The Journal of Arthroplasty xxx (2018) 1–7

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis

Yale A. Fillingham, MD [a,*], Dipak B. Ramkumar, MD [b], David S. Jevsevar, MD, MBA [b], Adolph J. Yates, MD [c], Peter Shores, MPH [d], Kyle Mullen, MPH [d], Stefano A. Bini, MD [e], Henry D. Clarke, MD [f], Emil Schemitsch, MD [g], Rebecca L. Johnson, MD [h], Stavros G. Memtsoudis, MD, PhD [i], Siraj A. Sayeed, MD [j], Alexander P. Sah, MD [k], Craig J. Della Valle, MD [a]

[a] Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL
[b] Department of Orthopaedic Surgery, Dartmouth Hitchcock Medical Center, Lebanon, NH
[c] Department of Orthopaedic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA
[d] Department of Research, Quality, and Scientific Affairs, American Academy of Orthopaedic Surgeons, Rosemont, IL
[e] Department of Orthopaedic Surgery, University of California San Francisco, San Francisco, CA
[f] Department of Orthopaedic Surgery, Mayo Clinic, Phoenix, AZ
[g] Department of Orthopaedic Surgery, University of Toronto, Toronto, Ontario, Canada
[h] Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN
[i] Department of Anesthesiology, Hospital for Special Surgery, New York, NY
[j] South Texas Bone and Joint Institute, San Antonio, TX
[k] Institute for Joint Restoration, Fremont, CA

ARTICLE INFO

Article history:
Received 17 April 2018
Received in revised form
7 June 2018
Accepted 18 June 2018
Available online xxx

Keywords:
tranexamic acid
antifibrinolytic
total hip arthroplasty
blood loss
transfusion

ABSTRACT

Background: Tranexamic acid (TXA) is an antifibrinolytic agent commonly used to reduce blood loss in total hip arthroplasty (THA). The purpose of our study was to evaluate the efficacy of TXA in primary THA to support 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: A search was performed using Ovid-MEDLINE, Embase, Cochrane Reviews, Scopus, and Web of Science databases to identify all publications before July 2017 on TXA in primary THA. We completed qualitative and quantitative homogeneity testing of all included studies. Direct and indirect comparisons were analyzed using a network meta-analysis followed by consistency testing of the results.
Results: Two thousand one hundred thirteen publications underwent critical appraisal with 34 publications identified as representing the best available evidence for inclusion in the analysis. Topical, intravenous, and oral TXA formulations provided reduced blood loss and risk of transfusion compared to placebo, but no formulation was clearly superior. Use of repeat doses, higher doses, or variation in timing of administration did not significantly reduce blood loss or risk of transfusion.
Conclusions: Strong evidence supports the use of TXA to reduce blood loss and risk of transfusion after primary THA. No specific routes of administration, dosage, dosing regimen, or time of administration provides clearly superior blood-sparing properties.

Primary total hip arthroplasty (THA) accounts for approximately one-third of the annual arthroplasties performed in the United States [1]. Although primary THA amounts to fewer annual procedures than primary total knee arthroplasty (TKA), it is associated with a higher quantity of postoperative blood loss [1,2]. Owing to the association between acute postoperative anemia and increased morbidity and mortality, research in blood management after total

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2018.06.023.

* Reprint requests: Yale A. Fillingham, MD, Department of Orthopaedic Surgery, Rush University Medical Center, 1611 West Harrison Street, Chicago, IL 60612.

https://doi.org/10.1016/j.arth.2018.06.023
0883-5403/

joint arthroplasty (TJA) has focused on various modalities to reduce blood loss and the use of allogeneic blood transfusions [3–5].

One of the commonly used methods to prevent blood loss in TJA has been tranexamic acid (TXA). TXA is a synthetic amino acid derivative of lysine, which inhibits binding of fibrin to plasminogen, thereby preventing degradation of the fibrin clot [6,7]. Despite the original application of TXA being used to prevent blood loss in dental procedures, it has become widely adopted in several medical specialties including orthopedic surgery [6,7]. A vast body of literature has provided overwhelming evidence supporting both the clinical and cost-effectiveness of TXA in primary THA.

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 conducted a series of studies including a network meta-analysis of randomized clinical trials of TXA in primary THA to support the efficacy recommendations of the clinical practice guideline. Our study aimed to answer a series of Population, Intervention, Comparison, and Outcome (PICO) questions related to the efficacy of TXA in the setting of primary THA (Table 1).

Direct meta-analysis has been commonly used to help coalesce publications investigating the same 2 treatments. For instance, when publications exist investigating treatment A vs B and B vs C, a direct meta-analysis allows the investigator to examine publications comparing treatment A vs B and B vs C. The investigator is not capable of examining the comparison of A vs C. Network meta-analysis is a more complex method to perform direct and indirect comparisons within the same analysis, which allows for the comparison of A vs B, B vs C, and A vs C all at once. The ability to perform direct and indirect comparisons within the same analysis is useful when a large number of randomized clinical trials exist with numerous treatments.

Material and Methods

Utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a network meta-analysis was performed on TXA in primary THA [8]. The search methodology, data collection, and statistical analysis were performed in the same manner as the sister study, "The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis."

Similar to the sister study, the outcomes included blood loss and transfusion. Reporting of blood loss utilized calculated blood loss instead of estimated intraoperative blood loss or drain outputs. Calculated blood loss is performed as a function of the patient's height, weight, and sex as well as the preoperative and postoperative changes in hemoglobin and potential transfusions [9–11]. Transfusions could be reported as allogeneic or autogenous blood transfusion. In addition, the stratification of TXA dose remained the same as the sister study, whereby high-dose intravenous (IV) TXA was defined as any dose ≥20 mg/kg or > 1g and high-dose topical TXA was defined as any dose >1.5g.

Table 1
PICO Questions.

Questions
1. For patients undergoing primary THA, what method of administration of TXA, compared to placebo, reduces the risk of transfusion and/or reduces blood loss?
2. For patients undergoing primary THA, 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 THA, does the dose of IV, topical, or oral TXA affect the risk of transfusion and/or reduction in blood loss?
4. For patients undergoing primary THA, does a repeat dose of IV or oral TXA affect efficacy?
5. For patients undergoing primary THA, 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; THA, total hip arthroplasty; TXA, tranexamic acid.

The 2 network plots for outcome comparison utilized identical themes as the sister study. The network plots are composed of nodes representing a TXA treatment with the line connection between the nodes, representing the presence of a direction comparison between the 2 nodes. The line becomes thicker when more publications exist comparing the 2 nodes. Therefore, the network plots provide a visual description of the direct comparisons and quantitative number of studies between each node. The first network plot concentrated on TXA formulation and dosage, which comprised 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 concentrated on the TXA formulation, timing of dosage, and number of doses, which comprised 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-dose preincision oral TXA, (7) multiple doses preincision and postincision oral TXA, and (8) single postincision topical TXA.

Because the 3 assumptions of a network meta-analysis include homogeneity, transitivity, and consistency of the data, a clinical statistician assessed all 3 assumptions in the same method as the sister study. The presence of homogeneity is important because it represents similarities between the data sets of the combined studies to help ensure confidence in the combined estimate of the outcome. Among the 5 direct comparisons, the heterogeneity under most circumstances was 0% while none of the direct comparisons had statistically significant heterogeneity greater than 40%. Because a network meta-analysis performs direct and indirect comparisons, transitivity and consistency are an evaluation that the generated estimates of the treatment effects are similar between direct and indirect comparisons. Evaluation for consistency demonstrated no significant differences between the direct and indirect comparisons [12–14]. Meanwhile, meta-regression was performed using the quality appraisal criteria, which showed no influence on the transitivity across trials [14].

The outputs of the direct and indirect comparisons of the network meta-analysis are mixed effects tables that provide the qualitative estimates of the outcome between the treatments. The intersecting cell between the treatments listed in the first column and top row is the result of the comparison between those 2 TXA treatments. When the reported outcome is blood loss, the value in the cell represents a mean difference, while the value for the outcome of transfusion is represented as a risk ratio. If the mean difference or risk ratio value is less than 1, the comparison favored the TXA treatment in the first column. Conversely, when the value was greater than 1, the comparison favored the TXA treatment in the top row. If the confidence limit did not span zero, the outcome was considered to be statistically significant.

Deviations from the methodology of the sister study occurred within the study selection criteria. In the present study, all study participants must have undergone a primary THA to be considered for inclusion in the network meta-analysis. Articles were excluded that consisted of patients undergoing revision THA, simultaneous or staged bilateral THA, and primary arthroplasty of joints other than the hip. The remainder of the exclusion criteria was the same as the sister study on primary TKA.

Results

Similar to the sister study, the literature search initially provided 2113 results that underwent the same screening and review process

to have 230 publications remaining that underwent data extraction and quality assessment in accordance with the AAOS Clinical Practice Guidelines and Systematic Review Methodology [14]. After completion of the data extraction and quality assessment, 34 publications on TXA in primary THA represented only level-I studies comprising the best available literature for the current network meta-analysis [15–48].

TXA Formulation and Dose Network Plot

The network plot focused on TXA formulation and dose examined the outcomes of blood loss (Fig. 1A) and transfusion (Fig. 1B). Owing to a lack of reported outcomes, the node of combined IV/oral TXA was omitted from the network plots examining blood loss and

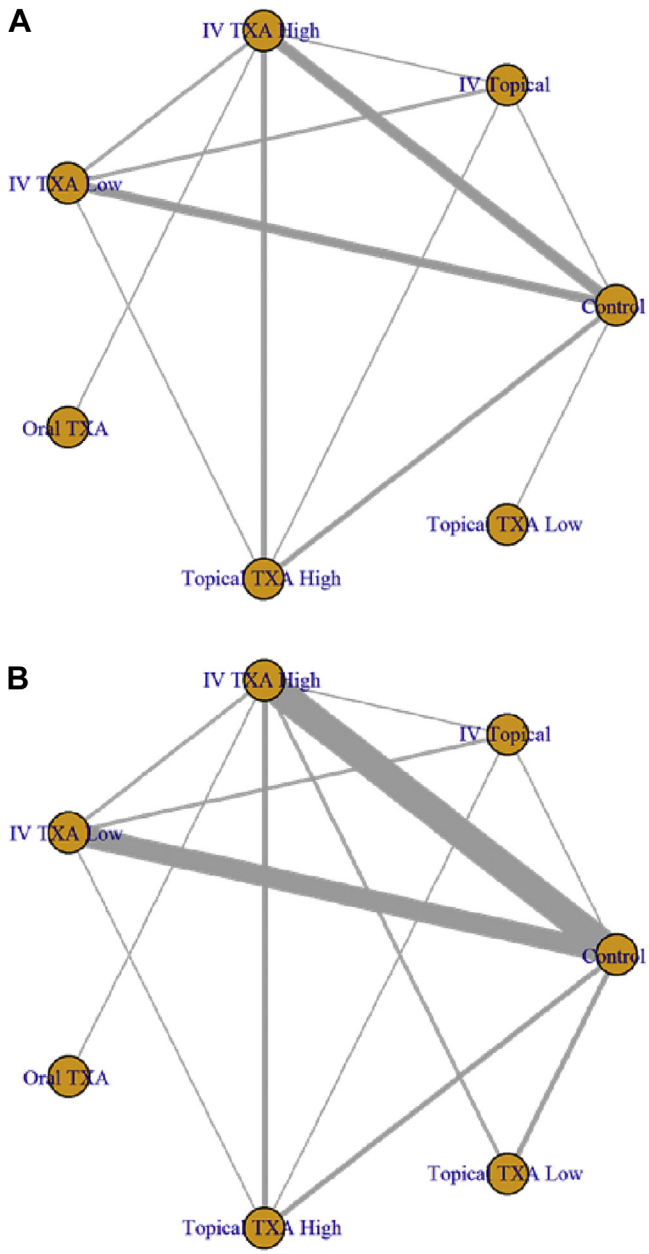

Fig. 1. (A) Network plot focused on TXA formulation and dosage for the outcome of blood loss in primary THA. (B) Network plot focused on TXA formulation and dosage for the outcome of transfusion in primary THA. IV, intravenous; THA, total hip arthroplasty; TXA, tranexamic acid.

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

THA	High IV	Low IV	High Topical	Low Topical	Oral	Control
IV/topical	−95.9 (−233.15 to 53.32)	−114.19 (−252.17 to 22.96)	−131.15 (−281.39 to 11.7)	−64.92[c] (−460.67 to 327.47)	−133.27[c] (−417.53 to 159.65)	**−427.91 (−568.55 to −294.12)**
High IV	–	−18.54 (−138.27 to 90.3)	−35.61[b] (−150.76 to 62.19)	30.07[c] (−354.59 to 406.69)	−37.84 (−289.35 to 213.05)	**−332.54[b] (−430.22 to −250.28)**
Low IV	–	–	−17.13 (−141.09 to 100.76)	49.59[c] (−334.66 to 430.11)	−18.91[c] (−291.16 to 261.63)	**−313.72[b] (−414.95 to −218.21)**
High topical	–	–	–	67.07[c] (−315.73 to 448.56)	−1.82[c] (−268.04 to 277.57)	**−296.66[b] (−392.97 to −200.82)**
Low topical	–	–	–	–	−68.47[c] (−519.38 to 392.2)	−363.75 (−733.03 to 6.87)
Oral	–	–	–	–	–	**−295.16[c] (−567.69 to −34.68)**

Bold values indicate a statistically significant result.
IV, intravenous; THA, total hip 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.

transfusion. The network meta-analysis on blood loss and transfusion included 16 (Appendix A) and 31 studies (Appendix B) in each network plot, respectively [15–23,25,26,28–48].

Network meta-analysis produced a mixed effects table examining blood loss between different TXA formulations and doses and a placebo (Table 2). With the exception of low-dose topical TXA, all TXA formulations and doses were considered statistically superior to placebo regarding the ability to reduce blood loss. Despite low-dose topical TXA being no different than placebo, we did not observe any statistically significant superiority for other treatments over low-dose topical TXA. Owing to the limited publications on low-dose topical TXA, the network plot (Fig. 1A) had fewer connections to low-dose topical TXA and consequently relied more heavily on indirect comparisons that resulted in broad confidence intervals in the comparison with a placebo. No difference in the volume of blood loss was detected between all TXA formulations and doses.

Network meta-analysis produced a mixed effects table examining transfusion between different TXA formulations and doses and a placebo (Table 3). With the exception of oral TXA, all TXA formulations and doses were considered statistically superior to placebo regarding the ability to reduce the risk of transfusion. Similar to low-dose topical TXA in the evaluation of blood loss, oral TXA was no different compared with other TXA formulations but was similarly burdened with limited publications and few connections in the network plot (Fig. 1B). The combination of IV/topical TXA was observed to have a lower risk of transfusion than all other TXA formulations and doses with the exception of oral TXA that was noted to be equivalent to combined IV/topical TXA. Interestingly, we did not observe the same results favoring combined IV/topical TXA for the outcome of blood loss. The inconsistency in the results is partially the consequence of limited connections to combined IV/topical TXA in the network plot (Fig. 1B). The remainder of the comparisons between TXA formulations and doses demonstrated no statistical difference in the risk of transfusion.

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

The network plot focused on TXA formulation, timing of dose, and number of doses examined the outcomes of blood loss (Fig. 2A) and transfusion (Fig. 2B). Owing to a lack of reported outcomes, the nodes of single-dose postincision IV TXA and multiple-dose preincision and postincision oral TXA were omitted from the network plot examining blood loss. Similarly, multiple doses preincision and postincision oral TXA were omitted from the network plot examining transfusions. The network meta-analysis on blood loss and transfusion included 17 (Appendix C) and 32 studies (Appendix D) in each network plot, respectively [15–48].

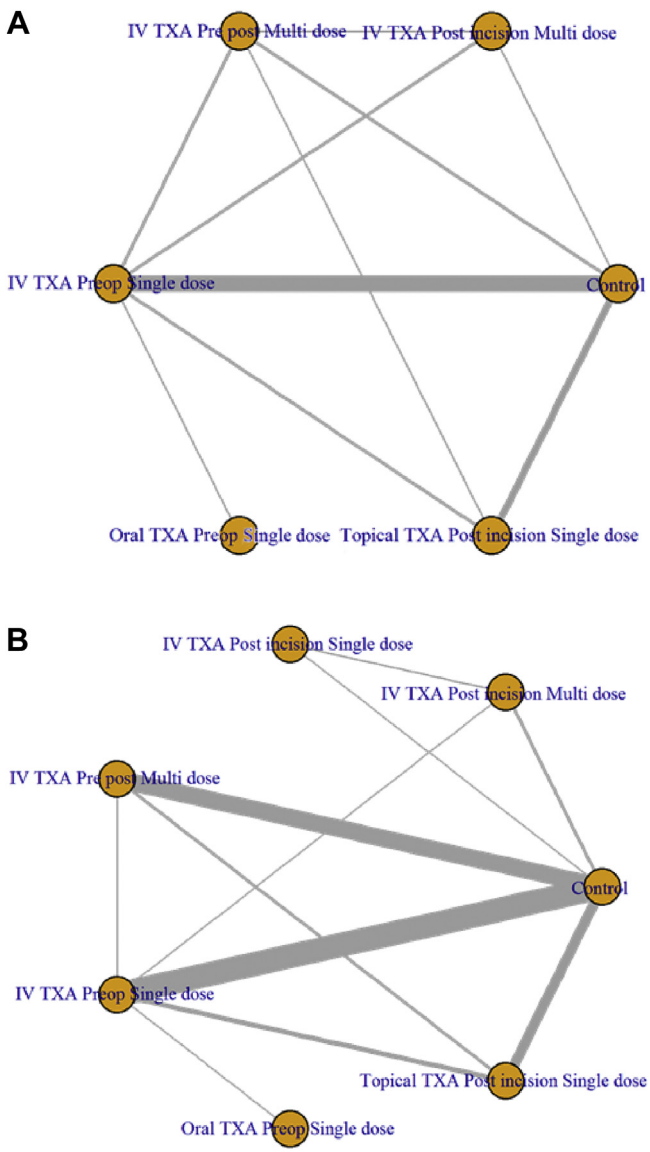

Fig. 2. (A) Network plot focused on TXA formulation, timing of dosage, and number of doses for the outcome of blood loss in primary THA. (B) Network plot focused on TXA formulation, timing of dosage, and number of doses for the outcome of transfusion in primary THA. IV, intravenous; THA, total hip arthroplasty; TXA, tranexamic acid.

Network meta-analysis produced a mixed effects table examining blood loss among different TXA formulations, timing of dose, number of doses, and a placebo (Table 4). All TXA formulations,

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

THA	High IV	Low IV	High Topical	Low Topical	Oral	Control
IV/topical	**0.19 (0.03-0.73)**	**0.15 (0.02-0.55)**	**0.19 (0.03-0.74)**	**0.19**[c] **(0.02-0.9)**	0.1[c] (0.01-1.18)	**0.05 (0.01-0.2)**
High IV	–	0.76 (0.49-1.17)	0.96[b] (0.57-1.64)	0.97 (0.45-2.35)	0.57 (0.07-3.85)	**0.28**[b] **(0.2-0.38)**
Low IV	–	–	1.27 (0.71-2.26)	1.28[c] (0.59-3.11)	0.75[c] (0.08-5.37)	**0.37**[b] **(0.26-0.5)**
High topical	–	–	–	1.01[c] (0.42-2.66)	0.59[c] (0.06-4.3)	**0.29**[b] **(0.17-0.47)**
Low topical	–	–	–	–	0.58[c] (0.06-4.59)	**0.29**[b] **(0.12-0.58)**
Oral	–	–	–	–	–	0.49[c] (0.07-4.25)

Bold values indicate a statistically significant result.
IV, intravenous; THA, total hip 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.

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

THA	Post Multi IV	Pre Single IV	Topical	Single Oral	Control
Pre/Post multi IV	−172.23[c] (−391.04 to 46.42)	−127.3 (−269.87 to 15.65)	−127.77 (−276.84 to 16.62)	−165.17[c] (−443.77 to 113.93)	**−431.9 (−574.33 to −294.69)**
Post multi IV	–	45.13 (−146.36 to 236.86)	44.62[c] (−163.55 to 248.97)	7.16[c] (−299.58 to 314.24)	**−259.7[c] (−456.6 to −67.46)**
Pre single IV	–	–	−0.07 (−101.36 to 93.51)	−38.1 (−277.18 to 202.08)	**−304.13[b] (−382.44 to −235)**
Topical	–	–	–	−37.62[c] (−293.21 to 224.15)	**−303.91[b] (−394.58 to −215.84)**
Single oral	–	–	–	–	**−266.23[c] (−521.71 to −19.3)**

Bold values indicate a statistically significant result.
IV, intravenous; THA, total hip 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.

timing of dose, and number of doses were statistically superior to placebo regarding the ability to reduce blood loss. No difference in the volume of blood loss was detected between all TXA formulations, timing of dose, and number of doses.

Network meta-analysis produced a mixed effects table examining transfusion between different TXA formulations, timing of dose, number of doses, and a placebo (Table 5). Other than oral TXA, all TXA formulations, timing of dose, and number of doses were considered statistically superior to placebo regarding the ability to reduce the risk of transfusion. Similar to the findings of low-dose topical and oral TXA in the network plot on TXA formulation and dose, oral TXA only had a single connection in the network plot (Fig. 2B). No difference was observed among the various TXA formulations, timing of dosing, and number of doses regarding the risk of transfusion.

Discussion

TXA has consistently demonstrated efficacy at limiting postoperative blood loss and the need for allogeneic transfusions. As a result, it has become a commonly used tool for blood management after primary THA. Despite a dramatic expansion in the scientific literature over the past decade on TXA in primary THA, we lack a comprehensive evaluation of the literature on the TXA formulations, dosage, timing of administration, and number of doses. Therefore, we performed a network meta-analysis on TXA in primary THA in conjunction with the sister study on primary TKA to help support the efficacy recommendations of 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.

The purpose of the network meta-analysis was to answer a series of 5 PICO questions regarding the efficacy of TXA in primary THA (Table 1). The first PICO question aimed to evaluate the effectiveness of the various methods of TXA administration compared with placebo at reducing blood loss and the risk of transfusion. We observed overwhelming support favoring all available methods of TXA administration. TXA provided dramatic reductions in the volume of blood loss compared to placebo with mean differences of 295 mL to 432 mL lower blood loss for the various TXA treatments with the exception of low-dose topical TXA that was not statistically superior to placebo. Similarly, we observed all methods of TXA except oral TXA to reduce the risk of transfusion compared to placebo. Despite the results for low-dose topical and oral TXA, we believe oral and topical TXA to still be superior to placebo. The inconsistency observed regarding oral and topical TXA is likely the result of a limited number of published studies on these specific TXA treatments. When a network plot only has a limited number of studies connecting the various nodes, the network meta-analysis must rely more heavily on indirect comparisons. As such, the outcomes of the mixed effects tables are vulnerable to providing results inconsistent with the broader outcomes. First, according to the mixed effects tables, oral TXA had a decreased volume of blood loss but no risk of transfusion compared with placebo. These results are contrary to the notion that patients who are at a higher risk of transfusion should experience larger volumes of blood loss. Second, we observed oral TXA to be equivalent to all other TXA treatments with regard to the risk of transfusion and low-dose topical TXA to be equivalent to all other TXA treatments with regard to the amount of blood loss. If the outcomes regarding oral and low-dose topical TXA compared with placebo were a true positive, we would not have expected to observe the results of equivalence among the various TXA treatments.

The second PICO question attempted to compare the blood-sparing properties among routes of administration for TXA. In general, we observed no difference in the risk of blood loss or need for transfusion between IV, topical, oral, and combined IV/topical TXA treatments. Both network plots demonstrated no statistical difference in the risk of blood loss between the available TXA formulations. Similarly, the risk of transfusion was observed to be equivalent among most TXA formulations except with combined IV/topical TXA presenting a lower risk of transfusion compared

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

THA	Post Multi IV	Post Single IV	Pre Single IV	Topical	Single Oral	Control
Pre/post multi IV	0.49[c] (0.23-1.08)	1.13[c] (0.24-9.22)	0.68 (0.42-1.1)	0.86 (0.51-1.43)	0.4[c] (0.04-2.88)	**0.24[b] (0.16-0.35)**
Post multi IV	–	2.31 (0.47-19.88)	1.41 (0.66-2.81)	1.76[c] (0.79-3.77)	0.81[c] (0.08-6.37)	**0.5 (0.24-0.92)**
Post single IV	–	–	0.61[c] (0.08-2.73)	0.76[c] (0.09-3.54)	0.33[c] (0.02-4.15)	**0.21 (0.03-0.93)**
Pre single IV	–	–	–	1.25[b] (0.78-2.02)	0.58 (0.06-4.01)	**0.35[b] (0.26-0.46)**
Topical	–	–	–	–	0.46[c] (0.05-3.37)	**0.28[b] (0.18-0.42)**
Single oral	–	–	–	–	–	0.6[c] (0.09-5.62)

Bold values indicate a statistically significant result.
IV, intravenous; THA, total hip 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.

with high-dose IV, low-dose IV, high-dose topical, and low-dose topical TXA. However, the same superiority of combined IV/topical TXA was not observed regarding the risk of blood loss. We believe the findings regarding risk of transfusion for combined IV/topical TXA represents a false-positive result for several reasons. First, similar to the inconsistencies noted with the results of the first PICO question, the limited number of studies investigating combined IV/topical TXA is more likely to produce an inconsistent result. Second, the use of transfusion as an outcome can be influenced by the use of subjective and objective criteria for triggering a transfusion. When studies are pooled for analysis of transfusion, the variations in the criteria to trigger a transfusion can have a profound influence. If studies provide an overwhelming treatment effect for a specific intervention, these results are further amplified in a network meta-analysis in the presence of a network plot with fewer connections to the intervention. Finally, we would expect an intervention that reduces the need for transfusion would reduce the amount of blood loss, which was not observed for combined IV/topical TXA. Meanwhile, the use of calculated blood loss as an outcome utilizes a standard calculation that is less prone to subjective biases of the criteria for triggering a transfusion. As a result, we conclude no support exists for a clearly superior route of TXA administration.

The third and fourth PICO questions sought to determine the optimal dose and number of doses of TXA. Under no circumstances did we identify a significant difference in favor of higher doses or multiple doses of TXA. We observed that higher doses of IV or topical TXA did not reduce the amount of blood loss or risk of transfusion compared with lower doses of IV or topical TXA. In addition, multiple doses of IV TXA given either before and after incision or all given after incision did not significantly reduce the risk of blood loss or transfusion compared with a single dose of IV or oral TXA. As a result, we could not support the use of higher doses or multiple doses of IV, topical, or oral TXA as a method to provide improved blood sparing after primary THA. However, we must note our findings do not preclude the presence of a dose response. It is possible that the doses being used in the published studies are not dramatically different on the dose-response curve for TXA. Despite the possibility for more blood-sparing properties with significantly higher TXA doses, we must use the principle of administering the lowest necessary dose of a medication. Given the efficacy of the current dosing of TXA, it does not appear higher doses are necessary.

The fifth PICO question investigated the effect of the timing of administration in relation to the time of incision of IV TXA to reduce blood loss and the risk of transfusion. Although we observed a difference in favor of preincision administration of TXA in the sister study on primary TKA, we did not observe a difference in the blood-sparing capabilities of TXA based on the timing of administration in the setting of primary THA. Under multiple comparisons, we were unable to provide evidence in favor of either preincision or postincision dosing of IV TXA. First, no difference was observed with administration of a single dose of IV TXA either before or after incision. Second, no difference was observed when multiple doses of IV TXA were administered with the doses either given before and after incision or all given after incision. Despite the lack of a significant difference based on the timing of administration of TXA in primary THA, we still advocate in favor of preincision administration of IV TXA owing to the potential benefits observed in the sister study with no apparent harm compared with postincision administration.

Even though the network meta-analysis was completed using only the highest quality of level-I evidence studies, we still have limitations with the interpretation of the results. First, we lacked available literature on certain nodes in the network plot, which were present in the sister study on primary TKA. In the network plot on TXA formulation and dose, we lacked the ability to discuss combined IV/oral TXA treatment. In the network plot on TXA formulation, timing of dose, and number of doses, we lacked the inclusion of nodes on multiple doses of oral TXA and single-dose IV postincision. However, because these nodes are not present in the published literature, the lack of these nodes should not significantly impede the interpretation of our results. We can presume the lack of publications on the specific TXA treatments represent their limited use in practice. Second, we observed that a few inconsistencies were because of fewer studies providing connections between the nodes within the network plot. When the network plots have fewer connections, the network meta-analysis must rely more heavily on indirect comparisons. As a result, the output from the network meta-analysis is more prone to producing false-negative or false-positive results. We observed low-dose topical and oral TXA under isolated circumstances to be equivalent to placebo. The observations regarding low-dose topical and oral TXA are contrary to the findings of equivalence to all other TXA treatments and superiority to placebo in certain circumstances. In addition, we observed combined IV/topical TXA to be superior to low and high doses of individual IV or topical TXA but equivalent to oral TXA regarding the risk of transfusion, but we did not see the same results regarding blood loss. The combination of these results is contrary to the notion a patient who experiences greater amounts of blood loss is at a higher risk of transfusion. Therefore, the contradictory results are likely a product of limited studies on combined IV/topical TXA and the pooling of studies that did not use the same thresholds for transfusion. As discussed regarding the second PICO question, transfusion triggers include a combination of subjective and objective criteria. Therefore, it makes the results of pooled studies with varying transfusion triggers likely more prone to biases. Given these isolated circumstances are contrary to the broader results, we believe these inconsistencies to represent false-negative and false-positive results.

Conclusion

Oral, IV, topical, and combined methods of TXA administration all significantly reduce the amount of blood loss and risk of transfusion compared with placebo, with no method of TXA administration shown to be clearly superior over the others for patients undergoing primary THA. Similar to TXA use for TKA, it appears that higher doses and multiple dosing strategies provide no added advantages of reducing blood loss or preventing transfusion for THA either, based on the available literature. Finally, preincision administration of IV TXA did not provide superior results in primary THA but would still be recommended based on the finding in the sister study on primary TKA.

Acknowledgments

The authors would like to thank the American Association of Hip and Knee Surgeons for providing funding for this study. They would like to thank Jayson Murray from the American Academy of Orthopaedic Surgeons Department of Research, Quality, and Scientific Affairs for his assistance with oversight of the quality assessment, data extraction, and statistical analysis. They would like to thank Thomas Mead for his expertise as a research librarian to assist with development of the database searches. Finally, they thank the leadership of the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, American Society of Regional Anesthesia and Pain Medicine, and the Hip and Knee Societies for help with organizational support.

References

[1] Registry AJR. American joint replacement registry annual report 2017. American Joint Replacement Registry; 2017. http://www.ajrr.net/images/annual_reports/AJRR-2017-Annual-Report—Final.pdf?hsCtaTracking=61a2fedc-0f48-4241-a282-2bca6e4b68ad%7Ce4ed88d8-6b8e-4d0c-9a47-d1c169759e83.

[2] Carling MS, Jeppsson A, Eriksson BI, Brisby H. Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study. J Orthop Surg Res 2015;10:48.

[3] Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055–60.

[4] Kirksey M, Chiu YL, Ma Y, Della Valle AG, Poultsides L, Gerner P, et al. Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998-2008. Anesth Analg 2012;115:321–7.

[5] Ponnusamy KE, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. J Bone Joint Surg Am 2014;96:1836–44.

[6] Okamoto SOU. Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of fibrinolysis. Keio J Med 1962;11:105–15.

[7] Okamoto SSS, Takada Y, Okamoto U. An active stereo-isomer (Trans-Form) of amcha and its antifibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med 1964;13:177–85.

[8] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9. W64.

[9] Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503–13.

[10] Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983;58:277–80.

[11] Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962;51:224–32.

[12] Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932–44.

[13] Dias S, Welton NJ, Sutton AJ, Ades AE. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London: NICE Decision Support Unit Technical Support Documents; 2014.

[14] American Academy of Orthopaedic Surgeons. AAOS Clinical Practice Guideline and Systematic Review Methodology. version 2, https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/Guideline%20and%20Systematic%20Review%20Processes_v2.0_Final.pdf.

[15] Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX-H) (Provisional abstract). J Bone Joint Surg Am 2013;95:1969–74.

[16] Barrachina B, Lopez-Picado A, Remon M, Fondarella A, Iriarte I, Bastida R, et al. Tranexamic acid compared with placebo for reducing total blood loss in hip replacement surgery: a randomized clinical trial. Anesth Analg 2016;122:986–95.

[17] Benoni G, Fredin H, Knebel R, Nilsson P. Blood conservation with tranexamic acid in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. Acta Orthop Scand 2001;72:442–8.

[18] Benoni G, Lethagen S, Nilsson P, Fredin H. Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. Acta Orthop Scand 2000;71:250–4.

[19] Castro-Menendez M, Pena-Paz S, Rocha-Garcia F, Rodriguez-Casas N, Huici-Izco R, Montero-Vieites A. Rev Esp Cir Ortop Traumatol 2016;60:315–24.

[20] Claeys M, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg 2007;107:397–401.

[21] Ekback G, Axelsson K, Ryttberg L, Edlund B, Kjellberg J, Weckstrom J, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000;91:1124–30.

[22] Emara WM, Moez KK, Elkhouly AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesth Essays Res 2014;8:48–53.

[23] Fraval A, Effeney P, Fiddelaers L, Smith B, Towell B, Tran P, et al. Outcome benefits of tranexamic acid in hip arthroplasty. A randomized double-blinded controlled trial. J Arthroplasty 2017;32:1516–9.

[24] Hourlier H, Fennema P. Single tranexamic acid dose to reduce perioperative morbidity in primary total hip replacement: a randomised clinical trial. Hip Int 2014;24:63–8.

[25] Hsu C, Lin P, Kuo F, Wang J. A regime of two intravenous injections of tranexamic acid reduces blood loss in minimally invasive total hip arthroplasty: a prospective randomised double-blind study. Bone Joint J 2015;97-B:905–10.

[26] Husted H, Blønd L, Sonne-Holm S, Holm G, Jacobsen T, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. Acta Orthop Scand 2003;74:665–9.

[27] Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N. Tranexamic acid for reduction of blood loss during total hip arthroplasty. J Arthroplasty 2012;27:1838–43.

[28] Jaszczyk M, Kozerawski D, Kolodziej L, Kazimierczak A, Sarnecki P, Sieczka L. Effect of single preoperative dose of tranexamic acid on blood loss and transfusion in hip arthroplasty. Ortop Traumatol Rehabil 2015;17:265–73.

[29] Johansson T, Pettersson L, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. Acta Orthop 2005;76:314–9.

[30] Kayupov E, Fillingham YA, Okroj K, Plummer DR, Moric M, Gerlinger TL, et al. Oral and intravenous tranexamic acid are equivalent at reducing blood loss following total hip arthroplasty: a randomized controlled trial. J Bone Joint Surg Am 2017;99:373–8.

[31] Kazemi S, Mosaffa F, Eajazi A, Kaffashi M, Besheli L, Bigdeli M, et al. Hip the effect of tranexamic acid on reducing blood loss in cementless total hip arthroplasty under epidural anesthesia. Orthopedics 2010;33:17.

[32] Lee Y, Park S, Kim J, Cho C. Effect of tranexamic acid on reducing postoperative blood loss in combined hypotensive epidural anesthesia and general anesthesia for total hip replacement. J Clin Anesth 2013;25:393–8.

[33] Lemay E, Guay J, Cote C, Roy A. Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. Can J Anaesth 2004;51:31–7.

[34] Malhotra R, Kumar V, Garg B. The use of tranexamic acid to reduce blood loss in primary cementless total hip arthroplasty. Eur J Orthop Surg Traumatol 2011;21:101–4.

[35] Na H, Shin H, Lee Y, Kim J, Koo K, Do S. The effect of tranexamic acid on blood coagulation in total hip replacement arthroplasty: rotational thromboelastographic (ROTEM®) analysis. Anaesthesia 2016;71:67–75.

[36] Niskanen R, Korkala O. Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. Acta Orthop 2005;76:829–32.

[37] North W, Mehran N, Davis J, Silverton C, Weir R, Laker M. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind, randomized controlled trial. J Arthroplasty 2016;31:1022–6.

[38] Oremus K, Sostaric S, Trkulja V, Haspl M. Influence of tranexamic acid on postoperative autologous blood retransfusion in primary total hip and knee arthroplasty: a randomized controlled trial. Transfusion 2014;54:31–41.

[39] Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br 2009;91:776–83.

[40] Sadeghi M, Mehr-Aein A. Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomized double blind study in 67 patients. Acta Med Iran 2007;45:437–42.

[41] Wang C, Kang P, Ma J, Yue C, Xie J, Pei F. Single-dose tranexamic acid for reducing bleeding and transfusions in total hip arthroplasty: a double-blind, randomized controlled trial of different doses. Thromb Res 2016;141:119–23.

[42] Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty 2014;29:2113–6.

[43] Xie J, Ma J, Yue C, Kang P, Pei F. Combined use of intravenous and topical tranexamic acid following cementless total hip arthroplasty: a randomised clinical trial. Hip Int 2016;26:36–42.

[44] Xu X, Li X, Liu W, Wang Z. Longtime soaking of high concentration tranexamic acid in total hip arthroplasty: a prospective randomized controlled trial in 224 patients. Pakistan J Med Sci 2015;31:1306–11.

[45] Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces blood loss after cementless total hip arthroplasty - prospective randomized study in 40 cases. Int Orthop 2004;28:69–73.

[46] Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic acid administration in primary total hip arthroplasty a randomized controlled trial of intravenous combined with topical versus single-dose intravenous administration. J Bone Joint Surg Am 2016;98:983–91.

[47] Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty 2014;29:2452–6.

[48] Zhang Y, Cheng T, Zhang X. Impact of tranexamic acid and autologous blood transfusion on postoperative complications after primary total knee arthroplasty: a retrospective comparative study. Int J Clin Exp Med 2016;9:3842–50.

Appendix

Table S1
Publications of Blood Loss Included in the TXA Formulation and Dose Network Plot.

Reference (Author/Year)	Treatment 1, Network Node	Group 1 (n)	Group 1, Mean Blood Loss (mL)	Treatment 2, Network Node	Group 2 (n)	Group 2, Mean Blood Loss (mL)	Treatment 3, Network Node	Group 3 (n)	Group 3, Mean Blood Loss (mL)
Alshryda, S., 2013 [15]	Low-dose topical TXA	56	1617	Placebo	38	1981	N/A	N/A	N/A
Barrachina, B., 2016 [16]	Low-dose IV TXA	35	1377	Placebo	37	2215	High-dose IV TXA	36	1308
Castro-Menendez, M., 2016 [19]	High-dose IV TXA	40	1320	Placebo	40	1694	N/A	N/A	N/A
Claeys, Ma., 2007 [20]	Low-dose IV TXA	20	801	Placebo	20	1038	N/A	N/A	N/A
Fraval, A., 2016 [23]	High-dose IV TXA	50	1084	Placebo	51	1394	N/A	N/A	N/A
Johansson, T., 2005 [29]	Low-dose IV TXA	47	969	Placebo	53	1324	N/A	N/A	N/A
Kayupov, E., 2017 [30]	Low-dose IV TXA	43	1301	Oral TXA	40	1339	N/A	N/A	N/A
North, Wt., 2016 [37]	High-dose IV TXA	70	1195	High-dose topical TXA	69	1443	N/A	N/A	N/A
Rajesparan, K., 2009 [39]	High-dose IV TXA	36	1372	Placebo	37	1683	N/A	N/A	N/A
Wang, C., 2016 [41]	Low-dose IV TXA	42	871	Placebo	38	1229	N/A	N/A	N/A
Wei, W., 2014 [42]	High-dose IV TXA	101	959	Placebo	100	1364	High-dose topical TXA	102	963
Xie, J., 2016 [43]	High-dose IV TXA	70	878	High-dose topical TXA	70	905	Combined IV/ topical TXA	70	777
Xu, X., 2015 [44]	High-dose topical TXA	113	730	Placebo	111	1048	N/A	N/A	N/A
Yamasaki, S., 2004 [45]	High-dose IV TXA	20	365	Placebo	20	522	N/A	N/A	N/A
Yi, Z., 2016 [46]	Low-dose IV TXA	50	1003	Placebo	50	1221	Combined IV/ topical TXA	50	835
Yue, C., 2014 [47]	High-dose topical TXA	52	946	Placebo	49	1256	N/A	N/A	N/A

IV, intravenous; N/A, not applicable; TXA, tranexamic acid.

Table S2
Publications of Transfusion Included in the TXA Formulation and Dose Network Plot.

Reference (Author/Year)	Treatment 1, Network Node	Group 1 (n)	Group 1, Transfusion (%)	Treatment 2, Network Node	Group 2 (n)	Group 2, Transfusion (%)	Treatment 3, Network Node	Group 3 (n)	Group 3, Transfusion (%)
Alshryda, S., 2013 (a) [15]	Low-dose topical TXA	80	12.50	Placebo	81	32.10	N/A	N/A	N/A
Barrachina, B., 2016 [16]	Low-dose IV TXA	35	22.86	Placebo	37	37.84	High-dose IV TXA	36	11.11
Benoni, G., 2000 [18]	High-dose IV TXA	20	45.00	Placebo	19	78.95	N/A	N/A	N/A
Benoni, G., 2001 [17]	Low-dose IV TXA	18	22.22	Placebo	20	40.00	N/A	N/A	N/A
Castro-Menendez, M., 2016 [19]	High-dose IV TXA	40	5.00	Placebo	40	17.50	N/A	N/A	N/A
Claeys, Ma., 2007 [20]	Low-dose IV TXA	20	5.00	Placebo	20	30.00	N/A	N/A	N/A
Ekback, G., 2000 [21]	High-dose IV TXA	20	5.00	Placebo	20	5.00	N/A	N/A	N/A
Emara, W. M., 2014 [22]	High-dose IV TXA	20	5.00	Placebo	20	35.00	Low-dose topical TXA	20	5.00
Fraval, A., 2016 [23]	High-dose IV TXA	50	2.00	Placebo	51	11.76	N/A	N/A	N/A
Hsu, Ch., 2015 [25]	High-dose IV TXA	30	6.67	Placebo	30	30.00	N/A	N/A	N/A
Husted, H., 2003 [26]	High-dose IV TXA	20	10.00	Placebo	20	35.00	N/A	N/A	N/A
Jaszczyk, M., 2015 [28]	Low-dose IV TXA	61	3.28	Placebo	63	22.22	N/A	N/A	N/A
Johansson, T., 2005 [29]	Low-dose IV TXA	47	17.02	Placebo	53	43.40	N/A	N/A	N/A
Kayupov, E., 2017 [30]	Low-dose IV TXA	43	2.33	Oral TXA	40	7.50	N/A	N/A	N/A
Kazemi, Sm., 2010 [31]	Low-dose IV TXA	32	12.50	Placebo	32	34.38	N/A	N/A	N/A
Lee, Yc., 2013 [32]	High-dose IV TXA	34	26.47	Placebo	34	58.82	N/A	N/A	N/A
Lemay, E., 2004 [33]	High-dose IV TXA	20	0.00	Placebo	19	42.11	N/A	N/A	N/A
Malhotra, R., 2011 [34]	Low-dose IV TXA	25	24.00	Placebo	25	72.00	N/A	N/A	N/A
Na, Hs., 2016 [35]	Low-dose IV TXA	29	6.90	Placebo	26	19.23	N/A	N/A	N/A
Niskanen, Ro., 2005 [36]	High-dose IV TXA	19	26.32	Placebo	20	40.00	N/A	N/A	N/A
North, Wt., 2016 [37]	High-dose IV TXA	70	11.43	High-dose topical TXA	69	17.39	N/A	N/A	N/A
Oremus, K., 2014 [38]	High-dose IV TXA	20	5.00	Placebo	22	77.27	N/A	N/A	N/A
Rajesparan, K., 2009 [39]	High-dose IV TXA	36	8.33	Placebo	37	27.03	N/A	N/A	N/A
Sadeghi, M., 2007 [40]	Low-dose IV TXA	32	37.50	Placebo	35	57.14	N/A	N/A	N/A
Wang, C., 2016 [41]	Low-dose IV TXA	42	2.38	Placebo	38	26.32	N/A	N/A	N/A
Wei, W., 2014 [42]	High-dose IV TXA	101	5.94	Placebo	100	26.00	High-dose topical TXA	102	5.88
Xie, J., 2016 (b) [43]	High-dose IV TXA	70	4.29	High-dose topical TXA	70	5.71	Combined IV/ topical TXA	70	0.00
Xu, X., 2015 [44]	High-dose topical TXA	113	5.31	Placebo	111	19.82	N/A	N/A	N/A
Yi, Z., 2016 [46]	Low-dose IV TXA	50	16.00	Placebo	50	38.00	Combined IV/ topical TXA	50	2.00
Yue, C., 2014 [47]	High-dose topical TXA	52	5.77	Placebo	49	22.45	N/A	N/A	N/A
Zhang, Y., 2016 [48]	High-dose IV TXA	23	4.35	Placebo	22	4.55	Low-dose topical TXA	24	0.00

IV, intravenous; N/A, not applicable; TXA, tranexamic acid.

Table S3
Publications of Blood Loss Included in the TXA Formulation, Timing of Dose, and Number of Doses Network Plot.

Reference (Author/Year)	Treatment 1, Network Node	Group 1 (n)	Group 1, Mean Blood Loss (mL)	Treatment 2, Network Node	Group 2 (n)	Group 2, Mean Blood Loss (mL)	Treatment 3, Network Node	Group 3 (n)	Group 3, Mean Blood Loss (mL)
Alshryda, S., 2013 [15]	Single postincision topical TXA	56	1617	Placebo	38	1981	N/A	N/A	N/A
Barrachina, B., 2016 [16]	Single-dose preincision IV TXA	35	1377	Placebo	37	2215	Multiple doses preincision and postincision IV TXA	36	1308
Castro-Menendez, M., 2016 [19]	Single-dose preincision IV TXA	40	1320	Placebo	40	1694	Multiple doses postincision IV TXA	40	1429
Claeys, Ma., 2007 [20]	Single-dose preincision IV TXA	20	801	Placebo	20	1038	N/A	N/A	N/A
Fraval, A., 2016 [23]	Multiple doses preincision and postincision IV TXA	50	1084	Placebo	51	1394	N/A	N/A	N/A
Imai, N., 2012 [27]	Multiple doses postincision IV TXA	20	675	Single-dose preincision IV TXA	25	638	Multiple doses preincision and postincision IV TXA	26	579
Johansson, T., 2005 [29]	Single-dose preincision IV TXA	47	969	Placebo	53	1324	N/A	N/A	N/A
Kayupov, E., 2017 [30]	Single-dose preincision IV TXA	43	1301	Single-dose preincision oral TXA	40	1339	N/A	N/A	N/A
North, Wt., 2016 [37]	Multiple doses preincision and postincision IV TXA	70	1195	Single-dose postincision topical TXA	69	1442.7	N/A	N/A	N/A
Rajesparan, K., 2009 [39]	Single-dose preincision IV TXA	36	1372	Placebo	37	1683	N/A	N/A	N/A
Wang, C., 2016 [41]	Single-dose preincision IV TXA	42	871	Placebo	38	1229	N/A	N/A	N/A
Wei, W., 2014 [42]	Single-dose preincision IV TXA	101	959	Placebo	100	1364	Single-dose postincision topical TXA	102	963
Xie, J., 2016 [43]	Single-dose preincision IV TXA	70	878	Single-dose postincision topical TXA	70	905	N/A	N/A	N/A
Xu, X., 2015 [44]	Single-dose postincision topical TXA	113	730	Placebo	111	1048	N/A	N/A	N/A
Yamasaki, S., 2004 [45]	Single-dose preincision IV TXA	20	365	Placebo	20	522	N/A	N/A	N/A
Yi, Z., 2016 [46]	Single-dose preincision IV TXA	50	1003	Placebo	50	1221	N/A	N/A	N/A
Yue, C., 2014 [47]	Single-dose postincision topical TXA	52	946	Placebo	49	1256	N/A	N/A	N/A

IV, intravenous; N/A, not applicable; TXA, tranexamic acid.

Table S4
Publications of Blood Loss Included in the TXA Formulation, Timing of Dose, and Number of Doses Network Plot.

Reference (Author/Year)	Treatment 1, Network Node	Group 1 (n)	Group 1, Transfusion (%)	Treatment 2, Network Node	Group 2 (n)	Group 2, Transfusion (%)	Treatment 3, Network Node	Group 3 (n)	Group 3, Transfusion (%)
Alshryda, S., 2013 [15]	Single postincision topical TXA	80	12.50	Placebo	81	32.10	N/A	N/A	N/A
Barrachina, B., 2016 [16]	Single-dose preincision IV TXA	35	22.86	Placebo	37	37.84	Multiple doses preincision and postincision IV TXA	36	11.11
Benoni, G., 2000 [18]	Multiple doses postincision IV TXA	20	45.00	Placebo	19	78.95	N/A	N/A	N/A
Benoni, G., 2001 [17]	Single-dose preincision IV TXA	18	22.22	Placebo	20	40.00	N/A	N/A	N/A
Castro-Menendez, M., 2016 [19]	Single-dose preincision IV TXA	40	5.00	Placebo	40	17.50	Multiple doses postincision IV TXA	40	5.00
Claeys, Ma., 2007 [20]	Single-dose preincision IV TXA	20	5.00	Placebo	20	30.00	N/A	N/A	N/A
Ekback, G., 2000 [21]	Multiple doses preincision and postincision IV TXA	20	5.00	Placebo	20	5.00	N/A	N/A	N/A
Emara, W. M., 2014 [22]	Multiple doses preincision and postincision IV TXA	20	5.00	Placebo	20	35.00	Single-dose postincision topical TXA	20	5.00
Fraval, A., 2016 [23]	Multiple doses preincision and postincision IV TXA	50	2.00	Placebo	51	11.76	N/A	N/A	N/A
Hourlier, H., 2014 [24]	Multiple doses postincision IV TXA	79	0.00	Single-dose postincision IV TXA	85	0.00	N/A	N/A	N/A
Hsu, Ch., 2015 [25]	Multiple doses preincision and postincision IV TXA	30	6.67	Placebo	30	30.00	N/A	N/A	N/A
Husted, H., 2003 [26]	Multiple doses preincision and postincision IV TXA	20	10.00	Placebo	20	35.00	N/A	N/A	N/A
Jaszczyk, M., 2015 [28]	Single-dose preincision IV TXA	61	3.28	Placebo	63	22.22	N/A	N/A	N/A
Johansson, T., 2005 [29]	Single-dose preincision IV TXA	47	17.02	Placebo	53	43.40	N/A	N/A	N/A
Kayupov, E., 2017 [30]	Single-dose preincision IV TXA	43	2.33	Single-dose preincision oral TXA	40	7.50	N/A	N/A	N/A
Kazemi, Sm., 2010 [31]	Single-dose peincision IV TXA	32	12.50	Placebo	32	34.38	N/A	N/A	N/A
Lee, Yc., 2013 [32]	Multiple doses preincision and postincision IV TXA	34	26.47	Placebo	34	58.82	N/A	N/A	N/A
Lemay, E., 2004 [33]	Multiple doses preincision and postincision IV TXA	20	0.00	Placebo	19	42.11	N/A	N/A	N/A
Malhotra, R., 2011 [34]	Single-dose preincision IV TXA	25	24.00	Placebo	25	72.00	N/A	N/A	N/A
Na, Hs., 2016 [35]	Single postincision IV TXA	29	6.90	Placebo	26	19.23	N/A	N/A	N/A
Niskanen, Ro., 2005 [36]	Multiple doses preincision and postincision IV TXA	19	26.32	Placebo	20	40.00	N/A	N/A	N/A
North, Wt., 2016 [37]	Multiple doses preincision and postincision IV TXA	70	11.43	Single-dose postincision topical TXA	69	17.39	N/A	N/A	N/A
Oremus, K., 2014 [38]	Multiple doses preincision and postincision IV TXA	20	5.00	Placebo	22	77.27	N/A	N/A	N/A
Rajesparan, K., 2009 [39]	Single-dose preincision IV TXA	36	8.33	Placebo	37	27.03	N/A	N/A	N/A
Sadeghi, M., 2007 [40]	Single-dose preincision IV TXA	32	37.50	Placebo	35	57.14	N/A	N/A	N/A
Wang, C., 2016 [41]	Single-dose preincision IV TXA	42	2.38	Placebo	38	26.32	N/A	N/A	N/A
Wei, W., 2014 [42]	Single-dose preincision IV TXA	101	5.94	Placebo	100	26.00	Single-dose postincision topical TXA	102	5.88
Xie, J., 2016 [43]	Single-dose preincision IV TXA	70	4.29	Single-dose postincision topical TXA	70	5.71	N/A	N/A	N/A
Xu, X., 2015 [44]	Single-dose postincision topical TXA	113	5.31	Placebo	111	19.82	N/A	N/A	N/A
Yi, Z., 2016 [46]	Single-dose preincision IV TXA	50	16.00	Placebo	50	38.00	N/A	N/A	N/A
Yue, C., 2014 [47]	Single-dose postincision topical TXA	52	5.77	Placebo	49	22.45	N/A	N/A	N/A
Zhang, Y., 2016 [48]	Single-dose preincision IV TXA	23	4.35	Placebo	22	4.55	Single-dose postincision topical TXA	24	0.00

IV, intravenous; N/A, not applicable; TXA, tranexamic acid.