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Original Article

The efficacy and safety of oral tranexamic acid for reducing blood loss after total joint arthroplasty: a meta-analysis

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Abstract: Objective: This meta-analysis aimed to illustrate the efficacy and safety of oral tranexamic acid (TXA) for reducing blood lossafter total joint arthroplasty (TJA). Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google database were searched for comparative studies comparing oral TXA versus control group or intravenous TXA for patients prepared for TJA. The outcomes including need for transfusion, hemoglobin drop, length of hospital stay and drain volume. We calculated risk ratio (RR) with a 95% confidence interval (CI) for need for transfusion, and the weighted mean difference (WMD) with a 95% CI for hemoglobin drop, length of hospital stay and drain volume. A random-effects model was used for all comparisons and Stata 12.0 was used for meta-analysis. Results: Six clinical trials (4 RCTs and 2 non-RCTs) involving 3258 patients were finally included for this meta-analysis. When compared with control group, oral TXA was associated with less need for transfusion, hemoglobin drop, drain volume and length of hospital stay ($P<0.05$). When compared with IV TXA, oral TXA was associated with more hemoglobin drop ($P<0.05$). However, there was no significant difference between the need for transfusion, drain volume and the length of hospital stay between oral TXA with IV TXA. Conclusion: Oral TXA has comparable hemostasis effects with IV TXA, and may reduce the costs for patients prepared for TJA. However, the limited quality and number of the included studies, more high quality and multi center RCTs are still need to recommend for routine administration.

Keywords: Tranexamic acid, total joint arthroplasty, oral, blood loss, meta-analysis

Introduction

Total joint arthroplasty (TJA) including total knee arthroplasty (TKA) and total hip arthroplasty (THA), has been identified as the most effective surgeries for knee or knee diseases [1]. Indeed, the number of primary TJA procedures is expected to reach 3.48 million in 2030 in the United States, soaring eightfold from 2005 [2]. TJA can be associated with considerable blood loss, and transfusion carries a substantial risk of immunologic reaction and transmission of disease [3, 4]. Methods to reduce postoperative blood loss and avoid homologous blood transfusion include tranexamic acid (TXA), fibrin sealant and tourniquet [5-7]. Surgical trauma and administration with tourniquet will stimulate fibrinolysis after TJA. TXA poses antifibrinolytic effects by reversible complex with plasminogen. Previous meta-analysis has been identified that intravenous TXA can decrease the perioperative blood loss without increase the thrombotic complications [8]. However, drug allergy with anaphylactic shock has been reported and concern has arisen concerning the safety of intravenous TXA [9]. Topical form carries the theoretical risk of periprosthetic infection due to needle contamination and may even aggravate sepsis [10]. Oral TXA has been shown to be equally or even more effective in primary TJA to reduce blood loss, hemoglobin drop, and blood transfusion [11]. However, the relatively small number of participants have made their conclusions inconclusive.

Based on the current clinical studies with oral TXA, we tried to pool the results in a meta-anal-

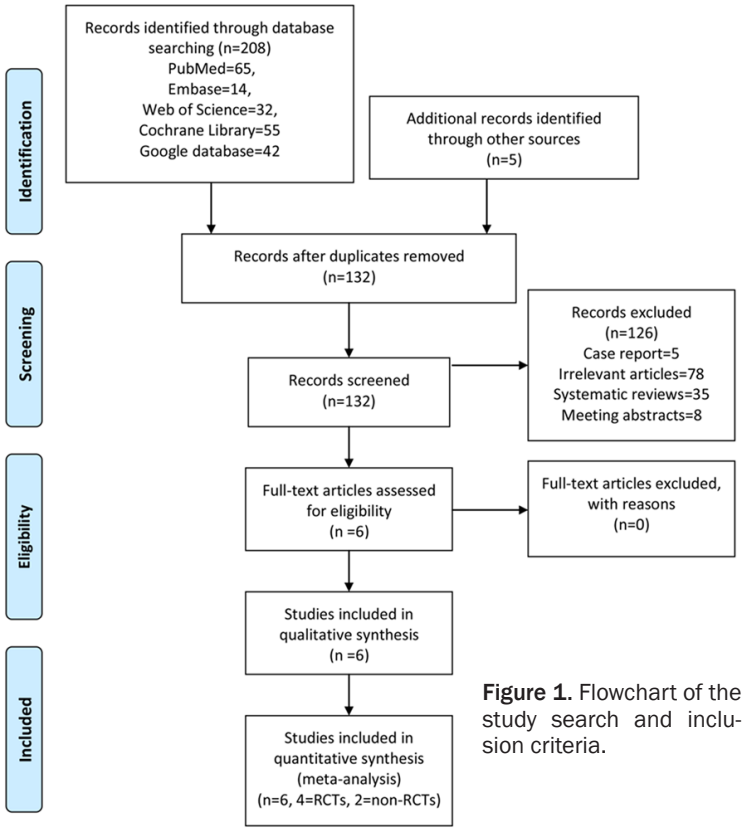

Figure 1. Flowchart of the study search and inclusion criteria.

ysis. The purpose of this meta-analysis was to study whether oral TXA was associated with less (1) need for transfusion, (2) hemoglobin drop, (3) drain volume, (4) length of hospital stay and complications than control group and IV TXA.

Material and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines for the meta-analysis of intervention trials [12].

Search strategies

PubMed, Embase, Web of Science and the Cochrane Library were searched up to December 2016 for comparative studies involving oral TXA for reducing blood loss in patients undergoing TJA. The search terms were as follows: "tranexamic acid", "total knee arthroplasty", "knee arthroplasty", "knee replacement", "oral", "joint arthroplasty", "joint replacement", "total hip arthroplasty", "hip arthroplasty", and "hip replacement". The language of publications was not limited. The title and abstract of studies identified in the search were reviewed to exclude clearly irrelevant studies. Reference lists of all eligible studies and relevant reviews were searched manually for additional trials.

Inclusion criteria and study selection

Inclusion criteria: Participants: patients undergoing primary TJA; Intervention: oral TXA; Comparison: IV TXA or control group; Outcomes: need for transfusion, hemoglobin drop, drain volume, length of hospital stay, and postoperative complications. Study: RCTs and non-RCTs were included. Articles that reported at least one outcome were included and those without the outcome measures of interest were excluded. Letters, comments, editorials and practice guidelines were excluded.

Data extraction and quality assessment

Two authors (Jian Zhang and Jian Liu) independently reviewed all titles and abstracts of studies identified by searches according to the eligibility criteria described above. Full texts of articles that met the inclusion criteria were reviewed thoroughly. Disagreements were resolved by discussion to reach consensus. The data on patient characteristics (age, sex and other baseline characteristics), interventions and outcomes were extracted in duplicate by the two authors using a standardized form predesigned Excel. The data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to mean ± standard deviation (SD) according to the Cochrane Handbook [13]. If data were not reported numerically, we extracted them by manual measurements from published figures.

Two authors (Weidong He and Min Wang) independently assessed the risk of bias of the included studies, based on the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other

Table 1. The general characteristic of the included studies

Author	Country	Control Group		Surgery	Intervention Group			Outcomes	Follow-up	Study
		No of patients	Doses		No of patients	Oral dose(g)	Intervals			
Alipour 2013	Iran	26	No TXA	TKA	27	1	2 h preoperatively, 6 hours and 18 hours postoperatively	1, 3, 4, 6, 7	6 weeks	RCT
Bradshaw 2012	USA	20	No TXA	TKA	26	1.5	8 h preoperatively, 3 dose 2 hours after surgery, and a 4 dose 6 h postoperatively	1, 3, 4, 6, 7	3 months	RCT
Fillingham 2016	USA	37	IV TXA (1 g)	TKA	34	1.95	2 h preoperatively	1, 2, 3, 4, 5, 6, 7	NS	RCT
Irwin 2013	USA	2638	IV TXA (15 mg/kg)	TKA+THA	302	25 mg/kg	2 h preoperatively		2 months	RCS
Lee 2017	China	54	No TXA	THA	54	1	2 h preoperatively, 6 hours and 12 hours postoperatively	1, 2, 3, 4, 6, 7	3 days	RCS
Zohar 2004	India	20	Arm1=No TXA Arm2=IV TXA short Arm3=IV TXA long	TKA	20	1	1 h preoperatively	1, 5	3 months	RCT

TXA, tranexamic acid, TKA, total knee arthroplasty, THA, total hip arthroplasty, RCT, randomized controlled trials, RCS, retrospective controlled trials, NS, not stated, 1, need for transfusion, 2, total blood loss, 3, hemoglobin drop, 4, drain loss, 5, length of hospital stay, 6, the occurrence of deep venous thrombosis, 7, the occurrence of infection.

sources of bias [13]. Each aspects were measured as "low bias", "unclear bias" and "high bias" according to the Cochrane Handbook [13]. Kappa values were used to measure the degree of agreement between the 2 reviewers and were rated as follows: fair, 0.40 to 0.59; good, 0.60 to 0.74; and excellent, 0.75 or more [14].

Statistical analysis

A random-effects model was used for all comparisons because the dose and other factors were inconsistent across trials. For each included study, the weighted mean differences (WMD) at 95% confidence interval (CI) were calculated for continuous outcomes, while risk ratios (RR) at 95% CI were calculated for dichotomous outcomes. All analyses were performed using the Stata 12.0 software (Stata Corp., College Station, TX) and *P* value less than 0.05 was considered as statistically significant. Because of the limited number of included RCTs, publication bias was not detected [15].

Results

Search results and study characteristics

The literature search and selection process were shown in **Figure 1**. The initial search yielded 213 articles, and 132 papers were read when excluded the duplicates. Next stage, 126 papers were excluded according to the inclusion criteria. Finally, we included 6 clinical studies with 3258 patients for meta-analysis [11, 16-20]. Among the included studies, 4 of were RCTs [11, 16-18] and 2 of were non-RCTs [19, 20]. The detailed baseline characteristics of the included studies were presented in **Table 1**. There were 6 studies included in our meta-analysis. All of the articles were published in English, between the year of 2004 and 2017. The sample size ranged from 20 to 2638 (total =3258) and mean age ranged from 63 to 70. The follow up ranged from 3 day to 3 month. The dose of oral TXA ranged from 1 g to 1.95 g. And the dose of IV TXA ranged from 900 mg to 1 g.

Risk of bias among the included studies

The summary risk of bias for RCTs can be seen in **Figure 2.** All of RCTs describe the random sequence generation, allocation concealment and blind to participant and personnel [11, 16-18]. Only one study has high risk of bias for blind to outcome assessor [11]. And one study did not reported the sample size calculations prior to interventions and assessed as unclear bias [11]. The summary risk of bias of non-RCTs can be seen in **Table 2**. The MINORS score of the study of Irwin et al. [19]. and Lee et al. [20] was 18 and 24 respectively. The overall kappa value regarding the evaluation of risk of bias of included RCTs was 0.903, indicating an excellent degree of agreement between the 2 authors.

Results of meta-analysis

Need for transfusion: Four studies including 3338 patients tested the effect of oral TXA ver-

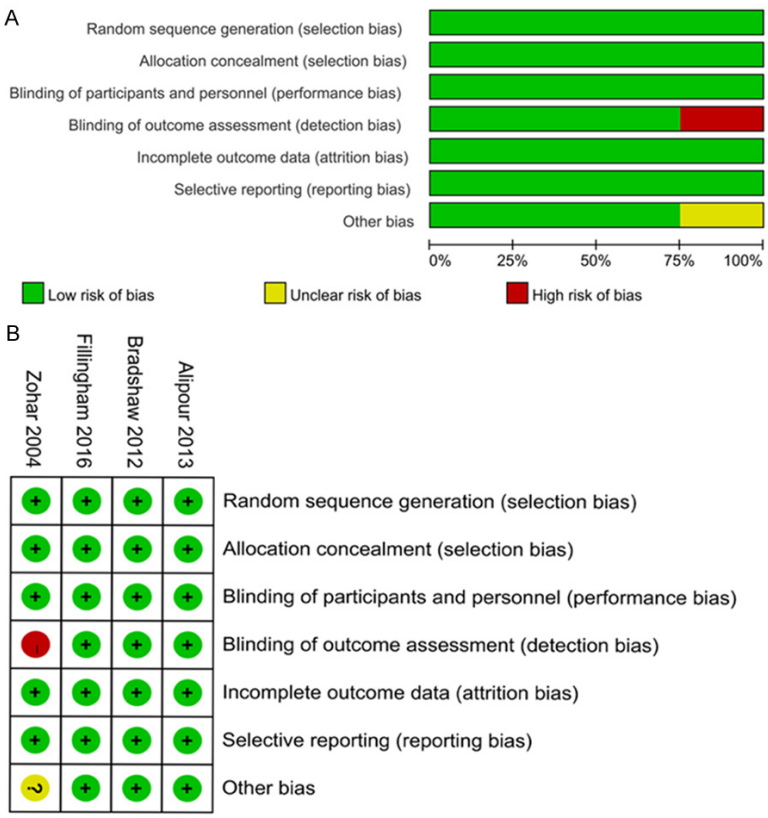

Figure 2. A: The risk of bias graph. B: Risk of bias of included in randomized controlled trials. +, no bias; -, bias; ?, bias unknown.

sus IV TXA on the need for transfusion. There was no significant difference between oral TXA with IV TXA in the need for transfusion (RR=0.77, 95% CI 0.44 to 1.33, P=0.340; I^2=8.5%) (**Figure 3**). Compared with control group, oral TXA was associated with less need for transfusion, however, the difference was not statistically significant (RR=0.52, 95% CI 0.17 to 1.57, P=0.243; I^2=66.3%, **Figure 3**).

Hemoglobin drop: Two studies including 3218 patients tested the effect of oral TXA versus IV TXA on the need for transfusion. Compared with IV TXA, oral TXA was associated with more hemoglobin drop (WMD=0.19, 95% CI 0.06 to 0.33, P=0.005; I^2=0.0%) (**Figure 4**). Compared with control group, oral TXA was associated with less hemoglobin drop (WMD=-1.01, 95% CI -1.48 to -0.53, P=0.000; I^2=27.0%, **Figure 4**).

Drain volume: One studies including 278 patients tested the effect of oral TXA versus IV TXA on the drain volume. Compared with IV TXA, no significant difference between oral TXA versus IV TXA in drain volume (WMD=0.19, 95% CI 0.06 to 0.33, P=0.815; I^2=0.0%) (**Figure 5**). Compared with control group, oral TXA was associated with less drain volume (WMD=-116.9, 95% CI -220.7 to -13.1, P=0.012; I^2=77.7%, **Figure 5**).

Length of hospital stay: Three studies including 299 patients tested the effect of oral TXA versus IV TXA on the length of hospital stay. Compared with IV TXA, no significant difference between oral TXA versus IV TXA in the length of hospital stay (WMD=0.00, 95% CI -0.41 to 0.41, P=1.000; I^2=0.0%) (**Figure 6**). Compared with control group, oral TXA was associated with less length of hospital stay (WMD=-1.08, 95% CI -1.57 to -0.60, P=0.000; I^2=0.0%, **Figure 6**).

Complications

Complications were reported in 2 RCTs, in which all patients received oral TXA or TXA group. The complications were related to DVT or infection. Fillingham et al. [18] reported 1 patient in control group underwent DVT and Bradshaw et al. [17] reported 1 patients in control group underwent infection.

Discussion

This is the first systematic review and meta-analysis that comparing oral TXA versus IV TXA and control group for reducing blood loss after TJA. The pooled results showed that oral TXA is effective and safe for reducing blood loss in TJA. However, there was no significant difference between oral TXA versus IV TXA in TJA. The level of evidence, which was undermined by heterogeneity and/or study design limitations, was low, indicating that the degree of benefit must be studied although the benefit is conclusive. The heterogeneity main comes fr-

Table 2. The Minors quality score of the non-RCTs

First Author, Year	Minors Scale												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
Irwin 2013	2	1	1	2	0	2	2	0	2	2	2	2	18
Lee 2017	2	2	2	2	2	2	2	2	2	2	2	2	24

Numbers 1-12 in heading signified: 1, a clearly stated aim; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to the aim of the study; 5, unbiased assessment of the study endpoint; 6, follow-up period appropriate to the aim of the study; 7, loss to follow-up less than 5%; 8, prospective calculation of the study size; 9, an adequate control group; 10, contemporary groups; 11, baseline equivalence of groups; and 12, adequate statistical analyses.

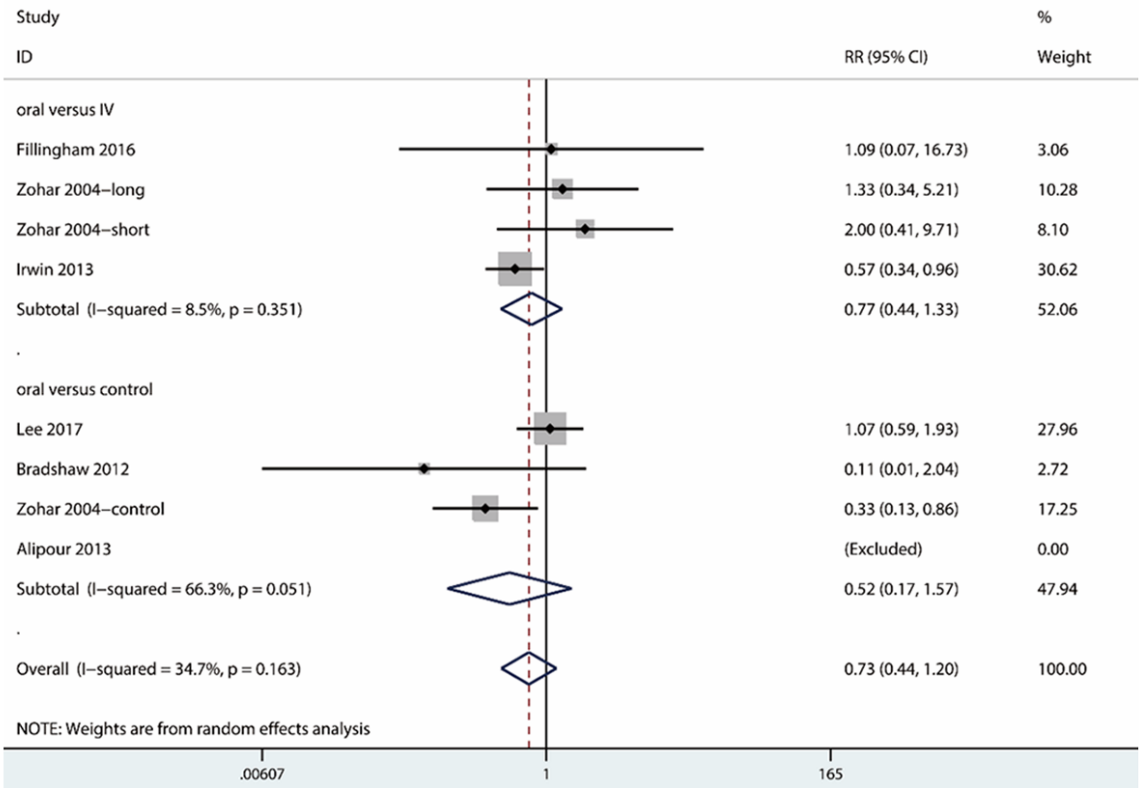

Figure 3. Forest plots of the included studies comparing need for transfusion between the two groups.

om the joint surgeries type and different dose of TXA. The subgroup analysis was not performed since the limited included number of studies.

A major highlight of current analysis is the comprehensive and systematic search with strict statistical calculations. IV TXA can decrease blood loss without increasing the occurrence of DVT a has accumulated a large body of evidence [8, 21]. However, limited research has been done on the orthopedic applications of the less expensive oral form of the TXA. Current meta-analysis indicated that oral TXA has comparable effect with IV TXA and was superior than control group in reducing blood loss after TJA. The most efficacious timing and dose protocol for intravenous TXA and oral TXA has not yet been clearly determined. For The more common IV TXA dose appears to be around 10 mg/kg, and this has been shown to be both effective and to maintain the minimum therapeutic level for approximately 3 hours [22]. Oral TXA dose ranging from 1 g to 1.95 g and the time interval always from 1 to 2 h before operation. The TXA bioavailability was to be around 34% and elimination in blood occurred mostly within 8 hours. Based on serum and pharmacokinetic studies, a 2-gram dose of oral TXA takes approximately 2 hours to achieve therapeutic

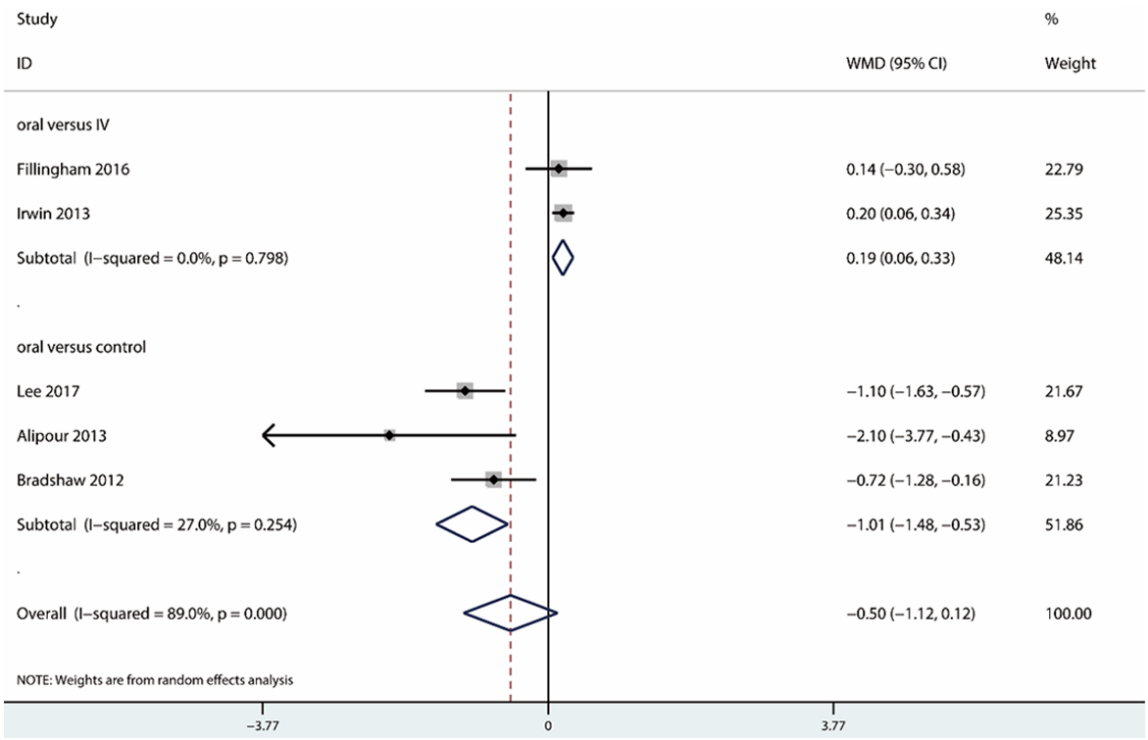

Figure 4. Forest plots of the included studies comparing hemoglobin drop between the two groups.

serum concentrations [23]. Inadequate dosing to reach the therapeutic threshold would account for Zohar et al. [11] showing a trend toward higher rates of transfusion for oral TXA compared to IV TXA groups and the lack of statistical significance in hematocrit on postoperative day 4 compared to placebo. Because oral and IV TXA are both systemically delivered drugs, oral TXA should be avoided in patients with contraindications to IV TXA such as renal impairment.

Although intravenous form has been shown to be safe and effective, there is a real risk anaphylactic shock [9]. So far, the allergic reactions, gastrointestinal disturbance, skin reactions and impaired color vision were reported for the oral form with milder and slower onset [24, 25]. Present meta-analysis indicated that oral TXA has no effect on the postoperative complications. The occurrence of infection and DVT was too small and thus meta-analysis was not proper to performed. Because oral TXA is cheaper than IV TXA, a transition to oral TXA would deliver even greater cost savings to the health care system. Fillingham et al. [18] reported that the oral TXA dosage cost $14 compared with $47-$108 depending on the availability of the generic IV formulation. Oral TXA seems to be a better choice than intravenous form, while provided similar drug efficacies with easily accessible and less costing than IV TXA.

Our meta-analysis also has several potential limitations: (1) patients treatment with different dose of TXA and different time to oral TXA preoperatively; (2) there was marked heterogeneity among the need for transfusion and hemoglobin drop between oral TXA with control group, reflecting the inconsistent benefit patients acquired from oral TXA, although these analyses were performed using a random effects model; (3) the follow-up in the included studies was limited after surgery. Thus, some adverse events may be underestimated. The occurrence of deep venous thrombosis and infection is too little to draw a final conclusion.

Conclusions

In conclusion, the present meta-analysis demonstrated Oral TXA has comparable hemostasis effects with IV TXA, and may reduce the costs for patients prepared for TJA. However, the limited quality and number of the included

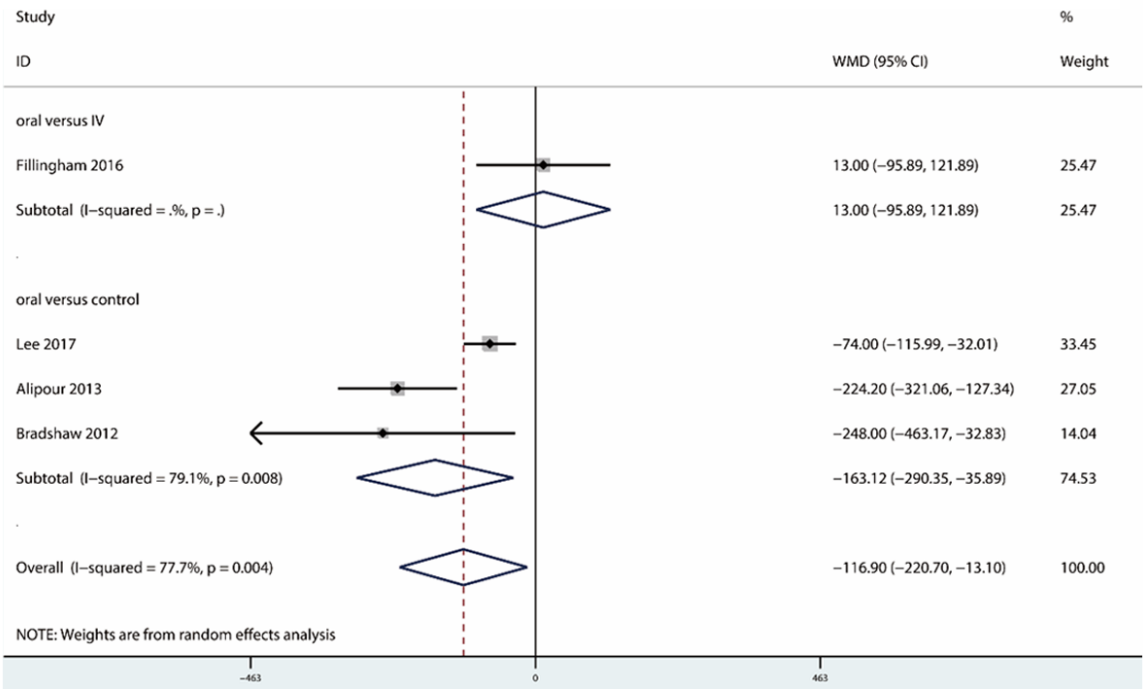

Figure 5. Forest plots of the included studies comparing the drain loss between the two groups.

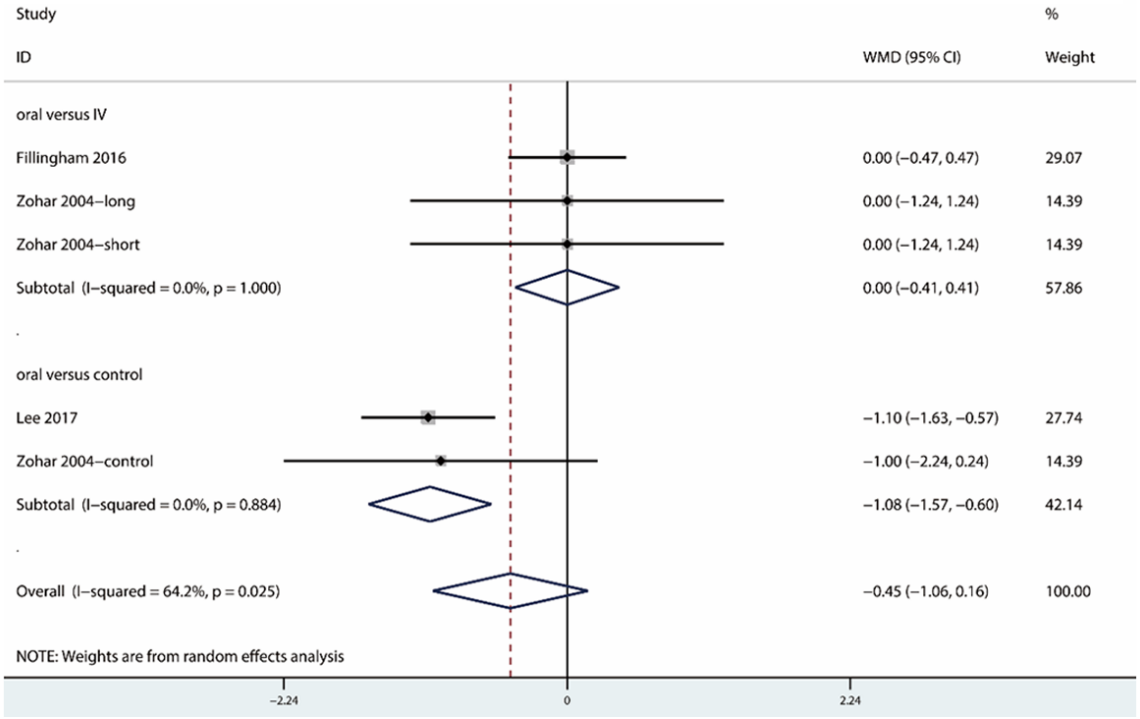

Figure 6. Forest plots of the included studies comparing the length of hospital stay between the two groups.

studies, more high quality and multi center RCTs are still need to recommend for routine administration.

Disclosure of conflict of interest

None.

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References

[1] Dong CC, Dong SL and He FC. Comparison of adductor canal block and femoral nerve block for postoperative pain in total knee arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore) 2016; 95: e2983.

[2] Kurtz S, Ong K, Lau E, Mowat F and Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89: 780-785.

[3] Gascon P, Zoumbos NC and Young NS. Immunologic abnormalities in patients receiving multiple blood transfusions. Ann Intern Med 1984; 100: 173-177.

[4] Heddle NM, Klama LN, Griffith L, Roberts R, Shukla G and Kelton JG. A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusions. Transfusion 1993; 33: 794-797.

[5] Li J, Li HB, Zhai XC, Qin L, Jiang XQ and Zhang ZH. Topical use of topical fibrin sealant can reduce the need for transfusion, total blood loss and the volume of drainage in total knee and hip arthroplasty: a systematic review and meta-analysis of 1489 patients. Int J Surg 2016; 36: 127-137.

[6] Sukur E, Ozturkmen Y, Akman YE, Senel A and Azboy I. The effect of tourniquet and knee position during wound closure after total knee arthroplasty on early recovery of range of motion: a prospective, randomized study. Arch Orthop Trauma Surg 2016; 136: 1773-1780.

[7] Lin C, Qi Y, Jie L, Li HB, Zhao XC, Qin L, Jiang XQ, Zhang ZH and Ma L. Is combined topical with intravenous tranexamic acid superior than topical, intravenous tranexamic acid alone and control groups for blood loss controlling after total knee arthroplasty: a meta-analysis. Medicine (Baltimore) 2016; 95: e5344.

[8] Fu DJ, Chen C, Guo L and Yang L. Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. Chin J Traumatol 2013; 16: 67-76.

[9] Lucas-Polomeni MM, Delaval Y, Menestret P, Delaval P and Ecoffey C. [A case of anaphylactic shock with tranexamique acid (Exacyl)]. Ann Fr Anesth Reanim 2004; 23: 607-609.

[10] Klak M, Anakkala N, Wang W, Lange S, Jonsson IM, Tarkowski A and Jin T. Tranexamic acid, an inhibitor of plasminogen activation, aggravates staphylococcal septic arthritis and sepsis. Scand J Infect Dis 2010; 42: 351-358.

[11] Zohar E, Ellis M, Ifrach N, Stern A, Sapir O and Fredman B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg 2004; 99: 1679-1683, table of contents.

[12] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.

[13] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011; [http://www.cochrane-handbook.org].

[14] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L and Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

[15] Song F, Eastwood AJ, Gilbody S, Duley L and Sutton AJ. Publication and related biases. Health Technol Assess 2000; 4: 1-115.

[16] Alipour M, Tabari M, Keramati M, Zarmehri AM and Makhmalbaf H. Effectiveness of oral Tranexamic acid administration on blood loss after knee artroplasty: a randomized clinical trial. Transfus Apher Sci 2013; 49: 574-577.

[17] Bradshaw AR, Monoghan J and Campbell D. Oral tranexamic acid reduces blood loss in total knee replacement arthroplasty. Current Orthopaedic Practice 2012; 23: 209-212.

[18] Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL and Della Valle CJ. The James A. Rand Young Investigator's Award: a randomized controlled trial of oral and intravenous tranexamic acid in total knee arthroplasty: the same efficacy at lower cost? J Arthroplasty 2016; 31: 26-30.

[19] Irwin A, Khan SK, Jameson SS, Tate RC, Copeland C and Reed MR. Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: results of 3000 procedures. Bone Joint J 2013; 95-b: 1556-1561.

[20] Lee QJ, Chang WY and Wong YC. Blood-sparing efficacy of oral tranexamic acid in primary total hip arthroplasty. J Arthroplasty 2017; 32: 139-142.

[21] Wu Q, Zhang HA, Liu SL, Meng T, Zhou X and Wang P. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. Eur J Orthop Surg Traumatol 2015; 25: 525-541.

[22] Benoni G and Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. J Bone Joint Surg Br 1996; 78: 434-440.

[23] Pilbrant A, Schannong M and Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol 1981; 20: 65-72.

[24] Kaku Y, Ito T, Kudo K, Kido-Nakahara M, Nakahara T, Moroi Y and Furue M. Generalized fixed drug eruption induced by tranexamic acid. Eur J Dermatol 2014; 24: 408-409.

[25] Imbesi S, Nettis E, Minciullo PL, Di Leo E, Saija A, Vacca A and Gangemi S. Hypersensitivity to tranexamic acid: a wide spectrum of adverse reactions. Pharm World Sci 2010; 32: 416-419.