraoperative transfusions (*U*)	0.86 ± 1.01	1.09 ± 1.01	0.142
Postoperative transfusions (*U*)	0.178 ± 0.56	0.43 ± 0.78	**0.015**
Post-op hematocrit (%)	26.48 ± 4.82	28.66 ± 4.79	**0.005**
Post-op hemoglobin (grs/dL)	8.87 ± 1.60	9.9 ± 1.70	**0.000**

Bold: Statistically significant ($p < 0.005$)

Table 6 Surgeries performed by the different surgeons

Surgeon	% AIS surgeries	% of NMS surgeries	Surgical time (min)	Intraoperative bleeding (mL)
1	21.2	0	280.16 ± 60.06	1917.48 ± 984.43
2	13.6	0	243.75 ± 65.6	996.25 ± 578.59
3	1.7	0	330.00 ± 42.42	650 ± 212.13
4	1.7	0	255.00 ± 106.06	1665 ± 657.6
5	52.5	100	201.36 ± 71.60	870.48 ± 589.14
6	11	0	207.73 ± 56.76	1050 ± 724.22

systemic fibrinolysis inhibition. In a topical fashion, plasma levels are 70% lower than when used IV [2]. Krhon et al. studied the use of tranexamic acid in orthopedic surgery and reported that by washing the wound with a tranexamic acid solution before closing, the fibrinolytic markers measured in the drain tube were significantly lower in the topical TXA group compared with the non-TXA group [18]. These results suggest that topical TXA acts very quickly, allowing IV infusion to stop sooner and at less cost.

When applied intravenously, high doses of TXA are more effective than low doses [16]; however, studies with 10 mg/kg in bolus and 1 mg/kg/hr (low dose) have shown important decrease in bleeding [19, 20]. The current study suggests that even smaller doses may be efficient when applied in a topical fashion (2 g of TXA per 1000 mL).

No complication-related to tranexamic acid was observed in this series, and there were overall no significant differences across the four studied groups. These findings are in line with the literature: the CRASH-2 [21] (clinical randomization of an antifibrinolytic in significant hemorrhage) study reported no increase in thromboembolic risk in trauma patients, other studies using topical tranexamic acid have not shown complications associated with its use [2, 9].

This study has limitations. The surgeon's expertise plays a significant role in the operative time and intraoperative bleeding. This did not alter our conclusion, but it should be taken into account when investigating peri-operative outcomes in multi-surgeon studies. Timing of tranexamic acid administration limited our ability to analyze its effectiveness intraoperatively; as the bolus was administered at incision, we benefited from effective plasmatic levels after one hour of surgical time.

The two TXA administration modalities complement each other and are not exclusive. From a timing point of view, we recommend the use of IV TXA during anesthesia induction to avoid bleeding during the intraoperative period and using TXA soaked sponges in the packing to decrease postoperative bleeding.

Conclusion

There is a significant decrease in postoperative bleeding and drain day removal in deformity spine surgery with the use of intravenous and topic tranexamic acid. No differences were found in total blood loss, intraoperative blood loss, surgical time, postoperative Ht/Hb, intraoperative and postoperative transfusion rates. The number of levels, surgical time, and surgeon in charge correlate with bleeding. No complication-related TXA was found in this series.

Availability of data and material Yes.

Compliance with ethical standards

Conflicts of interest Karen Weissmann, M.D. helped in consultant fees from Orthopediatrics, Medyssey, and Helico. Virginie Lafage, PhD contributed in Royalties: Nuvasive Inc., Consultant Globus Medical, Inc., Speaking and/or Teaching Arrangements: DePuy Synthes, Implanet. Carlos Barrios Pitaque M.D., PhD and Francoise M. Descazeaux M.D. were involved in no conflict of interest. Renaud Lafage M.Sc helped in Nemaris: stock option.

Ethical approval This project was presented to the hospital ethics committee (Approval 3/2018).

Consent to participate Retrospective study.

Consent for publication Yes.

References

1. Oetgen ME, Litrenta J (2017) Perioperative blood management in pediatric spine surgery. J Am Acad Orthop Surg 25(7):480–488. https://doi.org/10.5435/jaaos-d-16-00035
2. Winter SF, Santaguida C, Wong J, Fehlings MG (2016) Systemic and topical use of tranexamic acid in spinal surgery: a systematic review. Glob Spine J 6(3):284–295. https://doi.org/10.1055/s-0035-1563609
3. Vitale MG, Levy DE, Park MC, Choi H, Choe JC, Roye DP (2002) Quantifying risk of transfusion in children undergoing spine surgery. Spine Journal 2:166–172
4. Szpalski M, Gunzburg R, Sztern B (2004) An overview of blood-sparing techniques used in spine surgery during the perioperative period. Eur Spine J 13(Suppl 1):S18–27. https://doi.org/10.1007/s00586-004-0752-y
5. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussieres JS, Cote D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R, Investigators B (2008) A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 358(22):2319–2331. https://doi.org/10.1056/NEJMoa0802395
6. Verma K, Errico TJ, Vaz KM, Lonner BS (2010) A prospective, randomized, double-blinded single-site control study comparing blood loss prevention of tranexamic acid (TXA) to epsilon aminocaproic acid (EACA) for corrective spinal surgery. BMC Surg 10:13. https://doi.org/10.1186/1471-2482-10-13
7. Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC (2004) The effect of amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized double-blind study. Spine (Phila Pa 1976) 29(3):233–238. https://doi.org/10.1097/01.brs.0000109883.18015.b9
8. Kasimian S, Skaggs DL, Sankar WN, Farlo J, Goodarzi M, Tolo VT (2008) Aprotinin in pediatric neuromuscular scoliosis surgery. Eur Spine J 17(12):1671–1675. https://doi.org/10.1007/s00586-008-0790-y
9. Arun-Kumar V, Naresh-Babu J (2019) Is there a role for preoperative local infiltration of tranexamic acid in elective spine surgery? A prospective randomized controlled trial analyzing the efficacy of intravenous, local infiltration, and topical administration of tranexamic acid. Glob Spine J. https://doi.org/10.1177/2192568219888446
10. Jones KE, Butler EK, Barrack T, Ledonio CT, Forte ML, Cohn CS, Polly DW Jr (2017) Tranexamic acid reduced the percent

of total blood volume lost during adolescent idiopathic scoliosis surgery. Int J Spine Surg 11:27. https://doi.org/10.14444/4027
11. Yagi M, Hasegawa J, Nagoshi N, Iizuka S, Kaneko S, Fukuda K, Takemitsu M, Shioda M, Machida M (2012) Does the intraoperative tranexamic acid decrease operative blood loss during posterior spinal fusion for treatment of adolescent idiopathic scoliosis? Spine (Phila Pa 1976) 37(21):E1336–1342. https://doi.org/10.1097/BRS.0b013e318266b6e5
12. Wang M, Zheng XF, Jiang LS (2015) Efficacy and safety of antifibrinolytic agents in reducing perioperative blood loss and transfusion requirements in scoliosis surgery: a systematic review and meta-analysis. PLoS ONE 10(9):e0137886. https://doi.org/10.1371/journal.pone.0137886
13. Konig G, Hamlin BR, Waters JH (2013) Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty 28(9):1473–1476. https://doi.org/10.1016/j.arth.2013.06.011
14. Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM (2014) A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Jt J 96(8):1005–1015. https://doi.org/10.1302/0301-620X.96B8.33745
15. Fuentes IVJ (2009) Criterios de Indicación médica de trasfusiones. Componentes sangineos y hemoderivados., vol 1, 1 edn. Gobierno de Chile. Ministerio de Salud, Hospital Exequiel González Cortés
16. Jhonson DJ, Jhonson JC, Goobie S, Nami N, Wetzler J, Sponseller P, Frank S (2016) High-dose versus low-dose tranexamic acid to reduce transfusion requirements in pediatric scoliosis surgery. J Pediatr Orthop 0:1–6
17. Andersson L, Nilsson IM, Nilehn JE, Hedner U, Granstrand B, Melander B (1965) Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. Scand J Haematol 2(3):230–247. https://doi.org/10.1111/j.1600-0609.1965.tb01300.x
18. Krohn CD, Sorensen R, Lange JE, Riise R, Bjornsen S, Brosstad F (2003) Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. Eur J Surg Suppl 588:57–61
19. Wong J, El Beheiry H, Rampersaud YR, Lewis S, Ahn H, De Silva Y, Abrishami A, Baig N, McBroom RJ, Chung F (2008) Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesth Analg 107(5):1479–1486. https://doi.org/10.1213/ane.0b013e3181831e44
20. Goobie SM, Zurakowski D, Glotzbecker MP, McCann ME, Hedequist D, Brustowicz RM, Sethna NF, Karlin LI, Emans JB, Hresko MT (2018) Tranexamic acid is efficacious at decreasing the rate of blood loss in adolescent scoliosis surgery: a randomized placebo-controlled trial. J Bone Jt Surg Am 100(23):2024–2032. https://doi.org/10.2106/JBJS.18.00314
21. Collaborators C-t, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejia-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 376(9734):23–32. https://doi.org/10.1016/S0140-6736(10)60835-5