Comparative efficacy and safety of different hemostatic methods in total hip arthroplasty: a network meta-analysis

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Abstract

Background: It is unclear which kind of interventional therapy is the best when reducing blood loss in patients prepared for total hip arthroplasty (THA). We performed this network meta-analysis to rank the best intervention arm for blood loss control in THA patients.

Methods: We searched electronic databases about randomized controlled trials (RCTs) to compare three treatments (topical tranexamic acid (TXA), intravenous TXA, and topical fibrin sealant (FS)) versus placebo for the people prepared for THA. Traditional and network meta-analyses were performed. The quality assessment was conducted using Cochrane Collaboration’s tool. The network meta-analysis was conducted using Stata 13.0 software.

Results: Finally, a total of 32 RCTs were included in this network meta-analysis. Topical TXA, intravenous TXA, and topical FS significantly decreased the need for transfusion and total blood loss when compared with placebo. And intravenous TXA ranks the first hemostasis agent for reducing the need for transfusion and total blood loss. There was no significant difference between these three treatments (intravenous TXA, topical TXA, and topical FS) in the occurrence of deep venous thrombosis (DVT).

Conclusion: Intravenous TXA may be the best way to reduce the need for transfusion and total blood loss. More direct studies that focused on topical TXA versus FS are needed in the future.

Keywords: Tranexamic acid, Fibrin sealant, Total hip arthroplasty, Blood loss

Introduction

Total hip arthroplasty (THA) is associated with considerable blood loss, which can lead to a need for transfusion. It is reported that perioperative blood loss in THA can be as much as 700–2000 ml, and subsequently, 16 to 37% of patients need blood transfusion [1, 2]. Blood transfusion has several serious complications, such as virus transmission and immunological reaction [3, 4]. What is more, the economic burden caused by blood transfusion will be increased correspondingly. Substantial blood loss was mainly caused by the osteotomy of the femoral and surgical trauma and fibrinolysis. In order to reduce blood loss, several strategies have been managed to inhibit the fibrinolysis and surgical bleeding. Fibrin sealant (FS) is composed of fibrinogen and thrombin that mainly derived from human blood products [5, 6]. When those components mixed, fibrin formed and crosslinked directly with tissue collagen [7]. Tranexamic acid (TXA) is a synthetic amino acid, and its structure is analogous to lysine that can competitively inhibit plasminogen and reduce fibrinolysis locally [8]. There are two main administration routes to the management of TXA: topical TXA and intravenous TXA [9]. Clinical studies and meta-analysis found that both the topical and intravenous TXA can reduce blood loss without sacrificing the safety [10]. And several studies have identified the efficacy and safety of FS for reducing perioperative blood loss in THA. In the current clinical practice, which hemostasis agents were the most effective was in debate. In addition, the meta-analysis comparing topical
versus intravenous TXA in THA was limited. The purpose of this network meta-analysis was to compare the efficacy and safety of the three treatments (FS, topical TXA, and intravenous TXA) for patients prepared for THA. Our intention was to provide hierarchies of the need for transfusion, total blood loss, and incidence of deep venous thrombosis.

**Methods**

**Criteria for considering studies**

We only included RCTs which compared the need for transfusion, total blood loss, blood loss in drainage, and occurrence of DVT of the three main interventions (FS, topical TXA, and intravenous TXA) in people prepared for unilateral THA. Studies were included in the systematic review if they met the criteria: (1) primary unilateral THA; (2) RCTs; (3) intervention including FS, topical TXA, intravenous TXA, and control group; and (4) at least included one of the following outcomes: total blood loss, need for transfusion, and occurrence of deep venous thrombosis (DVT).

Trials were excluded if they (1) were meetings, letters, and protocols; (2) had repeated data or without insufficient data for meta-analysis; and (3) were retrospective design and prospective cohort studies.

**Search methods and study selection**

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and Web of Science from inception to August 2018. Keywords and MeSH terms including “total hip arthroplasty”; “total hip replacement”; “THA”; “THR”; “Arthroplasty, Replacement, Hip”[Mesh]; “fibrin glue”;

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Fig. 1 Flow diagram for the included studies
“fibrin sealant”; “fibrin tissue adhesive”; “Fibrin Tissue Adhesive[Mesh]”; and “tranexamic acid” were used in the search strategy. We also viewed a systematic review and meta-analysis for any omissive papers. Two independent authors selected the included studies based on the title and abstract. Any disagreement about whether included or not was resolved by a discussion or consulted to a senior reviewer.

**Table 1 The general characteristic of the included studies**

| Study           | Sample size | Comparators | Study design | Male, % | Mean age | Bone cement | Dose          |
|-----------------|-------------|-------------|--------------|---------|----------|-------------|---------------|
| Benoni 2000     | 40 (20/20)  | IV TXA/C    | RCT          | 42.5    | 69.5/68  | Cemented    | 10 mg/kg TXA  |
| Ekbaëck 2000    | 40 (20/20)  | IV TXA/C    | RCT          | 50      | 66.4/65.6| Cemented    | 10 mg/kg TXA  |
| Ido 2000        | 40 (20/20)  | IV TXA/C    | RCT          | NS      | NS       | NS          | 1000 mg TXA   |
| Husted 2003     | 40 (20/20)  | IV TXA/C    | RCT          | 32.5    | 65/67    | Cementless or Hybrid | 10 mg/kg TXA |
| Lemay 2004      | 39 (20/19)  | IV TXA/C    | RCT          | 64.1    | 59.7/53.6| Cemented or cementless | 10 mg/kg TXA |
| Garneti 2004    | 50 (25/25)  | IV TXA/C    | RCT          | NS      | 67.6/69.6| Cemented    | 10 mg/kg TXA  |
| Yamashaki 2004  | 40 (20/20)  | IV TXA/C    | RCT          | 67.5    | 55.5/61.2| Cementless  | 1 g TXA       |
| Johansson 2005  | 100 (47/53) | IV TXA/C    | RCT          | 43      | 69/68    | Cemented    | 15 mg/kg TXA  |
| Niskanen 2005   | 39 (19/20)  | IV TXA/C    | RCT          | 33.3    | 66/65    | Cemented    | 10 mg/kg TXA  |
| Claes 2007      | 40 (20/20)  | IV TXA/C    | RCT          | 30      | 73/68    | Hybrid      | 15 mg/kg TXA  |
| Rajespan 2009   | 73 (36/37)  | IV TXA/C    | RCT          | 35.6    | 67/67    | Cemented, cementless or Hybrid | 1 g TXA   |
| Kazemi 2010     | 64 (32/32)  | IV TXA/C    | RCT          | 67.2    | 46.6/45.4| Cementless  | 15 mg/kg TXA  |
| Singh 2010      | 42 (21/21)  | IV TXA/C    | RCT          | 45.2    | 69/73    | Cemented or cementless | 10 mg/kg TXA |
| McConnell 2011  | 66 (22/22/2)| IV TXA/FS/C | RCT          | 31.8    | NS       | Cemented    | 10 mg/kg TXA/10 ml FS |
| Malhotra 2011   | 50 (25/25)  | IV TXA/C    | RCT          | 44      | 52.6/54.7| Cementless  | 15 mg/kg TXA  |
| Clave 2012      | 70 (37/33)  | IV TXA/C    | RCT          | 35.7    | 69/73    | Cementless  | 1 g TXA       |
| Norio 2012      | 117 (95/22) | IV TXA/C    | RCT          | 17.9    | 64.4/60.2| Cementless  | 1 g TXA       |
| Falez 2013      | 69 (31/38)  | FS/C        | RCT          | NS      | NS       | NS          | 10 ml FS      |
| Lassen 2006     | 69 (33/36)  | FS/C        | RCT          | 39.1    | 67.1/63.1| Cemented or cementless | NS         |
| Mawatari 2006   | 100 (50/50) | FS/C        | RCT          | NS      | 60/60    | Cementless  | 10 ml FS      |
| Randelli F 2013 | 70 (35/35)  | FS/C        | RCT          | 41.2    | 63.1/64.2| Cementless  | 10 ml FS      |
| Wang 2003       | 81 (38/43)  | FS/C        | RCT          | 54.2    | 66.9/67.8| NS          | 10 ml FS      |
| Xie 2016        | 140 (70/70) | IV TXA/T TXA| RCT          | 45      | 59.5/62.2| Cementless  | 1.5g IV TXA/3g T TXA |
| Wei 2014        | 303 (100/102/101) | IV TXA/T TXA/ C | RCT | 37.3 | 63.6/60.2/63.9 | Cementless | 3g IV TXA/3g T TXA |
| North 2016      | 139 (70/69)| IV TXA/T TXA | RCT          | 55.5    | 64.1/65.7| Cementless  | 2g IV TXA/2 g T TXA |
| Zhang 2016      | 75 (25/25/25)| IV TXA/T TXA/ C | RCT | 52    | 44.5/44.3/43.4 | Cementless | 1g IV TXA/1 g T TXA |
| Martin 2013     | 50 (25/25)  | T TXA/C     | RCT          | 38.7    | 62.9/63.9| Cemented    | 2g T TXA      |
| Alshydra 2013   | 161 (80/81) | T TXA/C     | RCT          | 45.9    | 66/63    | Cementless  | NS            |
| Yue 2014        | 101 (52/49) | T TXA/C     | RCT          | 52.1    | 60.9/63.7| Cementless  | 3 g T TXA     |
| Yi 2016         | 100 (50/50) | IV TXA/C    | RCT          | 53      | 54/56.6  | NS          | 15 mg/kg TXA  |
| Lee 2013        | 68 (34/34)  | IV TXA/C    | RCT          | NS      | 51.4/52.8| Cementless  | 15 mg/kg TXA  |
| Benoni 2001     | 38 (18/20)  | IV TXA/C    | RCT          | 50      | 66/68    | Cemented    | 10 mg/kg TXA  |

*IV intravenous, T topical, TXA tranexamic acid, C control, FS fibrin sealant, NS not stated, RCT randomized controlled trials*
Comparators, study design, male patients, mean age, bone cement (cemented or uncemented), and dose of interventions. Meanwhile, we collected data about final outcomes: need for transfusion, total blood loss, and the occurrence of DVT. When relevant data was missing or needed to be identified, attempts were made to connect with the corresponding author by e-mail.

Cochrane risk of bias tool was used to assess the risk of bias. A total of seven domains were assessed and classified as low, unclear, and high risk of bias according to the suggestion of Cochrane risk of bias tool.

Data analysis
Data were recorded into Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) by two reviewers (Zhihu Zhao and Xinlong Ma). If there are differences between reviewers, re-review the literature to resolve. For continuous data (total blood loss), the mean difference (MD) with 95% confidence interval (CI) was used for direct comparisons. For network meta-analysis, MD with 95% credible intervals (CrI) was calculated by Stata software. Dichotomous data (need for transfusion and the occurrence of DVT) were used for odds ratio (OR) with 95% CI or 95% CrI to express indirect comparisons. Anna Chaimani model for network meta-analysis was used as previously described [11, 12]. Briefly, we calculate the inconsistency factor (IF) and its 95% confidence interval (IF) to evaluate the consistency of each closed loop. When the lower limit of the 95% confidence interval is equal to 0, it was considered to be consistent. Otherwise, there is a significant inconsistency in the closed loop.

Results
Study identification and selection
The literature search strategy process was shown in Fig. 1. Initially, we identified a total of 822 papers
from electronic databases, and no additional records identified from other sources. After the duplicates were removed, a total of 406 papers were going to the next process. After scanning the titles and abstracts of these papers, 374 papers were excluded. In total, 32 studies were included in the meta-analysis [13–44].

Study characteristics and risk of bias in included studies
As illustrated in Table 1, all the included studies provide detailed information about the general characteristics of the studies. A total of 31 clinical trials with 2476 patients were finally included in the meta-analysis. The sample size ranged from 20 to 102, and the age of the patients ranged from 45.4 to 73. Risk of bias summary and risk of bias graph can be seen in Figs. 2 and 3, respectively.

Effects of interventions on the need for transfusion
The network of four interventions on the need for transfusion was shown in Fig. 4. Table 2 provided hierarchies of effect size on the need for transfusion. Ranking graph of the distribution of probabilities on the need for transfusion was shown in Fig. 5. The direct and indirect comparisons indicated IV TXA, T TXA, and FS significantly decreased the need for transfusion compared with the control group. Based on SUCRA, control (0.97) ranked the first, the second was FS (0.66), the third was T TXA (0.23), and the last was IV TXA group (0.14).

Effects of interventions on the total blood loss
A total of 1287 THAs (IV TXA = 401, T TXA = 386, FS = 500, control = 562) were included for the analyses of total blood loss. The network of comparisons on total blood loss was shown in Fig. 6. Table 3 provided hierarchies of effect size on total blood loss. Figure 7 showed the ranking graph of the total blood loss between these treatments. The direct and indirect meta-analyses indicated IV TXA, T TXA, and FS significantly decreased total blood loss compared with the control group. Based on SUCRA value, Control (0.97) ranked the first, the second was FS (0.44), the third was T TXA (0.32), and the last was IV TXA group (0.27).

Effects of treatments on the DVT
A total of 476 patients were assigned to IV therapy and 297 to topical therapy, 556 patients were assigned to the FS group, and 713 patients were assigned to control therapy. The network of 4 comparisons (IV TXA, T TXA, FS, and control) on the occurrence of DVT was shown in Fig. 8. We also made a ranking graph of the distribution of probabilities on the occurrence of DVT in Fig. 9. Based on SUCRA, Co (0.67) ranked the first, the second was T TXA (0.56), the third was FS (0.52), and the last was IV TXA group (0.48).

Small-study effect and inconsistency test
Figure 10 shows that the funnel plot is symmetrical, indicating there is no publication bias in this network.
Discussion

This is the first systematic review and network meta-analysis that provided hierarchies for the need for transfusion, total blood loss, and the occurrence of DVT comparing two main hemostasis agents (FS and TXA) after THA. All the included studies were RCTs, and the general characteristic was comparable that all patients were old patients prepared for unilateral THA. There were several strengths in this network meta-analysis: (1) comprehensive search strategy by two authors was used to increase the robustness of the search results; (2) traditional and network meta-analysis were both performed to exhibit the evidence for hemostasis in THA patients; (3) we used SUCRA to rank these interventions; and (4) only RCTs were included in this article.

The meta-analysis indicated that (1) FS, IV TXA, and topical TXA can reduce total blood loss and need for transfusion after THA; (2) for decreasing the need for transfusion, the ranking of treatments was IV TXA, topical TXA, FS, and control; (3) for reducing total blood loss, the ranking of treatments was topical TXA, IV TXA, FS, and control group; (4) direct comparison indicated that there is no significant difference between IV TXA and topical TXA; (5) direct comparison showed that FS, IV TXA, and topical TXA can decrease blood loss and the need for transfusion compared with the control group; and (6) there is no direct comparison between topical TXA or intravenous TXA and FS.

The results of current network meta-analysis indicated that IV or topical TXA is the most preferable
hemostasis agent in THA. The efficacy of hemostasis was tested by the need for transfusion and total blood loss. Though the blood transfusion trigger is different between the included studies, the consistency test was performed and the included studies are consistent. There is a contradictory result for IV TXA versus topical administration TXA. As for the need for transfusion, IV TXA ranks the first, and for total blood loss, topical TXA ranks the first. Based on these results, a direct comparison was conducted between topical and intravenous TXA for THA. The results indicated that there is no significant difference between topical TXA and intravenous TXA in THA. These results were consistent with the previous meta-analysis. Until now, there is no evidence indicating that IV TXA is superior to topical TXA. Only one trial directly compared IV TXA with FS since there is no relevant data for blood loss and the need for transfusion for meta-analysis. Indirect data showed that whether IV TXA or topical TXA shows better hemostasis effects than FS. For TXA, there are no actual protocols that what dose is effective and safe. In the previous studies, intravenous 10 mg/kg, 15 mg/kg, or multiple doses are all been identified as effective and safe. The dose of topical TXA ranged from 1 to 3 g, and the administration routes included intra-articular and drain tube.

There is a previous meta-analysis comparing TXA with FS in total knee arthroplasty and found that there is no significant difference between the two agents. The meta-analysis including limited studies and non-RCTs will make the large heterogeneity for the final results. Another factor that affects the alternative choice for hemostasis agent is the price. FS is considerably costlier than TXA. The therapeutic dose of TXA (10 mg/kg) will cost about 8€, while FS will cost between 450€ and 675.00€. FS was manufactured from human plasma products, and in common with other blood-derived products, there is a risk of transmission of disease but concern may remain relating to unknown vectors.

There were several limitations for this meta-analysis: (1) the indirect comparison between FS and IV TXA was limited in total blood loss and the

|                | Co             | FS             | T TXA          | IV TXA         |
|----------------|----------------|----------------|----------------|----------------|
| -131.89(-258.11,-5.66) | 0.55(0.27,1.10) | 0.24(0.14,0.41) | 0.19(0.13,0.28) |
| -179.35(-196.72,-161.97) | -              | 0.44(0.18,1.06) | 0.34(0.15,0.77) |
| -317.00(-590.11,-43.89) | -              | 1.27(0.71,2.27) | 20.50(-24.04,65.04) |

For total blood loss, mean difference (MD) lower than 0 favor the column-defining treatment. Direct comparisons were shown in the upper right. Indirect comparisons were shown in the bottom left. The number which was painted by a style of overstriking indicated there was a significant difference between the two treatments. Co, control; FS, fibrin sealant; T TXA, topical tranexamic acid; IV TXA, intravenous tranexamic acid.
occurrence of DVT and thus may affect the precision of the final outcomes; (2) the follow-up in these studies was relatively short, and long-term follow-up was needed to identify the potential omitted complications; and (3) allocation concealment in some studies were limited and may cause heterogeneity between the studies.

In summary, our finding indicated that IV TXA was the most preferable hemostasis method for blood loss control in THA patients. And the use of IV TXA will not increase the occurrence of DVT. More direct evidence was needed to identify the optimal method for blood loss control in THA patients.
Abbreviations
CENTRAL: Cochrane Central Register of Controlled Trials; CI: Confidence interval; CrI: Credible intervals; DVT: Deep venous thrombosis; FS: Fibrin sealant; MDs: Mean differences; RCTs: Randomized controlled trials; THA: Total hip arthroplasty; TXA: Tranexamic acid

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Availability of data and materials
We state that the data will not be shared because all the raw data are present in the figures included in the article.

Authors’ contributions
ZZ, XM, and JM designed and conceived the experiment. JM and ZZ performed the experiments. ZZ and XM analyzed the data. ZZ, XM, and JM wrote the manuscript. All of the authors listed have reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
None

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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