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SYSTEMATIC REVIEW AND META-ANALYSIS OF INTRAVENOUS AND TOPICAL TRANEXAMIC ACID IN REDUCING BLOOD LOSS IN KNEE ARTHROPLASTY

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ABSTRACT

INTRODUCTION: The purpose of this review and meta-analysis is to compare tranexamic acid (TXA) administration via the intravenous route (IV-TXA) and topical route (T-TXA), in reducing blood loss in knee arthroplasty.

MATERIAL AND METHODS: A systematic literature search was performed using Medline, EMBASE, Scopus and CENTRAL databases till December 20, 2021. Outcomes of interest included blood loss, hematocrit and hemoglobin drop, and adverse events.

RESULTS: A total of 3,363 patients (n = 1,307 in IV-TXA group; n = 2,056 in T-TXA group) from 23 studies were included. There was no statistically significantly difference between IV-TXA and T-TXA among to: total blood loss (874.8 ± 349.7 mL vs 844.9 ± 366.6 mL, respectively; SMD = 0.13; 95% CI: −9.37 to 85.32; p = 0.15), as well as transfusion needed (10.9% vs 15.4% respectively (RR = 0.79; 95% CI: 0.60 to 1.04; p = 0.09). Blood loss from the drain in IV-TXA and T-TXA varied and occurred 377.9 ± 191.9 vs 302.9 ± 182.6 mL for IV-TXA and T-TXA, respectively: (SMD = 0.52; 95% CI: 0.02 to 1.02; p = 0.04).

CONCLUSIONS: Our clinical findings support that TXA can effectively, safely, and decrease the number of transfusions without severe side effects in patients undergoing TKA. However, given the reports from individual single clinical trials of the superiority of T-TXA, further clinical trials and meta-analyses based on these findings are needed to standardize the approach to TXA use in patients undergoing knee arthroplasty.

KEY WORDS: arthroplasty; knee; replacement; tranexamic acid; intravenous; topical; systematic review; meta-analysis

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INTRODUCTION

Knee arthroplasty (KA) has become a routine orthopedic procedure with tranexamic acid (TXA) used to prevent excessive bleeding [1–5]. Knee arthroplasty may be associated with blood loss of up to 800–1800 mL, making allogeneic blood transfusion necessary with a 10% to 62% [6–8]. This may expose the patient to related complications such as cardiopulmonary embarrassment, disease transmission, immunological reaction, and postoperative infection [9, 10]. Observational studies have reported associations between red blood cell transfusion and increased postoperative morbidity and mortality [11, 12]. Tranexamic acid (TXA) is an anti-fibrinolytic that inhibits fibrin's plasmin-mediated degradation, routinely used in KA but has not yet become the standard of care [12–14]. The absolute contraindications of intravenous TXA are not evident, as well the dose-related effects of TXA on the coagulation system are not clear.

Moreover, the route of TXA application can vary; intravenously (IV-TXA), topically (T-TXA), or orally [13, 15, 16]. T-TXA is considered to be comparable to IV-TXA in reducing postoperative blood loss after primary KA [17]. Topical administration has the theoretical benefits of limiting systemic toxicity and the advantage of locally increased concentrations compared to IV-TXA. It has been investigated as a safe alternative, especially regarding the systemic adverse effects of intravenous TXA [18]. However, most of those studies collectively focus on KA and total hip arthroplasty (THA) [4, 19]. Meta-analyses investigating data from two different procedures fail to capture the differences between the two procedures, their extent, and any differences between the doses of TXA applied topically. Considerations regarding the optimal administration of TXA are still controversial due to the still unclear comparison of the benefits and risks of using TXA by different approaches [16, 20–22].

The purpose of this review and meta-analysis is to compare data from various studies comparing intravenous and topical administration of TXA, which may help guide decisions on the administration of TXA during KA.

MATERIAL AND METHODS

The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement [23] and the recommendations of Cochrane Collaboration. The study is a continuation of the authors' research on the effectiveness and safety of TXA in orthopedics [24].

Search strategy

To identify all the eligible studies of IV-TXA versus T-TXA in patients with knee arthroplasty, a literature search was performed on the following online databases: Medline, EMBASE, Scopus, and Cochrane Central Register of Controlled Trials (CEN-TRAL) from database inception to December 20, 2021. The following keywords were used as search terms: "tranexamic acid" or "TXA" and "intravenous" or "topical" or "intraocular" and "knee arthroplasty".

Additionally, a manual search of the reference lists of studies and reviews on this topic was performed to identify additional eligible studies. To avoid double data counting, the one with the largest sample size was included when there were multiple publications from the same trial sample.

Eligibility criteria

Studies that were included in this meta-analysis had to fulfill the following PICOS criteria: (1) Participants: patients 18 years old or older requiring knee arthroplasty; (2) Intervention, tranexamic acid treatment administrated intravenously; (3) Comparison: tranexamic acid treatment administrated topically; (4) Outcomes: operative data and adverse events occurrence; (5) Study design: randomized controlled trials and retrospective trials comparing IV-TXA and T-TXA care for their effects in patients with knee arthroplasty. Animal studies, reviews, case reports, letters, conference or poster abstracts, or articles not containing original and not published in English were excluded.

Data extraction

From eligible studies, the following data were extracted into a predefined Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA): (1) study characteristic (*i.e.*, first author, year of publication, country, study design, inclusion and exclusion criteria, primary outcomes, findings); (2) participant characteristics (*i.e.*, number of participants, age, sex); (3) primary study outcomes (*i.e.*, blood volume loss, operative time, adverse events, hospital length of stay). Data extraction was performed independently by two authors (J.P. and M.P.). Potential disagreements were resolved by discussion with a third reviewer (L.S.).

Quality assessment

The quality of each study was independently evaluated by two authors (J.P. and M.A.-J.) using the RoB-2 tool (revised tool for risk of bias in randomized trials) was used to assess the quality of randomized studies [25], or the ROBINS-I tool (tool to determine the risk of bias in non-randomized studies of interventions) [26]. Any disagreements were resolved by discussion with a third author (M.A.-J.). The risk of bias assessments was visualized using the Robvis application [27].

Statistical analysis

As statistical analyses were performed using the Review Manager, version 5.4EN (RevMan; The Cochrane Collaboration, Oxford, UK) and STATA statistical software, version 17EN (StataCorp LLC, TX, USA). The results for dichotomous outcomes were presented as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs). The standard mean differences (SMDs) with 95% CI were used for continuous outcomes. In case when the continuous outcomes were reported in a study as median, range, and inter-quartile range, we estimated means and standard deviations using the formula described by Hozo et al. [28].

We quantified heterogeneity in each analysis by the tau-squared and I-squared statistics. Heterogeneity was detected with the chi-squared test with n – 1 degree of freedom, which was expressed as I2. Values of I2 > 50% and > 75% were considered to indicate moderate and significant heterogeneity among studies, respectively. A random-effects model was used to pool study results independently of the p-value for heterogeneity or I2 [29]. All the p-values are two-sided, and a $p < 0.05$ was considered statistically significant [30].

To evaluate the potential for publication bias, we plotted values against associated standard errors [31] and used Begg's test to assess the symmetry of the resulting funnel plot [32]. We considered publication bias present when the p-value was < 0.1 in the asymmetry test. However, publication bias was not evaluated when a limited number of studies (< 10) were included in the analysis.

RESULTS

Study selection

Figure 1 depicts the flow diagram for the search process. Overall, the combined search identified 517 articles, of which 470 were excluded (78 were duplicates, and 392 were excluded upon the title and abstract evaluation). The remaining 47 articles underwent full-text evaluation. Finally, 23 eligible articles were found and were included in the qualitative and quantitative analyses.

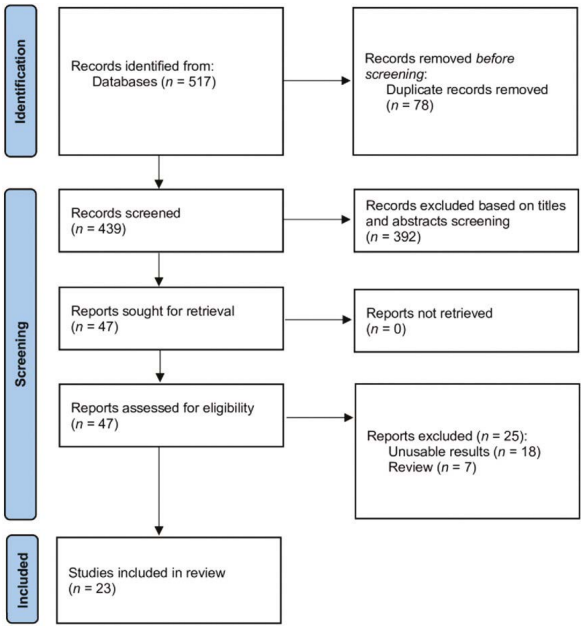

FIGURE 1. Database search and selection of studies according to PRISMA guidelines

Twenty-three trials [8, 9, 13–16, 20-21, including 3,363 patients with knee arthroplasty (1,307 with IV-TXA and 2,056 with T-TXA application) were published between 2012 and 2019. Table 1 displays the baseline characteristics of patients who underwent Knee arthroplasty and were treated with IV-TXA or T-TXA. Twenty-one studies were designed as randomized controlled trials [8, 9, 13–16, 21, 33, 35–42, 44–48]. The risk of bias among included studies is assessed in Figures S1–S4 (see Supplementary file).

There was no statistically significant difference in patient baseline characteristics between IV-TXA and T-TXA (Tab. 2).

Blood loss from the drain was reported in nine studies and was 377.9 ± 191.9 vs 302.9 ± 182.6 mL for IV-TXA and T-TXA respectively: (SMD = 0.52; 95% CI: 0.02 to 1.02; I2 = 92%; p = 0.04; Figure 2).

Fifteen studies reported hemoglobin differences between pre-surgery and post-surgery periods. Pooled analysis of hemoglobin drops in IV-TXA and T-TXA was 2.4 ± 1.1 in each group (SMD = 0.42; 95% CI: = −0.26 to 1.09; I2 = 98%; p = 0.23; Figure 4).

Table 1. Characteristics of included studies

Study	Country	Study design	Intravenous TXA group			Topical TXA group		
			No	Age	Sex, male	No	Age	Sex, male
Aguilera et al. 2015	Spain	RCT	50	72.49 ± 7.68	12 (24.0%)	50	72.53 ± 6.6	18 (36.0%)
Dronos et al. 2016	Greece	RCT	30	69.27 ± 7.21	6 (20.0%)	30	71.10 ± 6.32	6 (20.0%)
Hegde et al. 2013	India	PCS	30	66.57 ± 8.48	NS	30	65.48 ± 6.53	NS
Keyhani et al. 2016	Iran	RCT	40	68.4 ± 10.4	26 (65.0%)	40	67 ± 11.9	23 (57.5%)
Kyriakopoulos et al. 2019	Greece	RCT	41	69.73 ± 6.87	NS	42	70.74 ± 6.55	NS
Lacko et al. 2017	Slovakia	RCT	30	68.4 ± 7.2	12 (40.0%)	30	67.5 ± 7.7	13 (43.3%)
Laoruengthana et al. 2019	Thailand	RCT	76	64.01 ± 7.68	14 (18.4%)	75	64.81 ± 8.06	12 (16.0%)
López-Hualda et al. 2012	Spain	RCT	30	73.1 ± 7.3	24 (80.0%)	30	72.9 ± 7.1	19 (63.3%)
Maniar et al. 2012	India	RCT	40	67.3 ± 9.1	10 (25.0%)	40	67.4 ± 7.9	6 (15.0%)
Mehta et al. 2018	India	RCT	100	62.86 ± 6.08	41 (41.0%)	100	61.85 ± 4.81	44 (44.0%)
Oztas et al. 2015	Turkey	RCT	30	68.56 ± 5.38	5 (16.7%)	30	67.06 ± 6.54	4 (13.3%)
Pitta et al. 2015	USA	RS	202	65.3±10.6	61 (30.2%)	201	65.8 ± 10.9	68 (33.8%)
Sahin et al. 2019	Turkey	RCT	67	66.7 ± 9.5	8 (11.9%)	33	68 ± 7.5	4 (12.1%)
Sarzaeem et al. 2014	Iran	RCT	50	66.9 ± 7.2	7 (14.0%)	50	68.1 ± 6.8	7 (14.0%)
Seo et al. 2013	South Korea	RCT	50	66.8 ± 6.3	6 (12.0%)	50	67.5 ± 6.6	5 (10.0%)
Song et al. 2016	Korea	RCT	50	69.2 ± 6.4	6 (12.0%)	50	69.8 ± 6.8	8 (16.0%)
Tzatzairis et al. 2016	Greece	RCT	40	69.55 ± 6.61	9 (22.5%)	40	69.10 ± 8.68	7 (17.5%)
Uğurlu et al. 2016	Turkey	RCT	40	69.4 ± 7.5	11 (27.5%)	42	70.6 ± 8.6	9 (21.4%)
Wang et al. 2017	China	RCT	50	67.42 ± 8.202	14 (28.0%)	50	67.98 ± 5.971	14 (28.0%)
Wang et al. 2018	China	RCT	60	66.90 ± 9.48	15 (25.0%)	60	63.20 ± 11.75	16 (26.7%)
Yen et al. 2017	Taiwan	RCT	31	69.13 (7.94; 51–85)	4 (12.9%)	32	69.66 (5.53; 59–84)	13 (40.6%)
Yuan et al. 2017	China	RCT	140	63.74 ± 8.05	67 (47.9%)	140	63.26 ± 6.99	63 (45.0%)
Zekcer et al. 2016	Brazil	RCT	30	NS	6 (20.0%)	30	NS	9 (30.0%)

NS — not specified; PCS — prospective comparative study; RCT — randomized controlled trial; RS — retrospective study

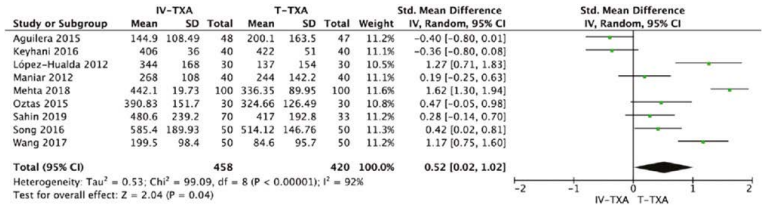

FIGURE 2. Forest plot of blood volume loss from the drain among IV-TXA and T-TXA groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds rep-resent pooled results

Hematocrit difference between pre- and post-surgery period was 7.5 ± 2.8% for IV-TXA group compared to 8.0 ± 2.9% for T-TXA group (SMD = −0.08; 95% CI: −1.42 to 1.26; I2 = 94%; p = 0.91; Figure 5).

Pooled analysis of nineteen studies showed that the need for transfusion in the IV-TXA and T-TXA groups varied and amounted to 10.9% vs 15.4% respectively (RR = 0.79; 95% CI: 0.60 to 1.04; I2 = 25%; p = 0.09).

A summary of the individual adverse events observed in the analyzed articles is presented in Table 3. Pooled analysis showed no statistically significant differences in the occurrence of particular

Table 2. Pooled analysis of patient characteristics among included trials

Outcome	No. of studies	Events / Participants or Mean ± SD		Events		Heterogeneity between trials		P-value for differences across groups
		IV-TXA	T-TXA	OR or SMD	95%CI	P-value	I2 statistic	
Age, years	22	66.6 ± 8.5	66.5 ± 8.7	0.00	−0.08 to 0.08	0.94	0%	0.98
Sex female, n (%)	22	327/1,208 (27.1%)	351/1,173 (29.9%)	1.13	0.94 to 1.36	0.80	0%	0.20
BMI	17	28.6 ± 6.2	28.1 ± 5.4	0.07	−0.18 to 0.33	< 0.001	86%	0.59
ASA								
1 class	5	67/321 (20.9%)	56/322 (17.4%)	1.34	0.85 to 2.11	0.92	0%	0.21
2 class	6	240/351 (68.4%)	247/352 (70.2%)	0.91	0.65 to 1.28	0.57	0%	0.59
3 class	5	39/321 (12.1%)	44/322 (13.7%)	0.87	0.54 to 1.41	0.43	0%	0.57
4 class	5	1/321 (0.3%)	1/322 (0.3%)	1.00	0.06 to 16.44	NA	NA	1.00
Pre-surgery hemoglobin, g/dL	19	13.1 ± 1.4	13.1 ± 1.6	0.00	−0.08 to 0.08	0.73	0%	0.99
Pre-surgery hematocrit, %	11	40.1 ± 3.5	40.1 ± 4.1	0.06	−0.09 to 0.22	0.18	27%	0.44

ASA — The American Society of Anesthesiologists physical status classification system; BMI — body mass index; CI — confidence interval; MD — mean difference; NA — not applicable

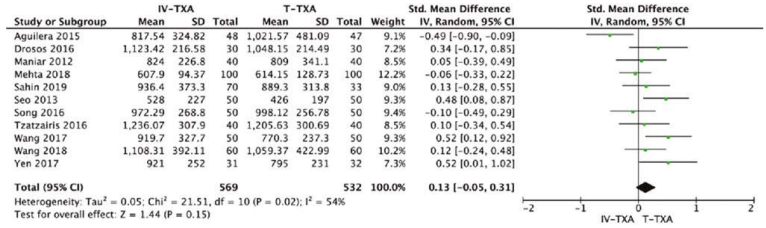

FIGURE 3. Forest plot of total blood volume loss among IV-TXA and T-TXA groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

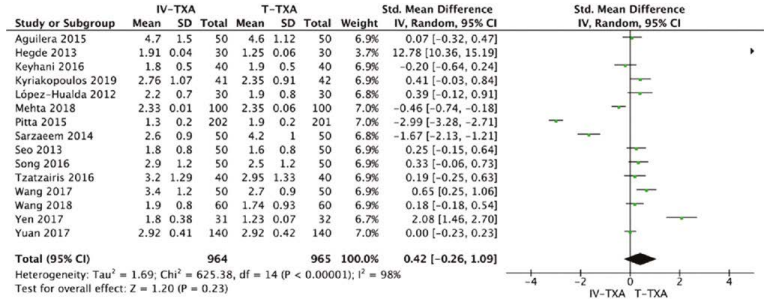

FIGURE 4. Forest plot of hemoglobin difference between pre-surgery and post-surgery period among IV-TXA and T-TXA groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

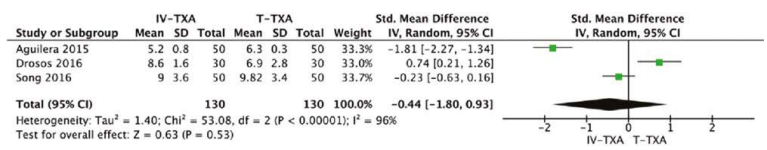

FIGURE 5. Forest plot of hematocrit difference between pre-surgery and post-surgery period among IV-TXA and T-TXA groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

Table 3. Pooled analysis of adverse events occurred among analyzed trials

Adverse event type	No. of studies	Events / Participants		Events		Heterogeneity between trials		p-value for differences across groups
		IV-TXA	T-TXA	RR	95%CI	p-value	I2 statistic	
DVT	6	4/345 (1.2%)	4/342 (1.2%)	1.10	0.26 to 4.62	0.37	7%	0.89
Pulmonary embolus	5	0/331 (0.0%)	0/332 (0.0%)	NE	NE	NA	NA	NA
Wound infection	3	0/230 (0.0%)	1/230 (0.4%)	0.33	0.01 to 8.02	NA	NA	0.50
Atrial fibrillation	1	0/50 (0.0%)	1/50 (2.0%)	0.33	0.01 to 7.99	NA	NA	0.50
Hematoma	2	7/91 (7.7%)	6/91 (6.6%)	1.17	0.43 to 3.19	0.90	0%	0.76
Gastric hemorrhage	1	0/60 (0.0%)	0/60 (0.0%)	NE	NE	NA	NA	NA

CI — confidence interval; DVT — deep vein thrombosis; NA — not applicable; NE — not estimable

types of adverse events between IV-TXA and T-TXA ($p > 0.05$ for every adverse event type).

Both the duration of the operation and the length of hospital stay between examined groups (IV-TXA and T-TXA) showed no statistically significant differences ($p > 0.05$; Figures S5–S6, see Supplementary file).

DISCUSSION

Knee arthroplasty can be associated with significant blood loss. Surgical primary concerns are intraoperative and postoperative period blood loss and secondary acute anemia [7]. Adequate use of antifibrinolytics contributes to decreased blood loss, and TXA has been used widely in total joint arthroplasty through intravenous or topical administration [10]. Routine use of TXA not only appears to increase a patient's prospects for faster and less complicated recovery subsequent to KA but also results in lower direct hospital charges by reducing costs associated with blood transfusion, laboratory testing, and room & board. Gillette et al. [48] report that hospitalization costs for a patient undergoing primary total hip or knee arthroplasty with TXA are lower by nearly $900. However, this study treats THA and KA collectively and refers to a single route of TXA administration. Also, Kyriakopoulos et al. [36] describe the cost reduction of KA with TXA, and the estimated saving is €386 per patient.

In order to compare the efficacy of the routes of administration of TXA used in KA, we conducted a meta-analysis in which eight parameters compared from individual studies were included; total blood loss, blood loss from the drain, hemoglobin drop difference between pre-surgery and post-surgery period, hemoglobin difference between pre- and post-surgery period, need of a transfusion, summary of the individual adverse events, duration of the operation and the length of postal stay.

A meta-analysis of 14 randomized controlled trials conducted by Alshryda et al. [49] in 2014 showed that T-TXA significantly reduced the rate of blood transfusions. Also, in a study by Hamlin et al. [50], it was reported that after T-TXA none of the patients required blood transfusion, while in the IV-TXA group, 2.4% of patients required transfusion. However, these findings are not consistent with our meta-analysis. In 19 analyzed studies, 10.8% of patients in the IV-TXA group required blood transfusion compared to 15.2% in the T-TXA group, and the hemoglobin difference between pre- and post-surgery period was 7.5 ± 2.8% for the IV-TXA group compared to 8.0 ± 2.9% for T-TXA group. These differences, however, must be considered concerning the other data analyzed and cannot unequivocally prove the superiority of IV-TXA because total blood loss in this group was higher than in the T-TXA group (874.8 ± 349.7 mL vs 844.9 ± 366.6 mL). Also, blood loss from drainage reported in ten analyzed

studies indicates an advantage of topical administration (377.9 ± 191.9 vs 302.9 ± 182.6 mL for IV-TXA and T-TXA, respectively).

Topical TXA application has the theoretical advantage of limiting systemic toxicity and benefits of locally increased concentrations, and it can potentially avoid the complications of intravenous TXA [51]. Topical intraoperative applications are easy to perform and therefore seem to be practical. Topical TXA rapidly diffuses into the synovial fluid and synovial membranes until the concentration of the TXA in synovial fluid reaches the concentration of serum, its biological half-life in the joint fluid is about 3 hours [52]. To maintain microvascular hemostasis, it is necessary to reach maximum concentrations at the surgical site. The minimum plasma concentration of TXA needed to inhibit fibrinolysis is 5–10 mg/L [53]. The potential mechanism and advantage of topical application of TXA into the surgical field is to directly reach the bleeding site, attenuating the marked increase in local fibrinolysis associated with a release of the tourniquet [54]. However, as mentioned, the additional costs after TKA are mainly generated by the postoperative need for blood transfusions, and thus analyzing the topic in terms of financial benefits indicates the advantage of IV-TXA again.

It is also valuable to point out that although absolute contraindications of intravenous TXA are not evident, one should remember about relative contraindications for TXA use, such as recent cerebrovascular accidents, deep vein thrombosis (DVT) or pulmonary embolism (PE) [48]. To evaluate the risk of adverse events, we summarized the individual adverse events, including DVT and PE. Pooled analysis showed no statistically significant differences in the occurrence of particular types of adverse events between IV-TXA and T-TXA. No statistical difference was also found in assessing the duration of the operation and the length of postal stay between the examined groups. However, TXA is not considered thrombogenic and prevents the degradation of existing blood clots, and some studies suggest no increase in the incidence of venous thrombosis among patients treated with TXA, even in patients at higher risk, and administration of IV-TXA does not necessarily correlate with an increased risk of venous thromboembolism [55, 56].

There are limitations to the meta-analysis conducted. First, there is a limitation in how results are reported. The different doses and administration times of TXA can contribute to confusion when comparing data. Moreover, there was substantial heterogeneity in the meta-analysis of several outcomes, such as differences in surgical time, technique, approaches, and postoperative measures. The meta-analysis conducted by our team does not allow concluding unequivocally on the superiority of one of the TXA application routes. The analyzed parameters of total blood loss and blood loss from the drain point favors T-TXA; however, the summary analysis of the need for transfusion points in favor of IV-TXA. Considering that the requirement for transfusion reflects the more severe condition of the patient after the procedure and carries the risk of post-transfusion complications, and is associated with additional costs, it seems that intravenous TXA may carry more benefits.

CONCLUSIONS

In conclusion, our clinical findings support that TXA can effectively, safely, and decrease the number of transfusions without severe side effects in patients undergoing TKA. However, given the reports from individual single clinical trials of the superiority of T-TXA, further clinical trials, and meta-analyses based on these findings are needed to standardize the approach to TXA use in patients undergoing TKA.

Author contributions

Conceptualization, J.P. and L.S.; methodology, J.P. and L.S.; software, L.S.; validation, J.P., M.A.-J. and L.S.; formal analysis, J.P. and L.S.; investigation, J.P., M.P., M.A.-J. and L.S.; resources, J.P.; data curation, J.P. and L.S.; writing — original draft preparation, J.P., L.S., MM., M.K. and E.M.; writing — review and editing, J.P., M.A.-J., M.M., M.P., A.M., M.K., E.M., J.S. and L.S.; visualization, L.S.; supervision, L.S.; project administration, J.P. and L.S.; funding acquisition, A.M. 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.

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