Original Article

DOI: 10.5582/ddt.2015.01018

Topical administration of tranexamic acid in total hip arthroplasty: A meta-analysis of Randomized Controlled Trials

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Summary **Tranexamic acid (TXA) is an antifibrinolytic drug which has been widely used in many areas of surgery. The purpose of our meta-analysis was to review randomized controlled trials (RCT) of the effectiveness and safety of topical TXA treatment in reducing total blood loss and transfusion rate for patients undergoing primary total hip arthroplasty (THA). A literature search was undertaken. Five eligible reports match the inclusion and exclusion standard. The topical administration of TXA groups revealed lower total blood loss(mean difference - 347ml, 95% CI, - 411 to - 282 mL; $p < 0.00001$) and transfusion rate (OR, 0.23 ($p < 0.00001$; 95% CI, 0.14-0.38)) compared with control groups. Meanwhile there was no statistically significant difference in the risk of developing thromboembolic events (OR, 1.64 (95% CI, 0.39-6.97); $p = 0.5$). Topical administration of TXA could significantly reduce total blood loss and transfusion requirements in primary THA, without increased thromboembolic complications.**

Keywords: Topical administration, tranexamic acid, total hip arthroplasty, intra-articular, meta-analysis

1. Introduction

Total hip arthroplasty (THA) is an effective treatment for osteoarthritis of the hip, femoral neck fracture, aseptic necrosis of femoral head and congenital developmental dysplasia of the hip. However, THA is associated with considerable perioperative blood loss and subsequently requires allogenic transfusion (*1,2*). Such allogenic transfusions may carry potential hazards of adverse immunological reactions, intravascular hemolysis, transfusion-related acute lung injury, disease transmission, transfusion-induced coagulopathy, renal failure, and even increased mortality (*3-5*).

Tranexamic acid (TXA), a synthetic derivative of lysine, prevents fibrinolysis by reversible blockade of the lysine-binding sites of plasminogen, thereby achieving the goal of local hemostasis and reducing bleeding (*6,7*). Currently, TXA has been widely used in many areas of surgery, such as, cardiovascular surgery, gastrointestinal bleeding, postpartum hemorrhage, orthotopic liver transplantation, and hip and knee arthroplasty (*8-11*). Intravenous administration of TXA has been reported to reduce blood loss in primary THA (*12-14*). However, one significant concern with TXA, is the risk of systemic thrombotic events which have been taken into consideration.

In consideration of thrombotic events with intravenous administration, more and more scholars have started to transfer their attention to topical use of TXA (*15,16*). Compared with IV-TXA, it has been hypothesised that topical application provides maximum concentration of TXA at the bleeding site, and is associated with little or no systemic absorption of TXA. However, clinical efficacy is inconsistent (*17,18*) and an optimal TXA treatment protocol is still unknown. We therefore performed a meta-analysis of randomized controlled trials (RCT) to investigate the effectiveness and safety of topical TXA treatment in reducing total blood loss and transfusion rate for patients undergoing primary THA.

2. Methods

This systematic review and meta-analysis was based on the standards described in Preferred reporting items for systematic reviews and meta-analyses (*19*).

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2.1. *Inclusion and eligibility criteria*

Only randomized controlled trials (RCTs) studies were eligible for this study, the inclusion criteria are as follows: (*i*) patients were adults who received primary unilateral THA regardless of the type or size of prosthesis implanted; (*ii*) the intervention was topical(intra-articular)administration of TXA; (*iii*) the full text of each article was available; (*iv*) outcome measures included total blood loss, transfusion rate, and incidence of thromboembolic complications. Exclusion criteria: (*i*) patients who had allergy to tranexamic acid; (*ii*) thrombotic disorder; (*iii*) patients who were on anticoagulant treatment.

2.2. *Search strategy*

Two independent reviewers searched the PubMed, Elsevier, Ebsco host, and OVId, to acquire all relevant articles. There were no restrictions as to the language and date. The key words used for the search included: "tranexamic acid" or "cyklokapron" and "total hip replacement" or "total hip arthroplasty" and "topical" or "intra-articular". The reference lists of related reviews and meta-analyses were reviewed for any potential studies.

2.3. *Extraction of data*

Each date extraction was reviewed and agreed upon by the authors, and a preliminary test was performed to ensure its consistency. The complete manuscript was obtained and carefully scrutinized by the two reviewers. Any disagreement between them was resolved by consensus or consultation with the senior authors. Data extracted included: author's name, publication year, sample size, dose of TXA, method of TXA administration, type of control, postoperative thromboprophylaxis, THA prothesis, anesthesia, DVT screening method, total blood loss, transfusion rate, and incidence of thromboembolic complications.

2.4. *Study quality*

The methodological quality of included studies was assessed with the use of Jadad Score by two independent reviewers (*20*). Any disagreement was resolved by consensus or the senior authors. Studies with a Jadad score of 1 were considered poor, scores of 2 were considered adequate and a score of 3 or higher was considered as high quality.

2.5. *Statistical analysis*

The meta-analysis program of the Review Manager Database (RevMan version 5.2, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.) was utilized to analyze selected data. Continuous data were summarized using the weighted mean differences and respective 95% confidence intervals (95% CI). Dichotomous data were summarized using odds ratio (OR) and 95% confidence intervals (95% CI). The presence of heterogeneity was assessed using Chi square test and I square test. A p value < 0.1 and I_2 > 50% were considered presence of statistical heterogeneity. A random-effects model analysis was used to estimate trials showing heterogeneity while a fixed-effect model analysis was used for the reverse. A non-significant test result(a p value > 0.1 and an I_2 value < 50%) only suggested that there was no evidence of heterogeneity; it did not necessarily signify homogeneity, as there may have been insufficient power to detect heterogeneity.

3. Results

A total of 277 abstracts and titles were reviewed. After screening, eventually five (*21-25*) eligible reports matched the inclusion and exclusion standard for analysis (Figure1). Two studies (*21,22*) included topical administration of TXA in total hip arthroplasty and total knee arthroplasty. One study (*25*) included two experimental groups (intravenous injection of TXA and topical administration of TXA). Only outcome

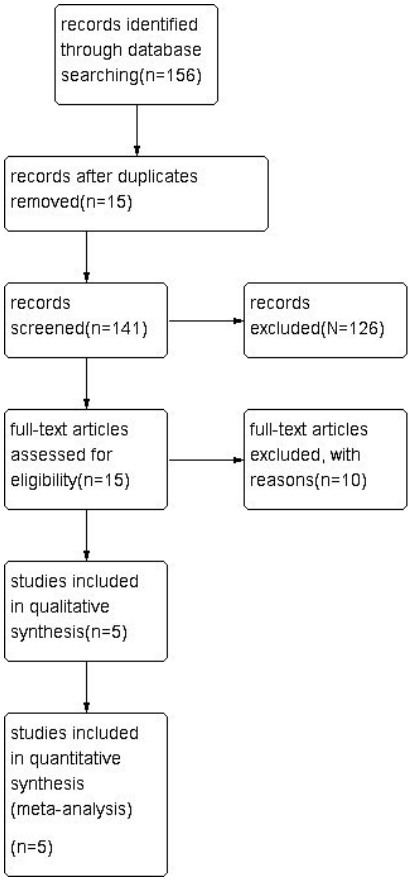

Figure 1. Flowchart of the study selection.

Table 1. Characteristics of included studies

Author	Number (TXA/Con)	Intervention (TXA)	Con	Thromboprophylaxis	Bone cement	Anesthesia	DVT screen
Konig (2013)	91/40	3gTXA/100mlNS topically used at three points during the procedure	None	Not mentioned	Cementless	Spinal	Not mentioned
Martin (2014)	25/25	2gTXA/100mlNS inject into the joint prior to surgical closure	100mlNS	Warfarin or aspirin	Cemented (15) cementless (35)	General or spinal	Clinical
Yue (2014)	52/49	3gTXA/150mlNS topically used 150mlNS at three points during the procedure	150mlNS	LMWH	Cementless	General or spinal	Ultrasound
Alshryda (2013)	81/80	Topical (intra-articular) application of tranexamic acid	Not mentioned	Mechanical and mechanical + LMWH when BMI>30 kg/m^2	Cemented (8) cementless (120) hybrid (33)	General or spinal	Doppler ultrasound
Wei (2014)	102/100	3gTXA/100mlNS topically used at three points during the procedure	100mlNS	LMWH	Cementless	Not mentioned	Ultrasound

TXA: tranexamic acid, Con: control, LMWH: low molecular weight heparin, DVT: deep vein thrombosis.

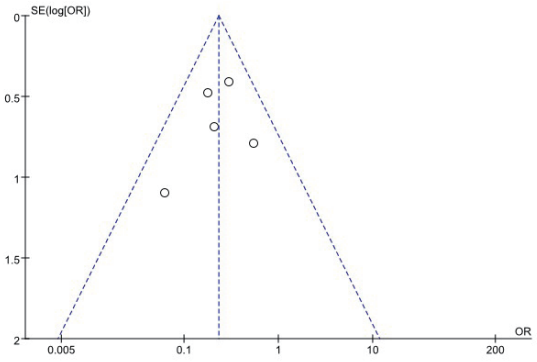

Figure 2. Funnel plot of transfusion rate. SE, standard error.

measurements referring to "THA" and "topical" group were analyzed in the present study. Only one report (*21*) did not mention thromboprophylaxis, and the method for screening thrombosis. The details of the included studies are listed in Table 1.

Figure 2 represents funnel plots examining for potential publication bias between studies. These funnel plots reports the logs OR of the numbers of patients requiring allogeneic transfusions as a measure of the treatment effect, and it shows moderate asymmetry, indicating mild publication bias.

3.1. *Total blood loss*

Four studies including 595 patients reported total blood loss (*21, 23-25*). The combination of data from the studies revealed lower total blood loss in topical administration of TXA groups compared with control groups (mean difference – 347 mL, 95% CI, − 411 to − 282 mL; $p < 0.00001$). Forest plots summarized the meta-analysis including data comparing total blood loss between TXA groups and control groups (Figure 3).

3.2. *Transfusion requirements*

The number of patients who needed allogenetic blood transfusion was recorded in five trials with 654 patients. Transfusion rate was significantly lower in the topical administration TXA group compared with the control group (OR, 0.23 (95% CI,0.14-0.38)) (Figure 4).

3.3. *Thromboembolic complications*

The data of thromboembolic complications was available in all five studies. Three studies (*21,24,25*) reported six thromboembolic events, four of 351 in the TXA group and two of 294 in the control group. However, there was no statistically significant difference in the risk of developing thromboembolic events (OR, 1.64 (95% CI, 0.39-6.97); $p = 0.5$) (Figure 5).

4. Discussion

This meta-analysis only analyzed randomized controlled trials (RCTs) so as to minimize the possibility of bias. Our results showed that topical (intra-articular) administration of TXA could effectively reduce total blood loss, and allogeneic blood transfusion rate. Also, topical (intra-articular) administration of TXA did not demonstrate increased risk of DVT, PE or other adverse events. This is consistent with the meta-analyses by Panteli in total knee replacement (*26*). However, given the relatively short duration of postoperative follow-up, and small sample involved, these findings require further confirmation.

All the five studies were graded with high quality scores, while the methodological quality of included trials was insufficient. Only three trials were almost identical, and one did not mention the placebo group

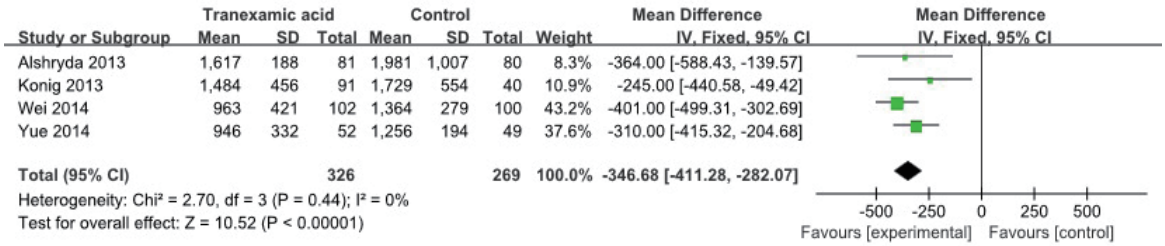

Figure 3. Trials of TXA versus control:forest plot of total blood loss.

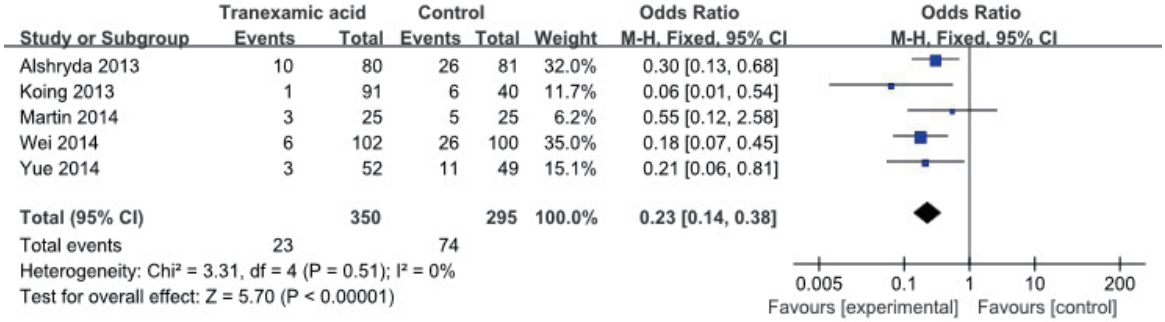

Figure 4. Trials of TXA versus control:forest plot of transfusion rate.

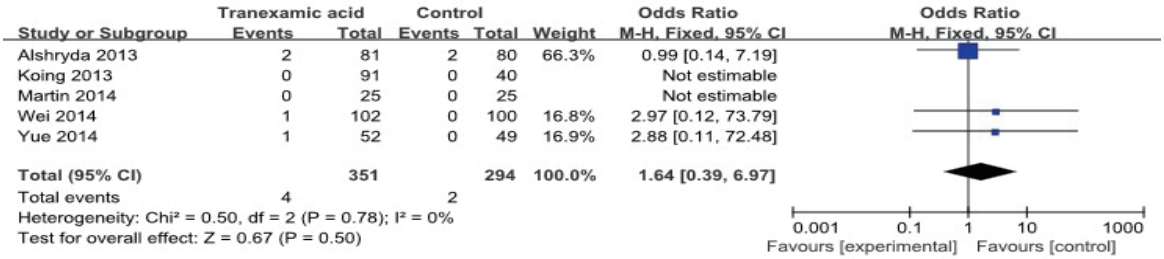

Figure 5. Trials of TXA versus control:forest plot of thromboembolic complications.

(*21*). The remaining two different method trials: one 2 g TXA/100 mL NS injected into the joint prior to surgical closure (*22*), the other topical (intra-articular) application of tranexamic acid (*24*) and did not mention the dose of TXA. These differences could have resulted in biased and flawed results. Furthermore, we believe that patient characteristics variation, postoperative thromboprophylaxis, anesthesia type, dose of TXA, method of TXA administration, and THA prothesis type, can distort the results. Although in this study heterogeneity is very low, it did not necessarily imply homogeneity. There may have been potential heterogeneity, because we lack sufficient power to detect it.

TXA is an antifibrinolytic agent and it has been confirmed that intravenous TXA could effectively reduce bleeding and transfusion rates in THA and TKA (*7,17*). Additional meta-analyses and systematic reviews about the efficacy of intravenous TXA in THA have been published (*27,28*). However, the risk of systemic thrombotic events must be taken into consideration and it is generally agreed that only a small percentage of the intravenously injected drug reaches the target location to inhibit tissue fibrinolysis and stabilize clots (*29*). Compared with IV-TXA, a topical (intra-articular) administration has the advantage of providing a maximum concentration of TXA at the bleeding site, and is associated with little or no systemic absorption of the TXA (*24*). So far,there are few meta-analyses about intra-articular injection of tranexamic acid and the efficacy of topical administration of TXA is obscure in THA and therefore we conducted this study.

The limitations of our study include small sample size (only 654 patients) and insufficient data are available to support the analysis of hip joint function and quality of life. Furthermore, the method of TXA administration, dose of TXA, THA prothesis type, and surgical technique may affect the outcome.

In conclusion, this meta-analysis demonstrated that topical administration of TXA could significantly reduce total blood loss and transfusion requirements in primary THA, without significant increase of thromboembolic complications. Because of the small sample size, more prospective randomized controlled studies with a larger scale of patients are necessary.

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(Received March 24, 2015; Revised May 9, 2015; Accepted June 20, 2015)