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EFFECTIVENESS AND SAFETY OF TRANEXAMIC ACID IN TOTAL KNEE ARTHROPLASTY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

INTRODUCTION: Major elective orthopedic surgery is often associated with blood loss, requiring the need for blood transfusion. A possible pharmacological option to reduce surgical blood loss in total arthroplasty is the use of tranexamic acid. The objective of the study was to undertake a meta-analysis investigating the effects of tranexamic acid on knee arthroplasty.

MATERIAL AND METHODS: The study was designed as a systematic review and meta-analysis. The PubMed, Central, Web of Science, and Scopus databases were searched up to March 23, 2022, to identify randomized controlled trials concerning tranexamic acid (TXA) administration during knee arthroplasty. Overall and stratified pooled odds ratios (ORs) or mean differences (MDs) with their 95% confidence intervals (Cis) were obtained.

RESULTS: Fifty-two articles were included. Pooled analysis showed that hemoglobin changes in TXA group was 3.4 ± 3.1, compared to 4.03 ± 2.62 for non-TXA group (MD = −1.30; 95% CI: −1.57 to −1.03; I2 = 99%; p<0.001). Total blood loss was reported in 31 trials and was statistically significantly lower in the TXA group compared to non-TXA (MD = –391.51; 95% CI: −454.29 to −328.73; p < 0.001). Intraoperative blood loss was lower when using TXA rather than non-TXA (MD = −32.10; 95% CI: −50.63 to −13.58; p < 0.001). 24-hours blood loss from the drain was also lower with TXA than with placebo (MD = −228.68; 95% CI: −293.31 to −164.05; p < 0.001). The above dependencies also applied to the intravenous as well as topical application of TXA. Blood transfusion was performed in 11.2% of patients from TXA group, compared to 34.3% of patients treated with placebo (OR = 0.16; 95% CI: 0.11 to 0.22; p < 0.001). Deep vein thrombosis (DVT) was observed in 4.6% of patients treated with TXA, compared to 5.8% of patients treated with placebo (OR = 0.81; 95% CI: 0.49 to 1.35; p = 0.42) and pulmonary embolism was 0.5% in TXA group and 1.4% in placebo group (OR = 0.44; 95% CI: 0.15 to 1.36; p = 0.15).

CONCLUSIONS: Tranexamic acid is effective and safe in reducing blood loss, the requirement for blood transfusion, and drain output in patients undergoing knee arthroplasty.

KEY WORDS: tranexamic acid; TXA; knee arthroplasty; blood loss; bleeding control; meta-analysis

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INTRODUCTION

Tranexamic acid is an antifibrinolytic drug that can significantly reduce blood loss in the perioperative period in the case of total primary knee arthroplasty [1]. In the light of current research, its use is important in reducing intraoperative bleeding and the need for blood transfusion in the postoperative period in patients undergoing total knee arthroplasty [2]. The use of tranexamic acid in the perioperative period does not increase the risk of adverse thromboembolic complications [1, 3]. In selected groups of patients, the use of TXA without the use of a tourniquet gives comparable results in terms of reducing the risk of bleeding during surgery as the use of only a tourniquet [4]. Moreover, the use of TXA alone without the use of a tourniquet leads to the occurrence of smaller limb edema in the postoperative period, a greater range of mobility of the operated jointly at discharge from the hospital, and increased patient satisfaction [4]. There are no unambiguous recommendations regarding the dosage of the drug or the route of administration, however, intravenous distribution seems to have advantages over oral or infiltration [2]. The results of some studies indicate that the effectiveness of both intravenous and local administration is comparable, taking into account the total blood loss, including drainage, the control level of hemoglobin 24 hours after the procedure, and the incidence of complications, including infectious complications [5]. The most promising seems to be the simultaneous local and intravenous administration of TXA [6], as well as local and intra-arterial administration [7], however, there are no clear guidelines as to the dosage or timing of drug administration [6]. When trying to determine a safe dose of tranexamic acid, the potential cytotoxic effect on articular cartilage, tendons and synovium should be taken into account, however, doses up to 20 mg/mL seem safe. There is evidence that caution should be exercised with intra-articular administration of TXA and long-term observations with topical administration [8]. According to the current state of knowledge, the incidence of complications is rare. However, tranexamic acid should not be administered to patients with recent bleeding from the urinary tract, pulmonary embolism, or myocardial infarction, after percutaneous transluminal coronary angioplasty (PTCA) or after stent implantation, as well as in patients with a history of epilepsy [9]. In patients with the above-mentioned risk factors, other methods of limiting perioperative blood loss, including clamping the tube for a period of 3 hours, should be considered. Moreover, the combined use of temporary clamping of the tube and intra-arterial administration of tranexamic acid should be considered in patients with a high risk of bleeding or in the group of patients with the lateral release of the patella patellar in order to reduce complications of surgical site healing [10].

The objective of the study was to undertake a meta-analysis investigating the effects of tranexamic acid on knee arthroplasty.

MATERIAL AND METHODS

The study was designed as a systematic review and meta-analysis and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11].

Search strategy

We searched PubMed, Central, Web of Science, and Scopus databases (from inception to 23 March 2022). The search was performed using the following terms: "TXA" or "TA" or "tranexamic acid" and "knee" and "arthroplasty" or "replacement".

Study selection

Two reviewers (J.P. and M.P.) independently determined whether eligible studies met the following PICOS criteria: (1) Population: adult patients treated with knee arthroplasty; (2) Intervention: treated with tranexamic acid; (3) Controls: patients without TXA; (4) Outcomes: operation time, length of hospital stay, blood loss and adverse events concerning to TXA administration; (5) Studies: randomized controlled trials.

Exclusion criteria were as follows: reviews, non-randomized studies, animal studies, editorials, letters, case reports, conference or poster abstracts, or articles not containing original data.

Data extraction

The initial and full-text reviews and data extraction from the included studies were performed independently by two reviewers (J.P. and M.A-L.). Any discrepancies were resolved by discussion with the third review (L.S.), and a decision was reached by consensus. Data were collected using a predesigned form. For each study, the following information was extracted: the last name of the first author, year of publication, country of publication, study design, inclusion and exclusion criteria, TXA dose, and patient

characteristics in each group (number of patients, age, sex male), outcomes (*i.e.* operation time, length of hospital stay, adverse events type, blood loss parameters, need of transfusion).

Assessment of risk of bias

The methodological quality of the studies that met the selection criteria was appraised by two of the researchers independently (J.P., M.P.) to assess the risk of bias using the revised tool for risk of bias in randomized trials (RoB-2 tool) [12]. The risk of bias assessments was visualized using the Robvis application [13].

Statistical analysis

The Review Manager, version 5.4 EN (RevMan; The Cochrane Collaboration, Oxford, UK) was used to perform data analysis. The results are presented as forest plots using odds ratios (ORs) for dichotomous data and the mean difference (MD) for continuous data with 95% confidence intervals (CIs). The heterogeneity was tested using I^2 percentages to consider the impact potential heterogeneity would have on the meta-analysis. When there was heterogeneity across studies ($I^2 > 50\%$), the random effect model was used, whereas the fixed-effect model was used.

RESULTS

Study characteristics

Our initial searches identified 1043 articles. After duplicate removal, 729 articles were screened based on titles and abstracts. 93 articles were eligible for full-text assessment. Finally, 52 articles were included [14–65]. Figure 1 depicts the PRISMA flow chart of the literature search and article selection. Figure S1 and S2 (see Supplementary file) show the assessment of the risk of bias, agreed on by three reviewers of the individual studies using the Cochrane Collaboration's tool for assessing the risk of bias.

Bleeding outcomes

Hemoglobin changes in 24 hours after surgery was reported in 20 trials. Pooled analysis showed that hemoglobin changes in TXA group was 3.4 ± 3.1, compared to 4.03 ± 2.62 for non-TXA group [MD = −1.30; 95% CI: −1.57 to −1.03; I^2 = 99%; $p < 0.001$ (Fig. 2)]. Subgroup analysis concerning to type of TXA administration showed that the use of TXA compared to non-TXA was associated with

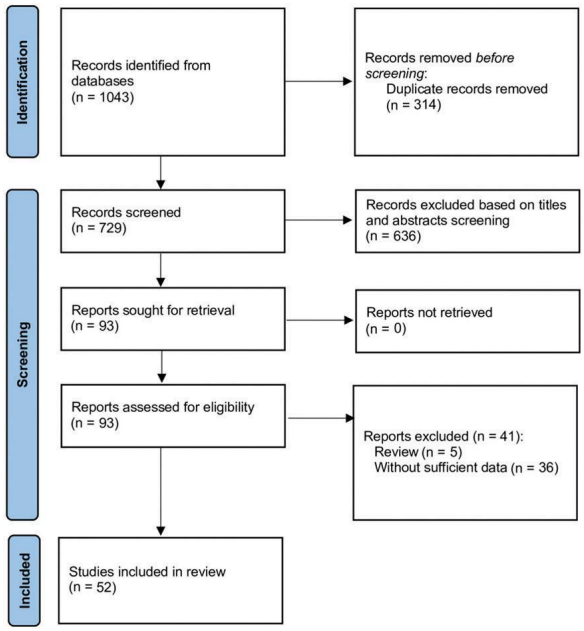

FIGURE 1. Meta-analysis flow chart of included and excluded studies

a statistically significantly lower decrease in hemoglobin levels both in terms of intravenous administration (4.15 ± 3.98 vs 4.36 ± 4.06, respectively; MD = −1.54; 95% CI: −1.89 to −1.19; $p < 0.001$) as well as in topical administration [2.4 ± 0.96 vs 3.1 ± 1.3; MD = −0.78; 95% CI: −1.03 to −0.54; $p < 0.001$ (Fig. S3, see Supplementary file)].

Total blood loss was reported in 31 trials and was statistically significantly lower in the TXA group compared to non-TXA [MD = −391.51; 95% CI: −454.29 to −328.73; $p < 0.001$ (Fig. 3)]. When analyzed in subgroups, applying TXA versus placebo-treated group showed a significant reduction in total blood loss for both intravenous (MD = −381.82; 95% CI: −461.48 to −302.15) and topical method of administration [MD = −436.21; 95% CI: −511.54 to −360.89; $p < 0.001$ (Fig. S4, see Supplementary file)].

Analysis of 14 trials showed that intraoperative blood loss was statistically lower when using TXA rather than non-TXA [MD = −32.10; 95% CI: −50.63 to −13.58; $p < 0.001$ (Fig. 4)]. Significant reductions in intraoperative blood loss have been observed with the intravenous administration of TXA compared to non-TXA treatment (MD = −31.12; 95% CI: −60.32 to −1.93; $p = 0.04$). A similar relationship was observed with the topical administration of TXA [MD = −28.41; 95% CI: −49.98 to −6.84; $p = 0.01$ (Fig. S5 , see Supplementary file)].

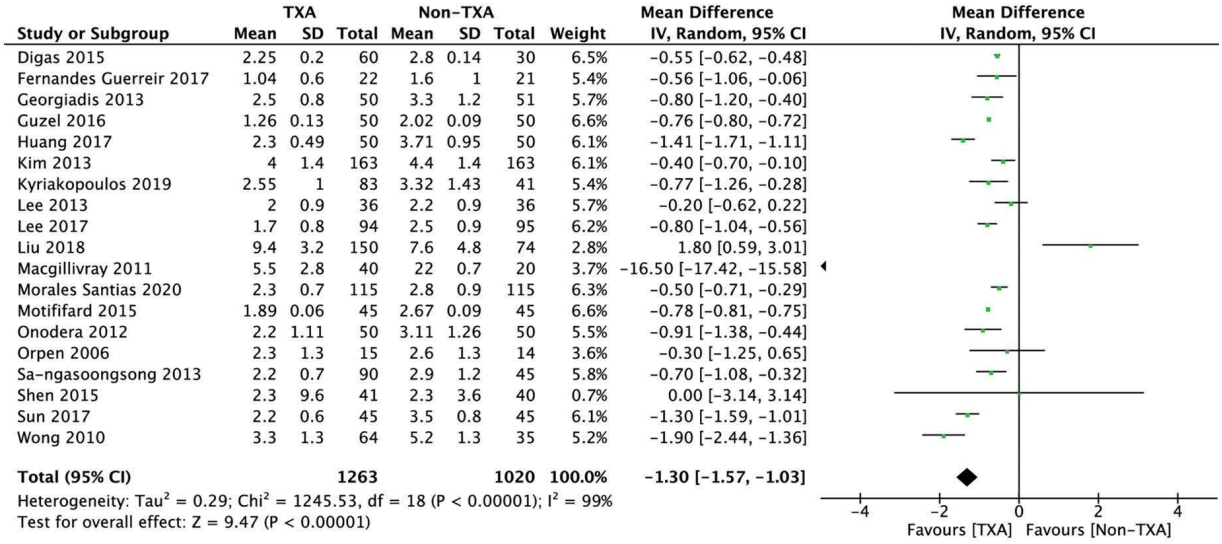

FIGURE 2. Forest plot of Hemoglobin changes in 24-hours after surgery among TXA and non-TXA groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

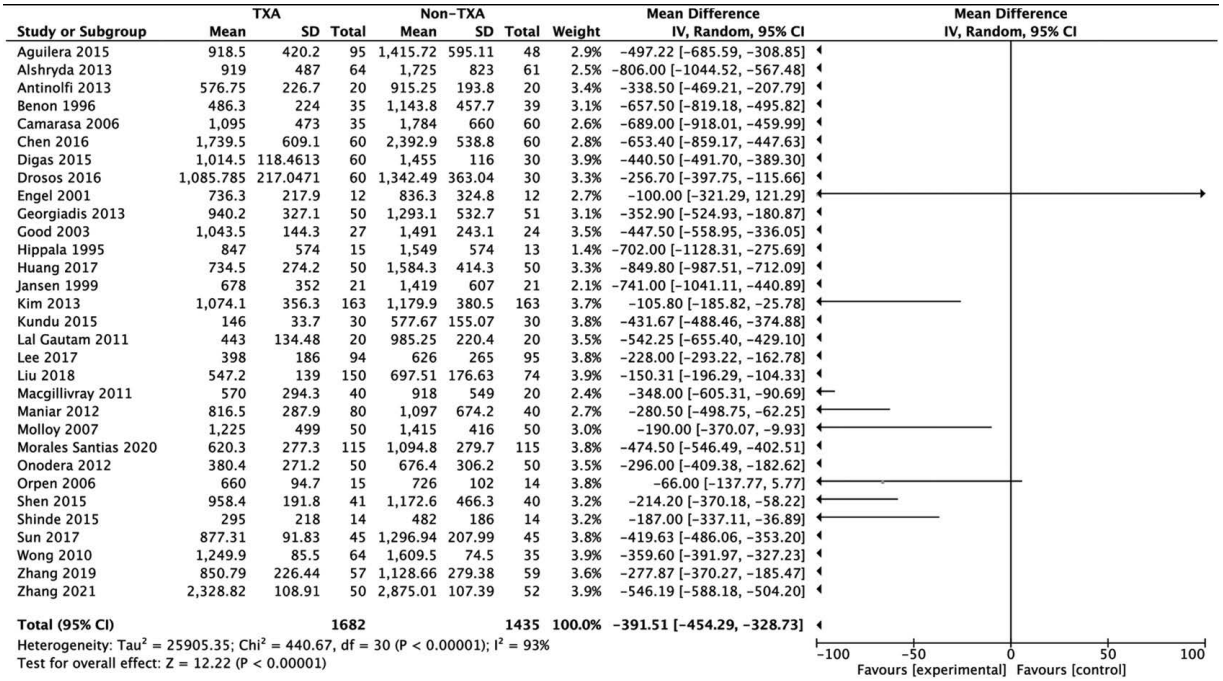

FIGURE 3. Forest plot of total blood loss among TXA and non-TXA group. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

24-hours blood loss from the drain was lower with TXA than with placebo [MD = −228.68; 95% CI: −293.31 to −164.05; p < 0.001 (Fig. 5)]. Similar relationship of occurrence during the subgroup analysis of intravenous TXA (MD = −243.25; 95% CI: −316.36 to −170.14; p < 0.001) as well as topical administration [MD = −202.89; 95% CI: −307.32 to −98.46; p < 0.001; (Fig. S6 , see Supplementary file)].

Blood transfusion was performed in 11.2% of patients from TXA group, compared to 34.3% of patients treated with placebo [OR = 0.16; 95% CI: 0.11 to 0.22; p < 0.001 (Fig. 6)]. Subgroup analysis showed that IV TXA compared to placebo was asso-

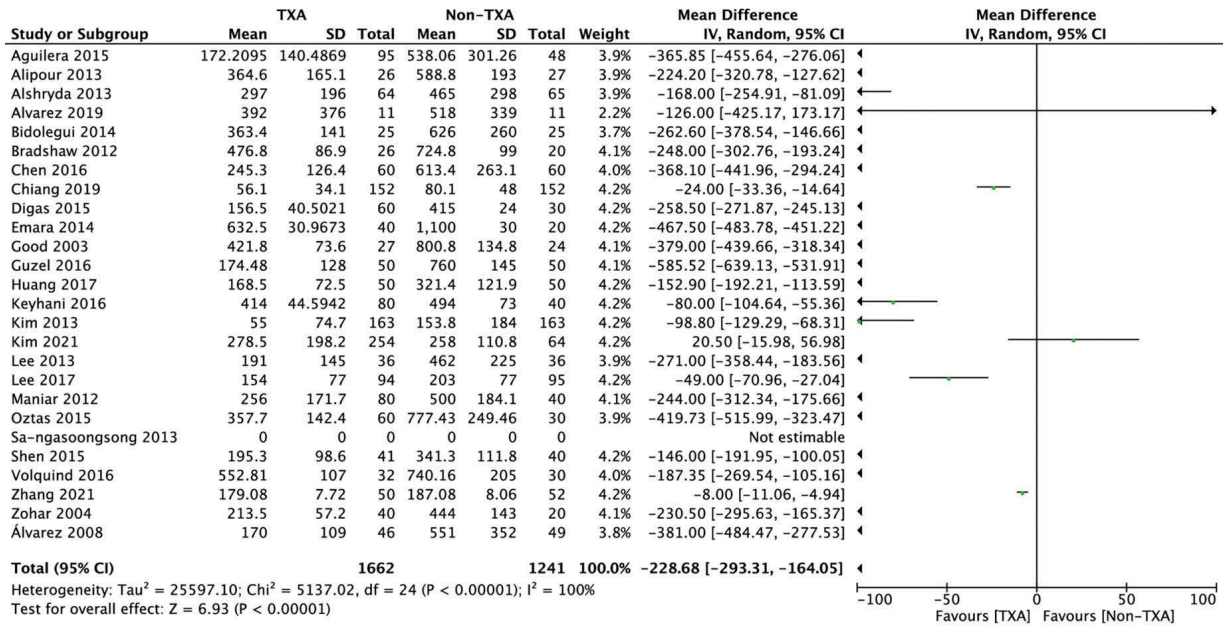

FIGURE 4. Forest plot of intraoperative blood loss among TXA and non-TXA group. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

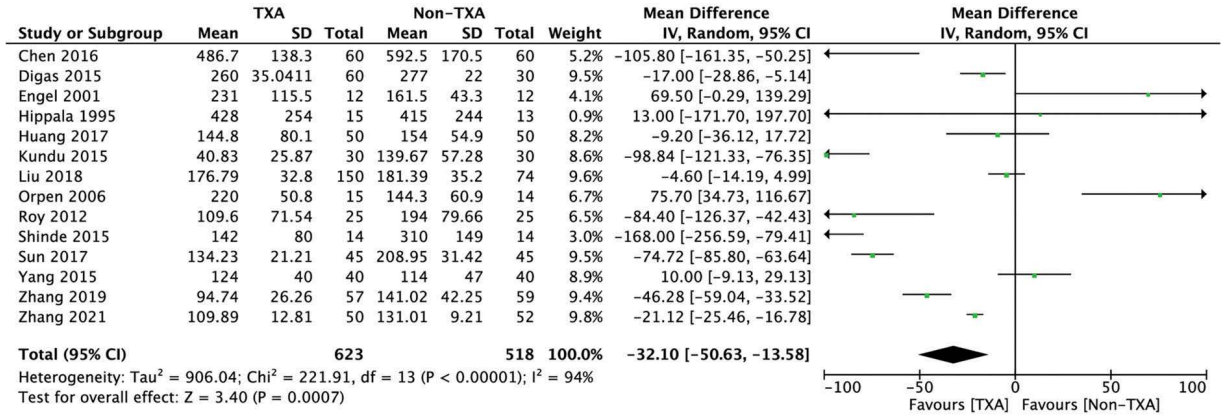

FIGURE 5. Forest plot of 24-hours blood loss from the drain among TXA and non-TXA groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

ciated with a reduction in the need for transfusions (12.7% vs 37.2%; OR = 0.13; 95% CI: 0.09 to 0.20; $p < 0.001$). The same relationship was observed with topical administered TXA [7.5% vs 30.0%; OR = 0.20; 95% CI: 0.14 to 0.28; $p < 0.001$ (Fig. S7, see Supplementary file)].

Adverse events

Twenty studies reported deep vein thrombosis. DVT was observed in 4.6% of patients treated with TXA, compared to 5.8% of patients treated with placebo (OR = 0.81; 95% CI: 0.49 to 1.35; p = 0.42). Pooled analysis showed that TXA administered intravenously compared to placebo is associated with the occurrence of DVT at the level respectively: 6.7% vs 6.0% (OR = 1.11; 95% CI: 0.61 to 2.02; p = 0.72). When topical TXA was used, the incidence of DVT was 2.9%, compared to 6.1% in placebo group (OR = 0.45; 95% CI: 0.20 to 1.02; p = 0.06).

Eleven studies reported pulmonary embolism as a potential adverse event. Polled analysis of TXA and non-TXA group showed, that pulmonary embolism was 0.5% in TXA group and 1.4% for placebo group (OR = 0.44; 95% CI: 0.15 to 1.36; p = 0.15). Subgroup analysis showed similar relationships between TXA and placebo for both intravenous TXA administration (0.0% vs. 1.5%; OR = 0.30; 95% CI: 0.06 to 1.55; p = 0.15) as well as in case topical TXA ad-

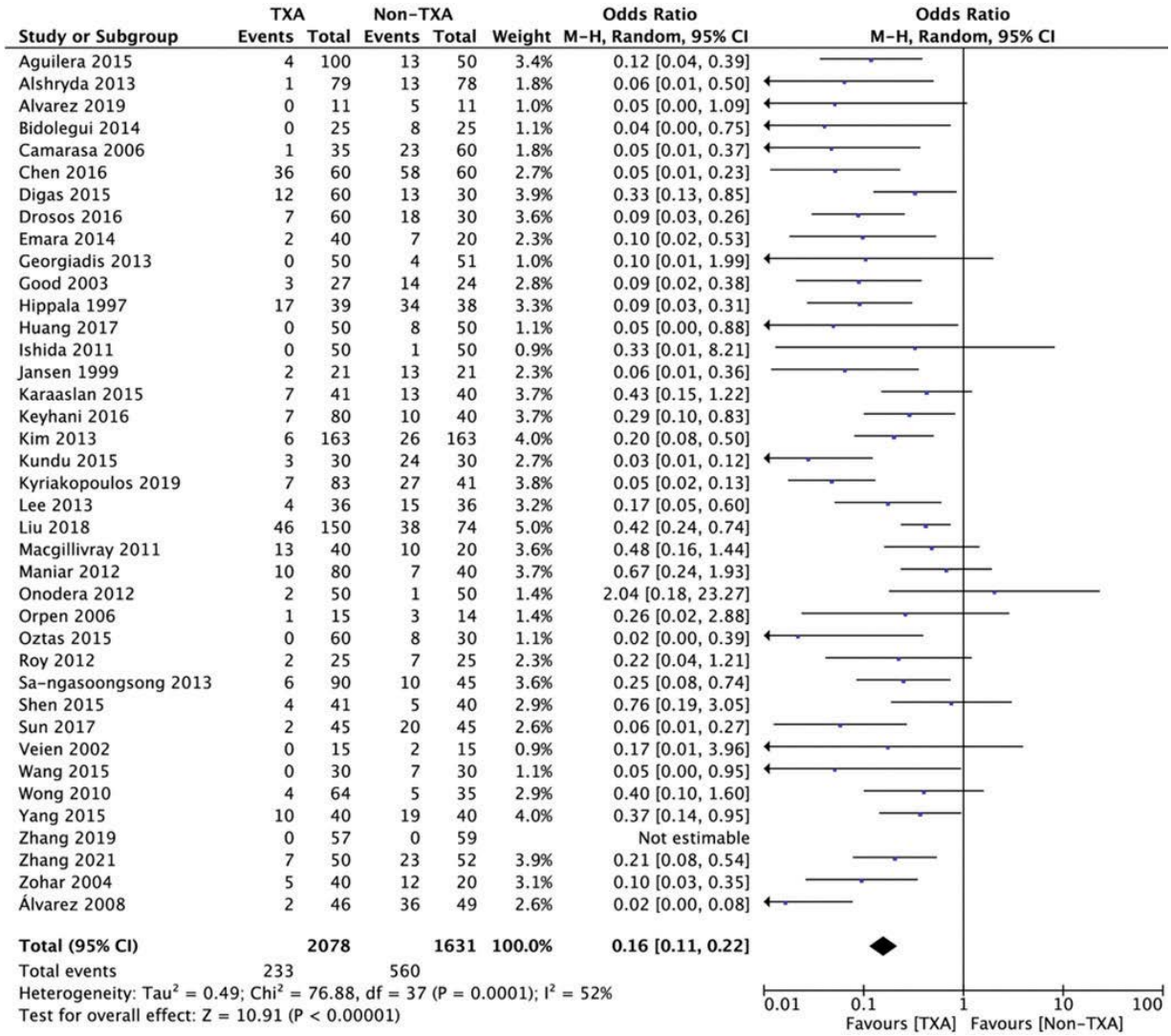

FIGURE 6. Forest plot of blood transfusion occurrence among TXA and non-TXA group. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

ministration (0.7% vs. 1.2% respectively; OR = 0.50; 95% CI: 0.08 to 3.16; p = 0.46).

DISCUSSION

Tranexamic acid is a commonly used anti-fibrinolytic agent that blocks the plasminogen lysine binding site, which can effectively reduce the duration and amount of blood loss, making it widely used in orthopedic surgery [66]. Along with the increase in the number of knee arthroplasty procedures performed and the continuous expansion of indications qualifying for the procedure, it is necessary to reduce complications during the procedure, and postoperative complications and increase the improvement of the results of the procedure. According to previous research, roughly 38% of knee arthroplasty patients require blood transfusions, resulting in a total blood loss of 1500 mL during the perioperative phase [67]. Many patients with tissue extravasation following knee arthroplasty have lower limb edema, discomfort, and functional activity limitations. Autologous blood transfusions, intraoperative hemodilution, hypotensive anesthesia, and current modified drainage procedures all add to the logistical issues while also being immunomodulatory. The use of tranexamic acid avoids many of these complications and is widely available and inexpensive.

In this meta-analysis, we evaluate results from fifty-two studies that compared outcomes in the TXA group and non-TXA group. The main findings of this study relate to several factors, which we have sorted out for clarity: Hemoglobin changes in 24 hours, total blood loss, intraoperative blood loss, 24-hours blood

loss from the drain, blood transfusion, comparisons of these categories for subgroup analysis concerning to type of TXA administration and also adverse events-deep vein thrombosis and pulmonary embolism. All the above-mentioned factors assessed by us in the analysis favor tranexamic acid. Its wide use in orthopedics will allow both to reduce the costs of surgery and the length of the patient's stay in the hospital, as well as significantly improve the patient's comfort and limit possible intraoperative and postoperative complications. The potential complications of using tranexamic acid should also always be considered - but does it really pose such a risk for patients without other loads? There are still concerns about the safety of different modes of administration of TXA and the risk of deep vein thrombosis and pulmonary embolism in high-risk groups with a history of thromboembolism, acute myocardial infarction, or ischemic cerebrovascular accident [68]. Considering these safety issues, topical TXA can be a safe route of administration to reduce postoperative bleeding without increasing the risk associated with knee arthroplasty, because using TXA administered intravenously compared to placebo is associated with the occurrence of DVT at the level respectively: 6.7% vs 6.0% and when topical TXA was used, the incidence of DVT was 2.9%, compared to 6.1% in the placebo group. The analysis for pulmonary embolism showed similar relationships between TXA and placebo for both intravenous TXA administration (0.0% vs 1.5%) as well as in case topical TXA administration (0.7% vs 1.2%). One aspect of TXA administration that needs to be considered and implemented in larger orthopedic research is the toxicity of TXA in human periarticular tissues. In current orthopedic practice, the interaction between critical tissues such as cartilage, tendons, subpatellar fat pads, and ligaments with TXA remains largely unclear [69]. We found substantial improvements for TXA in all of the parameters described in our statistical study.

The performed meta-analysis is not without limitations. The lack of information in many studies on the use of tourniquets and the duration of their use to reduce blood loss however, these limitations in a meta-analysis of tourniquet use in knee arthroplasty found no major differences, in whether or not a tourniquet was used when using TXA during knee arthroplasty [70]. Another limitation may be the lack of knowledge about blood transfusions and blood products that affect hemoglobin levels in addition, the estimation of blood loss was variable as blood loss due to hematomas or tissue extravasation was rarely measured, which could lead to inaccurate results. Arthroscopic surgery and trauma surgery should also be considered. However, the collected data indicate statistically and clinically significant findings regarding the use, route of administration, and safety of TXA in knee arthroplasty.

It is worth emphasizing, however, that this is the most complete meta-analysis from the studied range, including as many as 52 randomized trials. An additional advantage of meta-analysis is subanalysis divided into intravenous and topical application methods of TXA.

CONCLUSIONS

Tranexamic acid is effective and safe in reducing blood loss, the requirement for blood transfusion, and drain output in patients undergoing knee arthroplasty.

Author Contributions

Conceptualization, J.P.; methodology, J.P. and L.S; validation, J.P. and M.A-J.; formal analysis, J.P. and L.S.; investigation, J.P., M.A-J., I.N., M.P.; resources, L.S.; data curation, J.P.; writing — original draft preparation, J.P. and M.A-J.; writing — review and editing, all authors; visualization, L.S.; supervision, L.S. and J.P.; project administration, J.P. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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