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The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis

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ABSTRACT

Background: A growing body of published research on tranexamic acid (TXA) suggests that it is effective in reducing blood loss and the risk for transfusion in total knee arthroplasty (TKA). The purpose of this network meta-analysis was to evaluate TXA in primary TKA as the basis for the efficacy recommendations of the combined clinical practice guidelines of the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Medicine on the use of TXA in primary total joint arthroplasty.
Methods: We searched Ovid MEDLINE, Embase, Cochrane Reviews, Scopus, and Web of Science databases for publications before July 2017 on TXA in primary total joint arthroplasty. All included studies underwent qualitative and quantitative homogeneity testing. Direct and indirect comparisons were performed as a network meta-analysis, and results were tested for consistency.
Results: After critical appraisal of the available 2113 publications, 67 articles were identified as representing the best available evidence. Topical, intravenous (IV), and oral TXA formulations were all superior to placebo in terms of decreasing blood loss and risk of transfusion, while no formulation was clearly superior. Use of repeat IV and oral TXA dosing and higher doses of IV and topical TXA did not significantly reduce blood loss or risk of transfusion. Preincision administration of IV TXA had inconsistent findings with a reduced risk of transfusion but no effect on volume of blood loss.
Conclusions: Strong evidence supports the efficacy of TXA to decrease blood loss and the risk of transfusion after primary TKA. No TXA formulation, dosage, or number of doses provided clearly improved blood-sparing properties for TKA. Moderate evidence supports preincision administration of IV TXA to improve efficacy.

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Total knee arthroplasty (TKA) is an effective procedure in the treatment of degenerative joint disease but is associated with a substantial risk of blood loss requiring transfusion. Historically, approximately one-third of patients undergoing total joint arthroplasty (TJA) require 1 to 3 units of blood, postoperatively [1–5]. Acute postoperative anemia and transfusion has been linked to increased morbidity and mortality, including angina, myocardial infarction, heart failure, and delayed progression in rehabilitation [6,7]. Therefore, techniques such as the use of antifibrinolytics, desmopressin, hypotensive anesthesia, or normovolaemic hemodilution have all been utilized to reduce the need for allogeneic blood transfusion [8].

Tranexamic acid (TXA) is an antifibrinolytic agent discovered in the 1960s, which has become an integral component in postoperative blood management in orthopedic surgery [9,10]. TXA is a synthetic amino acid derivative of lysine, which binds to plasminogen and ultimately prevents fibrin degradation [9,10]. Ever since the initial publication on the use of TXA in TJA by Benoin et al [11], a significant body of literature has established its blood-sparing properties. As a result, TXA has become more commonly used in TJA.

The American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons (AAOS), Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Medicine have collaborated on the development of a clinical practice guideline on the use of TXA in primary TJA. We performed a network meta-analysis of randomized clinical trials on the use of TXA in primary TKA as part of the supporting documentation for the combined clinical practice guideline. The purpose of our study is not to provide additional evidence in the literature but to coalesce and synthesize the best available evidence on the many individual studies. The present study is not a classic "meta-analysis and systematic review," which is also referred to as a direct meta-analysis. The purpose of this study was to answer a series of Population, Intervention, Comparison, and Outcome (PICO) questions related to the efficacy of TXA in the setting of primary TKA (Table 1).

A direct meta-analysis is only capable of coalescing publications investigating the same 2 treatments. We have performed a network meta-analysis that is more complex than a standard direct meta-analysis. In a setting whereby publications exist investigating treatment A vs B and B vs C, the classic direct meta-analysis only allows for individually investigating publications comparing treatment A vs B and B vs C. Direct meta-analysis does not allow for comparison of A vs C. However, the network meta-analysis allows for direct and indirect comparisons that permit for the comparison of A vs B, B vs C, and A vs C within a single analysis. Because of the ability to perform indirect comparisons, the indication for a network meta-analysis is when there are several different published treatments among a large number of randomized clinical trials whereby too many treatments options exist to realistically perform a single randomized clinical trial.

Table 1
PICO Questions.

Questions
1. For patients undergoing primary TKA, what method of administration of TXA, compared to placebo, reduces the risk of transfusion and/or reduces blood loss?
2. For patients undergoing primary TKA, what method of administration of TXA, compared to a different method of administration, reduces the risk of transfusion and/or reduces blood loss?
3. For patients undergoing primary TKA, does the dose amount of IV, topical, or oral TXA affect the risk of transfusion and/or reduction in blood loss?
4. For patients undergoing primary TKA, does a repeat dose of IV or oral TXA affect efficacy?
5. For patients undergoing primary TKA, does the administration time in relation to the start of the procedure affect the efficacy of TXA?

IV, intravenous; PICO, population, intervention, comparison, and outcome; TKA, total knee arthroplasty; TXA, tranexamic acid.

Material and Methods

Before the initiation of the literature search, a study protocol was designed and maintained in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [12].

Search Methodology

Under the direction of a research librarian, we performed a literature search using Ovid MEDLINE, Embase, Cochrane Reviews, Scopus, and Web of Science databases. The search strategy was approached by first establishing the primary search themes—"arthroplasty" and "tranexamic acid." Exploded Medical Subject Headings (MeSH) terms were used whenever possible. Once the 2 search themes were established, the Boolean operators "AND" and "OR" were used to identify the intersection and union of the terminology sets. Individualized search strategies were implemented for each database (Appendix A). The database searches from Ovid MEDLINE, Cochrane Reviews, and Scopus included all published articles before July 2017. Because of limited database access to Embase and Web of Science, the search was only performed for all articles before October 2016. Meanwhile, no limitations were imposed on any of the database search results. We reviewed the bibliographies of relevant publications including reviews and meta-analyses to examine for additional publications and provide validation to the quality of the search methodology.

Because a sister study was performed on the efficacy of TXA in the setting of primary total hip arthroplasty, the search methodology included the identification of publications related to primary hip and knee arthroplasty. As a result, studies were separated based on the type of surgery as the last step in the process of the study selection for each individual analysis.

Study Selection Criteria

All study participants must have undergone a primary TKA to be considered for inclusion in the network meta-analysis, and the study must have reported the appropriate outcomes of blood loss and/or transfusion. Articles were excluded that consisted of patients undergoing revision TKA, simultaneous or staged bilateral TKA, and primary arthroplasty of joints other than the knee. Secondary source articles including review articles, systematic reviews, meta-analyses, and expert opinions were excluded from the network meta-analysis. Published abstracts from the proceedings of a scientific meeting were excluded; however, full-text publications associated with conference abstracts were included to help minimize publication bias. For PICO questions related to blood loss, the publication must have reported a standard deviation or 95% confidence interval to be included in the network meta-analysis.

Data Collection

Two authors independently performed a screening of all titles and abstracts to identify duplicate publications and studies meeting the exclusion criteria. If there was any doubt regarding the inclusion or exclusion status within the title and abstract screening, the study was kept for full manuscript review. Two authors independently assessed the full manuscripts of the remaining publications to assess for inclusion or exclusion of the studies. Any

disagreement between the authors was discussed, and a consensus was obtained regarding the status of the publication.

The AAOS Department of Research, Quality, and Scientific Affairs performed an assessment of the quality and data extraction of the publications from the full manuscript review in accordance with the AAOS Clinical Practice Guidelines and Systematic Review Methodology [13]. Reviewers evaluated the quality of the studies based on the following appraisal criteria: randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and conflict of interest. Based on the high volume of literature on the subject matter, further exclusions were applied to only include randomized clinical trials that were assigned a high-quality rating with the exception of 1 moderate quality study.

Outcomes and Network Plots

Reporting of the study outcomes was tracked to assess for consistency between studies. Blood loss in the studies was reported as calculated blood loss that used multiple variables to determine the blood loss instead of using estimated intraoperative blood loss. Transfusions were reported as allogeneic or autogenous blood transfusions. Stratification of the TXA dose could be performed for intravenous (IV) and topical TXA formulations. The definition for high-dose IV TXA included any dose ≥20 mg/kg or > 1 g, and the definition for high-dose topical TXA included any dose >1.5 g.

In the conception of the network plots for outcome comparison, 2 separate network plots were created. The network plots consist of nodes that represent a TXA intervention, which creates a visual description of the direct comparisons between each node and the quantitative number of studies for each comparison. A connection between 2 nodes represents the presence of a direct comparison in the literature, while the thickness of the line represents the number of studies for a given comparison. The first network plot focused on the TXA formulation and dosage, which included the following nodes: (1) placebo, (2) low-dose IV TXA, (3) high-dose IV TXA, (4) low-dose topical TXA, (5) high-dose topical TXA, (6) oral TXA, (7) combined IV/topical TXA, and (8) combined IV/oral TXA. The second network plot focused on the TXA formulation, timing of dosage, and number of doses, which included the following nodes: (1) placebo, (2) single-dose preincision IV TXA, (3) single-dose postincision IV TXA, (4) multiple doses preincision and postincision IV TXA, (5) multiple doses postincision IV TXA, (6) single preincision oral TXA, (7) multiple doses preincision and postincision oral TXA, and (8) single postincision topical TXA.

Statistical Analysis

As necessitated by the 3 assumptions of a network meta-analysis, a clinical statistician assessed the homogeneity, transitivity, and consistency of the data [14,15]. Homogeneity is useful in establishing the validity and interpretability of the results and strengthens the assumption of transitivity. Transitivity is the assumption that the indirect comparisons being generated are as qualitatively similar as the 2 or more direct comparisons that generated them. Transitivity was satisfied by using stringent inclusion criteria, quality appraisal, and homogeneity testing and is demonstrated by consistency testing [13]. The outcomes were first analyzed for heterogeneity using STATA software 12.1 (StataCorp, College Station, TX) to produce forest plots of direct comparisons [13]. Among the 17 direct comparisons, the heterogeneity under most circumstances was 0%, while 2 circumstances had a statistically significant heterogeneity greater than 40%. In the 2 situations when this exceeded 40%, we could not stratify or control for it any further. Though the heterogeneity was high for a couple of analyses, they tend to show agreement in the favored treatment and only seem to differ in the level of the treatment effect. The data were then entered into R open source software, specifically R-GeMTC (R-Project, Vienna, Austria), to generate precursory treatment rank and mixed effect comparison data. Weighted mean differences and risk ratios were calculated for continuous and dichotomous outcome measures using the R software. The resulting estimates of mixed (combined direct and indirect) effects were assessed for statistical significance. Indirect treatment effects were extrapolated from the differences of the mixed treatment effects and the direct treatment effects. Direct and indirect treatment comparisons were evaluated for consistency, which showed no significant differences for direct and indirect comparisons [13–15]. As far as consistency testing is concerned, the null hypothesis in this case is that there are statistically significant differences between direct, indirect, and mixed effects means and the alternative hypothesis is that there is no difference between means. At 95% (alpha = 0.05) and powered

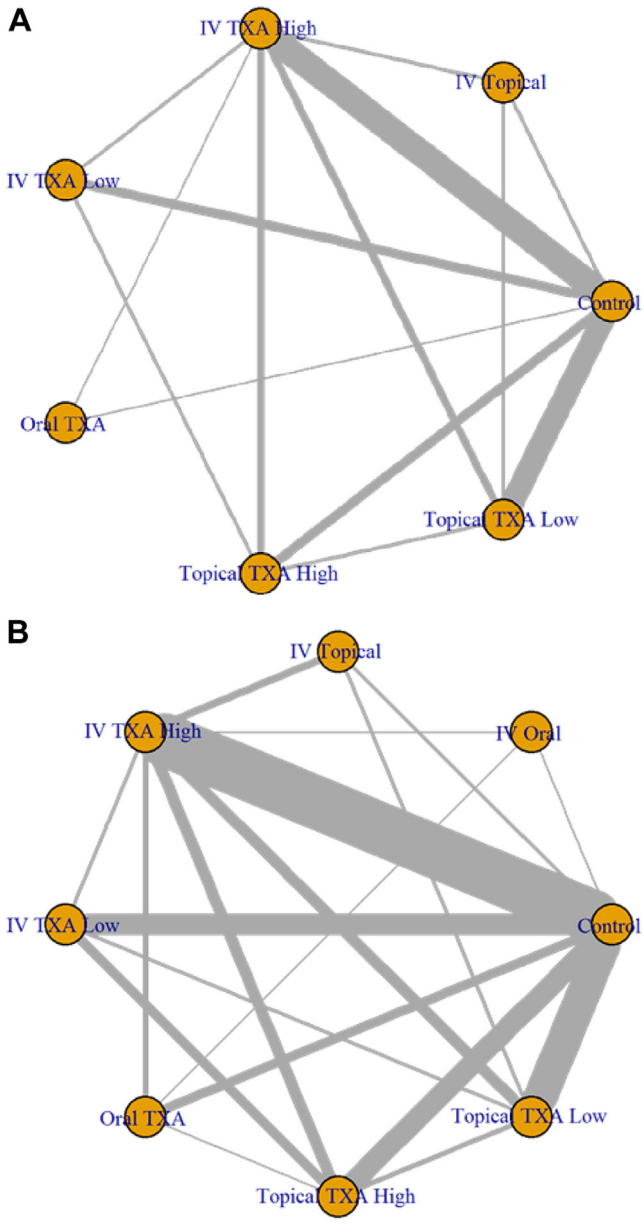

Fig. 1. (A) Network plot focused on TXA formulation and dosage for the outcome of blood loss in primary TKA. (B) Network plot focused on TXA formulation and dosage for the outcome of transfusion in primary TKA.

at 80% (beta = 0.8) to detect a difference of less than 1% in the means requires approximately 8000 patients. Our network contains over 9000 patients, so we are overpowered and still are not observing a difference between direct and indirect means. Therefore, we reject the null in favor of the alternative and conclude that our network is consistent and appropriately powered. Transitivity was assessed through the comparison of treatment effects across trials, and meta-regression was performed to assess the reliability of the quality appraisal criteria [13].

The mixed effects tables produced from the direct and indirect comparisons performed as part of the network meta-analysis provide a qualitative measure between the treatment comparisons. The intersecting cell between the treatment in the first column and row represent the comparison between those TXA interventions. The value presented in the cell either represents a mean difference when the reported outcome was calculated blood loss or a risk ratio when the outcome was transfusion. If the mean difference or risk ratio value is less than 1, the outcome favored the treatment in the first column. When the value was greater than 1, the outcome favored the treatment in the first row. Any comparison with a confidence limit not spanning zero was considered to be statistically significant.

Results

The initial search strategy provided 2113 results for title and abstract screening, whereby 867 were excluded for duplication and 596 excluded for meeting the exclusion criteria. The remaining 650 results underwent full manuscript review with 362 meeting the general exclusion criteria (19 had revision TJA or arthroplasty other than a hip or knee, 29 had bilateral TJA, 71 did not report blood loss or transfusion as an outcome, 151 were secondary source articles, and 92 were published abstracts from the proceedings of a scientific meeting). In addition, 31 were excluded for not having an English language translation and 27 were excluded for not having access to the full text. The 230 publications remaining after the full manuscript review underwent data extraction and quality assessment to provide 67 studies on the use of TXA in the setting of a primary TKA that were included in the network meta-analysis.

TXA Formulation and Dose Network Plot

The network plot for TXA formulation and dose was utilized to investigate the outcome of blood loss (Fig. 1A) and transfusion (Fig. 1B). The network meta-analysis investigating blood loss excluded the combined IV/oral TXA node due to a lack of reported outcomes for the specific TXA treatment and included a total of 32 studies within the network [3,16–46]. The network meta-analysis on transfusion encompassed all 8 nodes within the network plot with a total of 61 studies within the network [1,2,16–19,21–28,31–34,36–78].

Network meta-analysis output was used to produce a mixed effects table for blood loss between the various TXA formulations, TXA doses, and placebo (Table 2). All TXA formulations and doses provided a statistically significant decrease in the blood loss compared with placebo. No difference in the volume of blood loss was observed between the various TXA treatments regardless of TXA formulation or dose.

Network meta-analysis output was used to produce a mixed effects table for transfusion between the various TXA formulations, TXA doses, and a placebo (Table 3). Similar to the evaluation of blood loss, risk of transfusion was statistically lower for all TXA formulations and doses compared with placebo. Among the comparisons between TXA formulations and doses, only low-dose IV TXA was noted to have a higher statistically significant risk of transfusion compared with high-dose IV TXA and combined IV/topical TXA. The remaining comparisons between the TXA treatments demonstrated no difference in the risk of transfusion.

TXA Formulation, Timing of Dose, and Number of Doses Network Plot

The network plot for TXA formulation, timing of dose, and number of doses was used to investigate the outcome of blood loss (Fig. 2A) and transfusion (Fig. 2B). The network plots examining both blood loss and transfusion included all 8 of the nodes. The network meta-analysis on blood loss and transfusion included 32 and 60 studies within each network [1,2,16–27,29–56,58–64,66–80].

Network meta-analysis output was used to produce a mixed effects table for blood loss between the various TXA formulations, timing of dose, number of doses, and a placebo (Table 4). All TXA treatments with the exception of single-dose and multiple-dose oral TXA had a statistically significant decrease in the blood loss compared with placebo. Despite both oral TXA treatment groups being no different than placebo, we did not observe any statistical superiority of the other TXA treatments compared to the oral TXA treatments. In addition, no difference in the blood loss was observed between the various TXA treatments regardless of TXA formulation, timing of dose, and number of doses.

Network meta-analysis output was used to produce a mixed effects table for transfusion between the various TXA formulations, timing of dose, number of doses, and placebo (Table 5). With the exception of single-dose oral TXA, all TXA treatments

Table 2
TKA Mixed Effects (Mean Differences) for Blood Loss by TXA Formulation and Dose[a].

TKA	High IV	Low IV	High Topical	Low Topical	Oral	Control
IV/topical	−48.37 (−177.95, 82.02)	−59.21 [c] (−228.4, 112.9)	−1.95 [c] (−151.77, 149.37)	−64.98 (−196.13, 68.63)	−100.97 [c] (−317.24, 111.91)	**−331.18 (−464.59, −205.64)**
High IV	–	−10.75 (−133.71, 114.3)	46.47[b] (−48.39, 141.34)	−16.61[b] (−98.32, 66.23)	−52.64 (−233.36, 123.52)	**−283.06[b] (−353.6, −219.7)**
Low IV	–	–	57.26 (−79.17, 191.2)	−5.87 [c] (−139.5, 126.9)	−41.72 [c] (−255.28, 164.95)	**−272.29[b] (−397.42, −155.83)**
High topical	–	–	–	−63.05 (−162.79, 38.13)	−99.06 [c] (−296.33, 93.6)	**−329.4[b] (−426.63, −240.21)**
Low topical	–	–	–	–	−36.05 [c] (−226.34, 148.1)	**−266.32[b] (−341.69, −200.08)**
Oral	–	–	–	–	–	**−230.25 (−408.9, −55.88)**

Bold values indicate a statistically significant result.
TKA, total knee arthroplasty; TXA, tranexamic acid.
[a] Blood loss reported as weighted mean difference (confidence limits).
[b] Effect includes 3 or more high-quality studies of direct treatment comparison.
[c] Effect based on indirect estimates from network meta-analysis due to the lack of literature for direct treatment comparison.

Table 3
TKA Mixed Effects (Risk Ratios) for Transfusion by TXA Formulation and Dose[a].

TKA	IV/Oral	High IV	Low IV	High Topical	Low Topical	Oral	Control
IV/topical	0.83 [c] (0.13, 7.72)	0.5[b] (0.16, 1.34)	**0.3** [c] **(0.09, 0.88)**	0.4 [c] (0.12, 1.21)	0.42 (0.13, 1.2)	0.43 [c] (0.12, 1.45)	**0.1 (0.03, 0.28)**
IV/oral	–	0.61 (0.08, 2.72)	0.36 [c] (0.05, 1.71)	0.49 [c] (0.06, 2.33)	0.51 [c] (0.07, 2.34)	0.52 (0.06, 2.54)	**0.13 (0.02, 0.55)**
High IV	–	–	**0.6 (0.37, 0.98)**	0.8[b] (0.48, 1.37)	0.84[b] (0.55, 1.29)	0.85[b] (0.42, 1.8)	**0.21**[b] **(0.15, 0.27)**
Low IV	–	–	–	1.34[b] (0.76, 2.38)	1.41 (0.83, 2.32)	1.43 [c] (0.65, 3.23)	**0.35**[b] **(0.22, 0.51)**
High topical	–	–	–	–	1.05[b] (0.58, 1.82)	1.06 (0.48, 2.38)	**0.26**[b] **(0.15, 0.4)**
Low topical	–	–	–	–	–	1.01 [c] (0.48, 2.28)	**0.25**[b] **(0.17, 0.35)**
Oral	–	–	–	–	–	–	**0.24**[b] **(0.11, 0.47)**

Bold values indicate a statistically significant result.
TKA, total knee arthroplasty; TXA, tranexamic acid.
[a] Transfusions reported as risk ratio (confidence limits).
[b] Effect includes 3 or more high-quality studies of direct treatment comparison.
[c] Effect based on indirect estimates from network meta-analysis due to the lack of literature for direct treatment comparison.

demonstrated a statistically lower risk of transfusion compared with placebo. Despite the single dose of oral TXA not shown to be statistically superior to placebo regarding risk of transfusion, a single dose of oral TXA was not statistically different in comparison to all other TXA treatments. Other than the comparison between the preincision and postincision administration of a single dose of IV TXA, the remaining comparisons between the various TXA treatments were not statistically significant regarding the risk of transfusion. The preincision administration of a single dose of IV TXA reduced the risk of transfusion compared with postincision dosing (risk ratio 2.05; confidence limits 1.21-3.67).

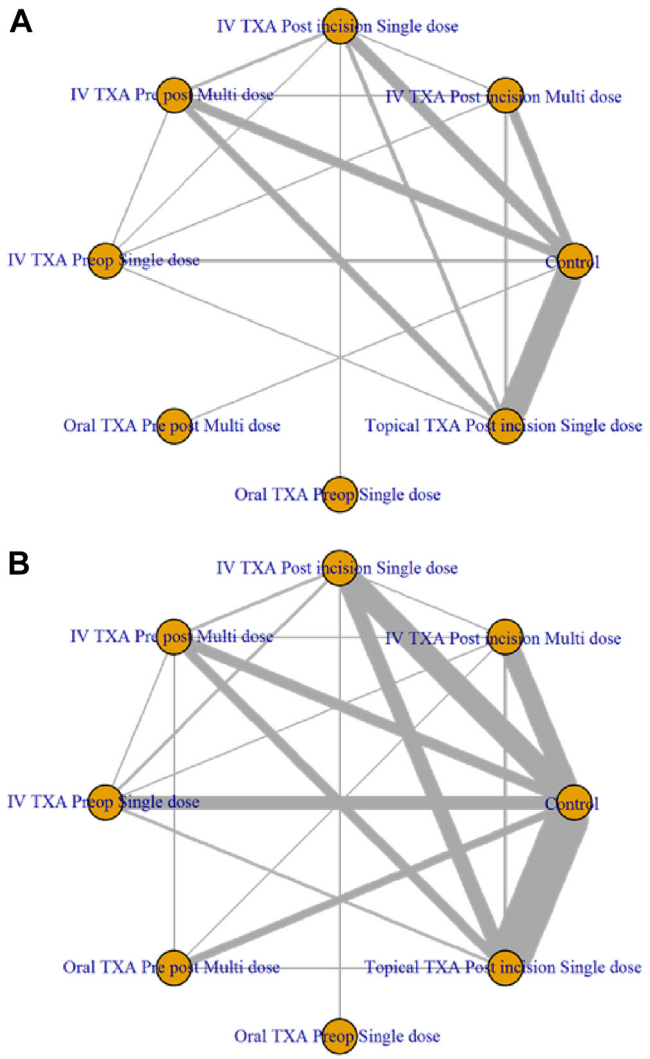

Fig. 2. (A) Network plot focused on TXA formulation, timing of dosage, and number of doses for the outcome of blood loss in primary TKA. (B) Network plot focused on TXA formulation, timing of dosage, and number of doses for the outcome of transfusion in primary TKA.

Discussion

TXA has become widely used in knee arthroplasty to help reduce perioperative blood loss and transfusions. The published literature on TXA has dramatically expanded over the past several years. Many of the publications have attempted to identify the formulation, dosage, number of doses, and timing of administration that provides the optimal blood-sparing properties. However, the literature lacks a comprehensive review on the efficacy of TXA in primary TKA. We performed a network meta-analysis of TXA in the setting of TKA to investigate the variables associated with TXA administration as part of the supporting evidence for the combined clinical practice guidelines of the American Association of Hip and Knee Surgeons, AAOS, Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Medicine.

This network meta-analysis was targeted to address a series of 5 PICO questions related to the efficacy of TXA in primary TKA. The first question aims to determine the effects of the administration of TXA compared with placebo on blood loss and the need for postoperative transfusion in patients undergoing primary TKA. Our results demonstrated a treatment effect significantly favoring all available forms of TXA compared with placebo. We observed relatively large reductions in the mean difference of blood loss between 225 mL and 331 mL in favor of TXA treatments compared with placebo. Although we believe oral TXA to be superior to placebo like all other investigated TXA treatments, we observed some inconsistencies in the results. A single dose of oral TXA was not statistically better than placebo with regards to blood loss and transfusion nor was multiple doses of oral TXA found to be statistically better than placebo regarding blood loss. However, the investigation of oral TXA in the first network plot that combined all single- and multiple-dose oral TXA studies demonstrated statistical superiority of oral TXA compared with placebo. Therefore, the inconsistency is likely the result of the small number of available studies resulting in wider confidence intervals. Moreover, if single and multiple doses of oral TXA were truly not effective compared with placebo, we would have expected that other TXA treatments would also be superior to these same oral TXA treatments. However, we did not observe any other TXA treatment to be superior to oral TXA. In addition, the observed difference could be the result of inappropriate dosing of oral TXA. Previous pharmacokinetic studies have established that a 2-g dose of oral TXA administered 2 hours before the incision allows for serum TXA concentrations to reach

Table 4
TKA Mixed Effects (Mean Differences) for Blood Loss by TXA Formulation, Timing of Dose, and Number of Doses[a].

TKA	Post Multi IV	Post Single IV	Pre Single IV	Topical	Pre/Post Multi Oral	Single Oral	Control
Pre/post multi IV	−101.63 (−232.52, 30.74)	−62.54 (−182.27, 57.19)	−5.49 (−160.16, 148.28)	−30.8[b] (−126.65, 65.83)	−98.03 [c] (−366.8, 158.5)	−112.23 [c] (−413.65, 188.55)	**−326.5[b] (−426.67, −235.02)**
Post multi IV	–	39.25 [c] (−95.52, 172.47)	96.27 (−67.65, 258.06)	70.92 (−43.69, 184.75)	3.67 [c] (−269.79, 263.87)	−10.77 [c] (−318.84, 295.85)	**−224.79[b] (−336.25, −122.95)**
Post single IV	–	–	57.05 (−95.41, 208.5)	31.69[b] (−73.15, 137.02)	−35.68 [c] (−305.43, 222.26)	−49.87 (−326.34, 226.3)	**−263.99[b] (−367.29, −169.43)**
Pre single IV	–	–	–	−25.28 (−170.27, 120.97)	−92.76 [c] (−380.94, 185.7)	−106.73 [c] (−421.51, 208.97)	**−321.05[b] (−467.86, −181.77)**
Topical	–	–	–	–	−67.26 [c] (−327.42, 180.06)	−81.52 [c] (−377.66, 213.7)	**−295.7[b] (−367.33, -233.14)**
Pre/post multi oral	–	–	–	–	–	−14.27 [c] (−390.13, 373.49)	−228.05 (−472.3, 16.98)
Single oral	–	–	–	–	–	–	−213.99 [c] (−512.12, 74.83)

Bold values indicate a statistically significant result.
TKA, total knee arthroplasty; TXA, tranexamic acid.
[a] Blood loss reported as weighted mean difference (confidence limits).
[b] Effect includes 3 or more high-quality studies of direct treatment comparison.
[c] Effect based on indirect estimates from network meta-analysis due to the lack of literature for direct treatment comparison.

the therapeutic threshold [81]. However, we observed most studies that included the use of oral TXA typically provided doses lower than 2 g and/or shorter than 2 hours before incision. If clinicians desire to use TXA orally, it is crucial for them to recognize the importance of using 2 g administered 2 hours preoperatively.

The second PICO question analyzes the most efficacious route of administration for TXA. We found that among the comparisons available, there was no difference in the observed risk of blood loss or need for transfusion between IV, topical, oral, combined IV/topical, or combined IV/oral TXA. Although we observed lower doses of IV TXA to have a significantly higher risk of transfusion compared with higher doses of IV TXA and combined IV/topical TXA, the same results were not observed for comparison regarding blood loss. Because these observed results are inconsistent with the more predominant findings between routes of administration, we believe the inconsistencies of a lack of difference are from the network relying more heavily on indirect comparisons for these TXA treatments. As a result, we conclude no evidence to show a clearly superior route of TXA administration.

The third PICO question sought to identify whether the dose of TXA affected the risk of blood loss or need for transfusion. Our results identify higher doses of IV TXA reduced the risk of transfusion compared with lower doses of IV TXA; however, the same was not observed for a reduction in blood loss. Nevertheless, we must consider the principle of providing the minimally effective dose of a medication to limit both risks and costs associated with the administration of any medication. Without consistent results supporting higher doses of IV TXA, it might not be warranted to provide adequate blood-sparing properties. In addition, we did not demonstrate a difference in the blood loss or risk of transfusion between lower and higher doses of topical TXA. We do not preclude the presence of a dose response for TXA, but it does not appear to be observed at the doses of TXA used or the amount of blood loss experienced in primary TKA.

The fourth PICO question investigated the effect of redosing TXA on the ability to reduce blood loss and the risk of transfusion. In patients undergoing TKA, regardless of whether IV TXA is administrated as a single dose or multiple doses, no statistically significant differences were noted in blood loss or transfusion rates. Similarly, we observed the same results between a single dose of oral TXA and multiple doses of oral TXA. Under no circumstances did the use of multiple doses of IV or oral TXA provide superior blood management compared with all other methods of TXA administration. In addition, the combination of IV/topical and IV/oral TXA formulations (amounting to multiple doses of TXA administration) failed to reduce the amount of blood loss or impact the risk of transfusion. As a result, we conclude additional doses of IV or oral TXA appear to be unnecessary to achieve results and may lead to less drug exposures and cost-saving benefits.

The fifth PICO question aims to determine whether the administration time of IV TXA, with respect to the start of the surgical procedure, affected the risk of transfusion or total blood loss. In the case of patients undergoing TKA, the timing of administration either before or after incision was only statistically significant under one comparison. Our results demonstrated preincision administration of a single dose of IV TXA reduced the risk of transfusion compared with a single dose of IV TXA given after the incision; however, the same results were not observed for a reduction in blood loss. In addition, we compared the administration of multiple doses of IV TXA whereby patients were given doses before and after the incision vs patients only given multiple doses of IV TXA after the incision. Under the circumstance with multiple doses of IV TXA, the inclusion of preincision administration did not provide additional blood-sparing properties. Despite the inconsistent results, it appears that there is a potential benefit to preincision

Table 5
TKA Mixed Effects (Risk Ratios) for Transfusion by TXA Formulation, Timing of Dose, and Number of Doses[a].

TKA	Post Multi IV	Post Single IV	Pre Single IV	Topical	Pre/Post Multi Oral	Single Oral	Control
Pre/post multi IV	0.85 (0.42, 1.68)	0.58 (0.31, 1.06)	1.19 (0.57, 2.49)	0.78[b] (0.42, 1.38)	0.75 (0.32, 1.76)	1.27 [c] (0.08, 47.17)	**0.19[b] (0.1, 0.32)**
Post multi IV	–	0.68 (0.4, 1.17)	1.4 (0.72, 2.81)	0.92 (0.54, 1.54)	0.88 (0.4, 2.05)	1.49 [c] (0.09, 55.36)	**0.22[b] (0.14, 0.34)**
Post single IV	–	–	**2.05 (1.21, 3.67)**	1.35[b] (0.91, 1.99)	1.3 [c] (0.61, 2.89)	2.19 (0.15, 78.38)	**0.33[b] (0.23, 0.45)**
Pre single IV	–	–	–	0.65 (0.36, 1.14)	0.63 [c] (0.26, 1.52)	1.06 [c] (0.07, 38.99)	**0.16[b] (0.09, 0.26)**
Topical	–	–	–	–	0.96 (0.46, 2.09)	1.63 [c] (0.11, 59.16)	**0.25[b] (0.18, 0.33)**
Pre/post multi oral	–	–	–	–	–	1.69 [c] (0.1, 64.09)	**0.25[b] (0.12, 0.5)**
Single oral	–	–	–	–	–	–	0.15 [c] (0, 2.26)

Bold values indicate a statistically significant result.
TKA, total knee arthroplasty; TXA, tranexamic acid.
[a] Transfusions reported as risk ratio (confidence limits).
[b] Effect includes 3 or more high-quality studies of direct treatment comparison.
[c] Effect based on indirect estimates from network meta-analysis due to the lack of literature for direct treatment comparison.

administration of IV TXA with no apparent downside compared with postincision administration. As a result, we believe there is a moderate level of evidence to support the use of preincision administration of IV TXA.

Despite the use of primarily high-quality, level-I evidence, this network meta-analysis has several limitations linked to inconsistencies in the results. First, we observed in the first network plot that oral TXA was statistically superior to placebo, but in the second network plot, single- and multiple-dose oral TXA at times were not statistically different from placebo. If the observation of no difference to placebo were a true positive result, we would have expected to observe results favoring other formulations over oral TXA. However, we found no statistical difference with all IV and topical TXA formulations compared with single- and multiple-dose oral TXA. Because the combination of the single- and multiple-dose oral TXA studies into a single node in the first network plot provides a statistical difference with placebo, the results of the second network plot are the result of fewer studies within each node. When a network plot has fewer studies providing connections between the nodes, the network meta-analysis relies more heavily on indirect comparisons that can result in the observed false negative findings. Second, we demonstrated that in 2 circumstances there was a statistical difference in the evaluation for risk of transfusion but no difference in the amount of blood loss. We would have anticipated patients who were placed at a higher risk for transfusion would have had higher amounts of blood loss. Nevertheless, our results demonstrated high-dose IV TXA to have a lower risk of transfusion than low-dose IV TXA, and the same was observed for preincision administration of IV TXA when compared to postincision administration. The inconsistency in the results between the outcomes of blood loss and transfusion could be the result of pooling studies that did not always utilize the same thresholds for transfusion. In addition, the use of calculated blood loss is still prone to variations secondary to issues with fluid shifts within the patient immediately after surgery.

Conclusion

Regardless of the formulation of TXA used, patients undergoing TKA show a significant reduction in blood loss and risk of transfusion compared to placebo with no clear difference observed between the available formulations of TXA administration. Based on the available literature, it appears higher doses and multiple doses of TXA are not necessary but preincision administration of IV TXA potentially provides superior results.

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Appendix A. Formal Database Search Strategies

Database: Complete OVID MEDLINE
Dates Covered: 1946 to 2017
Date of Search: July 5, 2017 (Most Recent Search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	exp arthroplasty/
2	(arthroplast$ or "hip replacement$" or total knee or total hip).af.
3	1 or 2
4	exp tranexamic acid/
5	(tranexemic acid or tranexamic acid).af.
6	exp antifibrinolytic agents/
7	(antifibrinolytic agent$ or aminocaproic acid).af.
8	4 or 5 or 6 or 7
9	**3 and 8**

Database: EMBASE (Excerpta Medica dataBASE)
Dates Covered: 1947 to 2016
Date of Search: October 3, 2016 (Most Recent Search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	exp arthroplasty/
2	(arthroplast$ or "hip replacement$" or total knee or total hip).af.
3	1 or 2
4	exp tranexamic acid/
5	(tranexemic acid or tranexamic acid).af.
6	exp antifibrinolytic agents/
7	(antifibrinolytic agent$ or aminocaproic acid).af.
8	4 or 5 or 6 or 7
9	**3 and 8**

Database: Web of Science (WOS)
Dates Covered: 1964 to 2017
Date of Search: October 5, 2017 (Most Recent Search)
Librarian: Tom Mead, MLS
Filters: Exclude MEDLINE database

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	1 AND 2
4	**Refined by: [excluding] Databases: (MEDLINE)**

Database: SCOPUS
Dates Covered: 1823 to 2017
Date of Search: July 10, 2017 (Most Recent Search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	**1 AND 2**

Database: Cochrane Library (DARE)
Dates Covered: 1994 to 2017
Date of Search: July 5, 2017 (Most Recent Search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	**1 AND 2**