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META-ANALYSIS

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Safety and Efficacy of Tranexamic Acid in Total Knee Arthroplasty

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The prevalence of total knee arthroplasty (TKA) is increasing, which is one of the most frequent operations in orthopedic practice. To further investigate the safe and effective role of using tranexamic acid (TA) in reducing transfusion rate and blood loss in total knee arthroplasty.

Material/Methods: This meta-analysis was conducted according to the Cochrane methodology. Twenty-eight superior quality and well designed randomized controlled trials (RCT) were collected to analyze for this study. Patients who had undergone primary unilateral TKA were chosen. The software, RevMan 5.2, was used to analyze collected data.

Results: Finally, 28 RCTs were collected to analyze for this study. Total blood loss was dramatically decreased via the application of TA, by a mean of 420 ml [95% CI: –514 to –327]. A significant reduction about blood transfusion rate was also found in patients who received TA. [RD: –0.26, 95%CI: –0.33 to –0.19]. Moreover, no significant differences were found between TA and control groups in incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Conclusions: This meta-analysis demonstrates that the application of TA in TKA could decrease total blood loss and transfusion rate. On the other hand, the application of TA is not associated with high incidence of DVT or other adverse events. TA should be taken into account in routine use in primary knee arthroplasty to benefit the patients.

MeSH Keywords: Arthroplasty, Replacement, Knee • Blood Loss, Surgical • Meta-Analysis • Tranexamic Acid

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Background

The prevalence of total knee arthroplasty (TKA) is increasing, which is one of the most frequent operations in orthopedic practice [1]. However, the considerable intraoperative and postoperative blood loss may be a trigger increasing risk of allogeneic blood transfusion, which causes subsequent complications, such as infections, intravascular hemolysis, and cardiopulmonary events [1–3]. Moreover, patients who underwent TKA are mostly aged people (65.7±8.2) [4,5], whose ability to replace lost blood is insufficient to maintain health. Therefore, they are more vulnerable to series of transfusion reactions, and even death. Thus, an effective and safe way to decrease complications of blood transfusion is to suppress intraoperative and postoperative blood loss [4,5].

Several methods had been applied for suppressing perioperative blood loss, including tourniquet, intraoperative blood salvage, and the application of antifibrinolytic agents [6,7]. Antifibrinolytic agents are widely used and potentially interrupt the cascade of haemostatic abnormalities and enhance hemostasis [8]. As a result, they may potentially reduce blood loss, blood transfusion, and transfusion reaction.

Tranexamic acid is a kind of synthetical antifibrinolytic agent, which blocks the activation of plasminogen to plasmin and blocks the fibrinolytic action of plasmin on fibrin. With the administration of TA, activation of plasminogen and fibrinolysis are both suppressed [9,10]. TA can prevent clots and reduce blood loss. Topical and intravenous administration of TA has been applied in many surgical practices, including TKA, which not only could reduce topical blood loss but also inhibits plasmin-induced platelet activation to affect hemostasis of the cardiopulmonary system [9].

More and more researchers have reported positive outcomes of administration of TA in TKA. However, the TA treatment administration varied among countries and surgeons. Several researchers have found that the use of TA could increase the risk of deep vein thrombosis and question the effectiveness and safety of TA [11]. The goal of this analysis is to further investigate the safe and effective role of using tranexamic acid (TA) in reducing transfusion rate and blood loss in total knee arthroplasty.

Material and Methods

This study was conducted in accordance with the guidelines described in the Cochrane Handbook for meta-analysis and also based on the recommended PRISMA checklist guidelines [12].

Search strategy

We searched PubMed, Web of Science, and EMBASE from 1950 to June 2015 to identify relevant studies. The following selected Medical Subject Headings terms were used for the initial literature search: 'Anti-fibrinolytics' or 'Tranexamic acid' or 'Cyklokapron' and 'total knee replacement'or 'total knee arthroplasty'.

Criteria of eligibility

Studies were considered eligible if they met the following criteria: 1) patients underwent a primary TKA; 2) the experiment group was considered as the administration of intravenous TA and placebo or no treatment for control group; 3) outcome measures included total blood loss, blood transfusion rate, and incidence of thromboembolism complications; 4) randomized controlled trials and prospective comparative studies. Exclusion criteria: 1) allergy to TA; 2) bleeding disorders; 3) thromboembolic complications.

Data extraction

Eligible articles were reviewed independently by 2 investigators (Yu Xiao and Weili Li). The titles and abstracts of the references were read. Any disagreement on a controversial study was settled by discussion and consensus.

Quality assessment

The methodological quality of included studies was evaluated with a generic evaluation tool [13]. The quality of each study was evaluated by a score from 0 to 24. Any disagreement on a controversial study was resolved by discussion and consensus.

Statistical analysis

Continuous variables were indicted as mean standard deviation, and the outcomes were analyzed by mean difference with 95% confidence interval. Dichotomous variables for each arm were indicted as risks, and the outcomes were analyzed by a risk difference with 95% CI.

Heterogeneity was conducted using Cochran's Q test and Higgins I-squared statistic. Heterogeneity was defined as $p<0.10$ or $I^2 >50\%$ [14]. The random-effects model was used if heterogeneity was observed ($P<0.10$), and the fixed-effects model was used in the absence of between-study heterogeneity ($P>0.1$). All of the above calculations were performed using RevMan 5.2 (Cochrane collaboration, Oxford, UK) software.

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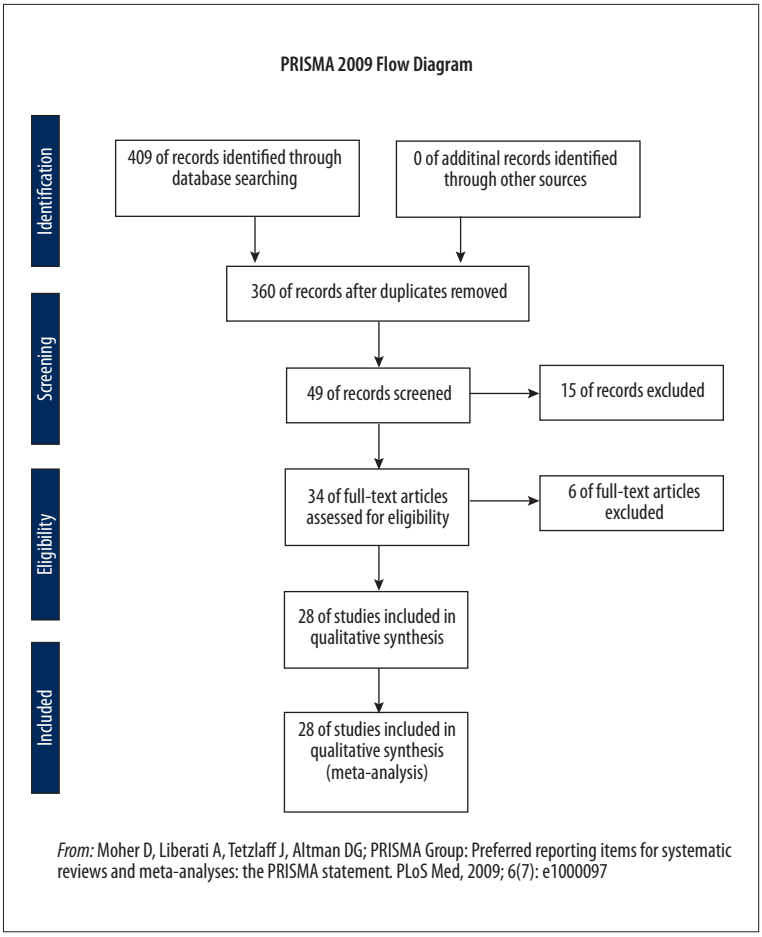

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Figure 1. Flow chart showing study identification, inclusion and exclusion.

Results

Characteristics of the eligible studies

We initially found 409 studies in our search of PubMed, Web of Science, and EMBASE. With the review of these abstracts, 49 potentially relevant studies were identified as eligible for full-text review, and 34 RCTs met the inclusion criteria. Among them, 6 trials were further excluded because TA was administered through knee joint injection in 2 trials, and placebo or blank control group was not set in 2 trials. Finally, 28 studies [15–41] were identified according to the inclusion criteria of the meta-analysis (Figure 1) and detail information were displayed in Table 1.

Total blood loss

Total blood loss was reported in 24 studies [15–17,19,20, 22–29,30–33,35–42]. Total blood loss was dramatically decreased via the application of TA by a mean of 420 ml [95% CI: –514 to –327, P<0.00001]. However, significant heterogeneity (I^2=90%) among included studies was detected, so the random-effects model was used. Based on data (420 ml [95% CI: –514 to –327, P<0.00001]) displayed in Figure 2A, we conclude that total blood loss volume decreased sharply with the use of TA in TKA.

Blood transfusion rate

Blood transfusions were recorded in 26 trials [15–26,28,30–42] including 2410 patients. Among them, there were 172 patients who took TA and 318 patients who took placebo who needed transfusion. TA significantly reduced the number of patients who needed transfusion [P<0.01, RD=–0.26, 95% CI –0.33 to –0.19]. Heterogeneity existed between trials [P<0.01, I^2=80%]. As shown in Figure 2B ([P<0.01, RD=–0.26, 95% CI –0.33 to –0.19]), TA can also reduce the blood transfusion rate of patients who underwent TKA.

Postoperative drainage

Fifteen studies (997 patients) reported postoperative drainage [15,19,20,24–29,31,33,38,40–42]. The application of TA significantly decreased postoperative drainage [MD: –275.47 mL, 95% CI –362.64 to –188.30; P<0.00001]. There was significant heterogeneity [P<0.00001; I^2=94%]. The TA group had less postoperative drainage compared to the control group (Figure 3).

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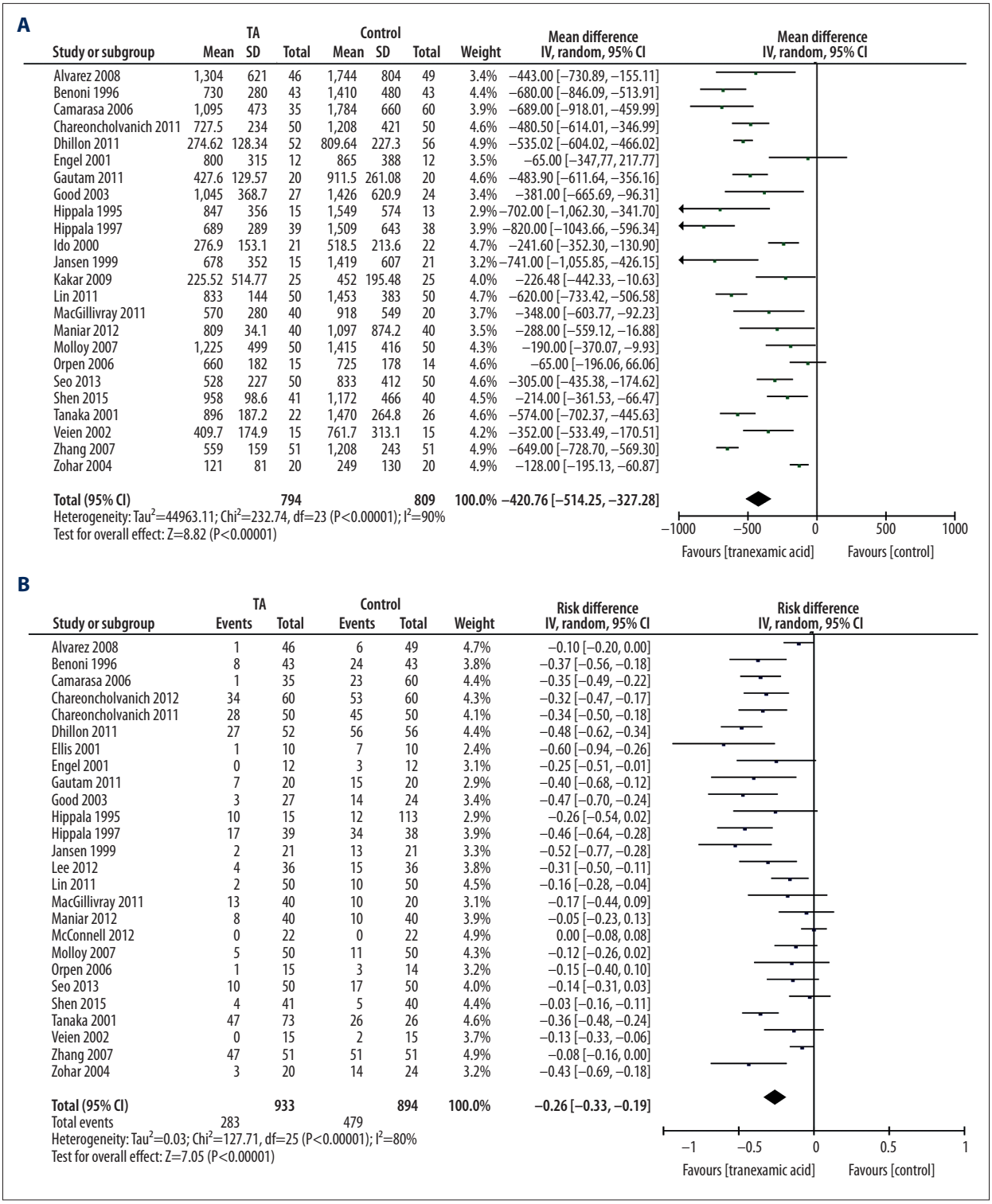

Figure 2. (**A**) Forest plot diagram showing the effect of TA on total blood loss. (**B**) Forest plot diagram showing the effect of TXA on blood transfusion rate.

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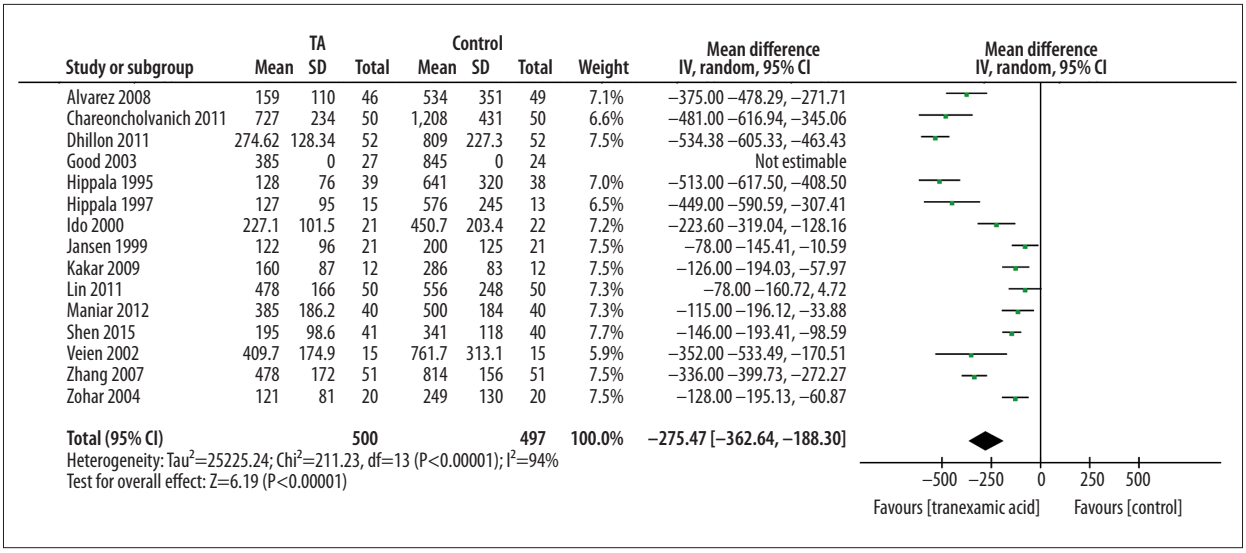

Figure 3. Forest plot diagram showing the effect of TA on postoperative drainage.

Incidence of DVT

In 26 trials [15–20,22–30,32–42], data on DVT were available. Studies included 919 and 877 patients in the TA group and control group, respectively. Among them, 22 patients in the TA group and 20 in the control group developed DVT. There was no statistically significant difference between TA and control groups (P=0.91) and no heterogeneity between trials (P=1.00, I^2=0) (Figure 4A).

Incidence of PE

In 15 trials, data were available on patient outcomes [16–19, 23,25–27,30,32,33,35,37–39,42]. In the TA group, no PE was reported. In the control group, 3 patients out of 550 developed PE. There was no statistically significant difference in the risk of developing PE between TA and control groups (P=0.47). There was no heterogeneity between trials (P=1.00, I^2=0) (Figure 4B).

Discussion

The results of the study demonstrate that the application of TA could significantly reduce total blood loss, allowing patients to benefit from it more. Moreover, the number of patients who needed to receive allogeneic transfusions in TKA was dramatically decreased with the application of TA. This study demonstrated that use of TA did not increase the incidence of DVT or PE. However, significant heterogeneity was detected between trials. Many factors may lead to the existence of heterogeneity, such as different types of anesthesia, surgical techniques, or TA use. The reasons for high heterogeneity may be that hidden bleeding was rarely measured or that different times of extraction of the drain tube were reported.

Among all antifibrinolytic agents, TA is not the only agent used in TKA. Other antifibrinolytic agents include fibrin spray, epsilon aminocaproic acid, and aprotinin, which have been used to decrease surgical blood loss [43]. However, some defects had been detected via clinical observations. These antifibrinolytic agents had been shown to be more costly and less effective than TA [44]. TA could bring better penetration into major joints than fibrin spray and it is less expensive and safer than aprotinin and more effective than EACA. The binding of TA to plasminogen is 6 to 10 times more potent than that of EACA [45].

Because of activation of fibrinolysis and the exposed surface of cancellous bone, TKA could cause significant blood loss. Here, the most noteworthy result of this study was the efficiency of TA in reducing total blood loss and transfusion rates after TKA. Our study indicates that intravenous use of TA results in sparing at a mean of 420 ml of total blood loss and significantly reduced transfusion rates. At the same time, the use of TA could effectively reduce postoperative drainage volume. Because of occurrence of the occasional thromboembolism events, some physicians are reluctant to use TA in TKA. However, the safety of TA could further be confirmed with the help of our study. In our study, 22 patients in the TA group and 20 patients in the control group developed DVT, with no significant difference (P=0.91). Only 3 patients developed PE events and they all belonged to the control group. The difference between TA and control group was also not statistically significant (P=0.47). With the evidence collected, TA did not increase risks of DVT or PE. Tourniquet use is common in TKA, which activates the local fibrinolysis system and significantly increases blood loss after surgery. TA has antifibrinolytic potency via blocking the lysine-binding sites of plasminogen and is mostly used in bleeding caused by local accentuation of fibrinolysis. On this point, TA mainly resists the fibrinolysis effect

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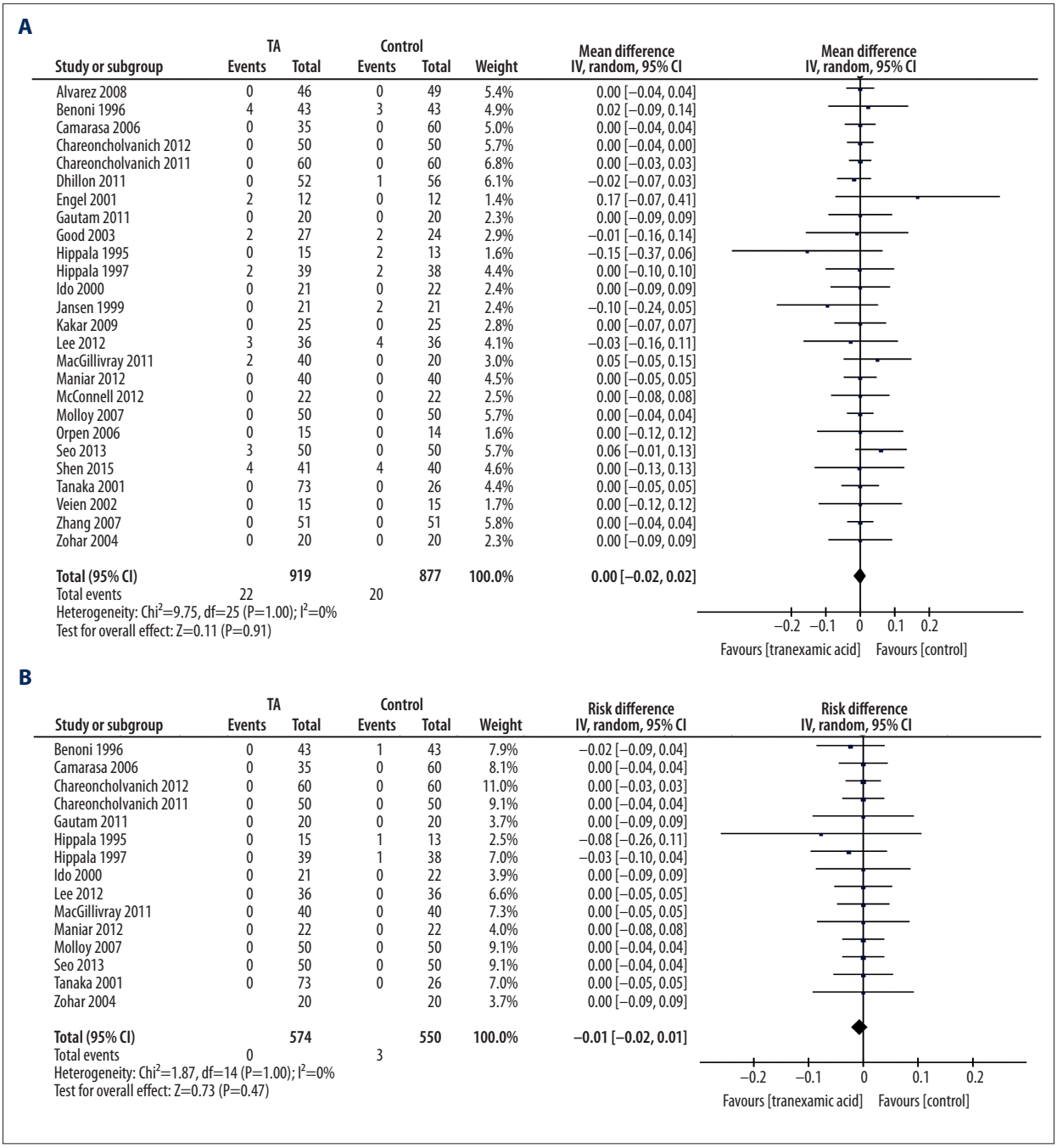

Figure 4. (**A**) Forest plot diagram of TA on incidence of DVT. (**B**) Forest plot diagram of TA on incidence of PE.

caused by tourniquet and generally has little influence on the normal fibrinolysis system. These results are consistent with other meta-analyses [46,47]. The major contraindication to administering TA is allergy. Because high doses of TA might increase the incidence of thrombosis, it is not recommended in patients who have PE history or state. Poeran [48] reported that patients who received TA had lower rates of blood transfusion (7.7 *vs.* 20.1%) as well as combined complications (1.9 *vs.* 2.6%). With an increasing dose of TXA (0–1 g, 1–2 g and >3 g), odds (OR: 0.31 to 0.38) of blood transfusion decreased and risk of complications did not increase significantly.

In our study, most of the trials were of high quality (QAS: 19–24), which makes the conclusions drawn from this meta-analysis more reliable, but there are still many limitations in our analysis: (I) Some uncontrolled factors among the studies may have accounted for the significant heterogeneity in total blood loss, transfusion requirements, and drain loss. (II) We

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Table 1. Characteristics of included studies.

Author, year	Cases	Intervention	Control	DVT prophylaxis	Blood transfusion	DVT screening method	QAS
Alvarez 2008	95 (46)	10 mg/kg 30 min before tourniquet deflation, 1 mg/kg/h infusion for 6 h	S	Bemiparin	Hb <90 g/L	Clinical exam	23
Benoni 1996	86 (43)	10 mg/kg before tourniquet deflation, 10 mg/kg after 3 h	S	LMWH	Hb <85 g/L	Clinical exam	23
Camarasa 2006	95 (35)	10 mg/kg before tourniquet deflation, repeated 3 h later	S	Dalteparin sodium	Hb <80 g/L	Clinical exam/ ultrasound	23
Chareancholvanich 2012	120 (60)	10 mg/kg 10 min before tourniquet deflation, then 10 mg/kg 3 h postoperatively	NA	Ankle motion	Hb <100 g/L	Clinical exam	21
Charoencholvanich 2011	100 (50)	10 mg/kg 10 min before tourniquet deflation, repeated 3 h later	S	Ankle motion	Hb <100 g/L	Clinical exam	21
Dhillon 2011	108 (52)	10 mg/kg IV 10 min tourniquet deflation and after 3 h	NA	LMWH	Hb <90 g/L	Clinical exam	22
Ellis 2001	20 (10)	15 mg/kg 30 min before tourniquet deflation, 10 mg/kg/h infusion for 12h	S	Enoxaparin	Hct <27%	NA	24
Engel 2001	24 (12)	15 mg/kg before tourniquet deflation, 10 mg/kg after 3 h	NA	Certoparin	Hb <100 g/L	Clinical exam	21
Gautam 2011	40 (20)	10 mg/kg 0.5 h before tourniquet deflation, 2 mg/kg after 3 h	S	NA	Hb <80 g/L	Clinical exam	20
Good 2003	51 (27)	10 mg/kg before tourniquet deflation, repeated 3 h later	S	Fragmin	Hb <90 g/L	Clinical exam/ ultrasound	20
Hiippala 1995	28 (15)	15 mg/kg before tourniquet deflation	NS	LMWH	Hb <100 g/L	Clinical exam	23
Hiippala 1997	77 (39)	15 mg/kg before tourniquet deflation, additional doses of 10 mg/kg after 3h	S	Enoxaparin	Hb <100 g/L	Clinical exam	23
Ido 2000	43 (21)	1 g before tourniquet release,1 g 3 h after operation	NA	NA	NA	Clinical exam	19
Jansen 1999	42 (21)	15 mg/kg 30 min before tourniquet deflation,repeated every 8 h for 3 d	S	Fraxiparine	PCV <26%	Clinical exam	21
Kakar 2009	24 (12)	10 mg/kg before tourniquet deflation, 1 mg/kg/h until wound closure	NS	NA	Hb <80 g/L	NA	23

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Table 1 continued. Characteristics of included studies.

Author, year	Cases	Intervention	Control	DVT prophylaxis	Blood transfusion	DVT screening method	QAS
Lee 2012	72 (36)	10 mg/kg before tourniquet deflation, repeated 6 h later	NA	LMWH	Hb <80 g/L	Clinical exam/ ultrasound	20
Lin 2011	100 (50)	10 mg/kg IV before deflation of the tourniquet	S	LMWH	Hb <85 g/L	NA	18
MacGillivray 2011	60 (20)	10-15 mg/kg tourniquet deflation and after 3 h	NS	Warfarin	Hb <80 g/L	Clinical exam/CT	24
Maniar 2012	80 (40)	10 mg/kg IV before deflation of the tourniquet	S	LMWH	Hb <85 g/L	Clinical exam	22
McConnell 2012	44 (22)	10 mg/kg at induction of anesthesia	NA	Aspirin	NA	Clinical exam	20
Molloy 2007	100 (50)	500 mg 5 min before tourniquet deflation, repeated 3 h later	NA	Aspirin	Hct <25%	Clinical exam	23
Orpen 2006	29 (15)	15 mg/kg at cement mixing commenced	NS	Fragmin	Hb <90 g/L	ultrasound	23
Seo 2013	100 (50)	1.5g TXA/100mL NS	S	NA	Hb <80 g/L	NA	19
Shen 2015	96 (46)	100 mL,15 min before tourniquet deflation	S	LMWH	Hb <80 g/L	ultrasound	22
Tanaka 2001	99 (73)	10 mg/kg before surgery, 10 mg/kg 10 min before tourniquet deflation	S	NA	NA	Venography	19
Veien 2002	30 (15)	10 mg/kg before tourniquet deflation, repeated 3 h later	NS	Fraxiparine	Hct <28%	Clinical exam	22
Zhang 2007	102 (51)	1 g before tourniquet deflation, repeated 3 h later	S	LMWH	NA	Clinical exam	19
Zohar 2004	40 (20)	15 mg/kg 15 min before tourniquet deflation,10 mg/kg/h infusion for 12h	NA	Enoxaparin	Hct <28%	Clinical exam/ ultrasound	21

NA – not available; S – saline; NS – normal saline; LMWH – low-molecular-weight heparin; QAS – quality assessment score.

selected studies that excluded high-risk patients, including patients with cardiovascular disorders, and DVT events. Thus, our results should be interpreted with caution.

Conclusions

This meta-analysis concludes that TA significantly reduces total blood loss and transfusion rate after TKA and does not apparently increase the risk of DVT or PE. Lager-scale prospective randomized controlled studies are needed and the optimal administration of TA in TKA still needs further investigation. Moreover, to better highlight the safety and efficacy of TA in TKA, studies that compare TA with other anti-fibrinolytics are needed.

Conflict of Interest

The authors have declared that no competing interests exist.

References:

1. Lemaire R : Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg Br, 2008; 90: 1128–36
2. Tobias JD: Strategies for minimizing blood loss in orthopedic surgery. Semin Hematol, 2004; 41: 145–56

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

3. Callaghan JJ, O'Rourke MR, Liu SS: Blood management: issues and options. J Arthroplasty 2005; 20: 51–54
4. Bierbaum BE, Callaghan JJ, Galante JO: An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am, 1999; 81: 2–10
5. Lotke PA, Faralli VJ, Orenstein EM, Ecker ML: Blood loss after total knee replacement: effects of tourniquet release and continuous passive motion. J Bone Joint Surg, 1999; 73: 1037–40
6. Zanasi S: Innovations in total knee replacement: new trends in operative treatment and changes in peri-operative management. Eur Orthop Traumatol, 2011; 2: 21–31
7. Rajesparan K, Biant LC, Ahmad M, Field RE: The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg, 2009; 91: 776–83
8. Henry DA, Carless PA, Moxey AJ et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev, 2001; (1): CD001886
9. Dunn CJ, Goa KL: Tranexamic acid: a review of its use in surgery and other indications. Drugs, 1999; 57: 1005–32
10. Lumsden MA, Wedisinghe L: Tranexamic acid therapy for heavy menstrual bleeding. Expert Opin Pharmacother, 2011: 12: 2089–95
11. Cid J, Lozano M: Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. Transfusion, 2005, 45: 1302–7
12. Moher D, Liberati A, Tetzlaff J et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ, 2009, 339: b2535
13. Handoll H et al: Cochrane Bone, Joint and Muscle Trauma Group. About the Cochrane collaboration (Cochrane Review Groups (CRGS)), 2008, Issue 4. Art. No: MUSKINJ
14. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med, 2002; 21: 1539–58
15. Alvarez JC, Santiveri FX, Ramos I et al: Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion, 2008; 48(3): 519–25
16. Benoni G, 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(3): 434–40
17. Camarasa MA, Ollé G, Serra-Prat M et al: Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth, 2006; 96(5): 576–82
18. Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, Pornrattanamaneewong C: Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. BMC Musculoskelet Disord, 2012, 13: 124
19. Charoencholvanich K, Siriwattanasakul P: Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. Clin Orthop Relat Res, 2011; 469(10): 2874–80
20. Dhillon MS, Bali K, Prabhakar S: Tranexamic acid for control of blood loss in bilateral total knee replacement in a single stage. Indian J Orthop, 2011; 45: 148–52
21. Ellis MH, Fredman B, Zohar E et al: The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. J Clin Anesth, 2001; 13(7): 509–13
22. Engel JM, Hohaus T, Ruwoldt R et al. Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. Anesth Analg, 2001; 92(3): 775–80
23. Gautam PL, Katyal S, Yamin M, Singh A: Effect of tranexamic acid on blood loss and transfusion requirement in total knee replacement in the Indian population: a case series. Indian J Anaesth, 2011; 55(6): 590–93
24. Good L, Peterson E, Lisander B: Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth, 2003; 90(5): 596–99
25. Hiippala S, Strid L, Wennerstrand M et al: Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth, 1995; 74(5): 534–37
26. Hiippala ST, Strid LJ, Wennerstrand MI et al: Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg, 1997; 4(4): 839–44
27. Ido K, Neo M, Asada Y et al: Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg, 2000; 120(9): 518–20
28. Jansen AJ, Andreica S, Claeys M et al: Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. Br J Anaesth, 1999; 83(4): 596–601
29. Kakar PN, Gupta N, Govil P, Shah V: Efficacy and safety of tranexamic acid in control of bleeding following TKR: a randomized clinical trial. Indian J Anaesth, 2009; 53(6): 667–71
30. Lee SH, Cho KY, Khurana S, Kim KI: Less blood loss under concomitant administration of tranexamic acid and indirect factor Xa inhibitor following total knee arthroplasty: a prospective randomized controlled trial. Knee Surg Sports Traumatol Arthrosc, 2013; 21(11): 2611–17
31. Lin PC, Hsu CH, Chen WS, Wang JW: Does tranexamic acid save blood in minimally invasive total knee arthroplasty. Clin Orthop Relat Res, 2011, 469: 1995–2002
32. MacGillivray RG, Tarabichi SB, Hawari MF, Raoof NT: Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. J Arthroplast, 2011; 26: 24–28
33. Maniar RN, Kumar G, Singhi T et al: Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res, 2012, 470: 2605–12
34. McConnell JS, Shewale S, Munro NA et al: Reducing blood loss in primary knee arthroplasty: a prospective randomized controlled trial of tranexamic acid and fibrin spray. Knee, 2012; 19(4): 295–98
35. Molloy DO, Archbold HA, Ogonda L et al: Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. J Bone Joint Surg Br, 2007; 89(3): 306–9
36. Orpen NM, Little C, Walker G, Crawfurd EJ: Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. Knee, 2006; 13(2): 106–10
37. Seo JG, Moon YW, Park SH et al: The comparative efficacies of intraarticular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc, 2013, 21: 1869–74
38. Shen PF, Hou WL, Chen JB et al: Effectiveness and safety of tranexamic acid for total knee arthroplasty: a prospective randomized controlled trial. Med Sci Monit, 2015; 21: 576–81
39. Tanaka N, Sakahashi H, Sato E et al: Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br, 2001; 83(5): 702–5
40. Veien M, Sørensen JV, Madsen F, Juelsgaard P: Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. Acta Anaesthesiol Scand, 2002; 46(10): 1206–11
41. Zhang F, Gao Z, Yu J: [Clinical comparative studies on effect of tranexamic acid on blood loss associated with total knee arthroplasty]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi, 2007; 21(12): 1302–4 [in Chinese]
42. Zohar E, Ellis M, Ifrach N et al: The postoperative bloodsparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg, 2004; 99(6): 1679–83
43. Niskanen RO, Korkala OL: Tranexamic acid reduces blood loss in cemented hip arthroplasty. Acta Orthop, 2005, 26: 829–32
44. Kagoma YK, Crowther MA, Douketis J et al: Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopaedic surgery: a systematic review of randomized trials. Thromb Res, 2009; 123: 687–96
45. Ellis MH, Fredman B, Zohar E et al: The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. J Clin Anesth, 2011; 13: 509–13
46. Cid J, Lozano M: Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. Transfusion, 2005; 45: 1302–7
47. Ho KM, Ismail H: Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. Anaesth Intensive Care, 2003; 31(5): 529–37
48. Poeran J, Rasul R1, Suzuki S et al: Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ, 2014; 349: g4829

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