A Single Preoperative Dose and an Additional Dose of Tranexamic Acid in Total Knee Arthroplasty: a Meta-analysis

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Abstract

Objective: To review the efficacy and safety of a single preoperative dose and an additional postoperative dose of tranexamic acid (TXA) in reducing blood loss in total knee arthroplasty (TKA).

Methods: PubMed, Embase, Cochrane Library and Web of Science were searched for randomized controlled trials (RCTs) in March 2021. Postoperative blood loss, transfusion rate, and deep vein thrombosis (DVT) incidence were studied. Data were analyzed using Review Manager 5.3 software and Stata 14.0 software.

Results: Intravenous (IV) TXA twice provided lower postoperative blood loss compared with placebo group ($P=0.001$) and IV TXA once group ($P=0.007$), but a higher postoperative blood loss as compared with combined TXA ($P=0.001$). IV TXA twice provided lower transfusion rate compared with placebo group ($P=0.001$). No significant difference was found in terms of DVT incidence ($P=0.05$). There was no significant publication bias for postoperative blood loss, transfusion rate, and DVT incidence.

Conclusion: When it comes to IV TXA in TKA, a single preoperative dose and an additional dose of TXA may be a better and more feasible way for blood control than a single preoperative dose.

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed orthopedic surgery, which is associated with a series of postoperative complications including blood loss[1, 2]. Intraoperative and postoperative bleeding is one of the main complications in TKA, and various blood-conserving strategies have been used in TKA. Hyperfibrinolysis following surgery is a major contributor to perioperative blood loss in TKA[3]. Tranexamic acid (TXA), a commonly used antifibrinolytic agent, inhibits fibrinolysis by blocking the lysine-binding site of plasminogen and has become the method of choice for controlling blood loss[4, 5]. Several studies have shown that intravenous (IV)[6–8], intra-articular (IA)[9–11] or oral[12–14] application of TXA can successfully reduce blood loss and transfusion rate in primary TKA without increasing the risk of thrombosis. But the most effective administration route of TXA remains controversial.

Recently, a meta-analysis[15] assessed the efficacy and safety of the efficacy and safety of a single dose of IV TXA given preoperatively. and it showed that preoperative IV TXA reduced perioperative blood loss and transfusion requirements in a variety of surgical disciplines without increasing the risk of thromboembolic events.

One RCT[7] showed that with the same total dose of TXA, the preoperative dose and an additional dose of TXA (IV TXA twice) were superior to a single preoperative dose of TXA (IV TXA once) in reducing blood loss in TKA. So this study aimed to assess the effect of a single preoperative dose and an additional postoperative dose of tranexamic acid more comprehensively. Postoperative blood loss, transfusion rate, and complication such as DVT incidence were the efficacy and safety points, respectively.

Methods

Search Strategy

The literature search using Embase, Cochrane Library, PubMed, and Web of Science databases until May 2021 were conducted. The search strategy included key search terms: (“tranexamic acid” or “TXA” or “TA”) and (“total knee arthroplasty” or “total knee replacement” or “TKA” or “TKR”). and (“randomized controlled trial” or “RCT”). Besides, the reference lists of previously published randomized trials, review articles, and meta-analyses were manually searched for additional eligible studies. Related articles and reference lists were searched to avoid original miss. Duplicate records were removed electronically and manually.

Eligibility Criteria

All citations were downloaded into Endnote X9. Two reviewers (LT and ZL) performed study selection independently, with disagreements solved through discussions and by consulting a third reviewer (HL) if necessary. The inclusion criteria for these studies were performed as follows: (1) Studies on patients with TKA; (2) RCTs; (3) IV TXA twice as intervening measure; (4) Studies reporting postoperative blood loss, transfusion rate, or DVT incidence. The exclusion criteria were: (1) Secondary analyses, including some pooled analyses; (2) Studies published not in English; (3) Abstract, case reports, letters, editorials, conference articles, or insufficient data.

Quality Assessment

The Cochrane risk of bias assessment tool was used to determine the methodological quality of included RCTs [16]. A total of six domains were evaluated: random sequence generation, allocation concealment, participant blinding, outcome assessor blinding, incomplete

outcome data and selective reporting. Each domain was assigned a judgment of low risk of bias, high risk of bias or unclear risk of bias. The judgments for each domain were made by strictly following the Cochrane Handbook V.5.1.0, Chapter 8.5.

Data Extraction

The following data were extracted: (1) Characteristics of the 24 trials selected showing general surgical information; (2) Outcome measures including postoperative blood loss, transfusion rate, and DVT incidence; (3) For continuous outcomes, we extracted the mean and standard deviation (SD). For dichotomous outcomes, we extracted the total numbers and the numbers of events in both groups.

Statistical Analysis

Heterogeneity among studies was tested using the Q statistic ($P < 0.05$ was considered heterogeneous) and I^2 statistic ($I^2 > 50\%$ was considered heterogeneous). If there was no significant heterogeneity among studies, a fixed-effects model was used; otherwise, a random-effects model was used[17]. The effect of publication bias was investigated by Egger's test[18]. Mean difference (MD) was calculated for continuous outcomes, and risk ratio (RR) was calculated for dichotomous outcomes. Statistical analyses were conducted using Review Manager 5.3 software (RevMan5.3, Cochrane Collaboration, Oxford, UK) and Stata software (Version 14.0, College Station, TX, USA).

Results

Study Characteristics and Quality Assessment

A total of 1754 potentially relevant articles were identified from the databases. After removal of duplicates, 1251 articles were screened for relevance in terms of the title and abstract. And then 109 articles were read the full text and 26 articles were reserved, in which 24 of them possibly eligible for inclusion. Two studies were excluded for reasons of "No available data" (Details are shown in Fig. 1). The remaining 24 RCTs were included in this meta-analysis. The characteristics of the ten included studies were summarized and showed in Table 1. The quality assessment of RCTs is presented in Fig. 2.

Table 1
Characteristics of the 16 trials selected showing general surgical information

Study	Experiment group	Blank control	TXA control group	Tourniquet	Thromboprophylaxis	DVT screening	Allogeneic transfusion criteria
Wang2019[22]	IV 20mg/kg TXA twice		IV 20mg/kg TXA twice 1g TXA orally 14 times	no	LMWH and a venous pump	doppler ultrasound	Hb<70g/L in asymptomatic or between 70g/L and 100 g/L in symptomatic patients
Tzatzairis2019[28]	IV 15mg/kg TXA twice		IV 15mg/kg TXA	no	LMWH and compression stockings	CT/Doppler ultrasound	Hb<10g/dl or any anemic symptoms or anemia-related organ dysfunction
Takuya2018[23]	IV 1g TXA twice		IV 1g TXA twice 1g IA 1g TXA	no	fondaparinux once every evening for 7 days	NR	Hb<7g/dL in asymptomatic or those with Hb<10g/ dL if they had symptoms
Yuan2017[14]	IV 20mg/kg TXA twice	placebo	3g topical TXA	yes	venous pump and rivaroxaban	doppler ultrasound	Hb<8.0g/dL or symptoms
Sun2017 [7]	IV 15mg/kg two times	saline	IV 30mg/kg	yes	LMWH for 3 days, and then rivaroxaban for 1 month	doppler ultrasound	Hb<8g/dL or 10g/dL and complicated with intolerable ischemic symptoms
Lee2017[24]	IV 10mg/kg twice		IV 10mg/kg twice 1g IA 1 g TXA	yes	individualized approach protocol	NR	Hb<7g/dL or if anemic symptoms in patients with Hb between 7.0 and 8.0 mg/dL
Lacko2017[29]	IV 10mg/kg twice	normal saline	IA 3g TXA	yes	NR	ultrasound of the venous system	Hb<8g/dL or < 9 g/dL when the patient had simultaneous signs of postoperative anemia
Castro-Menendez2016[30]	IV 1g TXA twice	placebo	IV 2g TXA	yes	3500 UI Bemiparin Sodium were used 35 days	doppler ultrasound	Hb<8g/dl in healthy patients without preoperative cardiopulmonary pathology, or Hb< 9g/dl with clinical symptoms of haemodynamic instability
May2016[31]	IV 1g TXA twice		IA 2g TXA	yes	LMWH or oral direct factor Xa inhibitor	NR	Hb<7g/dL or Hb<10g/dL if they had symptoms or ongoing blood loss

LMWH: low molecular weight heparin; NR: not reported; S.C.: Subcutaneous injection.

Study	Experiment group	Blank control	TXA control group	Tourniquet	Thromboprophylaxis	DVT screening	Allogeneic transfusion criteria
Motififard2015[32]	IV 0.5g TXA twice	saline		yes	LMWH for 14 days	NR	Hb<8g/dL or 10g/dL in patients with comorbidities and intolerated anemic symptoms
Aguilera2015[33]	IV 1g TXA twice		1g topical TXA(by syringe-spray to the following surfaces)	yes	LMWH	NR	Hb<8 or 8.5 g/dL in patients with heart disease or older than 70 years or when Hb between 8.5 and 9g/dL in patients with low orthostatic tolerance
Kim2014[34]	IV 10mg/kg TXA twice	saline		yes	orthopaedic Surgeons' Clinical Guidelines	NR	Hb<7mg/dL or if anaemic symptoms in patients with an Hb between 7 and 8mg/dL
Gomez-Barrena2014[26]	IV 15mg/kg TXA twice		IA 3g TXA	yes	40 mg enoxaparin for two weeks	NR	Hb<8g/dL or Hb<10g/dL if they had symptoms or ongoing blood loss
Bidolegui2014[35]	IV 15mg/kg TXA twice	placebo		no	40 mg enoxaparin for 30 days	NR	Hb<8 or 9 g/dl associated with either patients instability or with prior cardiac history
Lee2013[36]	IV 10mg/kg TXA twice	saline		yes	2.5 mg fondaparinux for 5 days	doppler ultrasound	Hb<8g/dL or clinical symptoms of
Aguilera2013[37]	IV 1g TXA twice	placebo		yes	LMWH for 30 days	NR	Hb<8 or 8.5g/dL in patients with heart disease or older than 70 years or when Hb between 8.5 and 9 g/dL in patients with low orthostatic tolerance
Maniar2012[38]	IV 10mg/kg TXA twice	saline	IV 10mg/kg TXA	yes	LMWH and below-knee stockings	NR	Hb<8.5g/dL or patients with cardiac disorders whose Hb<10g/dL or patients whose Hb 8.5 to 10g/dL but had symptoms.

LMWH: low molecular weight heparin; NR: not reported; S.C.: Subcutaneous injection.

Study	Experiment group	Blank control	TXA control group	Tourniquet	Thromboprophylaxis	DVT screening	Allogeneic transfusion criteria
Lin2012 [39]	IV 10mg/kg TXA twice	saline	IV 10mg/kg TXA	yes	20 mg enoxaparin until discharge	Antegrade enography/CT	Hb< 8g/dl or between 8g/dl and 9g/dl in patients with symptoms or cardiovascular disease
Molloy2007[40]	IV 0.5g TXA twice	placebo		yes	NR	NR	NR
Camarasa2006[41]	IV 10 mg/kg TXA twice	saline		yes	s.c. dalteparin sodium 5000 IU for 40 days	venous echo-Doppler	Hb<8g/dL or Hb<10g/dL if they had poor tolerance
Good2003[42]	IV 10 mg/kg TXA twice	saline		yes	S.C. dalteparin sodium 5000 IU for 11 days	NR	Hb <90g/L
Veien2002[43]	IV 10 mg/kg TXA twice	saline		yes	LMWH	NR	NR
Tanaka2001[44]	IV 10 mg/kg TXA twice	saline	IV 20 mg/kg TXA	yes	NR	radio-isotope venography	NR
Benoni1996[45]	IV 10 mg/kg TXA twice	placebo		yes	LMWH for 7-10 days	NR	NR
LMWH: low molecular weight heparin; NR: not reported; S.C.: Subcutaneous injection.							

Meta-analysis of Postoperative Blood Loss

Postoperative blood loss data were provided by 16 included studies (Fig. 3). Our meta-analysis indicated that patients receiving IV TXA twice had significantly lower postoperative blood loss as compared to the placebo group (MD=-378.28, 95% CI -483.62 to -264.91, $P<0.001$; $I^2=88.0\%$, $P<0.001$) or IV TXA once (MD=-82.32, 95% CI -141.96 to -22.67, $P=0.007$; $I^2=0.0\%$, $P=0.75$).

No significant difference was observed in postoperative blood loss (MD=-91.37, 95% CI -340.03 to 157.28, $P=0.47$; $I^2=68.0\%$, $P=0.08$) between IV TXA twice and topical TXA. IV TXA once and topical/oral TXA may reduce postoperative blood loss than IV TXA twice (MD=154.43, 95% CI 81.54 to 227.33, $P<0.001$; $I^2=48.0\%$, $P=0.14$).

Meta-analysis of Transfusion Rate

Transfusion rate data were provided by 22 included studies (Fig. 4). Our meta-analysis indicated that patients receiving IV TXA twice had significantly lower transfusion rate as compared to the placebo group (RR=0.27, 95% CI 0.21 to 0.34, $P<0.001$; $I^2=43.0\%$, $P=0.03$). No significant differences in were observed in IV TXA twice and topical TXA or IV once or topical TXA group.

Meta-analysis of DVT Incidence

18 randomized studies reported DVT incidence and no significant differences were observed (Fig. 5).

Publication bias

Egger's test was used to assess the potential publication bias of postoperative blood loss, transfusion rate, and DVT incidence studies included in this meta-analysis. The P values from Egger's test indicated that there was no significant publication bias for postoperative blood loss, transfusion rate, and DVT incidence ($P=0.936$, $P=0.224$ and $P=0.705$, respectively).

Discussion

Allogenic blood transfusions after TKA carried significant potential risks, which should be avoided as well as possible, so TXA should be applied. IV application of TXA has been confirmed as effectively decreasing postoperative blood loss and transfusion rate in TKA patients[19, 20]. However, there is no clear consensus on the optimal regimen of IV application of TXA. Administering one pre-operative dose and one subsequent post-operative dose is one of the most common IV application practices. The interval of doses is usually three hours, which is because TXA has a plasma half-life of three hours. This is the first meta-analysis to identify the efficacy and safety of a single preoperative dose and an additional dose of IV TXA in TKA.

This study showed that IV TXA twice could reduce postoperative blood loss than the placebo group and IV TXA once group, which was consistent with those of previous studies[7, 21]. There is a difference existing between single dose and multiple doses, and two doses of TXA may be the optimal regimen for blood loss. IV TXA twice had a higher postoperative blood loss as compared with the IV TXA once and topical/oral group, which may due to the total TXA dose. The efficacy of TXA was positively correlated with total dose, and the use of TXA at two intervals could maintain the exposure level of tranexamic acid to systemic circulation in order to achieve a better effect of reducing postoperative bleeding after TKA.

In three RCTs included, IV TXA twice with subsequent TXA was more effective than IV TXA twice group. Wang et al[22] compared IV 20mg/kg TXA twice with IV 20mg/kg TXA twice and subsequent long-term oral TXA for 14 days, finding the latter produced less blood loss and less swelling and ecchymosis without increasing the risk of complications. Takuya et al[23] compared IV 1g TXA twice with IV 1g TXA twice and intra-articular (IA) 1g TXA, showing IV and IA TXA regimen significantly reduced perioperative blood loss compared with only IV TXA. Lee et al[24] compared IV 10mg/kg TXA twice with IV 10mg/kg TXA twice and IA 1g TXA, concluding that combined IA TXA administration further reduces blood loss after TKA in comparison to IV use alone. IV TXA twice with subsequent TXA, either oral or IA, and either long or short term, bleeding could be better controlled.

In addition, IV TXA twice had a similar efficacy with topical TXA in terms of reducing postoperative blood loss. One study[25] indicated that topical 1g TXA and IV 10 mg/kg TXA once have similar safety and efficacy for reducing perioperative blood loss in TKA. Gomez-Barrena et al concluded[26] that a single topical dose of 3g of TXA was not inferior to two 15mg/kg IV TXA doses. We thought IV TXA twice and topical TXA achieved equal control of blood loss. TXA applied locally before wound closure targeted the bleeding, which could reduce the significant increase in local fibrinolysis associated with tourniquet release[27].

IV TXA twice had significantly lower transfusion rate as compared to the placebo group. No significant differences in were observed between IV TXA twice and TXA control group in terms of transfusion rate. No significant differences in were observed in terms of DVT incidence. When the patients determined to apply TXA during the perioperative period, IV TXA twice could be used without without safety concerns. Egger's test indicated that there was no significant publication bias for postoperative blood loss, transfusion rate, and DVT incidence. Therefore, the results of this study were relatively stable.

The authors acknowledge that the current study has several limitations. Firstly, the sample of IV TXA twice in this study was small. Secondly, we only pooled DVT complication. Finally, there may be high quality non-English studies that could have influenced the outcomes of our meta-analysis, but were excluded due to the selection criteria. A longer follow-up period is required to compare the safety profile and functional outcome differences.

Conclusion

When it comes to IV TXA in TKA, a single preoperative dose and an additional dose of TXA may be a better and more feasible way for blood control than a single preoperative dose.

Declarations

The authors declared that they had no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All methods in the included studies of this meta-analysis were carried out in accordance with relevant guidelines and regulations.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All relevant data (including raw-data) has been provided in figures, tables and supplements.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have full access to all data in the study. LT and ZL conducted the literatures screening and the statistical analysis. LT and HL wrote the manuscript. ZL reviewed the manuscript. All Authors read and approved the final version of the manuscript.

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Figures

Figure 1

Flowchart of the study selection process

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aguilera 2013	+	+	+	+	+	+	?
Aguilera 2015	+	+	+	+	+	+	?
Benoni 1996	+	+	+	+	+	+	?
Bidolegui 2014	+	+	+	+	+	+	+
Camarasa 2006	+	?	+	?	+	+	?
Castro-Menendez 2016	+	?	+	+	+	+	?
Gomez-Barrena2014	+	?	+	?	+	+	?
Good 2003	+	?	+	+	+	+	?
Kim 2014	+	+	+	+	+	+	+
Lacko 2017	+	+	+	+	+	+	?
Lee 2013	+	+	+	+	+	+	?
Lee 2017	+	+	+	+	+	+	?
Lin 2012	+	+	+	+	+	+	?
Maniar 2012	+	+	+	+	+	+	?
May 2016	+	+	+	+	+	+	?
Molloy 2007	+	+	+	+	+	+	+
Motiffard 2015	+	+	+	+	+	+	?
Sun 2017	+	+	+	+	+	+	?
Takuya 2018	+	+	+	+	+	+	?
Tanaka 2001	+	+	+	+	+	+	?
Tzatzairis 2019	+	+	+	+	+	+	?
Veien 2002	+	+	+	+	+	+	?
Wang 2019	+	+	+	+	+	+	?
Yuan 2017	+	+	+	+	+	+	?

Figure 2

Risks of bias summaries

Figure 3

Forest plot showing postoperative blood loss

Figure 4

Forest plot showing transfusion rate

Figure 5

Forest plot showing DVT Incidence

Supplementary Files

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