

A Single Preoperative Dose of Tranexamic Acid Reduces Perioperative Blood Loss

A Meta-analysis

Mieke Heyns, MD, Paige Knight, MD, Anna K. Steve, MD, and Justin K. Yeung, MD✉

Objective: To review the efficacy and safety of a single dose of intravenous tranexamic acid (TXA) given preoperatively.

Summary Background Data: TXA is a synthetic antifibrinolytic that has been used in various surgical disciplines to reduce blood loss, blood transfusions, ecchymosis, and hematoma formation. However, there is no universal standard on the most effective dose and route of TXA administration, limiting its routine use in many centers. This study evaluates the current evidence for the efficacy and safety of a single preoperative dose of TXA on surgical blood loss in all surgical disciplines.

Methods: With the guidance of a research librarian, in accordance with the Cochrane Handbook Medline, Cochrane Central and Embase were searched in November 2018. Search terms included “Tranexamic Acid” AND “Intravenous,” with studies limited to randomized controlled trials in adult humans. Two independent reviewers and an arbitrator assessed articles for inclusion. Criteria included a single preoperative bolus dose of intravenous TXA, surgical patients, and intraoperative blood loss measurement or perioperative blood loss up to 24 hours postsurgery. Quality assessment was done using the Cochrane Collaboration risk-of-bias tool by 2 reviewers. Statistical analysis was carried out using Cochrane Review Manager 5.3. The primary outcome was surgical blood loss. Secondary outcomes included venous thromboembolic complications, transfusion requirements, and dosing.

Results: A total of 1906 articles were screened, 57 met inclusion criteria. The majority of included studies were orthopedic (27), followed by obstetric and gynecological (16), oral maxillofacial and otolaryngology (10), cardiac (3), and 1 plastic surgery study focusing on acute burn reconstruction. Across all surgical specialties (n = 5698), the perioperative estimated blood loss was lower in patients receiving TXA, with a standard mean difference of -153.33 mL (95% CI = -187.79 to -118.87). Overall, surgical patients with TXA had a 72% reduced odds of transfusion (odds ratio = 0.28 [95% CI = 0.22–0.36]). The most frequently used dose of TXA was 15 mg/kg. There was no difference in the incidence of venous thromboembolic events between TXA and control groups.

Conclusions: While there is a growing body of evidence to support benefits of perioperative TXA use, this is the first meta-analysis to identify the efficacy and safety of a single preoperative dose of IV TXA. The potential implications for expanding the use of preoperative TXA for elective day surgery procedures is substantial. Preoperative intravenous TXA reduced perioperative blood loss and transfusion requirements in a variety of surgical disciplines without increasing the risk of thromboembolic events. Therefore,

it should be considered for prophylactic use in surgery to reduce operative bleeding.

Keywords: antifibrinolytic, blood, blood loss, blood transfusion, outcomes, perioperative medicine, tranexamic acid

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Perioperative blood loss is a common risk for surgical patients and can lead to increased morbidity and mortality. Postoperative anemia is associated with adverse outcomes, longer length of hospital stay, and increased impairment of functional ability.^{1,2} These risks are compounded when allogenic blood transfusion is required for correction.³ Allogenic blood transfusion increases the risk of postoperative infection, hemolysis, immunosuppression, transfusion-related acute lung injury, prolonged hospital length of stay, and even death.^{4–6} Furthermore, when considering resource allocation, the societal cost of 1 allogenic unit of red blood cells is upward of 200 USD.⁷ Therefore, decreasing perioperative blood loss and transfusion requirements for patient undergoing surgical procedures is paramount.

Tranexamic acid (TXA) (Cyclokapron [Pfizer, New York, NY]) is a pharmacologic agent used to minimize perioperative blood loss and the need for allogenic blood transfusions. TXA is a synthetic antifibrinolytic that acts by competitively binding to plasminogen, thereby slowing its conversion to plasmin at the end of the clotting cascade (Fig. 1).⁸ Due to its ability to reduce the local degradation of fibrin clot by plasmin, TXA has been successfully used in a variety of surgical procedures to minimize postoperative anemia and ultimately decrease transfusion rates.^{9–11} In early studies, TXA has shown a survival benefit in the setting of severe trauma and of postpartum hemorrhage, without an increase in thromboembolic events.^{12,13} Today, numerous research studies have reported favorable safety and efficacy outcomes with the use of tranexamic acid as intravenous, topical, and oral formulations.¹⁴ However, there is no universal standard on the most effective route, dosing, or timing of administration of TXA. Consequently, the use of TXA remains controversial and is not routine in many centers. Aside from multiple dosing forms, there have been mixed reports on bolus versus infusions of intravenous tranexamic.¹⁵ Overall, in the acute surgical setting bolus seems to be as effective as infusion.^{16,17} Plasma concentration required for the antifibrinolytic effect of TXA is as low as 10 µg/mL, which is achievable for up to 3 hours after IV bolus administration.^{18,19} Therefore, by evaluating 1 preoperative intravenous dose of TXA we hope to show evidence for a simpler regimen of administering TXA to patients.

The purpose of this meta-analysis was to evaluate the effect of a single preoperative IV dose of TXA on surgical blood loss across all surgical disciplines. Secondary outcomes were to evaluate the risk of perioperative transfusion and thromboembolic events following a single preoperative dose of TXA. We also aimed to clarify any dose response that may exist.

From the Department of Surgery, Plastic and Reconstructive Surgery, University of Calgary, Calgary, AB, Canada.

✉Justin.Yeung2@albertahealthservices.ca.

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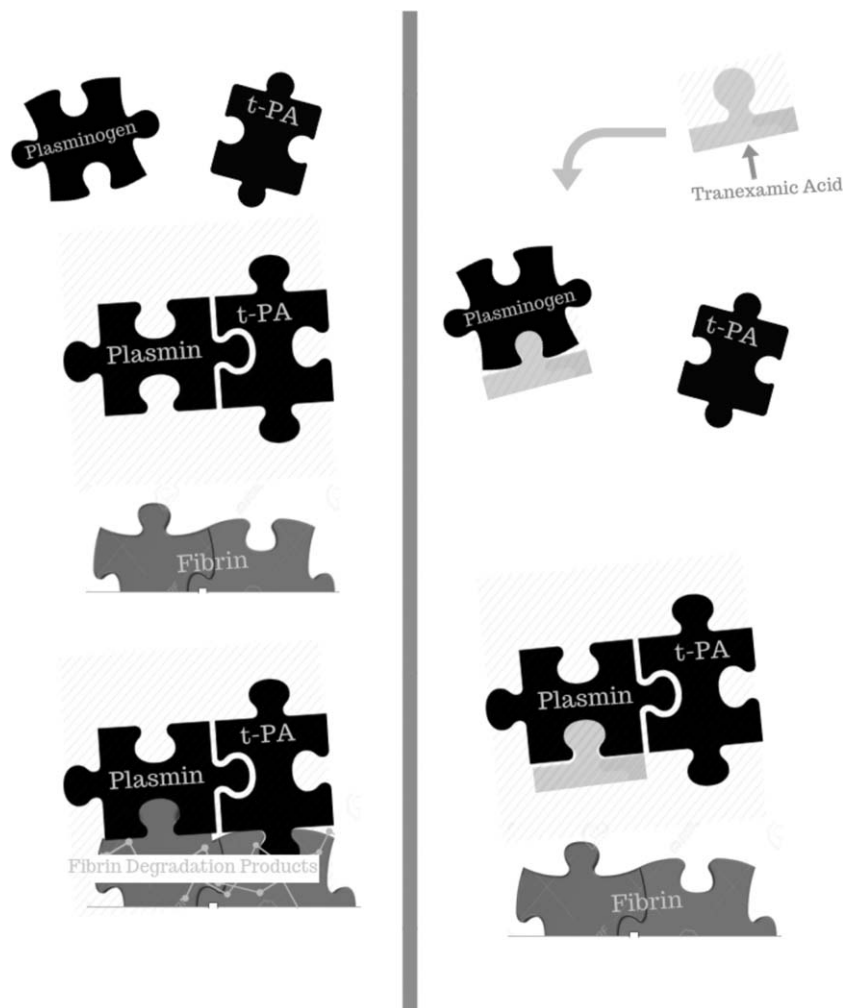


FIGURE 1. Mechanism of action of tranexamic acid. Tranexamic acid is a synthetic lysine analogue that competitively inhibits the activation of plasminogen, thereby inhibiting the degradation of fibrin.

METHODS

Search Strategy

With the guidance of an academic librarian, 3 authors searched EMBASE, Ovid MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCTs) up to November 2018. The key search terms included “Tranexamic Acid” (MeSH term) AND “Intravenous” (MeSH term). The full search strategy is presented in Appendix A, <http://links.lww.com/SLA/B982>.

Eligibility Criteria

RCTs that met the following inclusion criteria were analyzed in the meta-analysis: 1) adults undergoing surgery who were randomly assigned to a TXA; experimental or control group; 2) a single dose of intravenous (IV) TXA was administered as a bolus up to a maximum 30 minutes infusion time at the commencement of surgery; 3) intraoperative and perioperative blood loss was reported up to 24 hours after surgery; 4) a full-text article was available. Exclusion criteria included: 1) study could not be found in English; 2) nonsurgical procedures, including vaginal deliveries.

Quality Assessment

The Cochrane Collaboration risk-of-bias tool was utilized to assess the quality of included studies.²⁰ This tool assesses 6 types of bias in 7 domains including assessment of random sequence generation, allocation concealment, selective reporting, other sources of bias, blinding of participants and personnel, blinding of outcome, and incomplete outcome data. Each study was judged to be low risk of bias, high risk of bias, or unclear risk of bias. Two authors and an arbitrator used their judgement to categorize studies.

Data Extraction

Endnote X8 was used as a reference manager to extract data from all 3 databases.²¹ A single author (MH) performed the first review of all retrieved citations (1095 articles) after duplicates were removed. Three articles were sourced from the reference section of screened articles. Two authors (MH and PK) each independently completed a second review of citations (281 articles), which included a full article review. A third reviewer (AS) served as an arbitrator for any disagreements after the second review. All members of the team assisted in data extraction into a uniform excel spreadsheet. Demographic data was collected from all studies to ensure uniformity between and within groups, including name, age, sex, weight,

number of patients in each group, American Society of Anesthesia class, surgical procedure, and dose and duration of IV TXA bolus. Raw values, means, and standard deviations were also extracted when available. The primary outcome of interest was intraoperative and perioperative blood loss measured in any form within the first 24 hours after surgery. Intraoperative and postoperative blood loss values were extracted, as well as method of blood loss measurement and associated hematological parameters (such as hemoglobin, haematocrit, and coagulation markers). The secondary outcomes included blood transfusion rates and complications, such as deep vein thrombosis, and pulmonary embolism, as well as dosing. It was also recorded whether antihemorrhage agents or venous thromboembolism prophylaxis was given to patients.

Statistical Analysis

Categorical and numerical data were extracted pertaining to primary and secondary objectives and were statistically analyzed by an independent professional statistician. Data was analyzed as both pooled and separated into respective surgical disciplines as subgroup analysis. Specifically, for the dosing analysis data was divided into 10, 15, and 20 mg/kg regimens and analyzed in a similar fashion. Dosing reported in grams was divided by mean weight of participants when available. Statistical analyses were completed using Cochrane Review Manager 5.3.²² Random effects models were used if the χ^2 test for heterogeneity failed at $\alpha = 0.05$, otherwise fixed effects models were used. For each outcome, we produced forest plots along with numeric estimates of overall (common) effects along with 95% confidence intervals (CIs), and funnel plots to assess publication bias. The Cochrane Collaboration risk-of-bias tool was used to assess methodological heterogeneity, and funnel plots were used to evaluate for bias in publication.²⁰

RESULTS

Study Characteristics and Quality Assessment

A total of 1098 articles were screened, 57 met inclusion criteria (Fig. 2). Randomized controlled trials were performed across a wide variety of surgical subspecialties: orthopedic surgery (27), obstetrics and gynecology (16), oral maxillofacial surgery/otolaryngology (10), cardiac surgery (3), and plastic surgery (1). Sample sizes of the included trials ranged from 6 to 374, and mean age of

participants ranged from 22.8 to 79.3 years. Further demographic information of the 5698 patients included in the analysis is summarized in Supplementary Table 1, <http://links.lww.com/SLA/C819>. Three of the included studies had more than 1 dosage tested against placebo, these studies were analyzed multiple times, once for each dosage compared with placebo.^{23–25} Thirteen studies were not included in the statistical analysis for blood loss due to inadequate reporting on confidence interval or standard deviation, these values were either missing or expressed as a figure where exact values could not be extracted.

Fig. 3 summarizes methodological quality and the risk of bias of the included studies.

Overall, 30 studies (52%) had a low risk of bias for random sequence generations, 5 (9%) studies were high risk, and 23 (40%) studies had an unclear risk due to lack of information. Allocation was adequately concealed in 16 studies (28%), and inadequately concealed in 5 studies (9%). The risk of allocation concealment bias in the remaining 37 (64%) was deemed unclear due to lack of information. The risk of bias for selective reporting was low in 27 studies (47%), high in 18 studies (31%), and unclear in 13 studies (22%). The high incidence of studies with a high risk of selective reporting bias is partially due to lack of appropriate reporting of confidence interval or standard deviation of blood loss by 13 studies as stated above. Other bias was low in 16 (28%) of studies, and high in 15 (26%) of studies for a variety of reasons including using estimated blood loss by the anesthesiologist for outcome instead of gravimetric methods or small sample size. Other bias was deemed unclear in 58 (46%) of studies. There was appropriate blinding of the participants and personnel in 30 (53%) of studies, high risk of participant blinding bias in 8 (14%), and unclear risk in 19 (33%) of studies. There was appropriate blinding of outcome in 23 (40%) of studies, high risk of outcome blinding bias in 6 (11%), and unclear risk in 28 (49%) of studies. Data was deemed to be complete in 30 (53%) of studies, incompletely reported in 3 (5%), and there was an unclear risk of incomplete outcome data bias in 24 (42%) of studies.

Meta-analysis of Blood Loss

One perioperative dose of TXA had a strong effect on reduction of blood loss compared with control groups in all disciplines (Table 1). Across all surgical specialties ($n = 5698$), the perioperative estimated blood loss was lower in patients receiving TXA, with a standard mean difference of -153.33cc (95% CI = -187.79cc to

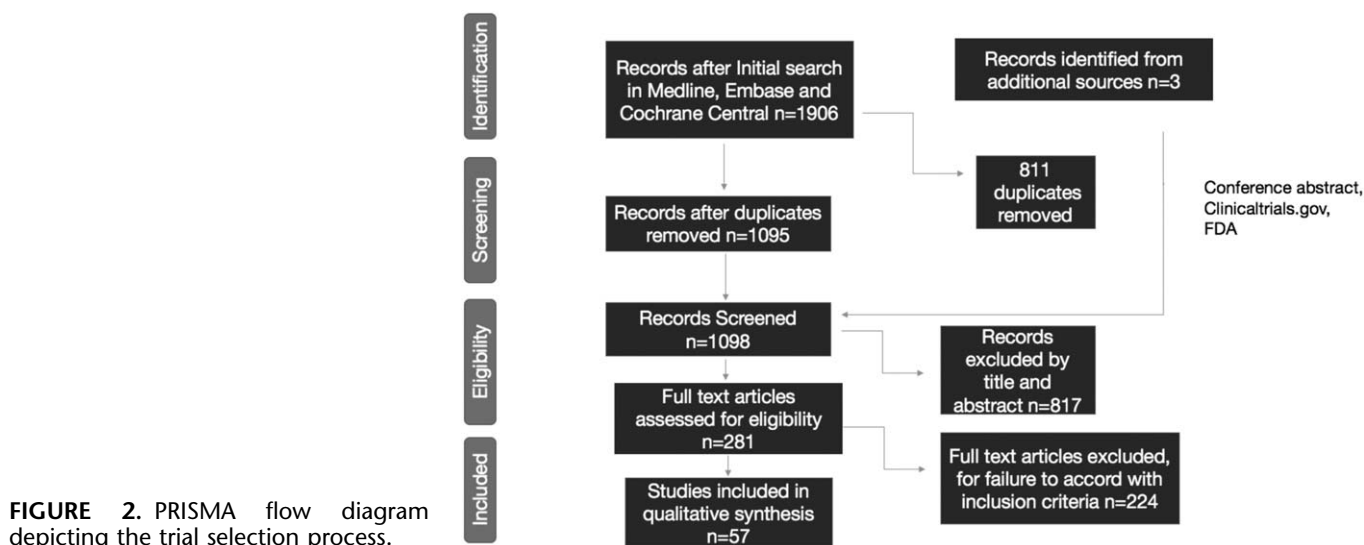


FIGURE 2. PRISMA flow diagram depicting the trial selection process.

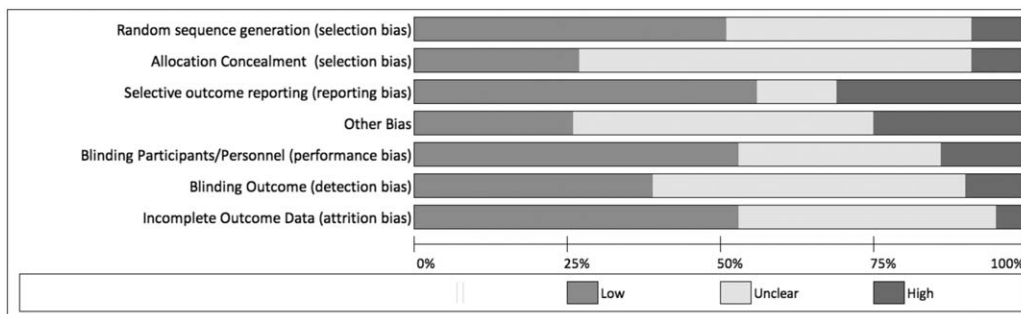


FIGURE 3. Risk of bias assessment. Appraisal of methodological quality of randomised controlled trials (cochrane collaboration’s tool for assessing risk of bias).

–118.87cc). The mean differences in blood loss after a single preoperative dose of TXA compared with controls are stratified by discipline in Table 1. While the largest number of randomized controlled trials comparing the effect of 1 preoperative TXA dose have been performed in orthopedic surgery, the highest number of patients enrolled in studies comparing a single dose of TXA to placebo were in the field of obstetrics and gynecology. While only 1 study came from plastic surgery (n = 50), the greatest reduction in blood loss with a single preoperative TXA dose was seen in this subgroup (–409.00cc [–600.97cc, –217.03cc]).

Meta-analysis of Transfusion Rate

There were 31 studies (n = 2342) that reported the number of patients needing blood transfusions in the TXA and placebo groups. In the TXA groups 154 out of 1177 (13%) patients needed at least 1 unit of packed red blood cells, in the placebo groups 340 of 1165 (29%) patients needed a transfusion. Overall, surgical patients with TXA had a 72% reduced odds of transfusion (odds ratio = 0.28 (95% CI = 0.22–0.36), Table 2). All surgical specialties showed a reduction in need for transfusions compared with placebo. Within treatment groups the reduction in relative risk was greatest in the orthopedic surgery studies with an odds ratio of 0.26 [95% CI = 0.19, 0.34], results for each surgical specialty are summarized in Table 2. A risk difference model for transfusion in the overall data gave a number needed to treat of 20 (NNT = 1/(absolute risk reduction) = 1/0.05 = 20).

Meta-analysis of VTE Incidence

Forty-two studies reported on deep vein thrombosis and pulmonary embolisms (VTE), which occurred in 15 of 2357 (0.64%) patients in the tranexamic acid group, and 15 of 2300 (0.65%) patients in the control groups. There was no difference in the incidence of venous thromboembolic events between TXA and control groups (OR 1.00, 95% CI [0.50, 1.99]). This remained true when data was pooled together, as well as stratified by surgical subspecialty. Of note, patients were prescribed anticoagulation with either lower molecular weight injections or oral anticoagulation for upward of 35 days postoperatively.

Meta-analysis of Dosing

Dosing ranged from 10 up to 100 mg/kg and from 0.5 to 10 g. All doses were given at most 30 minutes preoperatively or at the time of anesthesia induction. The most frequently used dose (mode) of TXA was 15 mg/kg, this was used on 21 studies (37%). Twelve studies used a TXA dose of 10 mg/kg (n = 1066), Twenty-one studies used a dose of 15 mg/kg (n = 1406) and 5 studies used a dose of 20 mg/kg (n = 381). Various other dosages were used such as a standard 1 or 1.5 mg of intravenous TXA in studies that did not report average weights of patients and therefore were not included in statistical analysis. Furthermore, 3 cardiac surgery studies used a dose of 100 mg/kg. Overall there was a nonsignificant trend toward less blood loss and lower odds of transfusion with an increase in the dosage of TXA from 10 to 20 mg/kg (Table 2, Fig. 4).

TABLE 1. Blood Loss in Tranexamic Acid Versus Placebo Groups Based on Surgical Discipline

Discipline	No. of RCTs	No. of Patients	Mean Difference in Blood Loss, cc (TXA, Control, 95% CI)
Orthopedic	27	1822	–86.79 [–113.75, –59.83]
Obstetrics and gynecology	16	2850	–166.92 [–198.82, –135.03]
Plastic surgery	1	50	–409.00 [–600.97, –217.03]
Oral maxillofacial/ Otolaryngology	10	776	–222.72 [–290.52, –154.91]
Cardiac surgery	3	200	–331.00 [–379.09, –282.91]
Total	57	5698	–153.33 [–187.79, –118.87]

TABLE 2. Odds Ratio of Transfusion in Tranexamic Acid Versus Placebo Groups Based on Surgical Discipline

Discipline	No. of RCTs	No. of Patients	Odds Ratio of Blood Transfusion in TXA Versus Placebo
Orthopedic	17	1206	0.26 [0.19, 0.34]
Obstetrics and gynecology	6	812	0.34 [0.19, 0.59]
Plastic surgery	1	50	0.29 [0.09, 0.98]
Oral maxillofacial/otolaryngology	7	274	0.39 [0.15, 0.96]
Cardiac surgery	0	—	—
Total	31	2342	0.28 [0.22, 0.36]

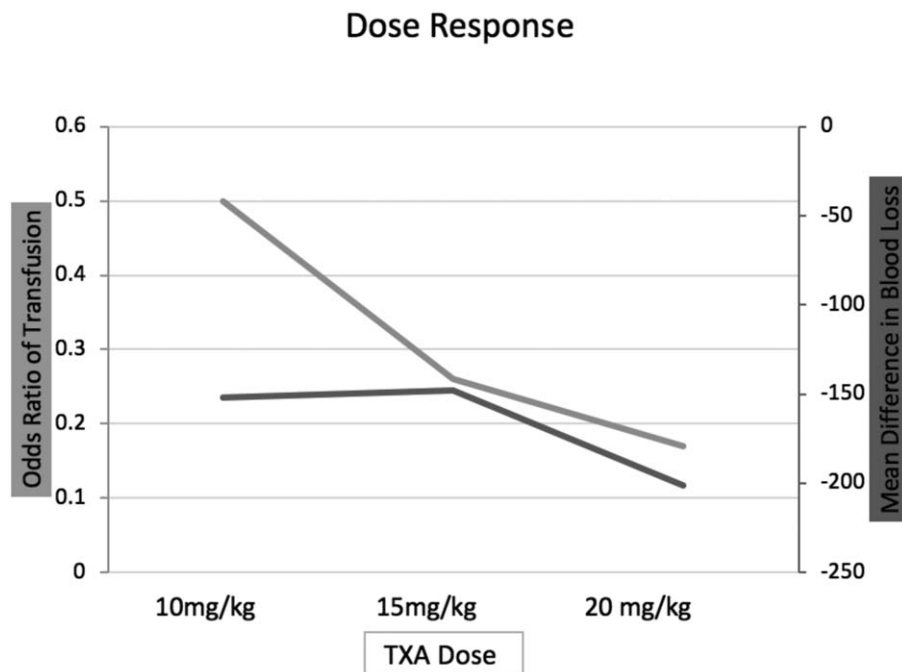


FIGURE 4. Mean difference in blood loss and odds ratio of blood transfusion at 10mg/kg (n = 12), 15mg/kg (n = 21) and 20mg/kg (n = 5) of intravenous tranexamic acid versus control group.

DISCUSSION

While there is a growing body of evidence to support benefits of perioperative TXA use,^{9–11} this is the first meta-analysis to identify the efficacy and safety of a single preoperative dose of intravenous tranexamic acid. This study shows application of this simpler dosing method of TXA which may transfer to its applicability in the elective day surgery setting. The efficacy of a single preoperative dose indicates that patients do not need to be admitted to hospital to receive additional postoperative doses of TXA to benefit from its administration. Furthermore, the lack of increased risk of thromboembolic events suggests that patients receiving TXA may not require hospital admission for postinfusion monitoring as part of safe administration practices.

The evidence in this review suggests that trials showing the efficacy of a single preoperative dose of tranexamic acid has been mounting for at least the past 20 years, with most studies being done over 5 years ago. For patients treated prophylactically with TXA we found a reduction in blood loss per procedure of 153.33cc (95% CI = -187.79cc to -118.87cc) using pooled data from all included studies regardless of discipline. This reduction in bleeding was reflected within each subgroup analyzed (Table 1). The largest RCT included in this review by Abdel-Aleem et al. had 745 women undergoing elective cesarean sections at >37 weeks also supported these findings.²⁶ They report an average 268.4mL reduction in intraoperative blood loss in the patients receiving 1g TXA preoperatively. In this review, when studies were grouped based on subspecialty the reduction in blood loss was smallest in orthopedic and gynecological groups; these were also the

specialties with the most published data. Taken together this points to a potential publication bias due to limited evidence in the surgical specialties with the least published data namely studies in oral surgery/otolaryngology, plastic surgery, and cardiac surgery.

Across all included studies the predominant trend was toward lower red blood cell (RBC) transfusions as a result of lower blood loss following preoperative TXA administration. Overall, the odds ratio of needing a blood transfusion in the TXA groups was 0.28 [0.22, 0.36], meaning that these patients were 72% less likely to need a blood transfusion than those not prophylactically treated with TXA with a number needed to treat of 20 to prevent 1 transfusion. This statistic was mirrored in the Orthopedic studies which had the most reported transfusion data and found a 74% reduction in patients requiring RBC transfusions (Table 2). In addition, the patients requiring transfusion were less in the tranexamic acid group for all surgical specialties analyzed (Table 2).

However, this data is not consistent across all individual studies. The largest study to report transfusion data was by Bhavana²⁷ published in 2016 reporting on 200 patient undergoing term C-sections. Of the 100 patients randomized to receive preoperative TXA, 2 needed blood transfusions whereas in the control group 3 patients needed blood transfusion, with 1 patient requiring 5 units of RBCs for a postpartum hemorrhage. There was no significant difference in transfusion rate from this study.²⁷ On the other hand, Baruah et al²⁸ randomized 60 patients to TXA and placebo preoperatively in patients undergoing dynamic hip screw plate fixation for trochanteric fracture concluding there was also no significant

TABLE 3. The Effect of Tranexamic Acid Dose on Odds Ratio of Blood Transfusion and Mean Blood Loss

Dose (mg/kg)	Odds Ratio of Blood Transfusion in TXA Versus Placebo	Mean Difference in Blood Loss, cc (TXA, Control, 95% CI)
10	0.50 [0.24, 1.03]	-152.14 [-192.28, -112.01]
15	0.26 [0.19, 0.36]	-148.04 [-194.03, -102.06]
20	0.17 [0.07, 0.41]	-201.51 [-303.40, -99.62]

difference in transfusion requirements, as all 60 patients needed a blood transfusion.

Decreasing perioperative blood loss can lead to a more functional postoperative course and shorter length of hospital stay.² Moreover, it is widely known that perioperative blood transfusions are associated with increased adverse events, and potentially life-threatening complications. The use of prophylactic TXA could theoretically reduce the risk of these adverse complications including severe anaphylaxis, transfusion-associated circulatory overload, and transfusions-associated lung injury.⁴ Although it is difficult to be certain using the data from this review given the overall low incidence of blood transfusions and low reporting by included studies. In addition to this clinical benefit, another benefit of TXA administration that was not assessed in this review is the cost benefit from spared blood transfusions.

When considering the optimal regimen for administering TXA, the reduction in transfusion rate as well as the potential for complications should be considered. There is a definite persistent uncertainty around the effect of tranexamic acid on thromboembolic events and mortality. Although there was no difference in VTE risk reported by any of the studies, nor when assessed cumulatively; no included studies were judged to be adequately powered or followed subjects rigorously enough to assess the possible adverse effects specifically thromboembolic complications associated with TXA. A recent retrospective cohort study including over 13,000 patients undergoing THA or TKA at the Mayo Clinic found no difference in VTE or mortality in this high risk group of patients treated with TXA within 30 days of surgery.²⁹ Along with high-risk orthopedic patients and pregnant women undergoing cesarean sections, this review also included studies with burn victims and those having gynecological cancer resections, with all populations not showing an increase in VTE.^{30,31} Most studies included in this trial were small including about 50 patients as controls and 50 patients in the tranexamic acid group, too small to resolve the uncertainties about the effects on thromboembolic events. Because thromboembolic events are relatively rare these trials lack the power to detect clinically significant increases in risk. We do acknowledge that this meta-analysis of smaller trials does remain vulnerable to publication bias, although the incidence of VTE was lower than other literature (0.64%), funnel plot analysis did not show publication bias for VTE risk.

Most studies used a dose between 10 and 20 mg/kg, except the 3 cardiac surgery studies that used much higher doses around 100 mg/kg.^{32–34} Although there was a blood loss reduction and reduction in odds of transfusion from 10 to 20 mg/kg (Fig. 4, Table 3), the reduction was not statistically significant in this review. However, this trend is supported by 3 included studies that looked at multiple doses. Apipan et al²³ found a reduction in blood loss per procedure compared with placebo from 355 to 380 to 455 mL when moving from 10 to 15 to 20 mg/kg, respectively. Two other studies also report more effect with an increased bolus dose of tranexamic acid from 10 to 15 mg/kg.^{24,25} Conversely, the authors of this review acknowledge that the nonsignificance of this trend can be interpreted as an argument to use the lowest effective dose which may be 10 mg/kg. Pharmacological studies have shown that all patients given a dose of 1 g TXA IV preoperatively sustained therapeutic levels for up to 150 minutes after administration¹⁹ Using a lower dose may also encourage more widespread use of TXA as it may offset some of the concern regarding the theoretical increase in VTE risk.

Although the intravenous route of administration remains the clinical standard, recent studies have demonstrated the benefits of intra-articular topical TXA as well as oral TXA for a limited number of orthopedic procedures.^{35,36} Oral TXA is inexpensive, has good oral bioavailability and a longer half-life compared with IV TXA,

making it an excellent medication for perioperative care.³⁷ Further study on the use of a single oral dose of TXA may have additional applications in surgery to improve postoperative patient outcomes.³⁸

Limitations

Frequently, there is a reluctance to generalize the evidence across multiple surgical disciplines, although there is no evidence showing that the relative effect of TXA on blood loss or transfusion rate varies by type of surgery; a statement consolidated further in this review. Still, this study does draw a conclusion based on somewhat vast groups of data with most evidence coming from orthopedic and obstetrical and gynecological studies leading to a potential bias toward supportive evidence in these areas. There was some heterogeneity within the studies assessing blood loss, this was managed by using random effect models to assess common effect when analyzing the data. However, there was no evidence of heterogeneity within the transfusion data which also showed a strong effect for transfusion reduction in the presence of TXA administration. As previously stated, the included studies were not adequately powered to analyze the potential adverse effects of TXA in high-risk surgical patients such as venous thromboembolic events or seizures.

CONCLUSIONS

A single preoperative dose of intravenous TXA reduces perioperative blood loss by 153.33 cc per procedure and transfusion odds by 72% in a variety of surgical disciplines without clinically increasing the risk of thromboembolic events. Therefore, a single preoperative dose of TXA should be considered, particularly for elective day surgery procedures to minimize risks of perioperative blood loss and adverse outcomes associated with red blood cell transfusion.

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