Safety and Efficacy of Tranexamic Acid in Total Knee Arthroplasty

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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 indicated as mean standard deviation, and the outcomes were analyzed by mean difference with 95% confidence interval. Dichotomous variables for each arm were indicated 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 I² >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.
### 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 detailed 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 (I²=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, I²=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; I²=94%]. The TA group had less postoperative drainage compared to the control group (Figure 3).
### 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.
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 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, I²=0) (Figure 4B).

Discussion

The results of the study show that the use 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.

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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

Figure 4. (A) Forest plot diagram of TA on incidence of DVT. (B) Forest plot diagram of TA on incidence of PE.
| 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 |
| Camara 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 12 h | 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 3 h | 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 |
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. Larger-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.

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