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TRANEXAMIC ACID IN ADOLESCENT SCOLIOSIS SURGERY: A SYSTEMATIC REVIEW

ÁCIDO TRANEXÂMICO NA CIRURGIA DE ESCOLIOSE EM ADOLESCENTES: REVISÃO SISTEMÁTICA

ÁCIDO TRANEXÁMICO EN LA CIRUGÍA DE ESCOLIOSIS EN ADOLESCENTES: REVISIÓN SISTEMÁTICA

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ABSTRACT

The objective of this study was to conduct a systematic literature review to evaluate the impact of perioperative blood loss reduction and blood transfusion rate in patients undergoing adolescent idiopathic scoliosis correction surgery and to correlate these results with the different doses of tranexamic acid used in the literature. Ten databases (BVS, COCHRANE, EBSCOHOST, EMBASE, EPISTEMONIKOS, PROQUEST, PUBMED PMC, PUBMED, SCOPUS, WEB OF SCIENCE) were searched to find studies on the effectiveness of tranexamic acid in idiopathic scoliosis surgery. The mean differences in bleeding and transfusions were combined using a random-effects meta-analysis. A total of 17 studies with 1608 patients were included in the evaluation, demonstrating an Odds Ratio of 2.8 (95% CI: 0.8-4.3) as a measure of association for the risk of bleeding and transfusion in the control group (non-users of tranexamic acid), efficiency in reducing bleeding (p=0.03). Additionally, a mean reduction in bleeding of approximately 700 ml was observed. There was no statistical difference between the doses used. The systematic review showed that tranexamic acid effectively reduces bleeding and the need for transfusions, but there were no significant differences in the results between different doses of tranexamic acid. ***Level of Evidence II; Systematic Review.***

Keywords: Scoliosis; Tranexamic Acid; Perioperative Period.

RESUMO

O Objetivo desse estudo foi realizar uma revisão sistemática da literatura com finalidade de avaliar o impacto da redução de sangramento perioperatório e taxa de transfusão sanguínea em pacientes submetidos a cirurgia de correção de escoliose idiopática do adolescente, e correlacionar esses resultados com as diferentes doses de ácido tranexâmico utilizadas na literatura. Foram pesquisados dez bancos de dados BVS, COCHRANE, EBSCOHOST, EMBASE, EPISTEMONIKOS, PROQUEST, PUBMED PMC, PUBMED, SCOPUS, WEB OF SCIENCE para encontrar estudos sobre a eficácia do ácido tranexâmico em cirurgia de escoliose idiopática. As diferenças médias de sangramento e transfusões foram combinadas usando uma meta-análise de efeito aleatório. Um total de 17 estudos com 1608 pacientes foi incluso na avaliação. Demonstrando Odds Ratio 2,8 (95% IC: 0,8-4,3) como medida de associação para risco de sangramento e transfusão no grupo de pacientes controle (não usuários de ácido tranexâmico), eficiência na redução de sangramento (p = 0,03). Ainda, verificou-se uma redução média no sangramento de aproximadamente 700 ml. Não houve diferença estatísticas entre as doses utilizadas. A revisão sistemática mostrou que o ácido tranexâmico é eficaz na redução do sangramento e na necessidade de transfusões, mas não houve diferenças significativas nos resultados entre diferentes doses de ácido tranexâmico. ***Nível de Evidência II; Revisão Sistemática.***

Descritores: *Escoliose; Ácido Tranexâmico; Período Perioperatório.*

RESUMEN

El objetivo de este estudio fue realizar una revisión sistemática de la literatura con el fin de evaluar el impacto de la reducción del sangrado perioperatorio y la tasa de transfusión sanguínea en pacientes sometidos a cirugía de corrección de escoliosis idiopática en adolescentes, y correlacionar estos resultados con las diferentes dosis de ácido tranexámico utilizadas en la literatura. Se investigó en diez bases de datos: BVS, COCHRANE, EBSCOHOST, EMBASE, EPISTEMONIKOS, PROQUEST, PUBMED PMC, PUBMED, SCOPUS y WEB OF SCIENCE para encontrar estudios sobre la eficacia del ácido tranexámico en la cirugía de escoliosis idiopática. Las diferencias medias de sangrado y transfusiones se combinaron utilizando un metaanálisis de efectos aleatorios. Un total de 17 estudios con 1608 pacientes fue incluido en la evaluación, demostrando una Odds Ratio de 2,8 (IC del 95%: 0,8-4,3) como medida de asociación para

Study conducted by the Hospital das Clínicas of the School of Medical Sciences at Universidade Estadual de Campinas (HC/FCM/UNICAMP), Campinas, SP, Brazil.
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el riesgo de sangrado y transfusión en el grupo de control (no usuarios de ácido tranexámico) y eficacia en la reducción del sangrado (p = 0,03). Además, se observó una reducción promedio en el sangrado de aproximadamente 700 ml. No se observaron diferencias estadísticas entre las dosis utilizadas. La revisión sistemática mostró que el ácido tranexámico es efectivo en la reducción del sangrado y la necesidad de transfusiones, pero no hubo diferencias significativas en los resultados entre las diferentes dosis de ácido tranexámico. ***Level of Evidence II; Systematic Review.***

Descriptores: *Escoliosis; Ácido Tranexámico; Periodo Perioperatorio.*

INTRODUCTION

Tranexamic acid (TXA) was first used in the 1970s to treat upper gastrointestinal bleeding. Since then, its use has expanded to heart, digestive tract, and gynecological surgeries.[1,2] In the 2000s, it began to be studied in hip arthroplasty surgeries, analyzing its effect on bleeding during the operation.[3] At the end of the 2010s, its usefulness in spinal arthrodesis surgeries was investigated, particularly in cases of scoliosis in adolescents undergoing surgical treatment.[4]

Due to the extensive tissue dissection and instrumentation used during spinal arthrodesis, intraoperative bleeding is possible in volumes ranging from 800 to 3000 ml. As a result, it is often necessary to resort to allogeneic blood transfusion to restore the patient's hemodynamic balance.[4-6]

Although blood transfusion is safe and extremely common,[7] it is not without its associated risks and complications, such as infections (HIV, HCV), alloimmunization, transfusion-related acute lung injury, and circulatory overload. This leads to greater post-operative complications, increased mortality, and costs.[7,8]

To mitigate these risks, the introduction of antifibrinolytic therapy (AT) seeks to reduce the occurrence of bleeding during the perioperative period. This therapy aims to block the conversion of plasminogen into plasmin, breaking down fibrin deposits and reducing the degradation of fibrin clots responsible for blood clotting.

Studies such as that by Goobie et al.[7] have shown that the use of AT, specifically with tranexamic acid (TXA), a synthetic antifibrinolytic analog of lysine, can significantly reduce bleeding and transfusion rates in patients undergoing posterior spinal fusion surgery for scoliosis. The results showed a 27% decrease in intraoperative bleeding and a twofold reduction in clinically relevant bleeding (>20 ml/kg) compared to placebo.[7,9,10]

However, other studies suggest TXA may increase the risk of postoperative complications such as surgical site infections, pneumonia, pulmonary embolism, and deep vein thrombosis.[7,11]

The recommended tranexamic acid dose (TXA) for spinal fusion in patients with idiopathic scoliosis should be determined considering clinical efficacy, safety, and cost. Based on data from researchers in various parts of the world, especially in the last decade, TXA appears to be a low-cost, effective, and safe option for reducing bleeding during surgery to correct idiopathic scoliosis. However, the ideal dose of TXA is still controversial, with a wide variation in the literature and a lack of standardization for its use in this type of surgery. The relationship between TXA dose and clinical efficacy in this population still needs to be standardized and better understood.[4,12,13]

This study aimed to systematically review the literature to assess the impact of reducing perioperative bleeding and blood transfusion rates in patients undergoing surgery to correct adolescent idiopathic scoliosis and to correlate these results with the different doses of tranexamic acid used in the literature.

METHODOLOGY

A systematic review of the literature, a type of secondary study, was carried out according to the Cochrane Model (Cochrane Handbook for Systematic Reviews of Interventions version 6.1, 2020) and according to the PRISMA recommendation (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Search strategy

The studies were identified through systematic searches of electronic databases and search portals and reading reference lists of articles, including ten databases. Keywords [medical subject descriptor (MeSH) terms and free terms] were used that included Scoliosis AND ("Postoperative Period" OR "Postoperative" OR postoperative OR "Post-operative" OR "post-operative period" OR "post-operative phase" OR "post-surgery period" OR "post-surgical period" OR "postoperative phase" OR "postsurgery period" OR "postsurgical period" OR "Perioperative Period" OR "peri-operative period" OR "peri-surgical period" OR "presurgical period") AND ("Tranexamic Acid" OR "Tranexamic acid (TXA) " OR "TXA = tranexamic acid" OR TXA).

Inclusion and exclusion criteria

We considered studies (randomized and non-randomized clinical trials, controlled observational studies, or case series, with no restrictions on year or language) that used tranexamic acid (TXA) preoperatively and postoperatively in surgeries to correct adolescent idiopathic scoliosis. Animal and in vitro studies, literature reviews, case reports, duplicate articles, interviews, or comments were excluded. In addition, studies that did not seek to evaluate the use of tranexamic acid in adolescent scoliosis correction surgery and articles that were not published in full after attempting to contact the authors to obtain the study data were also excluded. The outcomes evaluated included: the volume of total blood loss reported, including intra-operative, post-operative, and total blood loss, doses of tranexamic acid (loading and maintenance), number of patients who received a blood transfusion, and volumes of transfused red blood cells.

Literature search results

A systematic search identified 695 articles: VHL (n = 49), COCHRANE (n = 16), EBSCOHOST (n = 53), EMBASE (n = 223), EPISTEMONIKOS (n = 14), PROQUEST (n = 19), PUBMED PMC (n = 27), PUBMED (n = 49), SCOPUS (n = 146), WEB OF SCIENCE (n = 99). These were exported to the EndNote and Rayyan reference management programs with titles, abstracts, references, and the database name from which they were extracted. The programs above automatically removed duplicate studies (398 articles excluded), leaving 297 articles for eligibility analysis.

41 full-text articles were evaluated, and 17 relevant articles were selected for evaluation and data extraction, as shown in Figure 1.

Data extraction

Initially, the titles and abstracts of the studies identified from the electronic search were independently assessed by two reviewers. Subsequently, the full text of each study considered possibly relevant was retrieved and reviewed independently by two authors. Each author compiled a list of studies they believed met the inclusion criteria. The lists were compared, and disagreements were resolved by discussion and consensus. Subsequently, the full text of each study considered possibly relevant was retrieved and reviewed independently by two reviewers. Each reviewer compiled a list of studies that met the pre-established inclusion and exclusion criteria, with the aid of a standardized clinical form, to record the primary reason for exclusion and to compose the flow of article selection and the objectives of this systematic review. The lists were compared, and disagreements were resolved by discussion and consensus.

Assessment of the quality of evidence and strength of recommendation

The assessment of the evidence's quality and the information's reliability used the Newcastle-Ottawa Scale (NOS) system to

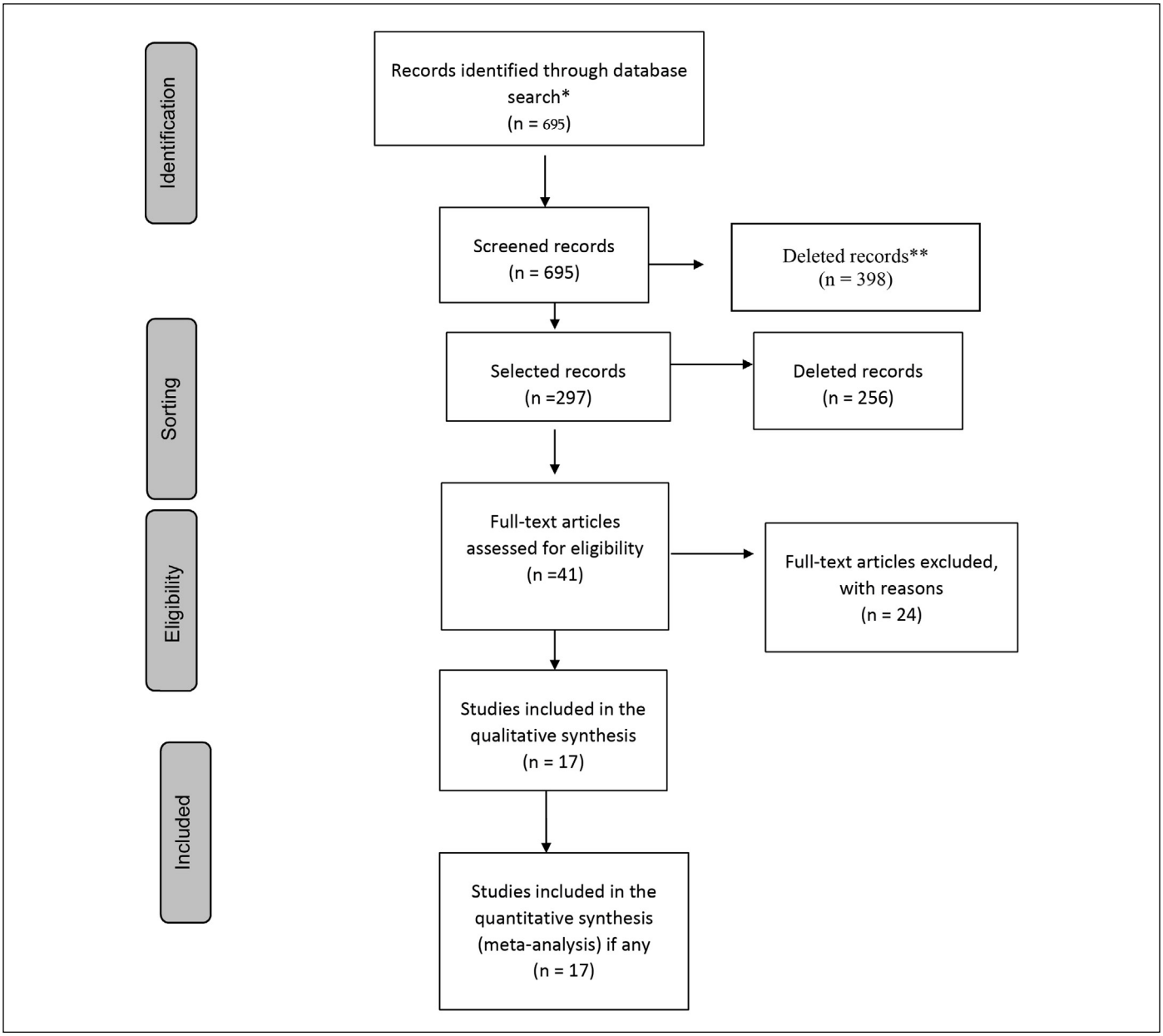

Figure 1. Flowchart illustrating the PRISMA methodology.

evaluate studies with non-randomized methodology, case controls, and cohorts. This assesses the quality of studies through a 'star system,' in which a study is judged from three broad perspectives: the selection of study groups, the comparability of the groups, and the verification of the exposure or outcome of interest for case--control or cohort studies.

A systematic review study was carried out to assess the factors associated with the drug's effectiveness in reducing blood loss and the consequent need for transfusions. To this end, measures of association applied in cohort studies and clinical trials, such as the Odds Ratio (OR) and the Relative Risk (RR), were considered. Given the different methodologies found in the texts, the analyses were carried out using the Mantel-Haenszel (MH) fixed model and the internal variance. These models consider the following components for calculation: Yj (desired effect) = $\theta M + \varepsilon j$ (where εj is the random error of the study, and θM is the effect common to all studies). In addition, the Higgins and Thompson models were used, the I 2 = (Q-gl) / Q x 100, where Q is based on Cochran's Q test ($Q = \Sigma wi (\theta i - \theta)$ 2, which presents the null hypothesis that the studies that make up the review are homogeneous.

Each of the 17 studies was measured based on the epidemiological methodology used (cohort or clinical trials), the risk of sampling bias, applied statistics, and the probabilistic and statistical inference method based on hypothesis tests (Student's t-test or Mann-Whitney test). Differences were inferred between groups treated or not with TXA about reduced blood loss and reduced need for transfusions in samples of adolescents (mean age 15 ± 4 years) undergoing spinal surgery.

The H0 of this study (null hypothesis) was defined as a statistical parameter in which the studies defined should be heterogeneous, based on average values of more than 50% between the MH and I2 tests, calculated on the geometric mean and variance of the statistical results of the 17 studies.

All statistical analyses were carried out using STATA software version 16 (2019), using an alpha of 5% (0.05) as the statistical parameter. We tried to distinguish between the variations in the use of TXA (high dose: from 50 mg/Kg, up to 100 mg/Kg, and less than 30 mg/Kg - low dose). Based on these parameters, the variations and risks associated with bleeding were calculated, considering the studies identified in the bibliographic survey.

RESULTS

After applying the inclusion and exclusion criteria, 17 articles were used for statistical analysis. The selected studies showed optimum homogeneity, revealing agreement between the analytical models of Relative Risk (with control groups not using TXA in surgery being considered as "exposed") for observational cohort studies (the most effective measure among those observed). It should be noted that in two experimental articles, the concordances were also significant regarding the results applicable to this review. Table 1 shows the absolute and relative frequencies associated with the quantitative (weighted average, patients, and confidence intervals) and qualitative (measures used) variables.

The characteristics involving the statistical analyses of the data and the evaluations of the degrees of systematic homogeneity, are described in Table 2.

The studies surveyed showed excellent homogeneity (average I2 and MH of 16%) regarding applications, objectives, and analytical designs. They are homogeneous in terms of the evidence's quality and the recommendation's strength, as shown in Table 3.

Table 1. Measures of association related to the risk of bleeding and transfusions in the control group (non-users of TXA).

Parameters	Number of studies	Number of patients	Weighted Average Measures of Association (RR, OD)	IC* -lower	IC* -superior
Grouped results	17	1608	2.8	0.8	4.3
Date of analysis					
Before 2010	1(6%)	52 (3.23%)	2.6	0.7	4.6
Between 2010 and 2021	16 (94%)	1556 (96.7%)	3.0	0.5	5.0
Type of Study					
Case series	1 (6%)	111 (7.0%)	2.1	0.4	3.9
Clinical trials	1 (6%)	254 (16%)	1.7	0.3	3.3
Observational	15 (88%)	1243 (77%)	3.2	1.6	4.2

*IC = Confidence Interval. Source: Data collected by the authors.

Table 2. The analytical weighting of the articles used and statistical methodologies.

Authors and year	Methodology	Weight of the average about homogeneity (MH and I2) for each article*
Hasan et al. (2021)[12]	Clinical trial	27%
Hideshima et al. (2021)[14]	Observational	12%
Halpern et al. (2021)[15]	Observational	8%
Tumber et al. (2021)[16]	Observational	9%
Bosch et al. (2019)[17]	Observational	13%
Goobie et al. (2018)[7]	Observational	7%
Jones et al. (2017)[18]	Observational	11%
Johnson et al. (2017)[4]	Observational	9%
Sui et al. (2016)[19]	Observational	6%
Ng et al. (2015)[20]	Observational	15%
Berney et al. (2015)[21]	Observational	19%
Rocha et al. (2015)[22]	Observational	26%
Ngo et al. (2013)[23]	Observational	18%
Lykissas et al. (2013)[24]	Review	21%
Verma et al. (2014)[25]	Observational	22%
Yagi et al. (2012)[26]	Observational	10%
Grant et al. (2009)[27]	Observational	11%

Source: Data collected by the authors.

Based on the results of this review, the null hypothesis was accepted, showing that the use of TXA effectively reduces bleeding ($p = 0.03$). Furthermore, based on the hypothesis tests (T), there was an average reduction in bleeding of approximately 700 ml when these patients were compared to the groups not exposed to TXA.[14-17] There was also a reduction in the need for transfusions ($p = 0.04$) based on comparisons made by Bosch et al.[17] and Yagi et al.[26] These data were confirmed by the RR and OR analyses shown in Table 1, where the unexposed groups had a higher incidence of blood loss and transfusions.

No statistical differences were observed in the results for the concentrations of doses under 30 mg, over 50 mg, and 100mg/Kg. The works of Tumber et al.[16] and Johnson et al. stand out. (2017),[4] who inferred dose comparisons and found reductions in blood loss in both dosages but demonstrated a greater impact in the high-dose group (>30mg/kg).

DISCUSSION

The homogeneity of the articles may be linked to the common methodology used by the authors, as well as the results corroborated by all the articles evaluated.

Overall, the TXA-using groups showed reductions in bleeding (OR 2.8, 95% IC 0.8-4.3), less need for transfusion, and an average reduction in bleeding of approximately 700ml. The studies by Goobie et al. can demonstrate this,[7] Johnson et al.[4], and Ng et al.[20], which showed reductions in bleeding after adjusting for weight, number of fused vertebrae, and curve severity. They had average bleeding values of 695ml, 968ml, and 794.3ml, respectively. These volumes are lower than the expected averages for posterior spinal arthrodesis for AIS correction.[4-6,16]

In addition, low doses were as effective as high doses of TXA in reducing blood loss and the need for allogeneic blood transfusion when adolescent patients were considered. These results corroborate those observed in a previous evaluation.[27]

Despite the impact observed on the blood transfusion rate in this group of patients with the use of TXA, as shown in Table 1, the lack of standardization in the transfusion criteria in the analyzed studies is evident. Different criteria were adopted for the transfusion of blood components, as exemplified by the work of Bosch et al., who used hemoglobin (hb) of less than 7g/dl as a criterion; on the other hand, Hideshima et al., and Conolley et al. were less permissive with the drop in hematometry. And thus, establishing higher hb criteria (9g/dl and 8g/dl, respectively). Therefore, the failure to standardize universally accepted criteria between studies can lead to fragility in the analysis of the relative risk of transfusion.

However, a reduction in the transfusion rate as well as a reduction in the volume of packed red blood cells transfused has been observed in patients using TXA.[20,23]

Table 3. Escala Newcastle-Ottowa.

Authors and year	Selection criteria	Comparability criterion	Outcome criteria
Grant et al. (2009)[27]	4	2	1
Lykissas et al. (2013)[24]	3	2	1
Jones et al. (2017)[18]	4	2	1
Halpern et al. (2021)[15]	4	2	2
Ngo et al. (2013)[23]	2	2	2
Rocha et al. (2015)[22]	3	2	3
Ng et al. (2015)[20]	4	2	2
Johnson et al. (2017)[4]	4	2	2
Tumber et al. (2021)[16]	4	2	2
Berney et al. (2015)[21]	4	2	2
Hideshima et al. (2021)[14]	3	2	2
Sui et al. (2016)[19]	3	2	2
Yagi et al. (2012)[26]	4	2	2
Bosch et al. (2019)[17]	4	2	2

One factor to consider is that there was no standardization in the use of TXA (Table 4) when considering the dosages for each patient's epidemiological profile, the surgical procedure performed, and any damage and immediate side effects. However, no statistical differences were found in the results for the concentrations of doses lower than 30 mg, higher than 50 mg, and 100mg/Kg. The works of Tumber et al.[16] and Johnson et al. stand out. (2017),[4] who inferred dose comparisons and found reductions in blood loss and transfusion rates in both dosages but demonstrated a greater impact with a 30% reduction in intraoperative bleeding and a 60% reduction in transfusion rates in the high-dose group (>30mg/kg). However, these findings diverge when compared to the randomized study by Hasan et al.,[12] which showed no statistical difference between high and low doses when assessing the reduction in total intraoperative bleeding. However, the three articles mentioned above were the only ones among the 17 articles that set out to evaluate and compare different TXA dose regimes with each other. The other articles made retrospective, non-randomized comparisons between tranexamic acid and placebo doses.

The clinical use of tranexamic acid (TXA) is based on a balance between clinical efficacy, safety, and cost, seeking to use the minimum effective dose with the lowest risk of adverse effects. However, there are reports in the current literature of an association between the use of TXA and seizures, pulmonary thromboembolism, and deep vein thrombosis. The articles selected in the systematic review showed four cases of surgical infection in the works by Halpern et al.[15] and Johnson et al.[4] and three cases of respiratory morbidity.[4] The studies evaluated did not report serious complications such as pulmonary thromboembolism, deep vein thrombosis, seizures, or mortality.

Observational trials (cohorts) were the most common type of study, given the practicality of the model in terms of comparing risk between exposed and unexposed groups, and the vast majority of studies were single-center, with small populations evaluated, and without established criteria for randomizing the sample. Therefore, some sampling biases should be borne in mind. These include failing to explicitly define randomized allocations between TXA-treated and untreated patients, a substantial lack of clinical trials with more detailed randomization and sample profiles, and inhomogeneity in blood management strategies. The procedures varied greatly between the institutions identified in the selected articles, and the concentrations did not follow a methodological pattern either.

Table 4. Tranexamic acid dose and % reduction in bleeding.

Authors and year	Dose (Attack/ Maintenance)	% Reduction in bleeding
Hasan et al. (2021)[12]	Low dose:10mg/kg-1mg/kg/h High dose: 30mg/kg-10mg/kg/h	no difference between high and low dose
Hideshima et al. (2021)[14]	1000mg, 1000mg every 5h surgery	73%
Halpern et al. (2021)[15]	10mg/kg-5mg/kg/h	18%
Tumber et al. (2021)[16]	Low dose: 20mg/kg-10mg/kg/h High dose: 50mg/kg-10mg/kg/h	37.5% HIGH DOSE GROUP
Bosch et al. (2019)[17]	30mg/kg-10mg/kg/h	No reduction identified
Goobie et al. (2018)[7]	50mg/kg-10mg/kg/h	27%
Jones et al. (2017)[18]	10mg/kg-1mg/kg/h	57%
Johnson et al. (2017)[4]	50mg/kg-5mg/kg/h	28%
Sui et al. (2016)[19]	100mg/kg-10mg/kg/h	57%
Ng et al. (2015)[20]	100mg/kg-10mg/kg/h	53%
Berney et al. (2015)[21]	15mg/kg-10mg/kg/h	45%
Rocha et al. (2015)[22]	100mg/kg-30mg/kg/h	29.7%
Ngo et al. (2013)[23]	50mg/kg-5 to 10mg/kg/h	20.54%
Lykissas et al. (2013)[24]	100mg/kg-10mg/kg/h	57%
Verma et al. (2014)[25]	10mg/kg-1mg/kg/h	14%
Yagi et al. (2012)[26]	1000mg-100mg/kg/h	43%
Grant et al. (2009)[27]	20mg/kg-10mg/kg/h	50%

CONCLUSION

Based on the systematic review, tranexamic acid effectively reduces bleeding OR 2.8 ($p = 0.03$), reduces average blood volume, and reduces the need for transfusions ($p = 0.04$). However, there were no statistical differences in the results for the concentrations of doses under 30 mg, over 50 mg, and 100mg/Kg. There was no standardization of the doses used between the studies.

It is therefore suggested that intervention research be carried out to effectively prove the efficacy of TXA in reducing the need for blood transfusion, controlling multifactorial phenomena that may increase the demand for transfusion, and establishing a protocol with adequate doses for clinical use.

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