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Editorial Board Member of *World Journal of Clinical Cases*, Pietro Scicchitano, MD, Professor, Research Scientist, Department of Emergency and Organ Transplantation, School of Medicine, University of Bari, Bari 70124, Italy. piero.sc@hotmail.it

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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META-ANALYSIS

Efficacy of topical *vs* intravenous tranexamic acid in reducing blood loss and promoting wound healing in bone surgery: A systematic review and meta-analysis

Jian-Wen Xu, Hong Qiang, Ting-Li Li, Yi Wang, Xiao-Xiao Wei, Fei Li

ORCID number: Jian-Wen Xu 0000-0002-1360-6795; Hong Qiang 0000-0001-7436-5764; Ting-Li Li 0000-0003-4709-1010; Yi Wang 0000-0003-3756-6801; Xiao-Xiao Wei 0000-0001-5173-5400; Fei Li 0000-0002-8810-1759.

Author contributions: Xu JW and Li F conceptualized this study; Xu JW, Qiang H, and Li F collected the data; Xu JW, Wang Y, and Wei XX performed the formal analysis; Xu JW and Wang Y drafted the manuscript; Li F edited and reviewed the manuscript.

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Jian-Wen Xu, Hong Qiang, Ting-Li Li, Xiao-Xiao Wei, Nursing Department, Yangpu District Shidong Hospital, Shanghai 200438, China

Yi Wang, Emergency Services Department, Yangpu District Shidong Hospital, Shanghai 200438, China

Fei Li, The Second Neurological Department, Yangpu District Shidong Hospital, Shanghai 200438, China

Corresponding author: Fei Li, MD, Chief Doctor, The Second Neurological Department, Yangpu District Shidong Hospital, No. 999 Shiguang Road, Yangpu District, Shanghai 200438, China. lifeimedicine@163.com

Abstract

BACKGROUND

Tranexamic acid (TXA) has been used as an anti-fibrinolytic drug for over half a century and has received much attention in recent decades.

AIM

To evaluate the efficacy of topical *vs* intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

METHODS

From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resource. Searches were performed with mesh terms. The data were retracted blindly by two independent reviewers. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. Chi-square (I^2) tests were used to quantify the extent of heterogeneity ($P < 0.01$ was considered statistically significant). The efficacy of topical TXA in reducing blood loss and promoting wound healing in bone surgery was compared with intravenous TXA and placebo.

RESULTS

According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches, and 18 papers remained in

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agreement with our inclusion criteria. It was found that TXA reduced 277.51 mL of blood loss compared to placebo, and there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery. Our analyses also showed that TXA significantly reduced blood transfusion compared to placebo and there was no significant difference between topical TXA and IV TXA.

CONCLUSION
The use of both topical and intravenous TXA are equally effective in reducing blood loss in bone surgery, which might be beneficial for wound healing after surgery.

Key Words: Tranexamic acid; Blood loss; Wound healing; Bone surgery; Meta-analysis

Core Tip: Although tranexamic acid (TXA) is regularly used by surgeons, a comprehensive guideline on safe topical doses and methods for TXA administration has remained controversial. This study showed that both topical and intravenous TXA are equally effective in reducing blood loss in bone surgery, which is thus beneficial for wound healing after surgery.

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INTRODUCTION

Wound healing is a natural biological process, in which all four stages, including homeostasis (stop bleeding), inflammation, proliferation, and maturation, must occur within a time frame for successful wound healing[1,2]. The use of tranexamic acid (TXA) as an anti-fibrinolytic drug has been available for over half a century and has received much attention in recent decades[3]. By binding to plasminogen, TXA prevents the conversion of plasminogen to plasmin, thus preventing fibrinolysis[4]. The use of TXA reduces blood loss and blood transfusion in major orthopedic surgery, and the safety is also well recognized[5-8]. Previous studies have not confirmed any increased risk of thromboembolism after the use of TXA in various surgeries[9-11]. Topical use of TXA is increasingly popular today, but surgeons do not have a comprehensive guideline on safe topical doses and methods of administration, as topical use is still off-label[12]. There have been two meta-analysis studies discussing efficacy of topical *vs* intravenous TXA in total hip arthroplasty and total knee arthroplasty, respectively[13,14]. However, the efficacy of topical *vs* intravenous TXA in reducing blood loss and promoting wound healing in bone surgery remains to be systemically reviewed.

Therefore, the aim of this systematic review and meta-analysis was to evaluate the efficacy of topical *vs* intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

MATERIALS AND METHODS

Search strategy techniques

From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resources. Searches were performed with mesh terms: ("Tranexamic Acid/administration and dosage"[Mesh]

OR "Tranexamic Acid/adverse effects"[Mesh] OR "Tranexamic Acid/blood"[Mesh] OR "Tranexamic Acid/standards"[Mesh] OR "Tranexamic Acid/toxicity"[Mesh])) AND ("Wound Healing/blood"[Mesh] OR "Wound Healing/blood supply"[Mesh] OR "Wound Healing/complications"[Mesh] OR "Wound Healing/drug effects"[Mesh] OR "Wound Healing/drug therapy"[Mesh] OR "Wound Healing/innervation"[Mesh] OR "Wound Healing/pharmacology"[Mesh] OR "Wound Healing/surgery"[Mesh] OR "Wound Healing/therapy"[Mesh])) OR ("Blood Loss, Surgical"[Mesh] OR "Hemorrhage"[Mesh] OR "Postoperative Hemorrhage"[Mesh])) OR "Homeostasis"[Mesh]) OR "Bleeding Time"[Mesh]) OR "Inflammation"[Mesh]) OR "Cell Proliferation"[Mesh].

The present systematic review and meta-analysis protocol was prepared by PRISMA checklist[15], and Population/Patient, Exposure/Intervention, Comparison, and Outcome strategy (Table 1).

Selection criteria

Inclusion criteria: Randomized controlled trials, controlled clinical trials, and prospective and retrospective cohort studies; human; topical TXA or intravenously administered TXA; adults; bone surgery trials; and in English.

Exclusion criteria: *In vitro* studies, case studies, case reports, and reviews; animal studies; oral TXA; and studies without a control group.

Data extraction and method of analysis: The data were extracted from the related studies including years, study design, number of patients, mean/range of age, interventions group, control group, and clinical endpoints. The quality of studies included was assessed using the Cochrane Collaboration's tool[16]. The scale score for low risk was 1 and that for high and unclear risk was 0. Scale scores ranged from 0 to 6. A higher score indicated higher quality.

Two reviewers blindly and independently extracted the data. Odds ratio (OR) with 95% confidence interval (CI), fixed effects model and Mantel-Haenszel method and mean difference with 95%CI, random effect model and restricted maximum likelihood method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. Chi-square (I^2) tests were performed to quantify the extent of heterogeneity (P value < 0.01 was considered statistically significant). I^2 values > 50% indicated moderate-to-high heterogeneity. Software Stata/MP v.16 (fastest version of Stata) was used for statistical analysis.

RESULTS

According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches. In the first phase of the study selection, 1312 studies were left after removing copies. Then 1247 *in vitro* studies, case studies, case reports, and reviews or those that did not meet the eligibility criteria were excluded. Therefore, we fully assessed the complete full-text papers of the remaining 65 studies in the second stage, and 47 publications were excluded due to the lack of the defined inclusion criteria. Finally, 18 papers remained in agreement with our inclusion criteria required (Figure 1).

Characteristics

Eighteen studies (randomized controlled trials) were included. The total sample size was 1994. All of the studies evaluated the efficacy of TXA in bone surgical patients. In detail, nine studies evaluated the efficacy of TXA in total knee arthroplasty, two evaluated the efficacy of TXA in trochanteric fracture surgery, one evaluated the efficacy of TXA in intertrochanteric fractures, two evaluated the efficacy of TXA in total shoulder arthroplasty, two evaluated the efficacy of TXA in total hip replacement and one evaluated the efficacy of TXA in orthognathic surgery (Table 2)[17-34].

Transfusion rate

The effects of TXA and placebo were compared in 10 studies about bone surgery. The OR was -1.56 (95%CI: -1.96 to -1.17; P = 0.00), and moderate heterogeneity was found (I^2 = 35.63%). Our results showed that TXA significantly reduced blood transfusion compared to placebo (Figure 2).

The effects of topical TXA and IV TXA were compared in five studies about bone surgery. The OR was 0.20 (95%CI: -0.50 to 0.89; P = 0.58), and there was mild hetero-

Table 1 Population/Patient, Exposure/Intervention, Comparison, and Outcome strategy

PICO or PECO strategy	Description
P	Population/Patient: Adult patients
E	Exposure/Intervention: Tranexamic acid
C	Comparison: Placebo or standard care
O	Outcome: Blood loss

PECO: Population/Patient, Exposure, Comparison, and Outcome; PICO: Population/Patient, Intervention, Comparison, and Outcome.

Table 2 Studies selected for systematic review and meta-analysis

	Ref.	Study design	Sample size	Procedure	Intervention group and control group
1	Lei *et al*[17], 2020	RCT	132	Total knee arthroplasty	IV TXA, placebo
2	Luo *et al*[18], 2019	RCT	90	Trochanteric fracture surgery	IV TXA, placebo
3	Chen *et al*[19], 2019	RCT	166	Trochanteric fracture surgery	IV TXA, placebo
4	Zhang *et al*[20], 2019	RCT	50	Total knee arthroplasty	Topical TXA, IV TXA
5	Zhou *et al*[21], 2019	RCT	100	Intertrochanteric fractures	Topical TXA (1 g), placebo
6	Cvetanovich *et al*[22], 2018	RCT	110	Total shoulder arthroplasty	TXA, placebo
7	Huang *et al*[23], 2017	RCT	150	Total knee arthroplasty	Topical TXA (1 g), IV TXA, placebo
8	Vara *et al*[24], 2017	RCT	102	Total shoulder arthroplasty	Topical TXA, placebo
9	Goyal *et al*[25], 2017	RCT	168	Total knee arthroplasty	TXA, IV TXA
10	Chen *et al*[26], 2016	RCT	100	Total knee arthroplasty	Topical TXA, IV TXA
11	Drosos *et al*[27], 2016	RCT	90	Total knee arthroplasty	Topical TXA: 1 g, placebo, IV TXA
12	Keyhan *et al*[28], 2016	RCT	120	Total knee arthroplasty	Topical TXA: 3 g, placebo, IV TXA (500 g)
13	North *et al*[29], 2016	RCT	139	Total hip replacement	Topical TXA: 2 g, IV TXA (2 g)
14	Aguilera *et al*[30], 2015	RCT	150	Total knee arthroplasty	Topical TXA: 1 g, IV TXA (2 g), placebo
15	Eftekharian *et al*[31], 2015	RCT	56	Orthognathic surgery	Topical TXA: 1 g, placebo
16	Gillespie *et al*[32], 2015	RCT	111	Total shoulder arthroplasty	Topical TXA: 2 g, placebo
17	Taheriazam *et al*[33], 2015	RCT	80	Total hip replacement	Topical TXA, IV TXA
18	Yang *et al*[34], 2015	RCT	80	Total knee arthroplasty	Topical TXA, placebo

RCT: Randomized Controlled Trial; TXA: Tranexamic acid.

geneity (I^2 < 0%). Our results showed there was no significant difference between topical TXA and IV TXA in reducing blood transfusion in bone surgery (Figure 3).

Blood loss

The blood loss after topical TXA *vs* IV TXA was compared among six studies about bone surgery, and the mean difference was 74.06 mL (mean difference [MD]: 74.06, 95%CI: -8.17 to 156.39; P = 0.08), with high heterogeneity found (I^2 = 88.98%). Our results showed there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery (Figure 4).

The blood loss after TXA *vs* placebo administration was compared among 12 studies about bone surgery, and the mean difference was -277.51 mL (MD: -277.51, 95%CI: -410.47 to -144.5; P = 0.00), with high heterogeneity (I^2 = 97.94%). The results showed that TXA reduced 277.51 mL of blood loss compared to placebo (Figure 5).

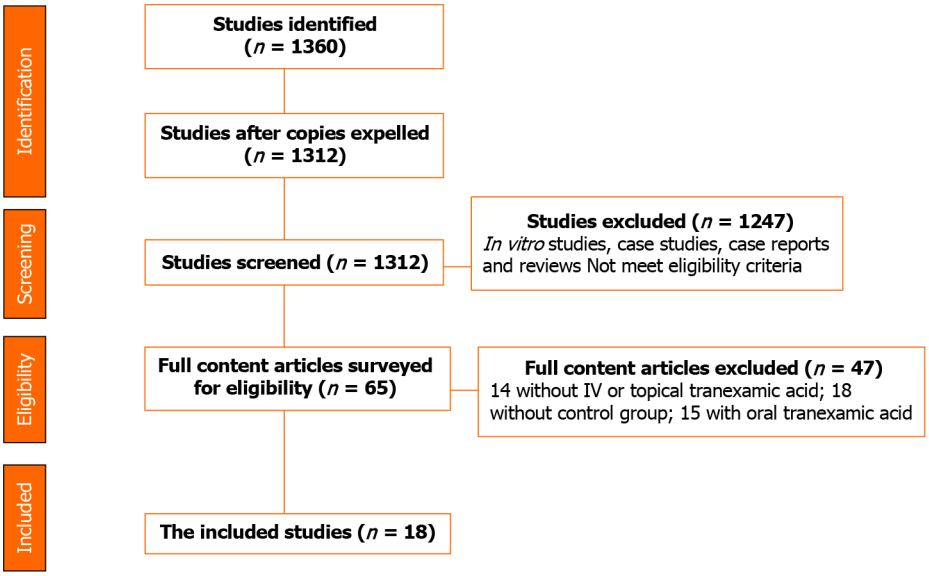

Figure 1 Study attrition. Eighteen papers were finally included in the meta-analysis.

DISCUSSION

The present meta-analysis showed that TXA reduced 277.51 mL of blood loss compared to placebo in bone surgery, and there was no significant difference between topical TXA and IV TXA in reducing blood loss. Moreover, TXA significantly reduced blood transfusion compared to placebo in bone surgery and there was no significant difference between topical TXA and IV TXA. In a systematic review and meta-analysis study with a sample size of 10488 patients[35], regardless of the type of TXA administration, it was shown that 30% of patients only needed an injection. These results were consistent with our study. If a theoretical comparison is made between the topical TXA and IV TXA, the topical TXA would result in a 90% reduction in plasma concentrations[36-38]. Also, a study with regression analysis showed no significant relationship between topical TXA and reduced dose-dependent risk of transmission, and topical TXA also has the advantage of lower doses and medical costs[39,40]. Moreover, previous studies have shown that there is no significant advantage of systemic TXA in various surgical and non-surgical procedures compared to topical TXA[39,41]. Taken together, these findings indicate that topical TXA is recommended to reduce blood loss and transfusion at least in bone surgery.

Much blood loss is common in bone surgery, which is a major source of mortality, and blood transfusions are often required during the perioperative period. However, blood transfusions may lead to increased length of hospital stay, a raised risk of infection, and an increased medical cost[42-44]. TXA prevents the conversion of plasminogen to plasmin, thus preventing fibrinolysis and blood loss[4]. Thus, it is clinically significant to use TXA to reduce blood loss and transfusion in bone surgery, which might be beneficial for wound healing.

However, our study also had some limitations. First, the optimal dose and timing of the topical TXA were not evaluated in our study due to lack of clinical guideline for TXA and inconsistency in dose and timing of TXA across studies, which remain to be evaluated in the further research. Second, significant heterogeneity was detected in blood loss and our findings remain to be further verified by more well-designed studies.

CONCLUSION

We found that the use of both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery. Given the consideration of smaller dose and less medical cost, topical TXA is recommended for bone surgery. However, more studies are needed to further verify our findings in the future.

Risk of bias assessment

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome Assessment	incomplete outcome data	Selective reporting	Total score
Lei *et al*[17], 2020	+	+	+	+	+	+	6
Luo *et al*[18], 2019	+	+	+	+	+	+	6
Chen *et al*[19], 2019	?	+	+	+	+	+	5
Zhang *et al*[20], 2019	+	+	+	+	+	+	6
Zhou *et al*[21], 2019	+	?	?	+	+	+	4
Cvetanovich *et al*[22], 2018	+	+	+	?	+	+	5
Huang *et al*[23], 2017	+	+	+	+	?	+	5
Vara *et al*[24], 2017	+	+	-	+	+	+	5
Goyal *et al*[25], 2017	+	?	?	+	+	+	4
Chen *et al*[26], 2016	+	+	+	?	+	+	5
Drosos *et al*[27], 2016	+	+	+	-	?	+	4
Keyhan *et al*[28], 2016	+	+	-	+	+	+	5
North *et al*[29], 2016	+	+	+	?	?	+	4
Aguilera *et al*[30], 2015	+	+	+	+	-	+	5
Eftekharian *et al*[31], 2015	+	+	?	+	-	+	4
Gillespie *et al*[32], 2015	+	-	+	+	?	+	4
Taheriazam *et al*[33], 2015	+	+	?	+	+	+	5
Yang *et al*[34], 2015	+	+	?	+	?	+	4

(+): Low; (?): Unclear; (-): High.

Figure 2 Risk of bias assessment. (+): Low; (?): Unclear; (-): High.

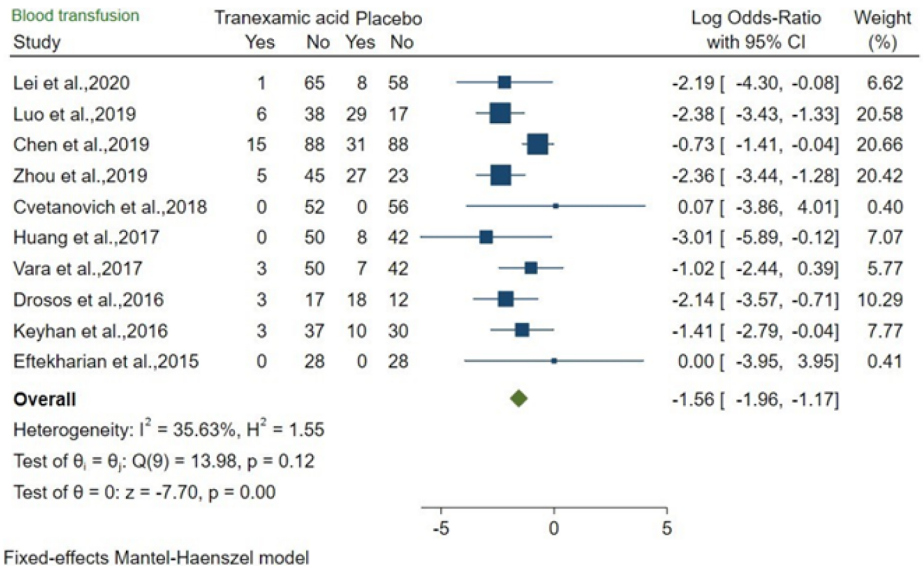

Figure 3 Forest plot showed odds ratio (95% confidence interval) for risk of blood transfusion between tranexamic acid and placebo in bone surgery. CI: Confidence interval.

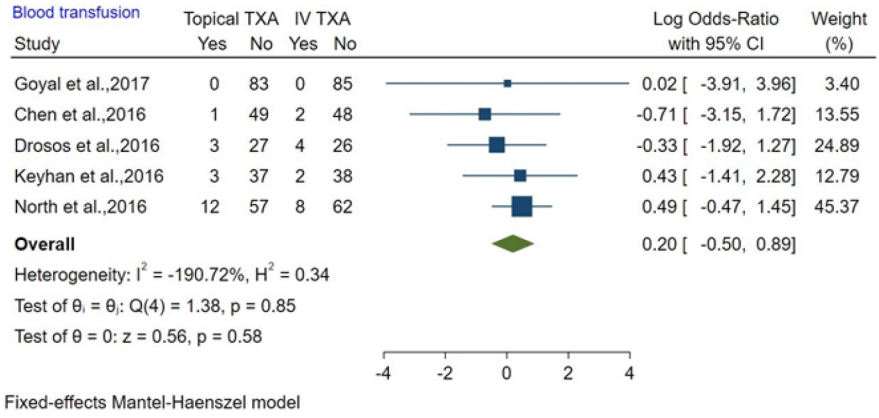

Figure 4 Forest plot showed odds ratio for risk of blood transfusion between topical tranexamic acid and IV tranexamic acid in bone surgery. CI: Confidence interval; TXA: Tranexamic acid.

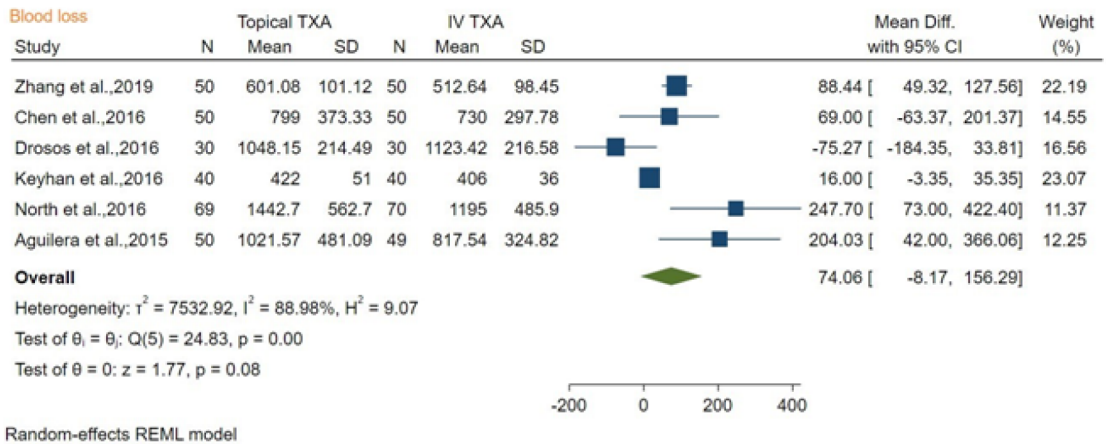

Figure 5 Forest plot showed mean difference (95% confidence interval) of blood loss between topical tranexamic acid and IV tranexamic acid in bone surgery. CI: Confidence interval; SD: Standard deviation; TXA: Tranexamic acid.

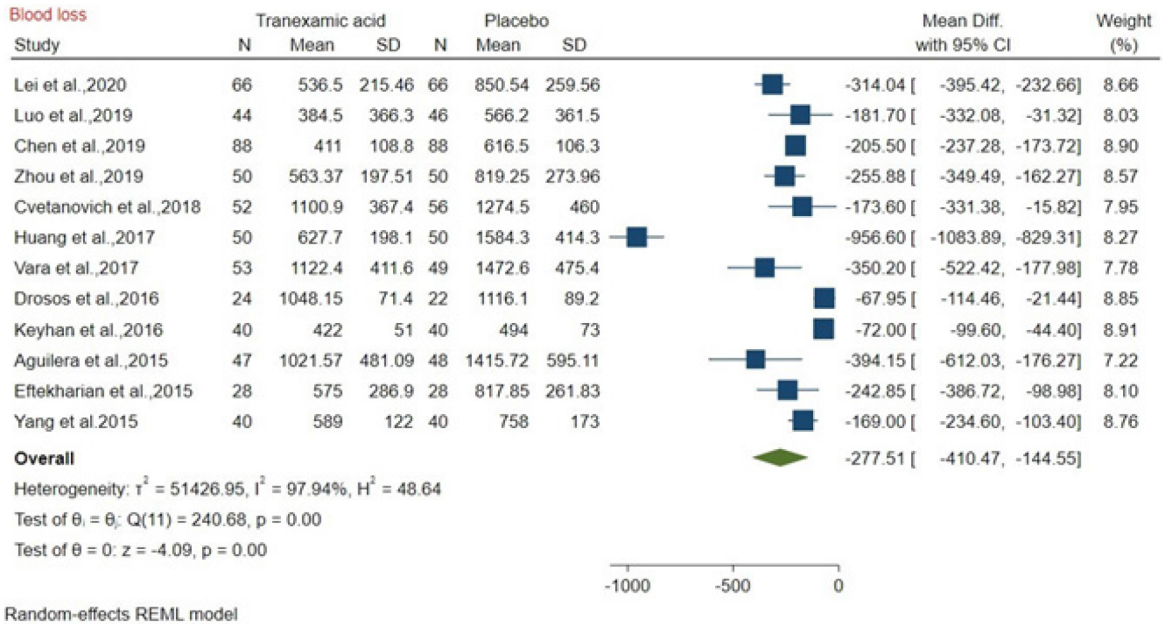

Figure 6 Forest plot showed mean difference (95% confidence interval) for blood loss between tranexamic acid and placebo in bone surgery. CI: Confidence interval; SD: Standard deviation.

ARTICLE HIGHLIGHTS

Research background

Tranexamic acid (TXA) as an anti-fibrinolytic drug has been available for over half a century and Topical use of TXA is more and more popular today.

Research motivation

Although TXA is regularly used in surgeons, a comprehensive guideline on safe topical doses and methods for TXA administration has remained controversial.

Research objectives

This study evaluated the efficacy of topical *vs* intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

Research methods

From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resource. Searches were performed with mesh terms. The data were retracted blindly by two independent reviewers. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. Chi-square (I^2) tests were used to quantify the extent of heterogeneity ($P < 0.01$ was considered statistically significant). The efficacy of topical TXA in reducing blood loss and promoting wound healing in bone surgery was compared with intravenous TXA and placebo.

Research results

According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches, and eighteen papers remained in agreement with our inclusion criteria required. It was found that TXA reduced 277.51 mL of blood loss compared to placebo, and there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery. Our analysis also showed that TXA significantly reduced blood transfusion compared to placebo and there was no significant difference between topical TXA and IV TXA.

Research conclusions

This meta-analysis showed that both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery. Given the consideration of smaller dose and less medical cost, topical TXA is recommended

for bone surgery.

Research perspectives

Both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery.

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