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USE OF TRANEXAMIC ACID IN ADULTS SCOLIOSIS SURGERY: SYSTEMATIC REVIEW AND META-ANALYSIS

USO DO ÁCIDO TRANEXÂMICO NA CIRURGIA DE ESCOLIOSE EM ADULTOS: REVISÃO SISTEMÁTICA E METANÁLISE

USO DE ÁCIDO TRANEXÁMICO EN CIRUGÍA DE ESCOLIOSIS EN ADULTOS: REVISIÓN SISTEMÁTICA Y METAANÁLISIS

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ABSTRACT

To evaluate the effects of using tranexamic acid in scoliosis surgeries in adults. This meta-analysis considered bleeding as the main outcome, using the Mantel-Haenszel fixed model. Cochran's Q test was also used, whose null hypothesis is that the studies that make up the meta-analysis are homogeneous. After applying the exclusion criteria, seven of the eight papers previously selected were included in the statistical analyses, adding up to 911 patients (76 to 355 patients). The incidence rates of efficacy among experimentally treated patients were a geometric mean of 45%. Concerning blood loss, mean values were 1302 ± 490 in the control group versus 1108 ± 150 mL in the experimental group. Biological factors such as male gender and type of surgery did not influence the protective outcome of tranexamic acid in terms of reducing bleeding ($p > 0.05$). Age over 65 was statistically significant ($p = 0.04$) using the x2 test. This meta-analytical study showed that age over 65 is a factor that negatively influences the effects of tranexamic acid in reducing bleeding in scoliosis correction surgeries. ***Level of Evidence I; Randomized and Controlled Clinical Studies with homogeneous results.***

Keywords: Tranexamic Acid; Scoliosis; Surgery; Spine.

RESUMO

Avaliar os efeitos anti-hemorrágicos da utilização do ácido tranexâmico (TXA) nas cirurgias de escoliose em adultos. Nesta metanálise, considerou-se como principal desfecho o sangramento, utilizando-se o modelo fixo de Mantel-Haenszel. Também se empregou o teste Q de Cochran que apresenta como hipótese nula a afirmação de que os estudos que compõem a metanálise são homogêneos. Após a aplicação dos critérios de exclusão, dos 8 artigos previamente selecionados, 7 foram incluídos nas análises estatísticas, somando 911 pacientes (amplitude entre 76 e 355 pacientes). As taxas de incidência de eficácia entre os pacientes tratados experimentalmente foram, em média geométrica, de 45%. Em relação a perda de sangue, foram observados valores médios de 1302 ± 490 no grupo controle versus 1108 ± 150 mL no grupo experimental. Fatores biológicos como sexo masculino e tipo de cirurgia não influenciaram no desfecho protetor do TXA quanto à redução do sangramento ($p > 0,05$). Já a idade superior a 65 se mostrou estatisticamente significativa ($p = 0,04$) pelo teste de x2. Este estudo metanalítico demonstrou que a idade acima de 65 anos é um fator que aumenta o sangramento nessas cirurgias tendo o TXA pouca ação na redução do sangramento nesse grupo. ***Nível de Evidência I; Estudos Clínicos Randomizados e Controlados de Nível 1 cujos resultados foram homogêneos.***

Descritores: *Ácido Tranexâmico; Escoliose; Cirurgia; Coluna Vertebral.*

RESUMEN

Evaluar los efectos del uso de ácido tranexámico (TXA) en cirugías de escoliosis en adultos. Este metaanálisis consideró la hemorragia como resultado principal, utilizando el modelo fijo de Mantel-Haenszel. También se utilizó la prueba Q de Cochran, cuya hipótesis nula es que los estudios que componen el metaanálisis son homogéneos. Tras aplicar los criterios de exclusión, de los 8 artículos previamente seleccionados, 7 fueron incluidos en los análisis estadísticos, totalizando 911 pacientes (rango de 76 a 355 pacientes). Las tasas de incidencia de la eficacia entre los pacientes tratados experimentalmente fueron de una media geométrica del 45%. En cuanto a la pérdida de sangre, se observaron valores medios de 1302 ± 490 en el grupo de control frente a 1108 ± 150 mL en el grupo experimental. Factores biológicos como el sexo masculino y el tipo de cirugía no influyeron en el resultado protector del TXA en cuanto a la reducción de la hemorragia ($p > 0,05$). La edad superior a 65 años fue estadísticamente significativa ($p = 0,04$) mediante la prueba x2. Este estudio metaanalítico demostró que la edad superior a 65 años es un factor que influye negativamente en los efectos del TXA en la reducción de la hemorragia en las cirugías de corrección de la escoliosis. ***Nivel de Evidencia I; Estudios Clínicos Aleatorizados y Controlados de Nivel 1 cuyos resultados fueron homogéneos.***

Descriptores: *Ácido Tranexámico; Escoliosis; Cirugía; Columna Vertebral.*

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INTRODUCTION

Degenerative scoliosis (DS) is a three-dimensional spine deformity with a coronal deviation greater than ten degrees by the Cobb method. This pathology is associated with advanced ages, making it increasingly common as the population progressively ages and an important public health concern.[1]

Pathophysiologically, DS results from the asymmetric degeneration of the intervertebral discs and facet joints, unbalancing the axial forces that pass through the spine. The progression is dynamic and has three dimensions: forming osteophytes and narrowing the spinal canal. This instability destroys the facets and discs, culminating in spondylolisthesis, laterolisthesis, and imbalances in the coronal and sagittal planes.[2-7] The restoration of spinopelvic alignment in these planes is the main goal of surgical treatment (which has proven superior to conservative treatment).[8]

Patients with a large and rigid curve are often subjected to osteotomies (Smith-Petersen, Pedicle Subtraction, or Bridge) involving three columns and an anterior and posterior approach.[9] However, these surgical techniques have significant potential morbidity.

The corrective surgery for deformity involving many levels like this is associated with significant blood loss (which can reach an average volume of 3,000 mL) as it may require a large incision, long surgical time, and extensive bone resection. Blood transfusions to restore hemodynamic balance are necessary. Consequently, the chances of potential complications inherent to this procedure (such as infections, coagulopathies, immune reactions, circulatory overload, lung injuries, epidural hematomas, paralysis, and paraplegia) also significantly increase potential morbidity.[10-13]

Tranexamic acid (TXA) is one of the most effective and safe antifibrinolytic agents in hemorrhages. Its applicability has been recognized for about fifty years in major orthopedic surgeries, cardiac surgery, digestive tract surgery, gynecological surgery, liver transplantation, and cerebral hemorrhage surgery.[14,15]

The proteolytic enzyme plasmin is responsible for fibrinolysis and platelet activation. Its inhibition will reduce bleeding by reducing fibrin degradation and preserving platelets.[7] In turn, plasminogen is the inert precursor of plasmin and has several binding sites for the amino acid lysine. When lysine binds to the surface of fibrin or plasminogen receptors, it causes a conformational change in the molecule, allowing its activation. The tissue plasminogen activator released by the damaged endothelium binds to the one attached to fibrin, and proteolytic degradation occurs.[1,7]

TXA is a synthetic analog of lysine that blocks its binding site to plasminogen, preventing its activation.[7] It can also act as a competitive antagonist to inhibitory neurotransmitters that act on glycine and GABA (A) receptors in the central nervous system, causing hyperexcitability: a plausible explanation for the increase in seizures after intravenous administration of high doses.[16,17]

The efficacy of TXA in spinal deformity correction surgery is already known. However, evaluating the impact of reducing perioperative bleeding and blood transfusion rates in patients undergoing surgery for degenerative scoliosis correction and correlating these results with the different doses of tranexamic acid used in the literature is necessary and is the objective of this meta-analysis.

METHODS

This study was guided by the need to control perioperative complications (such as hemorrhages) in patients undergoing corrective surgeries for increasingly long-lived adult scoliosis. The selection of works used research in important scientific databases and was armed with a careful search strategy, as described below. The works were then exported to the reference management program Rayyan so that the author and a collaborator could evaluate them double-blindly, including their titles and abstracts, followed by the full texts.

Studies with animals, *in vitro* research, those that deviated from the use of tranexamic acid in the age group over 18 years, duplicates, incomplete studies, interviews, other meta-analyses, comments, comparisons between TXA and other drugs, as well as those involving this drug in surgeries other than adult deformity correction, were excluded from the research. On the other hand, studies that dealt with the use of the drug in the pre- and post-operative periods of corrective surgeries for degenerative scoliosis, case series, controlled observational studies, randomized or not, regardless of time or language, were utilized. The evaluated variables were the total number of patients, gender, age, BMI (Kg/m2), estimated blood volume-EBV (mL), the dose (loading and maintenance) of TXA administered in the pre, intra, and postoperative periods, pre and postoperative hemoglobin (Hb) (g/L), pre and postoperative hematocrit (%), duration of surgery (minutes), fixation and fused levels, decompression levels, osteotomy levels, intraoperative blood loss-IBL (ml), postoperative drainage (mL), total blood loss (mL), intra and postoperative red blood cell concentrates (units/mL), intra and postoperative transfusion rate (n, %), patients treated with transfusion, units of red blood cell concentrates administered during hospital stay, and postoperative complications.

The databases used for the selection of articles were Pubmed, Pubmed PMC, Web of Science, and Embase, using the following search strategy: *(((((((Adult OR Adults) OR ("Young Adult" OR "Young Adults")) OR ("Middle Aged" OR "Middle Age")) OR (Aged OR Elderly)) AND (("Degenerative Scoliosis"[Title/Abstract]) OR ((Scoliosis[MeSH Terms]) OR (Scoliosis[Title/Abstract] OR Scoliosis[Title/Abstract]))))) AND (((((((Postoperative Period[MeSH Terms]) OR ("Postoperative Period"[Title/Abstract] OR "Period, Postoperative"[Title/Abstract] OR "Periods, Postoperative"[Title/Abstract] OR "Postoperative Periods"[Title/Abstract])) OR ("Post-operative"[Title/Abstract] OR postoperative[Title/Abstract] OR "Post-operative"[Title/Abstract] OR "post-operative period"[Title/Abstract] OR "post-operative phase"[Title/Abstract] OR "post-surgery period"[Title/Abstract] OR "post-surgical period"[Title/Abstract] OR "postoperative phase"[Title/Abstract] OR "postsurgery period"[Title/Abstract] OR "postsurgical period"[Title/Abstract])) OR ((Perioperative Period[MeSH Terms]) OR ("Perioperative Period"[Title/Abstract] OR "Period, Perioperative"[Title/Abstract] OR "Periods, Perioperative"[Title/Abstract] OR "Perioperative Periods" [Title/Abstract]))) OR ("peri-operative period"[Title/Abstract] OR "peri-surgical period"[Title/Abstract] OR "perisurgical period"[Title/Abstract])) OR ((Surgical Procedures, Operative[MeSH Terms]) OR ("Surgical Procedures, Operative"[Title/Abstract] OR "Operative Procedures"[Title/Abstract] OR "Operative Procedure"[Title/Abstract] OR "Operative Surgical Procedures"[Title/Abstract] OR "Surgical Procedures"[Title/Abstract] OR "Surgical Procedure"[Title/Abstract] OR "Operative Surgical Procedure"[Title/Abstract]))) OR (surgery[Title/Abstract] OR operation[Title/Abstract]))) AND (("Tranexamic Acid"[MeSH Terms]) OR ("Tranexamic acid (TXA) "[Title/Abstract] OR "TXA - tranexamic acid"[Title/Abstract] OR TXA[Title/Abstract]))) AND (((((((Hemorrhage[MeSH Terms]) OR (Hemorrhage[Title/Abstract] OR Hemorrhages[Title/Abstract] OR Bleeding[Title/Abstract])) OR ((Blood Loss, Surgical[MeSH Terms]) OR ("Blood Loss, Surgical"[Title/Abstract] OR "Surgical Blood Loss"[Title/Abstract] OR "Surgical Blood Losses"[Title/Abstract] OR "Surgical Hemorrhage"[Title/Abstract] OR "Surgical Hemorrhages"[Title/Abstract]))) OR ("operative bleeding"[Title/Abstract] OR "operative haemorrhage"[Title/Abstract] OR "operative hemorrhage"[Title/Abstract] OR "peroperative bleeding"[Title/Abstract] OR "peroperative blood loss"[Title/Abstract] OR "peroperative haemorrhage"[Title/Abstract] OR "peroperative hemorrhage"[Title/Abstract])) OR ((Postoperative Hemorrhage[MeSH Terms]) OR ("Postoperative Hemorrhage"[Title/Abstract] OR "Postoperative Hemorrhages"[Title/Abstract] OR "Postoperative Blood Loss"[Title/Abstract]))) OR ("postoperative bleeding"[Title/Abstract])) OR ((Blood Transfusion[MeSH Terms]) OR ("Blood Transfusion"[Title/Abstract] OR "Blood Transfusions"[Title/Abstract]))) OR ("transfusion therapy"[Title/Abstract] OR hemotherapy[Title/Abstract] OR "blood replacement"[Title/Abstract]))*.

The systematic literature review was based on the Cochrane Model (Cochrane Handbook for Systematic Reviews of Interventions version 6.1, 2020) and the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The

titles, abstracts, references, and names of the selected database were exported to Rayyan's reference management program. A systematic review and meta-analytic study were developed to evaluate the interference factors in therapeutic efficacy by comparing the use of tranexamic acid in two situations: the reduction of blood loss {a} and the other related to the demand for blood transfusion {b}. To this end, the outcome complications were applied as one of the analysis measures, using the fixed model of Mantel-Haenszel (MH) for risk factors, especially the age range of the patients.

The MH statistical model considers the following components for calculation: Yj (desired effect / less blood loss or no need for transfusions) = $\theta M + \varepsilon j$ (where, εj is the random error of the study, and θM is the effect common to all studies, based on applied sampling and statistical methodology). The Q test by Cochran, a key tool in our meta-analysis, was employed to present a null hypothesis that the studies comprising the meta-analysis are homogeneous regarding the randomized analyses and the therapeutic interventions proposed based on the efficacy percentages of the therapies applied randomly in the hypothesis tests performed, and in the association measures identified in the articles with adjustments by the I^2 test, = (Q-df)/Q x 100, where Q is based on Cochran's Q test (as proposed by Higgins & Thompson.[18] The association measures Relative Risk (RR) or Odds Ratio (OR) will be evaluated elements for the consecration of clinical trial studies.

Initially, 223 studies were identified that met the previously established search string. The inclusion criteria consider only articles that describe quantitative or qualitative studies discussing the use of tranexamic acid in adult scoliosis correction surgeries. After reading the titles and abstracts of the 223 previously selected articles, 208 were excluded from the sample based on the already described criteria. Eight of the 15 remaining studies were also excluded after a detailed reading of their content, leaving seven articles included in the sample for the meta-analysis. The work was measured based on the epidemiological methodology taken as a basis for its development (cohort or clinical trials), in addition to risks of sampling biases, applied statistics, and probabilistic and statistical inference methods based on hypothesis tests (Student's T-test or Mann-Whitney test), based on the results of the symmetrical measurement of the Gaussian curve (parametricity), calculated by the Shapiro-Wilk test.

The X2 test will analyze quantitative variables with more implicated outcomes to assess associative significance. All statistical analyses were performed in STATA, version 16 (2019) software, using an alpha of 5% (0.05) as the statistical parameter. Regarding the variables involved in the outcomes, age group, sex, and surgical procedures were analyzed in the studies identified in the bibliographic survey.

RESULTS

After applying the exclusion criteria, of the eight previously selected articles, seven were included in the statistical analyses considering only clinical trials that grouped control patients (without the use of tranexamic acid) and experimental patients (with the use of tranexamic acid) in addition to sample robustness (Figure 1). The selected works showed good heterogeneity when grouped. However, when evaluating the outcomes individually, the need for transfusions did not show agreement, with the reduction of bleeding in the experimental groups being more consistent among the analytical models of Standard Error (stipulated at 3%), sampling, and description implied by the use of association measures (Tables 1 and 2).

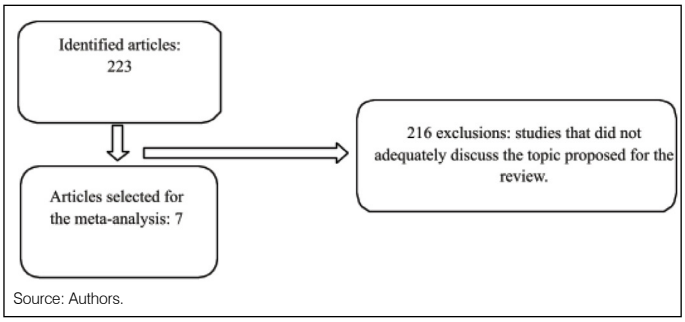


Figure 1. Flowchart of the process of inclusion/exclusion of articles.

As for the causal factors for the processes involving bleeding in the experimental group, age was the most influential variable, with an Odds ratio of 3.2 (CI: 1.6 – 4.7) and a p-value = 0.039. In total, the seven selected studies included 911 patients, ranging between 76 and 355. In this sample group, the average age was 61 years (CI: 20 – 85 and a range of 18 years), with 52% being male. The incidence rates of efficacy among experimentally treated patients were, on a geometric average, 45%. Regarding blood loss, mean values of 1302 ± 490 were observed in the control group *versus* 1108 ± 150 mL in the experimental group. The calculations were performed after consolidating the parametricity of the data (Shapiro-Wilk Test – p = 0.03), followed by the confidence intervals of the percentages with the standard error-SEa-corrected by stratification: √p (1-p) /n and with 95% confidence = p'- 1.96xSEa; p" + 1.96SEa), as shown in Table 3.

The characteristics involving the data collection of each evaluated work are described in Table 4. Biological factors such as male sex and type of surgery did not influence the protective outcome of tranexamic acid in terms of bleeding reduction (p > 0.05). Age over 65 was statistically significant (p = 0.04) by the x^2 test.

In Figure 2, it is possible to observe the Forest Plot which included the articles that effectively compared the age under 65 years and the reduction in bleeding rates based on the I^2 statistic considering the patients in the control group, experimental group, and weight in relation to heterogeneity*.

Table 1. Q Test values and I2 test for meta-analysis of the seven articles that evaluated therapeutic efficacies, considering the period between 2015 and 2020, regarding blood loss.

	Test Q	Value of p	I^2
Coefficient	1.327	0.00021	80%
Heterogeneity residue test	0.158	0.01084	-

Source: Authors.

Table 2. Q Test Values and I2 test for meta-analysis of the seven articles that evaluated therapeutic efficacies, considering the period between 2015 and 2020, regarding the demand for transfusions.

	Test Q	Value of p	I^2
Coefficient	1.327	0.062	34%
Heterogeneity residue test	2.18	> 0.05	-

Source: Authors.

Table 3. Frequency of bleeding reduction rates, sample numbers, and temporal variation of data collection.

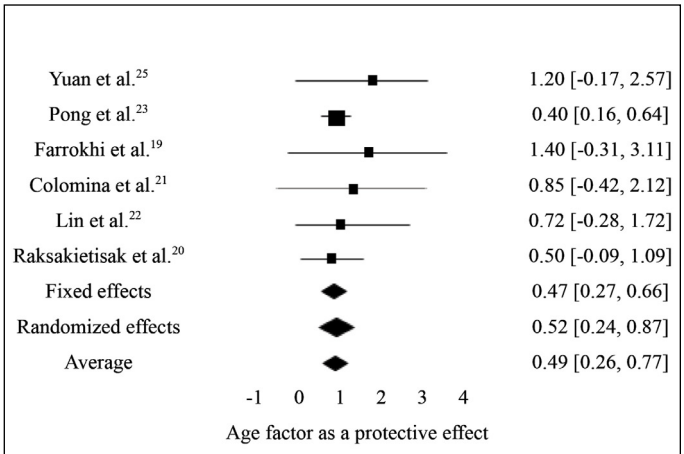
Parameters	Number of studies	Number of patients	Average reduction (%)	CI - inferior	CI - superior
Grouped results	7	911	45%	38%	52%
Analysis date					
Between 2011 and 2018	5 (71%)	383 (42%)	32%	21%	47%
Between 2019 and 2021	2 (29%)	528 (58%)	68%	42%	85%

CI = Confidence Interval. Source: Authors.

Table 4. Risk factors associated with reduced bleeding in samples of tranexamic acid users and values of association measures calculated by X^2.

Authors and year	Number of patients	Data source	Age risk factors > 65 years and low % reduction in bleeding with the use of acid	Weighted average of association measures (RR, OD)	IC* -lower	IC* -upper
Farrokhi et al. (2011)[19]	76	Shiraz Neuroscience Research Center; and Department of Anesthesiology, Shiraz University of Medical Sciences, Shiraz, Iran.	$p < 0.05$	3.2	1.98	4.7
Raksakietisak et al. (2015)[20]	78	Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand	$p < 0.05$	2.1	1.6	3.0
Colomina et al. (2017)[21]	95	Department of Anesthesia, Vall d'Hebron University Hospital, Barcelona	$p < 0.05$	2.8	0.9	5.2
Lin et al. (2017)[22]	100	Department of Orthopedic Surgery at Columbia University	$p < 0.05$	1.75	0.87	2.26
Pong et al. (2018)[23]	34	Virginia Mason Medical Center, Seattle, Washington	$p < 0.05$	3.6	2.1	5.5
Li et al. (2020)[24]	355	Jiamus University Affiliated Hospital - People's Republic of China	$p < 0.05$	1.3	0.75	1.81
Yuan et al. (2021)[25]	173	Department of Orthopedics, Third Hospital of Peking University, Beijing, People's Republic of China	$p < 0.05$	1.64	0.26	3.41

P values were observed by the X^2 adherence test. Source: Authors.



I2: 80%: Good heterogeneity. *Weight of the mean in relation to heterogeneity (MH and I2) for each article: Farrokhi et al.19 (13%), Raksakietisak et al.20 (17%), Colomina et al.21 (12%), Lin et al.22 (22%), Pong et al.23 (37%), Li et al.24 (12%) and Yuan et al.25 (11%). Source: Authors.

Figure 2. Forest plots based on the association measures implied the groups treated in relation to age < 65 years.

There was no significant difference identified in two articles, Colomina et al.[21] and Farrokhi et al.[19] considering the need for blood transfusions even in the treated group as well as the low heterogeneity analyzed among the data. In this case, there was no association of the studied phenomena with other variables, such as: sex and age.

DISCUSSION

The heterogeneity of the selected articles may be linked to the common methodology carried out by the authors, as well as to the results corroborated by all the evaluated articles, with emphasis given to the work of Pong et al.,[23] which implies significance in the protective factor compared to the other evaluated works. Overall, the TXA user groups showed reductions in bleeding, linking this outcome to age under 65 years (OR 0.83 – 95% CI 0.48 – 1.2). Thus, it was observed that the age group was the most influential variable in the incidence of bleeding in the experimental group, allowing us to state that individuals over 65 years old obtained worse results.

One factor to be considered in this meta-analysis is that no standardization was observed in the epidemiological variables along with the use of TXA, as differences were seen when considering the drug dosages, age factors, morbidity profile, and comorbidities among the studies. According to Colamina et al.,[21] spinal surgeries are associated with considerable blood loss during the perioperative period, making transfusion a frequent necessity. For the authors, the main factors influencing the occurrence of bleeding in this type of procedure include the extent of the surgery, careful tissue handling, the quality of the patient's vascular tissues, pre-existing medical comorbidities, the use of anticoagulant medications, specific surgical techniques, and the possibility of hidden blood loss. These results are corroborated by Li et al.,[20] who obtained the largest sample among the analyzed articles, reaching similar conclusions.

Through a retrospective cohort study, Tumber and colleagues,[26] compared high doses *versus* low doses of TXA as part of a strategy aimed at reducing blood loss in patients undergoing posterior fusion surgery for the treatment of scoliosis. To that end, they reviewed clinical records of 223 patients with scoliosis undergoing posterior spinal fusion of five or more levels over a period of six years. The normalized blood loss, the estimated total blood loss (EBL), and the need for transfusion were compared between patients who received high-dose TXA (loading dose ≥ 30 mg/kg) *versus* low-dose TXA (loading dose < 30 mg/kg). Both groups received maintenance infusions of TXA at 10 mg/kg/h until skin closure. As a result, it was observed that the demographic data, curves, and surgical characteristics of the patients were similar in both groups. Patients who were on high-dose TXA therapy had a 36% reduction in normalized blood loss (1.8 cc/kg/fused level *versus* 2.8 cc/kg/fused level, $p < 0.001$) and a 37.5% reduction in total EBL (1,000 cc *versus* 1,600 cc, $p < 0.001$). Still, patients in the high-dose group had a 48% reduction in packed red blood cells (pRBC) transfusion, with only 19% receiving a pRBC transfusion compared to 67% in the low-dose group ($p < 0.001$). For the authors, when combined with other proven patient blood management strategies, the use of high doses of TXA compared to low doses of TXA could be beneficial in reducing blood loss in patients with idiopathic scoliosis undergoing posterior spinal fusion surgery.

Colomina et al.,[27] commented that several factors could negatively influence the action of TXA. In addition to advanced age (particularly over 65 years), which may be associated with changes in renal and hepatic function, other factors include pre-existing renal disease, hepatic dysfunction, coagulation disorders (active

intravascular coagulation, acute occlusive vasculopathy), history of thromboembolic events (such as deep vein thrombosis or pulmonary embolism) and the concomitant use of certain anticoagulant or antiplatelet medications. These factors may interfere with the effectiveness of TXA in controlling bleeding, increasing the risk of hemorrhagic complications and thrombosis during surgical or traumatic procedures.

On the other hand, the patient's sex, as well as the type of surgery performed, did not influence the protective effect of TXA in reducing bleeding. Shrestha and colleagues,[28] in their meta-analysis, also concluded that the patient's sex would not affect the protective effects of TXA, nor the type of surgery performed.

It is important to point out that the analyzed studies were clinical trials modeled by Odds ratio measures, measured for the forest plot configuration (Figure 2), allowing the identification of age group as a protective measure, and that they were based on unicentric analyses, with predefined samples (ranging from 76 to 355 patients). However, the works do not consider the randomization factor, suggesting the need for further studies with this epidemiological modeling, thus minimizing potential sampling and blinding biases.

CONCLUSION

This meta-analytic study demonstrated that age over 65 is a factor that increases the chances of bleeding to the detriment of the effects of TXA in reducing bleeding in surgeries for the correction of adult scoliosis, and this result is not influenced by the patient's sex. Based on the systematic review, it was possible to verify that TXA has protective efficiency among the younger population (45% less bleeding - 95% CI 38-52% and $p < 0.05$), as well as a significant average reduction in blood loss (1302 $\pm$ 490 in the control group *versus* 1108 $\pm$ 150 mL in the experimental group $<$ 65 years, p-value = 0.03). Thus, it is suggested to conduct intervention research to effectively prove the efficacy of TXA in surgeries performed in blinded groups, with the use of TXA associated with specific comorbidities among patients, in addition to surgical indications, so that protocols for the use of TXA more appropriate to the factors identified here can be established, especially the advanced age of the patients.

All authors declare no potential conflict of interest related to this article.

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REFERENCES

1. Silva FE, Lenke LG. Adult degenerative scoliosis: evaluation and management. Neurosurg Focus. 2010;28(3):E1.
2. Roughley PJ. Biology of intervertebral disc aging and degeneration: involvement of the extracellular matrix. Spine. 2004;29(23):2691–9.
3. Bao H, Zhu F, Liu Z, Zhu Z, He S, Ding Y, et al. Coronal curvature and spinal imbalance in degenerative lumbar scoliosis: disc degeneration is associated. Spine (Phila Pa 1976). 2014;39(24):E1441-7.
4. Kotwal S, Pumberger M, Hughes A, Girardi F. Degenerative scoliosis: a review. HSS J. 2011;7(3):257-64.
5. Zirbel SA, Stolworthy DK, Howell LL, Bowden AE. Intervertebral disc degeneration alters lumbar spine segmental stiffness in all modes of loading under a compressive follower load. Spine J. 2013;13(9):1134-47.
6. Homminga J, Lehr AM, Meijer GJ, Janssen MM, Schlösser TP, Verkerke GJ, et al. Posteriorly directed shear loads and disc degeneration affect the torsional stiffness of spinal motion segments: a biomechanical modeling study. Spine (Phila Pa 1976). 2013;38(21):E1313-9.
7. Boström J, Grant JA, Fjellström O, Thelin A, Gustafsson D. Potent fibrinolysis inhibitor discovered by shape and electrostatic complementarity to the drug tranexamic acid. J Med Chem. 2013;56(8):3273-80.
8. Le Huec JC, Cogniet A, Mazas S, Faundez A. Lumbar scoliosis associated with spinal stenosis in idiopathic and degenerative cases. Eur J Orthop Surg Traumatol. 2016;26(7):705-12.
9. Aebi M. The adult scoliosis. Eur Spine J. 2005;14(10):925-48.
10. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg. 2009;108(3):759-69.
11. Katz EA. Blood transfusion: friend or foe. AACN Adv Crit Care. 2009;20(2):155-63.
12. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med. 2007;356(22):2301-11.
13. Amiri AR, Fouyas IP, Cro S, Casey AT. Postoperative spinal epidural hematoma (SEH): incidence, risk factors, onset, and management. Spine J. 2013;13(2):134-40.
14. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999;57(6):1005-32.
15. Horrow JC, Hlavacek J, Strong MD, Collier W, Brodsky I, Goldman SM, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg. 1990;99(1):70-4.
16. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. Ann Neurol. 2016;79(1):18-26.
17. Sharma V, Katznelson R, Jerath A, Garrido-Olivares L, Carroll J, Rao V, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia. 2014;69(2):124-30.
18. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.
19. Farrokhi MR, Kazemi AP, Eftekharian HR, Akbari K. Efficacy of prophylactic low dose of tranexamic acid in spinal fixation surgery: a randomized clinical trial. J Neurosurg Anesthesiol. 2011;23(4):290-6.
20. Raksakietisak M, Sathitkarnmanee B, Srisaen P, Duangrat T, Chinachoti T, Rushatamukayanunt P, et al. Two Doses of Tranexamic Acid Reduce Blood Transfusion in Complex Spine Surgery: A Prospective Randomized Study. Spine (Phila Pa 1976). 2015;40(24):E1257-63.
21. Colomina MJ, Koo M, Basora M, Pizones J, Mora L, Bagó J. Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial†. Br J Anaesth. 2017;118(3):380-390.
22. Lin JD, Lenke LG, Shillingford JN, Laratta JL, Tan LA, Fischer CR, et al. Safety of a High-Dose Tranexamic Acid Protocol in Complex Adult Spinal Deformity: Analysis of 100 Consecutive Cases. Spine Deform. 2018;6(2):189-194.
23. Pong RP, Leveque JA, Edwards A, Yanamadala V, Wright AK, Herodes M, et al. Effect of Tranexamic Acid on Blood Loss, D-Dimer, and Fibrinogen Kinetics in Adult Spinal Deformity Surgery. J Bone Joint Surg Am. 2018;100(9):758-764.
24. Li W, Guan J, Guo Y, Wang J, Wang Y, Qu Y. Application of tranexamic acid for the perioperative period of patients undergoing scoliosis correction surgery. FARMACIA. 2020;68(6):1081–90.
25. Yuan L, Jiang Y, Liu Y, Zeng Y, Chen Z, Li W. Cost-Benefit Analysis of Using A Single Dose of Tranexamic Acid in Degenerative Lumbar Scoliosis Patients Undergoing Long-Segment Spinal Fusion Surgery: A Retrospective Study. Med Sci Monit. 2021;27:e930352.
26. Tumber S, Bacon A, Stondell C, Tafoya S, Taylor SL, Javidan Y, et al. High- versus low-dose tranexamic acid as part of a Patient Blood Management strategy for reducing blood loss in patients undergoing surgery for adolescent idiopathic scoliosis. Spine Deform. 2022;10(1):107-113.
27. Colomina MJ, Contreras L, Guilabert P, Koo M, M Ndez E, Sabate A. Clinical use of tranexamic acid: evidences and controversies. Braz J Anesthesiol. 2022;72(6):795-812.
28. Shrestha IK, Ruan TY, Lin L, Tan M, Na XQ, Qu QC, et al. The efficacy and safety of high-dose tranexamic acid in adolescent idiopathic scoliosis: a meta-analysis. J Orthop Surg Res. 2021;16(1):53.