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Transfusions and cost-benefit of oral versus intravenous tranexamic acid in primary total hip arthroplasty

A meta-analysis of randomized controlled trials

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Abstract

Background: The purpose of this study was to assess the cost benefit and transfusions of oral and IV tranexamic acid (TXA) in primary total hip arthroplasty (THA).

Methods: PubMed, Embase, Web of Science, and the Cochrane Library were systematically searched for randomized controlled trials (RCTs) comparing oral and IV TXA in primary THA. Primary outcomes were total blood loss, maximum hemoglobin drop, transfusion requirements, and cost benefit. Secondary outcomes were length of stay, deep venous thrombosis (DVT) and/or pulmonary embolism (PE).

Results: Four independent RCTs were included involving 391 patients. There was no difference in the total blood loss ($P = .99$), maximum hemoglobin drop ($P = .73$), and the length of stay ($P = .95$) between the 2 groups. Transfusion requirements ($P = .97$) were similar. The total mean cost was the US $75.41 in oral TXA group and the US $580.83 in IV TXA group. The incidence of DVT ($P = .3$) did not differ significantly between the 2 groups, and no PE was reported in all studies.

Conclusion: Oral TXA shows similar efficacy and safety as IV TXA in reducing total blood loss, maximum hemoglobin drop and transfusion requirements in primary THA. However, oral TXA may be more cost-benefit than IV TXA.

Level of Evidence: Level I, therapeutic study.

Abbreviations: CI = confidence interval, DVT = deep vein thrombosis, IV = intravenous, MD = mean difference, PE = pulmonary embolisms, RCTs = randomized controlled trials, TKA = total knee arthroplasty, TXA = tranexamic acid.

Keywords: intravenous, oral, total hip arthroplasty, tranexamic acid

1. Background

Primary total hip arthroplasty (THA) is considered to be potentially advantageous for patients who have the severe hip disease.[1–3] However, as previously reported, the total blood loss associated with has been reported ranges from 700 to 2000 mL, and the incidence of transfusion requirements ranged from 16% to 38%.[4–7] Minimizing the risk of blood loss has always been a goal for surgeons because perioperative anemia is potentially associated with increased morbidity and costs.[8–10]

As a type of antifibrinolytic agent, tranexamic acid (TXA) is a synthetic amino acid that can also prevent plasminogen activation and delay fibrinolysis, thereby stabilizing the clot.[6,11,12] TXA could be performed intravenously[13,14] topically[15,16] and orally.[17,18] Evidence from the past decades has confirmed that IV or topical TXA can effectively reduce blood loss, decrease knee swelling, and less postoperative blood transfusion requirements in most studies.[6,11,13,15–17] Although multiple studies over the recent years have evaluated different possible alternatives for the route of application, the most suitable route of administration, dosage, and duration were still controversial.[11,12,14]

Recently, oral TXA has been demonstrated that it can be used as a simple and cost-benefit way to minimize blood loss, without increasing the risk of thrombotic events in THA.[18,19] However, none of the studies assessed all available level I trials (defined as prospective randomized trials)[20] to evaluate the effectiveness, risk of cost benefits, and complications of oral TXA in THA. Therefore, the purpose of our study is to assess the highest evidence-based (level I) studies in order to compare total blood loss, maximum hemoglobin drop, transfusion requirements, length of stay, deep venous thrombosis (DVT), pulmonary embolism (PE), and cost benefit with the use of oral TXA in THA.

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2. Methods

The method used in this meta-analysis is based on the recommended PRISMA checklist guideline.[21] Ethical approval is unnecessary because it is a review of previously published articles and does not involve any processing of individual patient data.

2.1. Search strategy

These electronic databases were queried by PubMed, Embase, Web of Science, the Cochrane Library related reporting databases until March 2018, using the keywords "Tranexamic acid," "TXA," "TA," "total hip arthroplasty," "total hip replacement," "THA," and "THR."

2.2. Inclusion criteria

The meta-analysis met the following criteria: PICOS (population, intervention, comparator, outcome, study design). Population: patients were performed for primary THA; Intervention: The intervention was oral TXA; Comparison: the comparator was IV TXA; Outcomes: the outcomes were total blood loss, maximum hemoglobin drop, transfusion requirements, mean cost, the length of stay, DVT and/or PE. Study design: the study design was performed by randomized controlled trials (RCTs). We then excluded studies that were performed in animals, non-English, or single case reports or abstract. Two reviewers independently evaluated the title and abstract to find potential studies, and finally obtained eligible research based on the full text. When there was a disagreement, it can be resolved by discussion or by consulting a third reviewer.

2.3. Assessment of methodological quality

Following the criteria in the Cochrane Handbook for Systematic Reviews of methodological quality and the risk of bias, 2 reviewers independently assessed study quality, including assessment of sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias. Each study was judged as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (unclear risk of bias).[22]

2.4. Outcome measures

We compared oral TXA and IV TXA in terms of hemostatic effect and safety in THA. Primary outcomes were the total blood loss, maximum hemoglobin drop, transfusion requirements, and cost benefit. Secondary outcomes were length of stay, DVT, and/or PE.

2.5. Data extraction

The following data were extracted from the included trials: author, published date, age, gender, the number of participants, TXA interventions, DVT prophylaxis, DVT screening, and transfusion protocol. All data were independently extracted by reviewers from eligible studies in the predefined data fields.

2.6. Data synthesis

Statistical analysis was performed using RevMan 5 software (version 5.3, Cochrane Collaboration). Continuous data were calculated by mean difference (MD) and 95% confidence interval (CI), such as blood loss, maximum hemoglobin drop, and length of stay. Dichotomous data were calculated by risk ratio (RR) and 95% CI, such as transfusion requirements, wound complications, DVT, and PE. Chi-squared test and I^2 statistic was used to assess statistical heterogeneity. If the chi-squared test > 0.1 or the $I^2 < 50\%$, the fixed-effects model was used. Otherwise, a random-effect model was chosen. Publication bias was tested using blood loss, and if the funnel plot was symmetric, there was a low potential for publication bias, or vice-versa.

3. Results

Figure 1 summarizes the identification of studies. A total of 226 studies were screened out through initial searches. After reading the titles, abstracts and full text, 4 independent RCTs[18,19,23,24] finally satisfied the predefined inclusion criteria in this meta-analysis. A total of 391 patients were included in the meta-analysis: 194 patients in the oral TXA group and 197 patients in the IV TXA group. All included studies were published in English between 2017 and 2018. The sample sizes included in these studies ranged from 34 to 60, and the average age ranged from 55.7 to 67.60 years. All studies reported DVT prophylaxis such as warfarin,[18] Low molecular weight heparin and rivaroxaban,[19,23,24] Doppler ultrasound was used screening for DVT. All studies have similar standards for blood transfusions (Hb < 7 g/dL or has symptoms of anemia). Tables 1 and 2 summarize the baseline characteristics of the included studies.

One study reported that the randomization method was performed using the random number algorithm,[18] and one study was conducted using sealed envelopes[23] and 2 studies were performed using computer-generated list.[19,24] There was a clear blind methodology in all studies. Figure 2 summarizes the methodological quality of the included studies. The plots of blood loss were symmetrical generally, suggesting considerable control of publication bias (Fig. 3).

3.1. Total blood loss

Three studies[18,19,24] reported data on total blood loss (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated that the blood loss was similar between the 2 groups (MD 0.31, 95% CI −57.93–58.56, $P = .99$). The fixed model was used ($P = .84$, $I^2 = 0\%$) (Table 3).

3.2. Maximum hemoglobin drop

Three studies[18,19,24] reported data on maximum hemoglobin drop (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated no significant difference between the 2 groups (MD, 0.04; 95% CI, –0.17–0.24; $P = .73$). The fixed model was used ($P = .75$, $I^2 = 0\%$) (Table 3).

3.3. Transfusion requirements

Four studies[18,19,23,24] reported data on transfusion requirements. Transfusions requirements were reported in 8 of 194 patients (4.12%) in the oral TXA group, compared with 8 of 197 patients (4.06%) in the TXA group. Pooling the data demonstrated that the transfusion requirements were similar between the 2 groups (RR, 1.02; 95% CI, 0.39 to 2.63; $P = .97$). The fixed model was used ($P = .47$, $I^2 = 0\%$) (Table 3).

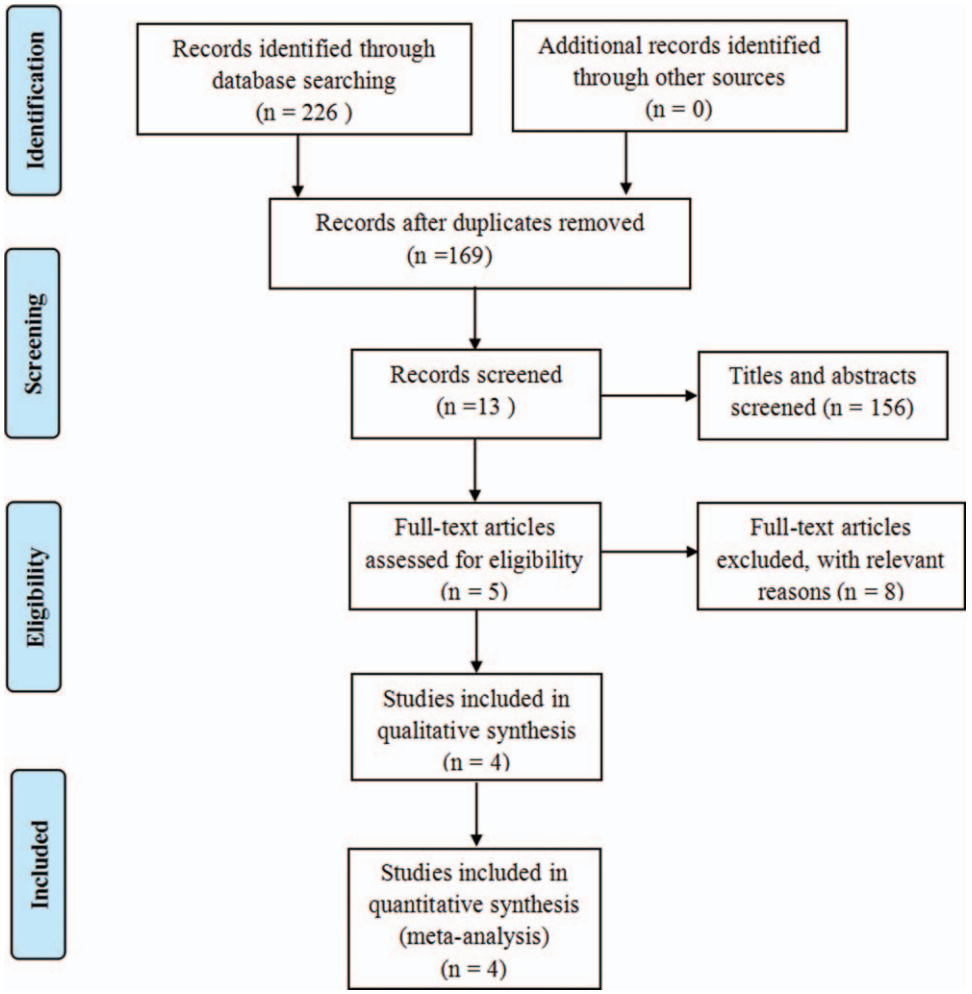

Figure 1. Flowchart of inclusion and exclusion for eligible studies.

Table 1

Characteristics of included trials.

Authors	Date	Age, years		Participants		Gender (F/M)		BMI, kg/m^2		Preoperative Hb, g/dL	
		Oral TXA	IV TXA	Oral TXA	IV TXA	Oral TXA	IV TXA	Oral TXA	IV TXA	Oral TXA	IV TXA
Kayupov et al[18]	2017	60±10	55±12	40	43	20/20	23/20	29±5	31±6	13.6±1.3	13.8±1.5
Luo et al[19]	218	67.60±10.38	66.98±8.57	60	60	28/32	27/33	24.59±3.09	24.51±3.87	13.85±1.01	13.71±0.75
Cao et al[23]	2018	55.7	55.7	54	54	23/31	20/34	23	23.6	13.23	13.31
Zhao et al[24]	2018	60.47±10.35	59.50±1.42	40	40	42/18	43/17	22.24±1.91	22.46±1.89	13.2±1.1	13.5±1.8

BMI = body mass index, F = female, Hb = hemoglobin, IV = intravenous, M = male, TXA = tranexamic acid.

Table 2

Characteristics of included trials.

Authors	Surgical approach	TXA interventions		DVT prophylaxis	DVT screening	Transfusion protocol
		Oral TXA	IV TXA			
Kayupov et al[18]	Posterior approach	1950 mg TXA approximately 2 h before the incision	1 g TXA before wound closure	Warfarin	Doppler ultrasound	Hb<7 g/dL or has symptoms of anemia
Luo et al[19]	Posterolateral approach	2 g TXA approximately 2 h before the incision	20 mg/kg TXA 5 minutes before the skin incision	LMWH Rivaroxaban	Doppler ultrasound	Hb<7 g/dL or 7–10 g/dL with symptoms of anemia
Cao et al[23]	Posterolateral approach	20 mg/kg IV TXA 5–10 min before skin incision, and received 2 g of oral TXA 4 h, 10 h, 16 h after surgery	20 mg/kg IV TXA 5–10 min before skin incision, and received 1 g TXA 6 h, 12 h, 18 h after surgery	LMWH Rivaroxaban	Doppler ultrasound	Hb<7 g/dL or 7–8 g/dL with symptoms of anemia
Zhao et al[24]	Direct anterior approach	20 mg/kg at 2 h before and 3 h after surgery	15 mg/kg at 10 minutes before and 3 h after surgery	LMWH Rivaroxaban	Doppler ultrasound	Hb<7 g/dL or has symptoms of anemia

DVT = deep venous thrombosis, Hb = hemoglobin, IV = intravenous, LMWH = low molecular weight heparin, TXA = tranexamic acid.

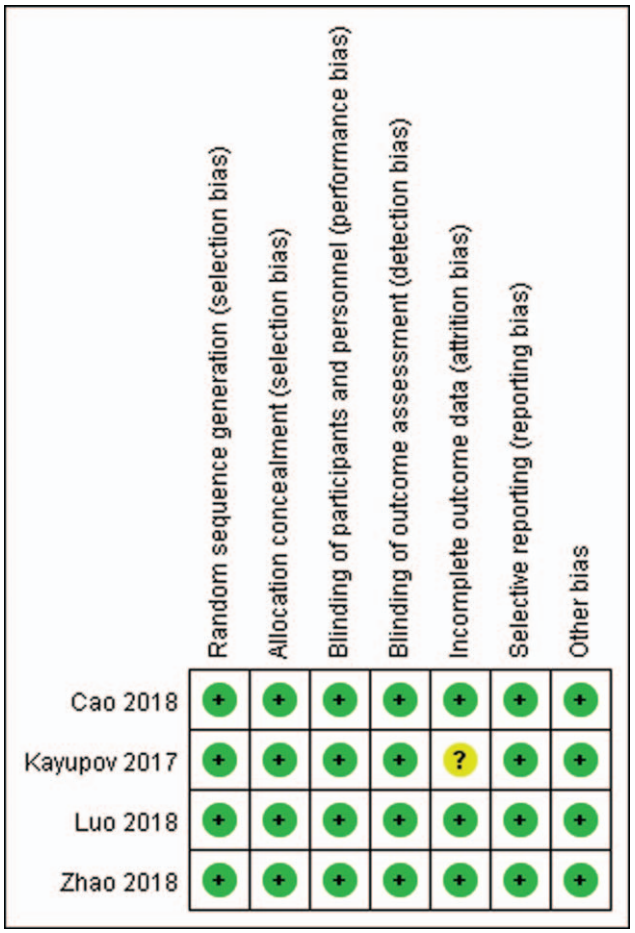

Figure 2. Risk of bias summary.

3.4. Length of stay

Three studies[18,19,24] reported data on length of stay (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated that the length of stay was similar between the 2 groups (MD, −0.00; 95% CI, −0.03–0.03; $P = .95$). The fixed model was used ($P = .74$, $I^2 = 0\%$) (Table 3).

3.5. DVT and PE

Four studies[18,19,23,24] reported data on DVT. DVT were reported in 0 of 194 patients (0%) in the oral TXA group, compared with 2 of 197 patients (1.02%) in the TXA group, no difference was found between the 2 groups ($P = .30$). No PE was reported in all studies (Table 3).

3.6. Cost-benefits analysis

Two studies[23,24] reported data on cost benefits. After all data were compiled for THA, the total average cost was US $75.41 in oral TXA and US $580.83 in IV TXA (see Table 4). Specifically, of the studies that provided specific data for oral TXA, the cost ranged from US $70.56 to $80.26, and the study providing specific data for IV TXA reported from US $489.4 to $672.26. Thus, patients in the oral TXA group had an average total cost savings of US $505.42 compared to patients in the IV TXA.

4. Discussion

In light of new healthcare policies, it is crucial to save medical costs without increasing the incidence of complications. Therefore, we hope to analyze the level I trial that have evaluated the use of oral TXA from the highest possible evidence in primary THA. This meta-analysis demonstrated that, based on the available evidence, the oral and IV routes of administration of TXA in primary THA were associated with similar total blood loss, maximum hemoglobin drop, transfusion requirements,

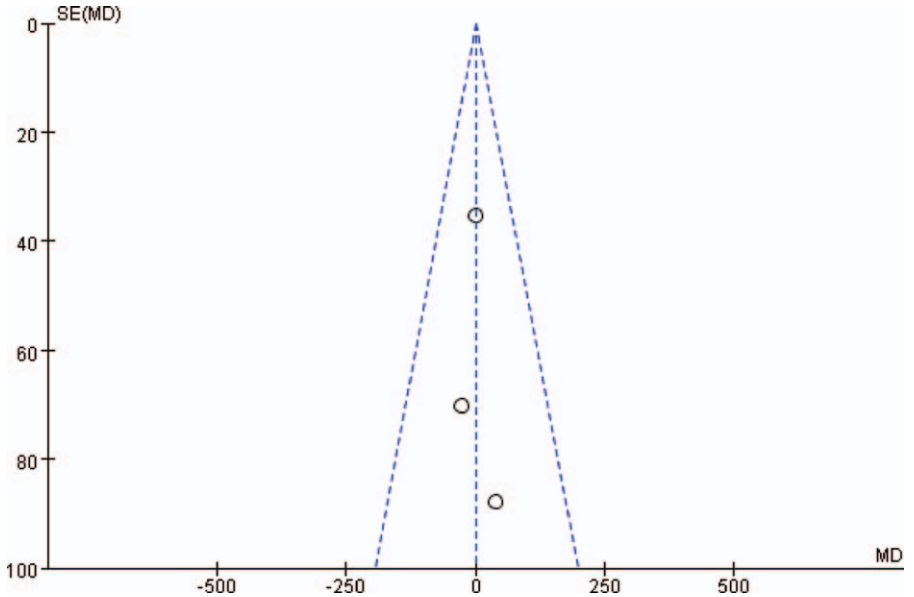

Figure 3. Funnel plot of total blood loss indicates minimal publication bias.

Table 3

Clinical results of meta-analysis.

Clinical results	Studies	Participants			Incidence				Model
		Total	Oral TXA	IV TXA	*P*	MD/RR	95% CI	Heterogeneity *P* (I^2)	
Total blood loss	3	283	140	143	.99	0.31	−57.93 to 58.56	.84 (0%)	Fixed
Maximum hemoglobin drop	3	283	140	143	.73	0.04	−0.17 to 0.24	.75 (0%)	Fixed
Transfusion requirements	4	391	194	197	.97	1.02	0.39 to 2.63	.47 (0%)	Fixed
Length of stay	3	283	140	143	.95	-0.00	−0.03 to 0.03	.74 (0%)	Fixed
DVT	4	391	194	197	.30	0.20	0.01 to 4.07	n.s.	Fixed
PE	4	391	194	197	n.s.	n.s.	n.s.	n.s.	n.s.

CI = confidence interval, DVT = deep venous thrombosis, IV = intravenous, MD = mean difference, n.s. = not state, PE = pulmonary embolism, RR = risk ratio, TXA = tranexamic acid.

Table 4

Cost-benefit analysis.

Authors	Surgery	Total cost		Cost savings	Mean cost		Average total cost savings	Value
		Oral TXA	IV TXA		Oral TXA	IV TXA		
Luo et al[19]	THA	$70.56 (¥ 480)	$489.40 (¥ 3329.28)	$418.84				Positive
Zhao et al[24]	THA	$80.26 (¥ 546)	$672.26 (¥ 4573.2)	$592	$75.4	$580.83	$505.42	Positive

IV = intravenous, THA = total hip arthroplasty, TXA = tranexamic acid.

Costs were calculated in Chinese yuan (¥): 1¥ = 0.147 United States dollars (USD, $).

length of stay and incidence of DVT, and/or PE. However, the oral route is associated with a significantly smaller cost of TXA.

Similar studies evaluating the effectiveness of oral TXA have also been reported in another surgical field. Among these, a randomized rhinoplasty clinical trial[25] demonstrated an average reduction in the bleeding volume of 50 mL in oral TXA group than with control group, without any significant adverse events. Other studies in the obstetrics gynecology[26] and urology surgery[27] literature have also evaluated the use of oral TXA or did not receive TXA, finding a difference in reducing blood loss and improving pain.

The use of tranexamic acid in total hip arthroplasty has been widely accepted as part of routine practice because it has been shown to provide clinical benefit.[5,12–16] However, the optimal administration route of TXA was unclear. An updated meta-analysis[28] included 18 RCTs comparing patients who received IV or topical TXA in primary THA or TKA indicated that both IV and topical TXA are similar benefits in reducing blood loss and transfusion rates. Zhao et al[24] reported that patients treated with oral or intravenous TXA showed similar efficacy for reducing hemoglobin drop, blood loss, and transfusion rate by the direct anterior approach. Similarly, Kayupov et al[18] prospectively evaluated 89 THAs randomized to receive orally 1.95 g TXA or intravenously 1 g TXA. They found that oral TXA provides equivalent reductions in blood loss compared with the IV formulation. In the current study, our results were also similar to those previously reported[17,18,24] The total blood loss, maximum hemoglobin drop, and transfusion requirements were not the significant difference between the oral TXA and IV TXA routes.

Our results suggest that oral TXA, the total average cost was the US $75.41, may be much more cost benefit than IV TXA, the total average cost was US $580.83, for achieving similar efficacy in reducing blood loss and transfusion requirements. Consequently, patients in the oral TXA group had an average cost savings of the US $505.42 compared to patients in the IV TXA group. Gillette et al[29] retrospectively reviewed 1018 patients, finding that a mean savings of $879 with TXA use when estimating total hospital cost for patients in total joint arthroplasty. As Luo et al[19] reported the lowest cost of TXA in oral TXA group ($70.56)), compared with IV TXA group ($520.38). The use of oral was relatively more cost benefit compared with the additional cost associated with IV TXA without sacrificing efficacy or safety.

The effect of TXA on thromboembolic events in TKA is unclear. It is well known that TXA has been successfully used in clinical practice for the past decades, and it has not been clinically proven to increase the risk of DVT and/or PE.[6,14,18,23] Alshryda et al[30] even believe that TXA can reduce the risk of thrombosis by reducing the transfusion requirement for thrombotic interventions. In the current study, DVT was reported in 0 of 194 patients in the oral TXA group, compared with 2 of 197 patients in the TXA group. No statistical difference in the rate of DVT ($P = .30$) between the 2 groups. No PE was reported in all studies. These results were consistent with other trials. Theoretically, many clinicians are hesitant to use TXA intravenously because of concerns about the risk of thromboembolic complications after systemic administration. Therefore, there is an increasing interest in the prevention of THA bleeding by oral TXA.

A recent meta-analysis by Zhang et al[17] evaluated the use of oral versus IV TXA in total knee and hip arthroplasty. The authors enrolled 3 studies[31–33] with TKA, 1 study[18] with THA, and 1 study[34] with THA and TKA. It also included a retrospective study of level III.[34] As they included THA and THA in their analysis and did not account for cost or difference in the type of surgery, we were unable to reach a meaningful conclusion. Therefore, we believe that more stringent criteria need to be applied in the meta-analysis to determine the benefits of oral or IV TXA. The meta-analysis offers several advantages over previously published meta-analysis[17] because it includes recently published RCTs; more stringent inclusion criteria have also been adopted. Second, this is the first independent study on the effectiveness and safety of oral or IV TXA only in the THA.

Third, more results have been analyzed, such as the benefits of TXA, and our study found that oral TXA is more likely to give patients optimal TXA costs.

Although the meta-analysis included well-designed RCTs, our study has some limitations. First, our selection criteria were used to choose only the studies with the best evidence, and then nonlevel I studies were excluded, which may potentially ignore other high-quality case series; Second, sample sizes of the most included studies were calculated by the reduction in hemoglobin, it may result in insufficient sample size to detect other outcomes, such as blood loss, transfusion requirements and thrombosis events. Third, publication bias may exist because of only English language publications. However, the plot of blood loss was symmetrical generally, suggesting considerable control of publication bias. Hence, we believe the factor would not affect our results.

5. Conclusions

The available evidence demonstrates that oral and IV of TXA administration shows similar benefits in total blood loss, maximum hemoglobin drop, transfusion requirements and, length of stay without sacrificing safety in the primary THA. However, oral TXA may be more cost-benefit than IV TXA.

Author contributions

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References

[1] Rykov K, Reininga IHF, Sietsma MS, et al. Posterolateral vs direct anterior approach in total hip arthroplasty (POLADA Trial): a randomized controlled trial to assess differences in serum markers. J Arthroplasty 2017;32:3652–8.
[2] Nishio S, Fukunishi S, Fukui T, et al. Comparison of continuous femoral nerve block with and without combined sciatic nerve block after total hip arthroplasty: a prospective randomized study. Orthop Rev (Pavia) 2017;9:47–50.
[3] Archibeck MJ, Tripuraneni KR, Carothers JT, et al. Prospective, randomized, surgeon-blinded comparison of standard magnification assumption vs magnification marker usage for preoperative templating in total hip arthroplasty. J Arthroplasty 2017;32:3061–4.
[4] Gibon E, Courpied JP, Hamadouche M. Total joint replacement and blood loss: what is the best equation? Int Orthop 2013;37:735–9.
[5] Hallstrom B, Singal B, Cowen ME, et al. (2016) The michigan experience with safety and effectiveness of tranexamic aciduse in hip and knee arthroplasty. J Bone Joint Surg Am 2013;98:1646–55.
[6] Zeng Y, Shen B, Yang J, et al. 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.
[7] Kim C, Park SSH, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. J Blood Med 2015;6:239–44.
[8] Henry DA, Carless PA, Moxey AJ, et al. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2002;2:CD003602.
[9] Paul JE, Ling E, Lalonde C, et al. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: a meta-analysis of randomized controlled trials. Can J Anaesth 2007;54:799–810.
[10] Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. New Engl J Med 1996;334:1685–90.
[11] Wang CD, Kang PD, Ma J, et al. 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.
[12] North WT, Mehran N, Davis JJ, et al. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind, randomized controlled trial. J Arthroplasty 2016;31:1022–6.
[13] Wei W, Wei BF. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty 2014;29:2113–6.
[14] Xie J, Hu Q, Ma J, et al. Multiple boluses of intravenous tranexamic acid to reduce hidden blood loss and the inflammatory response following enhanced-recovery primary total hip arthroplasty: a randomised clinical trial. Bone Joint J 2017;99B:1442–9.
[15] Yue C, Kang PD, Yang PQ, et al. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty 2014;29:2452–6.
[16] Nielsen CS, Jans O, Orsnes T, et al. Combined intra-articular and intravenous tranexamic acid reduces blood loss in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am 2016;98:835–41.
[17] Zhang LKMJ, Kuang MJ, Zhao J, et al. Comparison of oral versus intravenous application of tranexamic acid in total knee and hip arthroplasty: a systematic review and meta-analysis. Int J Surg 2017;45:77–84.
[18] Kayupov EFY, Okroj K, Plummer DR, 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.
[19] Luo ZYWH, Wang D, Zhou K, et al. Oral vs Intravenous vs topical tranexamic acid in primary hip arthroplasty: a prospective, randomized, double-blind, controlled study. J Arthroplasty 2018;33:786–93.
[20] Marx RG, Wilson SM, Swiontkowski MF. Updating the assignment of levels of evidence. J Bone Joint Surg Am 2015;97A:1–2.
[21] Moher D, Shamseer L, Clarke M, et al. PRISMA-P GroupPreferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Rev Esp Nutr Hum Die 2016;20:148–60.
[22] Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;J 343:d5928.
[23] Cao G, Huang Z, Xie J, et al. The effect of oral versus intravenous tranexamic acid in reducing blood loss after primary total hip arthroplasty: a randomized clinical trial. Thromb Res 2018;164:48–53.
[24] Zhao H, Xiang M, Xia Y, et al. Efficacy of oral tranexamic acid on blood loss in primary total hip arthroplasty using a direct anterior approach: a prospective randomized controlled trial. Int Orthop 2018;42:2535–42.
[25] Eftekharian HR, Rajabzadeh Z. The efficacy of preoperative oral tranexamic acid on intraoperative bleeding during rhinoplasty. J Craniofac Surg 2016;27:97–100.
[26] Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol 2010;116:865–75.
[27] Kumar S, Randhawa MS, Ganesamoni R, et al. Tranexamic acid reduces blood loss during percutaneous nephrolithotomy: a prospective randomized controlled study. J Urology 2013;189:1757–61.
[28] Xie JW, Hu QS, Huang Q, et al. Comparison of intravenous versus topical tranexamic acid in primary total hip and knee arthroplasty: an updated meta-analysis. Thromb Res 2017;153:28–36.

[29] Gillette BP, Kremers HM, Duncan CM, et al. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. J Arthroplasty 2013;28:137–9.
[30] Alshryda S, Sukeik M, Sarda P, et al. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J 2014;96B:1005–15.
[31] Fillingham YAKE, Plummer DR, Moric M, et al. 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.
[32] Zohar E, Ellis M, Ifrach N, et al. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg 2004;99:1679–83.
[33] Yuan XW, Li B, Wang QJ, et al. Comparison of 3 routes of administration of tranexamic acid on primary unilateral total knee arthroplasty: a prospective, randomized, controlled study. J Arthroplasty 2017;32:2738–43.
[34] Irwin A, Khan SK, Jameson SS, et al. Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: results of 3000 procedures. Bone Joint J 2013;95B:1556–61.