Original Research Article

The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty-A meta-analysis

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Abstract

Introduction: Total hip and knee arthroplasty is known as one of the most successful surgeries for relieving pain and improving physical function. However, perioperative blood loss is one of the major complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA).**Materials and Methods:** We systematically searched randomized controlled trials (RCTs) from Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google scholar. Eligibility criteria: Patients: adult patients with end-stage joint osteoarthritis, rheumatoid arthritis, and osteonecrosis of the femoral head, who prepared for JTA; Interventions: The experiential group received the intravenous form of TXA; Comparisons: An oral form of TXA; Outcomes: Total blood loss, hemoglobin reduction, transfusion requirements, duration of hospitalization, and thrombotic complications including deep vein thrombosis (DVT) and pulmonary embolism (PE); Study design: Randomized control trials (RCTs) and non-RCT. Meta-analysis results were collected and analyzed by the software STATA 11.0. After testing for heterogeneity between studies, data were aggregated for random-effects models when necessary.**Results:** Four RCTs and two non-RCTs were included in the meta-analysis. The present meta-analysis revealed that there were no significant differences regarding total blood loss (WMD=_25.013, 95% CI: _51.002 to 0.977, P=.059), postoperative hemoglobin decline (WMD=_0.090, 95% CI: _0.205 to 0.024, P=.122), or transfusion rate (RD=_0.039, 95% CI: _0.080 to 0.002, P=.062) between the 2 groups.**Conclusion:** Oral TXA shows comparable Efficacy to that of the intravenous forms after total knee and hip arthroplasty. Due to the limited quality of evidence currently available, higher quality RCTs is necessary.

Keywords: THA, TKA, Medline, Embase, PE

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Introduction

Total hip and knee arthroplasty are known as one of the most successful surgeries for relieving pain and improving physical function. However, perioperative blood loss is one of the major complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA)[1].There are several steps used to minimize blood loss in patients who undergo THA and TKA, such as Use of a tourniquet, deliberate hypotension, antifibrinolytics, cell salvage, etc [2]. Among these strategies, tranexamic acid (TXA) has been identified as a useful step in reducing blood loss and the transfusion rate in THA and TKA. Patients undergoing THA and TKA can receive TXA intravenously (IV), topically, or orally. Some studies have reported that both IV and topical administration were effective in reducing perioperative blood loss without increasing thrombotic complications after THA and TKA. However, IV administration of TXA increases the workload of nurses, the cost, and the risk of anaphylactic reaction compared with oral TXA[3]. Topical TXA administration carries a theoretical risk of periprosthetic infection due to contamination of the needle and dispensing process, and the topical form may increase the risk of forming clots and blocking drainage tubes[4]. Oral TXA administration is easy to access and administer, which decreases the workload of nurses, and its absorption is quick and complete. Additionally, the cost could decrease dramatically with oral TXA administration[5,6].

The ideal route of TXA administration remains controversial. Recently, researchers have paid more attention to oral TXA administration. However, the Efficacy and safety of oral TXA remain controversial because of the small number of clinical studies[7].

To our knowledge, this is the first meta-analysis and Grading of Recommendations,Assessment,Development,Evaluation(GRADE) analysis of only randomized controlled trials (RCTs) comparing the safety and Efficacy of oral TXA and IV TXA in primary THA and TKA. We found four meta-analyses comparing oral TXA and IV TXA administration in primary THA and TKA [8].However, the inclusion criteria of the previous four meta-analyses included retrospective cohort studies that may involve recall and interviewer bias[9,10]. Thus, based on the current RCTs comparing oral and IV TXA, we used the GRADE system to assess the quality of the evidence for each outcome and Conducted a meta-analysis of RCTs to Demonstrate the Efficacy and safety of oral and IV administration of TXA.

Material and Methods

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. No ethical approval was required because this paper was based on the previous articles.

Search methodology

Studies were retrieved from the databases of Pubmed (1966–2018.06),Embase(1980–2018.06),and the Cochrane Central Register of Controlled Trials (1980–2018.06), Web of Science (1966–2018.06), and Google scholar (1966–2018.06). Reference lists of

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relevant articles were manually searched to identify additional trials. No restrictions were imposed on language. A structured search was performed using the following search string: "Total knee replacement or arthroplasty," "Total hip replacement or arthroplasty," "tranexamic acid," "intravenous,"and "oral."

Inclusion criteria

(1) Patients: adult patients with end-stage joint osteoarthritis, rheumatoid arthritis, and osteonecrosis of the femoral head who prepared for TJA.

(2) Interventions: The experiential group received the intravenous form of TXA.

(3) Comparisons: An oral form of TXA.

(4) Outcomes: Total blood loss, hemoglobin reduction, transfusion requirements,duration of hospitalization, and thrombotic complications, including deep vein thrombosis (DVT) and pulmonary embolism (PE).

(5) Study design: Randomized control trials (RCTs) and non-RCT.

Selection criteria

All relevant studies were collected, and duplicate literature were excluded. Then, two researchers independently excluded studies by reading titles and abstracts. At last, the irrelevant studies were removed following inclusion criteria. If no consensus was reached, a third investigator was consulted.

Data extraction

The available data were extracted independently from the included studies by two reviewers. The information included author name, publishing year, age, sample size, gender, intervention procedure, transfusion trigger, and follow-up. We send emails to authors to obtain incomplete outcome data.

Quality assessment

The methodological qualities of included studies were assessed independently by the two reviewers described by the Cochrane Collaboration for Systematic Reviews. We conducted a "risk of bias" table including the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias, and each item was recorded by "Yes"- "No"- or "Unclear." The Methodological Index for Nonrandomized Studies (MINORS) scale was applied to evaluate non-RCTs with scores ranging from 0 to 24.

Statistical methods

Stata 11.0 software was utilized for the meta-analysis. Continuous various outcomes, such as the total blood loss, hemoglobin decline, and length of stay, were all expressed as the weighted mean difference (WMD) with 95% confidence intervals (CIs). The results of dichotomous outcomes (transfusion rate, DVT, PE) were expressed as a risk difference (RD) with 95% confidence intervals (CIs). The statistical heterogeneity was determined by the Chi-squared test in accordance with the value of P and I2. If I2>50%, P<.05, statistical was considered to be heterogeneous, we used a random-effects model to analyze the data. Otherwise, the fixed-effects model was performed to conduct a meta-analysis.

Results

Four hundred twenty-five studies were identified from databases. According to the inclusion criteria, 419 studies were excluded. No gray paper was included. Finally, 4 RCTs and two non- RCT published from 2004 to 2017 were included in our study and include 621 participates in the TXA groups and 2963 patients in the control groups.

Study Characteristics: The basic information of the included articles are concluded in Table 1. The included articles were published from 2004 to 2017. The sample size ranged from 40 to 2940, and the mean age of patients ranged from 55 to 69 years. Duration follow-up ranged from 2 to Six months.

Risk of bias assessment: Cochrane Collaboration's tool is applied to evaluate the risk of bias (Tables 2 and 3). Randomization was performed in all RCTs, which mentioned that the list of random numbers was generated from computers. All articles used sealed envelopes for allocation concealment. Double blinding was shown in 3 RCTs. It was not clear whether assessors were blinded. Two non-RCTs were appraised by the MINORS.

Meta-analysis results

Total blood loss. All studies provided the total blood loss after TJAs. No significant statistical heterogeneity was found (x2=1.03, df=5, I2=0.0%, P=.960), and a fixed-effects model was adopted. Our study revealed that there was no significant difference in terms of total blood loss (WMD=25.013, 95% CI: _51.002 to 0.977, P=.059;).

Hemoglobin decline. Six studies showed the postoperative hemoglobin decline after TJA. There was no significant heterogeneity (x2=0.25, df=5, I2=0.0%, P=.998). Hemoglobin decline did not show significant differences between groups (WMD=_0.090, 95% CI: _0.205 to 0.024, P=.122;).

Transfusion rates. Transfusion requirements were shown in six articles.[10–15] We found no significant heterogeneity (x2=3.78, df=5, I2=0.0%, P=.581); a fixed-effects model was adopted. There was no significant difference between groups regarding transfusion rates (RD=_0.039, 95% CI: _0.080 to 0.002, P=.062;).

Duration of hospitalization. All RCTs provided the duration of hospitalization.[10–15] There was no significant heterogeneity among articles (x2=2.80, df=5, I2=0.0%, P=.731). No significant difference in the duration of hospitalization was observed (WMD=_0.093, 95% CI: _0.280 to 0.094, P=.331).

Deep vein thrombosis. Six studies showed the thrombotic complications of DVT. No significant statistical heterogeneity was found, and a fixed-effects model was used (x2=0.14, df=5, I2=0.0%, P=1.000). A similar incidence of the risk of DVT was identified between groups (RD=_0.002, 95% CI: _0.010 to 0.006, P=.597;).

Pulmonary embolism. Six articles reported the thrombotic complications of PE following TJA. A fixed-effects model was adopted (x2=0.14, df=5, I2=0.0%, P=1.000). No significant difference was found in the PE incidence between the two groups (RD=_0.002, 95% CI: _0.012 to 0.008, P=.722).

Subgroup analysis. Subgroup analysis was conducted for the outcome of blood loss, hemoglobin reduction, transfusion rates, and duration of hospitalization (Table 5). The overall results demonstrated there was no significant difference between groups.

Table 1: Cohort characteristics

Reference	Study design	Cases (T/C)	Mean Age (T/C)	Female patients (T/C)	Surgical Procedure	TXA Intervention	Transfusion Trigger	Follow UP
Zohar et al	RCT	20/20	69/69	12/16	TKA	E: intravenous 15mL/kg TXA; C: 1 g oral TXA	Hematocrit<28%	Three mo
Irwin et al	CCT	302/2638	67.6/68.2	68/1442	TKA and THA	E: intravenous 15mg/kg TXA; C: 25 mg/kg, maximum 2 g	HB less than seven g/dL	Two mo
Fillingham et al	RCT	34/37	62/63	21/26	TKA	E: intravenous 1g TXA; C: 1.95 g oral TXA	HB less than 7 g/dL	NS
Kayupov et	RCT	40/43	60/55	40/33	THA	E: intravenous 1g TXA; C:	HB less than	

al						1.95 g oral TXA	7 g/dL	
Two mo Gottemoeller et al	CCT	165/165	67/68	110/101	TKA and THA	E: intravenous 15mL/kg TXA; C: 1 g oral TXA	HB less than 7 g/dL	Six mo
Luo et al	RCT	60/60	67/68	33/32	THA	E: intravenous 20mg/kg TXA; C: 2 g oral TXA	HB less than 7 g/dL	Three mo

Table 2: Methodological quality of the nonrandomized controlled trials

Quality assessment for nonrandomized trials	Irwin et al	Gottemoeller et al
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective data collection	2	2
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	0	0
A follow-up period appropriate to the aims of the study	2	2
Less than 5% loss to follow-up	2	2
Prospective calculation of the sample size	0	2
An adequate control group	2	2
Contemporary groups	2	2
Baseline equivalence of groups	2	2
Adequate statistical analyses	2	2
Total score	20	22

Discussion

To the best of our knowledge, this is the first systemic review to assess the Efficacy between intravenous and oral forms of TXA application in TKA and THA[11].We found that oral TXA shows comparable Efficacy to that of the intravenous forms after TKA and THA[12].TXA, which acts as an antifibrinolytic agent, is famous for proven success in reducing peri and postoperative blood loss and widely used in a surgical procedure[13].TXA could be applied by various routes, including intravenous, intraarticular, oral, and intramuscular [14]It was reported that TKA without antifibrinolytics was associated with massive blood loss ranging from 761 to 1784 mL, and allogenic blood transfusion was frequently performed to relieve anemia[15].Potential side effects might occur, for instance, the transmission of infection, possible hemolytic transfusion reactions, etc. Substantial high-quality RCTs and meta-analysis have been published to confirm that both intravenous and topical administration of TXA could diminish the need for allogeneic blood transfusions in patients undergoing TJA[16]Seol et al. observed a 24% decrease in the requirement for transfusion in the intravenous TXA group compared control group after TKA[17].Whether oral administration of TXA was superior to intravenous TXA for reducing transfusion rate in TJA remained controversial. Meta-analysis is performed as a major statistical method in the present study [18]. It could strengthen statistical power and enlarger sample size by pooling results of published articles that could point out stronger evidence. The current meta-analysis revealed that the difference in transfusion requirements between oral and intravenous groups was not significant[19].DVT is considered a common postoperative complication, which may develop into PE and even result in death following total joint arthroplasty. Published articles had suggested a potential higher risk of thrombotic complication when TXA was used[20].This result might be due to the tendency of TXA, which is an antifibrinolytic agent, to promote the risk of clotting. However, the intravenous administration of TXA might be more likely to result in the formation of a thrombus because of the higher TXA level of blood concentration. There was no significant difference between both groups in terms of the risk of DVT or PE in the present analysis. However, further study was still necessary.

Conclusion

Oral TXA shows comparable Efficacy to that of the intravenous forms after total knee and hip arthroplasty. Due to the limited quality of evidence currently available, higher quality RCTs is necessary.

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