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Intraoperative High-Dose Tranexamic Acid Infusion in Vertebral Surgeries: Our Clinical Experiences

Vertebra Cerrahisinde İntraoperatif Yüksek Doz Traneksamik Asit İnfüzyonu: Klinik Deneyimlerimiz

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ABSTRACT Objective: We aimed to share our experiences on perioperative blood loss and the prevalence of side effects of high-dose tranexamic acid (TXA) used intraoperatively in vertebral surgeries. **Material and Method:** Thirty-four patients with the class of American Society of Anaesthesiology(ASA) I–III who underwent posterior spinal instrumentation and osteotomy at ≥5 vertebral levels were retrospectively analysed. TXA was administered intravenously from beginning to end of surgery at a loading dose of 50 mg/kg and a maintenance dose of 10 mg/kg/h. In addition to routine monitoring, minimal invasive cardiac output measurement was also used. Operative parameters, intraoperative-postoperative blood loss, mean volume of blood transfusion and fluids, hospitalization time, Hb, BUN, creatinine, Plt, INR levels, side effects and complications were recorded and evaluated. **Results:** Median value of fused spinal segments was 12 (7-13). Intraoperative blood loss was 1448.53±767.18 ml, 133.85±61.77 ml per fused spinal segment and 172.79±82.12 ml per hour during the operation. While intraoperative blood loss was significantly lower in patients undergoing primary surgery than in revision patients, there was no difference in terms of postoperative blood loss. It was directly correlated with the number of fused vertebrae, duration of surgery, age and ASA. Mean amount of red blood cell transfused was 1.5±1.29U. There were no significant complications or side effects such as thromboembolism, seizure or renal failure in our patients. **Conclusion:** Although appropriate dosages are not yet established, we think that a loading dose of 50 mg/kg TXA can be used safely in vertebral surgeries without causing significant side effects.

Keywords: Tranexamic acid; scoliosis; spinal fusion; blood loss, surgical; antifibrinolytic agents

ÖZET Amaç: Vertebra ameliyatlarında intraoperatif olarak kullanılan yüksek dozda traneksamik asitin (TXA) perioperatif kan kaybı ve yan etkilerin yaygınlığı konusundaki deneyimlerimizi paylaşmayı amaçladık. **Gereç ve Yöntemler:** Amerikan Anesteziyoloji Derneği (ASA) I-III, ≥5 seviye posterior spinal enstrümantasyon ve osteotomi uygulanmış, 34 hasta retrospektif olarak incelendi. TXA 50 mg/kg yükleme ve 10 mg/kg/saat idame dozda cerrahi başından sonuna kadar intravenöz olarak uygulanmıştı. Rutin monitörizasyona ek olarak minimal invaziv kardiyak output ölçümü de kullanıldı. Ameliyat parametreleri, intraoperatif-postoperatif kan kaybı, ortalama kan transfüzyonu ve sıvı hacmi, hastanede yatış süresi, Hb, BUN, kreatinin, Plt, INR düzeyleri, yan etkiler ve komplikasyonlar kaydedildi ve değerlendirildi. **Bulgular:** Füzyon uygulanan omurga segmentlerinin median değeri 12 (7-13) idi. İntraoperatif kan kaybı operasyon sırasında 1448.53 ± 767.18 ml, füzyon uygulanan spinal segment başına 133.85 ± 61.77 ml ve operasyon süresine göre saatte 172.79 ± 82.12 ml idi. Primer cerrahi geçiren hastalarda intraoperatif kan kaybı revizyon hastalarına göre anlamlı olarak düşük olmakla birlikte, postoperatif kan kaybı açısından fark yoktu. Spinal segment sayısı, ameliyat süresi, yaş ve ASA ile doğru orantılıydı. Transfüze edilen ortalama kırmızı kan hücresi miktarı 1.5 ± 1.29 U idi. Hastalarımızda tromboemboli, nöbet veya böbrek yetmezliği gibi önemli bir komplikasyon ve yan etki ile karşılaşılmamıştı. **Sonuç:** Uygun dozajlar henüz belirlenmemesine rağmen, vertebra ameliyatlarında TXA'in 50 mg / kg yükleme dozunun önemli yan etkilere neden olmadan güvenle kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Traneksamik asit; skolyoz; spinal füzyon; kan kaybı,cerrahi; antifibrinolitik ajanlar

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Spinal instrumentation applications including soft tissue dissection, bone decortication, osteotomies, and surgical correction during vertebral surgeries can cause significant blood loss.[1] It is known that the amount of blood loss increases in proportion to the duration of surgery, male sex, the presence of preoperative kyphosis and revision surgeries.[2] Despite advances in surgical techniques, blood loss up to 500-2000 ml can be observed in these surgeries. Bleeding and blood transfusion may result in undesirable conditions such as increased postoperative infection rates, delayed wound healing, impaired respiratory function, long hospital stays and increased costs for patients.[3,4] Therefore, various techniques are applied to minimise perioperative blood loss and reduce the need for allogeneic blood products in vertebral surgeries. Modified anesthesia techniques, surgical dissection techniques, use of cell salvage systems, local hemostatic agents and intraoperative antifibrinolytic agents have yielded effective results in safely reducing blood loss during surgery.[5,6] Maintaining intravascular volume and ensuring haemodynamic optimisation plays an important role in reducing postoperative morbidity and mortality. Minimally invasive cardiac output and index monitoring methods can be useful to personalise perioperative fluid therapy and avoid administering excess fluids.[7]

Frequently, antifibrinolytic drugs such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are used in order to reduce blood loss and transfusion need in patients undergoing spinal surgery. TXA is a synthetic lysine analogue that reversibly blocks lysine binding sites on plasminogen molecules and prevents fibrinolysis.[8] TXA is used in a wide dose range in patients of different ages undergoing a variety of surgical procedures.[9] Even though antifibrinolytic agents are typically considered safe, they may be associated with side effects such as thrombotic events and seizures. Appropriate dosages to maximise effect and minimise risk remains not to be fully established.[9,10]

In this retrospective study, we aimed to evaluate the amount of blood loss, need of transfusion and postoperative side effects in the patients who underwent vertebral surgery due to deformities such as scoliosis, kyphosis or kyphoscoliosis and received high doses of TXA intraoperatively.

MATERIAL AND METHODS

After receiving study approval from the University of Health Sciences Istanbul Fatih Sultan Mehmet Health Research and Training Centre Scientific Studies Commission (Date: 26/06/2019, Issue: 17073117-050.06-E.147) and in accordance with the Helsinki Declaration Principles, this retrospective study was conducted by evaluating the records of 34 patients aged ≥ 10 years with the American Society of Anaesthesiology (ASA) physical status I–III who underwent level ≥5 vertebral surgery in the orthopaedics clinic between January and June 2019. Patients with diagnosed coagulopathy were excluded from the study. Age, gender, height, weight, body mass index (BMI), ASA physical status, duration of operation (incision to skin closure), number of fused spinal segments, preoperative vertebral deformity level (Cobb angle), perioperative haemoglobin (Hb) levels, platelet count, international normalised ratio (INR), blood urea nitrogen (BUN) and creatinine levels, perioperative hemodynamic parameters, intraoperative and postoperative blood loss within the first 24 h, intraoperative and postoperative urine output within the first 24 h, the amount of blood and blood products used, TXA amount, postoperative side effects and complications observed within the first 24 h and length of stay in hospital of the patients were recorded. All patients were operated by the same surgical team. Anaesthesia was administered by different anaesthesiologists using the same anaesthetic method. Propofol (2-2.5 mg/kg), fentanyl (1-2 µg/kg) and rocuronium (0.6 mg/kg) were used for anaesthesia induction; anaesthesia was maintained using propofol (4-12 mg/kg/h) and remifentanil (0.05-0.5 µg/kg/min), and anaesthesia depth was maintained using intravenous anaesthesia with a bispectral index value between 40 to 60. Central venous catheterisation, invasive arterial blood pressure monitoring, and minimally invasive cardiac output monitoring (FloTrac/Vigileo/EV1000, Edwards Life sciences, Irvine, CA, USA) were performed in addition to the routine monitoring. To prevent intraoperative hypothermia, active

heating was applied with compressed air heating blankets under the patient.

After surgical incision, the patients received 50 mg/kg of TXA infused in 1 hour, followed by a maintance infusion of 10 mg/kg/h intravenously until skin closure. Intraoperative blood loss for each patient were measured by anesthesiologists by weighing surgical sponges and measuring the volume of blood collected by suction canisters. The weight of irrigation fluids added to the surgical field and the sponge weight were then subtracted from this value. Intraoperative blood loss was calculated in ml for each hour of duration of operation and per number of fused vertebrae. Postoperative blood loss was measured from the volume of blood accumulated in the drainage bags during the first 24 hours. Total blood loss was calculated as the sum of intra and postoperative blood loss. Estimated preoperative total blood volume was calculated by multiplying the ideal body weight by 70 ml for each patient. Postoperative urine volume is the total amount of urine in millilitres in the first 24 h. Intraoperative transfusion was performed when acute blood loss reached 20% of estimated total blood volume for any patient or in case of fluid refractory hypotension or Hb<8 g/l. To provide hemodynamic optimization, stroke volume variation (SVV) guidance was used in fluid replacement. When the SVV is greater than 10 %, the fluid replacement rate has been increased. Crystalloids (Biofleks Izoleks-S, Osel, Turkey and Polifleks Lactated Ringer,Polifarma, Turkey) and colloid fluids (Voluhes-HES 6%, Polifarma, Turkey) were used in fluid replacement. Collois fluids were used in a balanced manner with crystalloid fluids in order to delay transfusion early in the operation and for rapid volume replacement in the period with acute blood loss during surgery. The volumes of administered fluids were calculated separately in millilitres. The following considerations were made for transfusions: one packed of erythrocyte suspension (ES) = 1 unit (U) (285 ml) and one packed of fresh frozen plasma (FFP) = 1 U (250 ml) used. The recorded data were statistically evaluated.

STATISTICAL ANALYSIS

Descriptive statistics are presented as mean ± standard deviation for normally distributed continuous variables, median (min-max) for non-normally distributed continuous variables, whereas frequency values and percentages are presented for qualitative variables. Mann-Whitney U test was used for between-group comparisons. Repeated measures ANOVA was used for the analysis of time-dependent measurements. Bonferroni test, a multiple comparison test, was used for results that were found to be significant. The correlations between the variables were analysed using Pearson and Spearman correlation coefficients. Significance level was defined as $\alpha = 0.05$. The statistical analysis of the data was performed using IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) programme.

RESULTS

The demographic data of the patients, preoperative mean arterial pressure (MAP), Cobb angles, duration of operation, diagnosis, surgery type, number of fused segments and length of stay in hospital (LOS) are presented in Table 1.

The total amount of TXA used, intraoperative and postoperative blood loss, the amount of fluid administered, erythrocyte suspension, blood products and urine output are given in Table 2.

1U thrombocyte apheresis was administered to one patient when platelet count was 67,000/µl within the first 24 h postoperatively.

When the preoperative and postoperative 0^{th} and 24^{th} hour values of Hb, Plt, BUN, creatinine and INR variables were compared, a significant difference was observed for all (Table 3). Preoperative measurements differed for all variables. Hb, Plt, BUN and creatinine values decreased postoperatively, whereas the INR value increased.

The side effects observed within the first 24 h postoperatively and their incidences are presented in Table 4.

A positive, moderately significant correlation was found between the number of fused segments and intraoperative blood loss ($r = 0.473$; $p = 0.005$) (Figure 1).

Furthermore, a positive, moderately significant correlation was found between duration of operation

TABLE 1: Demographic data, preoperative MAP, Cobb angle, duration of operation, surgery type, number of fused segments, LOS and diagnosis.

Variable	
Age (years) (mean ± sd)	21.24 ± 13.78
Age <18 vs. ≥18 (n,%)	21 (61.8%) / 13(38.2%)
Sex (M/F) (n,%)	7 (20.6%)/27 (79.4%)
BW (kg) (mean ± sd)	53.88 ± 13.73
Height (cm) (mean ± sd)	159.79 ± 9.24
BMI (kg/m^2) (mean ± sd)	21.04 ± 4.86
ASA (n,%)	
1	6 (17.6%)
2	17 (50%)
3	11 (32.4%)
Preoperative MAP (mmHg) (mean ± sd)	83.65 ± 10.74
Cobb angle (°) (mean ± sd)	58.53 ± 18.43
Duration of operation (min) (mean ± sd)	494.12 ± 119.37
Surgery type (primary/revision surgery) (n,%)	29 (85.3%)/5 (14.7%)
Number of fused segments [median(min-max)]	12 (7-13)
LOS (days) (mean ± sd)	6.38 ± 1.94
Diagnosis (n,%)	
Scoliosis	
Adolescent idiopathic scoliosis	16 (47.1%)
Neuromuscular scoliosis	4 (11.8%)
Revision	5 (14.7%)
Kyphosis	
Scheuermann kyphosis	5 (14.7%)
Posttraumatic kyphosis	1 (2.9%)
Kyphoscoliosis	3 (8.8%)

Descriptive statistics are presented as mean±standard deviation, median(min-max) or frequency and percentages.
BW: body weight, BMI: body mass index, ASA: American Society of Anaesthesiology, MAP: mean arterial pressure, LOS: length of stay in hospital.

and intraoperative blood loss (r = 0.541; p = 0.001) (Figure 2).

A significant difference was found between patients undergoing primary and revision surgeries in terms of intraoperative and total blood loss; however, no significant difference was found in terms of postoperative blood loss. Intraoperative and total blood loss was higher in patients who underwent revision surgery than in those who underwent primary surgery (Table 5).

When correlations of age and ASA physical status with intraoperative, postoperative and total blood loss were examined, a positive moderate correlation was found between age and blood loss in all periods. While ASA physical status did not show a significant correlation with postoperative blood loss, it showed a positive and moderately significant correlation with intraoperative and total blood loss (Table 6).

No significant difference was found between the sex in terms of intraoperative, postoperative and total blood loss.

DISCUSSION

In this retrospective study, we aimed to evaluate the amount of blood loss, need of transfusion and postoperative side effects in the patients who underwent vertebral surgery and received high doses of TXA intraoperatively.

The data of 34 patients were retrospectively analysed in this study. Of all, 25 patients were diagnosed with scoliosis, 6 with kyphosis and 3 with kyphoscoliosis, and posterior spinal instrumentation and osteotomy were performed for all patients. Median value of fused segments was 12 (7-13), and the mean duration of operation was 494.12 ± 119.37 min. We observed a significant and moderate correlation among the number of fused segments, duration of operation and intraoperative blood loss. In the study of Shapiro et al. including patients who underwent posterior spinal fusion due to Duchenne muscular dystrophy, intraoperative blood loss was 1944 ± 789 ml in patients who were administered TXA (100 mg/kg bolus dose and infusion dose of 10 mg/kg) and 3382 ± 1795 ml in those who were not administered TXA; and the authors reported that there was no correlation between duration of operation and intraoperative blood loss in patients in the TXA group.[11] Goobie et al. reported that the blood loss amount per hour was 190 ± 73 ml/h in the TXA group and 230 ± 80 ml/h in the placebo group in the intraoperative period in adolescent idiopathic scoliosis patients.[9] They used the TXA at a loading dose of 50 mg/kg and a maintenance dose of 10 mg/kg/hour. Lykissas et al. reported that the mean intraoperative blood loss was significantly lower in the receiving high doses (100 mg/kg bolus dose and infusion dose of 10 mg/kg) TXA (537 ml) than in the placebo group (1245 ml). The mean volume of blood transfused intraoperatively was 426 ml

TABLE 2: Evaluation of the TXA amount used intraoperatively in patients, intraoperative and postoperative blood loss, fluid administered, blood products and urine output.

Variable	Mean ± SD	Median (Min-max)
Intraoperative TXA total dosage (mg)	6142.65 ± 2016.64	5925 (2750-11200)
Intraoperative blood loss		
Total blood loss (ml)	1448.53 ± 767.18	1350 (400-3300)
Blood loss per number of fused segments (ml/segment)	133.85 ± 61.77	125 (30-272)
Blood loss per hour (ml/h)	172.79 ± 82.12	161.5 (57-412)
Intraoperative urine output		
Total urine output (ml)	1298.53 ± 782.91	1100 (350-4000)
Urine output per hour (ml/h)	160.5 ± 89.8	142 (45-375)
Intraoperative ES (U)	1.5 ± 1.29	1 (0-4)
Intraoperative FFP (U)	0.71 ± 0.91	0 (0-3)
Intraoperative crystalloid (ml)	5205.88 ± 1638.17	5500 (1500-8500)
Intraoperative colloid (ml)	588.24 ± 398.3	500 (0-1500)
Postoperative 24th h blood loss (ml)	282.35 ± 199.96	250 (50-1000)
Postoperative 24th h urine output (ml)	1505.59 ± 775.41	1325 (400-3500)
Postoperative ES(U)	1.21 ± 1.01	1 (0-3)
Postoperative FFP (U)	0.32 ± 0.47	0 (0-1)
Postoperative crystalloid (ml)	1748.53 ± 682.96	1725 (550-4000)

Descriptive statistics are presented as mean ± standard deviation and median(min-max).TXA: tranexamic acid, ES: erythrocyte suspension, FFP: fresh frozen plasma, U: unit.

TABLE 3: Hb, INR, BUN and creatinine values.

	Preoperative	Postoperative Hour 0	Postoperative Hour 24	p-value
Hb (g/dl)	13.23 ± 1.31	9.55 ± 1.23*	9.81 ± 0.97*	<0.001
Plt (10^3/ul)	282.35 ± 81.08	182.19 ± 69.78*	185.38 ± 55.64*	<0.001
BUN (mg/dl)	10.53 ± 3.78	8.97 ± 2.77*	8.94 ± 3.21*	0.002
Creatinine (mg/dl)	0.7 ± 0.1	0.59 ± 0.08*	0.58 ± 0.09*	<0.001
INR	1.03 ± 0.09	1.26 ± 0.12*	1.29 ± 0.14*	<0.001

*p < 0.05 (compared to preoperative values) Repeated measures ANOVA was used. In case of significance, Bonferroni test was used. Hb: haemoglobin, Plt: platelet count, BUN: blood urea nitrogen, INR: international normalised ratio.

TABLE 4: Incidence of side effects.

Variable	n (%) (n = 34)
Nausea	3 (8.8%)
Vomiting	1 (2.9%)
Thromboembolism	0 (0%)
Seizure	0 (0%)
Renal failure	0 (0%)
Other (allergic reaction, defect of vision)	0 (0%)

Descriptive statistics are presented as frequency and percentages.

and 740 ml for group TXA and group placebo.[12] Sui et al. found that in their study involving AIS patients, the estimated blood loss was 619 ml in the TXA group and 1125 ml in the non-TXA group.[13] In another study, high-dose TXA was reported to significantly reduce blood loss compared with the placebo, even though TXA did not reduce the transfusion rate in posterior spinal instrumentation surgeries.[14] In our patients, the mean total blood loss in the intraoperative period was 1448.53 ± 767.18 ml

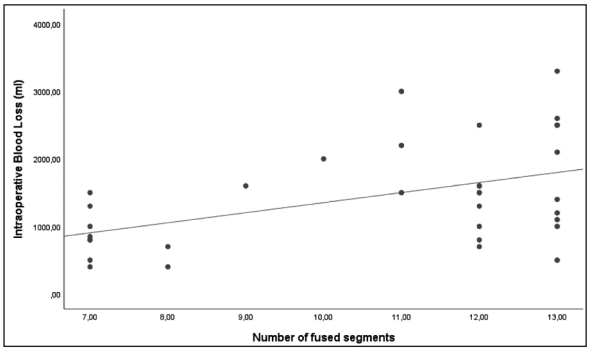

FIGURE 1: Relationship between intraoperatif blood loss and number of fused segments.

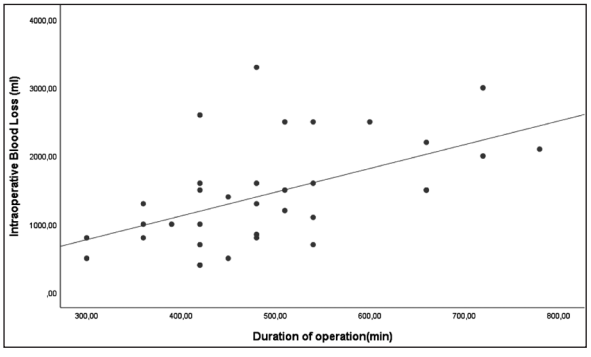

FIGURE 2: Relationship between intraoperatif blood loss and duration of operation.

and the mean blood loss according to duration of operation was 172.79 ± 82.12 ml/h. The ES amount administered per patient was 1.5 ± 1.29 U intraoperatively and 1.21 ± 1.01 U postoperatively. The fact that intraoperative blood loss in our patients was higher than some studies may have been due to our group having a heterogeneous diagnosis.

Minimal invasive cardiac output monitoring was used to guide fluid management in addition to conventional haemodynamic monitoring to avoid excess fluid administration; 5205.88 ± 1638.17 ml of crystalloid and 588.24 ± 398.3 ml of colloid fluids were used in the intraoperative period in addition to the blood products.

In our study, intraoperative blood loss of 29 (85.3%) patients who underwent primary surgery was significantly lower than 5 (14.7%) patients who underwent revision surgery. The age distribution of our patients included children and adults. We observed a directly proportional, moderate correlation between age and blood loss in all periods. Although a moderately positive correlation of ASA physical status was observed with intraoperative blood loss and total blood loss, no significant correlation was observed between sex and blood loss.

In our study, TXA was used in all of our patients and we do not have a placebo group. Therefore, we cannot evaluate the bleeding-reducing effect of TXA in our patient distribution. However, the use of TXA during vertebral surgery has been shown to be an effective, safe and inexpensive method to reduce blood loss in many prospective and retrospective studies.[14] In a meta-analysis including 644 patients of all age groups in whom different doses of TXA were used in spine surgery, TXA was found to reduce blood loss during and following the surgery as well as the total blood loss.[15] This study did not rule out concerns regarding the potential thrombogenic effect of TXA and reported that one patient in the TXA group developed myocardial infarction and one patient in the placebo group developed deep vein thrombosis. Verma et al. reported that TXA at a loading dose of 10 mg/kg and infusion dose of 1 mg/kg/h in spine surgeries, was effective in reducing intraoperative blood loss; furthermore, they did not report any renal, thromboembolic or other significant complication.[16] In another study comparing low dose TXA with placebo, it was stated that TXA reduced bleeding in adult spinal scoliosis cases, although there was no statistical difference. However, pulmonary embolism was detected in one of the patients a few weeks after the operation.[17] Neilipovitz et al. reported that there was no significant reduction in intraoperative blood loss using low dose of TXA.[18]

In a study in which intraoperative TXA was used at a loading dose of 50 mg/kg and infusion dose of 10 mg/kg/h in adolescent idiopathic scoliosis patients, it was reported that intraoperative blood loss decreased by 27% compared with that in the placebo group and that none of the patients developed postoperative complications such as thromboembolic events or clinical seizures.[9] In another study, TXA was reported to reduce intraoperative blood loss when administered at a loading dose of 100 mg/kg and infusion dose of 10 mg/kg; furthermore, no negative side effects were observed.[8]

The administration dose of TXA varies between 10 and 100 mg/kg for loading dose and between 1 and 10 mg/kg/h for continuous infusion dose.[8,10,19] The outcomes of dose-response trials of adults who underwent cardiac surgeries have shown the clinical benefit of high-dose TXA. [20] In one clinical trial, a dose of 100 mg/kg was found to be more effective than 50 mg/kg but equally effective compared with 150 mg/kg.[20]

TXA has been reported to increase the frequency of postoperative seizures, particularly at high doses, and it has been reported that the lowest effective TXA dose should be identified to reduce the risk.[21] In our patients, we administered TXA at a dose of 50 mg/kg, followed by an infusion dose of 10 mg/kg/h during the course of the surgery according to the preference of the orthopaedic surgical team. We did not encounter any serious complications or side effects such as thromboembolism, seizures or renal failure in our patients in the intraoperative or postoperative period. However, we observed nausea requiring additional medical treatment in three patients and vomiting in one patient. We considered that nausea and vomiting might have been induced by other drugs.

The heterogeneous distribution of our patients as a diagnostic group and the small number of cases are the limitations of our study.

CONCLUSION

Although the appropriate dosage of TXA to maximise its effect and minimise the risk remains not to be fully established, we did not observe any serious side effects of TXA in the dose ranges used by us. Although appropriate dosages are not yet established, we think that a loading dose of 50 mg/kg TXA can be used safely in vertebral surgeries without causing significant side effects.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Öznur Demiroluk, Ceren Köksal; **Design:** Öznur Demiroluk, Ceren Köksal, Dilek Erdoğan Arı; **Control/Supervision:** Öznur Demiroluk, Ceren Köksal, Ahmet Onur Akpolat; **Data Collection and/or Processing:** Öznur Demiroluk, Ceren Köksal, Ahmet Onur Akpolat, Mehmet Bülent Balioğlu; **Analysis and/or Interpreta tion:** Öznur Demiroluk, Ceren Köksal, Dilek Erdoğan Arı; **Literature Review:** Öznur Demiroluk, Ceren Köksal, Ahmet Onur Akpolat; **Writing the Article:** Öznur Demiroluk, Ceren Köksal; **Critical Review:** Öznur Demiroluk, Ceren Köksal, Dilek Erdoğan Arı; **References and Fundings:** Öznur Demiroluk, Ceren Köksal; **Materials:** Öznur Demiroluk, Ceren Köksal, Dilek Erdoğan Arı, Ahmet Onur Akpolat, Mehmet Bülent Balioğlu.*

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