Transfusions and cost-benefit of oral versus intravenous tranexamic acid in primary total hip arthroplasty

A meta-analysis of randomized controlled trials

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Abstract

Background: The purpose of this study was to assess the cost benefit and transfusions of oral and IV tranexamic acid (TXA) in primary total hip arthroplasty (THA).

Methods: PubMed, Embase, Web of Science, and the Cochrane Library were systematically searched for randomized controlled trials (RCTs) comparing oral and IV TXA in primary THA. Primary outcomes were total blood loss, maximum hemoglobin drop, transfusion requirements, and cost benefit. Secondary outcomes were length of stay, deep venous thrombosis (DVT) and/or pulmonary embolism (PE).

Results: Four independent RCTs were included involving 391 patients. There was no difference in the total blood loss (P= .99), maximum hemoglobin drop (P=.73), and the length of stay (P=.95) between the 2 groups. Transfusion requirements (P=.97) were similar. The total mean cost was the US $75.41 in oral TXA group and the US $580.83 in IV TXA group. The incidence of DVT (P=.3) did not differ significantly between the 2 groups, and no PE was reported in all studies.

Conclusion: Oral TXA shows similar efficacy and safety as IV TXA in reducing total blood loss, maximum hemoglobin drop and transfusion requirements in primary THA. However, oral TXA may be more cost-benefit than IV TXA.

Level of Evidence: Level I, therapeutic study.

Abbreviations: CI = confidence interval, DVT = deep vein thrombosis, IV = intravenous, MD = mean difference, PE = pulmonary embolisms, RCTs = randomized controlled trials, TKA = total knee arthroplasty, TXA = tranexamic acid

Keywords: intravenous, oral, total hip arthroplasty, tranexamic acid

1. Background

Primary total hip arthroplasty (THA) is considered to be potentially advantageous for patients who have the severe hip disease.[1–3] However, as previously reported, the total blood loss associated with has been reported ranges from 700 to 2000 mL, and the incidence of transfusion requirements ranged from 16% to 38%. [4–7] Minimizing the risk of blood loss has always been a goal for surgeons because perioperative anemia is potentially associated with increased morbidity and costs.[8–10]

As a type of antifibrinolytic agent, tranexamic acid (TXA) is a synthetic amino acid that can also prevent plasminogen activation and delay fibrinolysis, thereby stabilizing the clot.[6,11,12] TXA could be performed intravenously[13,14] topically[15,16] and orally.[17,18] Evidence from the past decades has confirmed that IV or topical TXA can effectively reduce blood loss, decrease knee swelling, and less postoperative blood transfusion requirements in most studies.[6,11,13,15–17] Although multiple studies over the recent years have evaluated different possible alternatives for the route of application, the most suitable route of administration, dosage, and duration were still controversial.[11,12,14]

Recently, oral TXA has been demonstrated that it can be used as a simple and cost-benefit way to minimize blood loss, without increasing the risk of thrombotic events in THA.[18,19] However, none of the studies assessed all available level I trials (defined as prospective randomized trials)[20] to evaluate the effectiveness, risk of cost benefits, and complications of oral TXA in THA. Therefore, the purpose of our study is to assess the highest evidence-based (level I) studies in order to compare total blood loss, maximum hemoglobin drop, transfusion requirements, length of stay, deep venous thrombosis (DVT), pulmonary embolism (PE), and cost benefit with the use of oral TXA in THA.
2. Methods

The method used in this meta-analysis is based on the recommended PRISMA checklist guideline.[21] Ethical approval is unnecessary because it is a review of previously published articles and does not involve any processing of individual patient data.

2.1. Search strategy

These electronic databases were queried by PubMed, Embase, Web of Science, the Cochrane Library related reporting databases until March 2018, using the keywords “Tranexamic acid,” “TXA,” “TA,” “total hip arthroplasty,” “total hip replacement,” “THA,” and “THR.”

2.2. Inclusion criteria

The meta-analysis met the following criteria: PICOS (population, intervention, comparator, outcome, study design). Population: patients were performed for primary THA; Intervention: The intervention was oral TXA; Comparison: the comparator was IV TXA; Outcomes: the outcomes were total blood loss, maximum hemoglobin drop, transfusion requirements, mean cost, the length of stay, DVT and/or PE. Study design: the study design was performed by randomized controlled trials (RCTs). We then excluded studies that were performed in animals, non-English, or single case reports or abstract. Two reviewers independently evaluated the title and abstract to find potential studies, and finally obtained eligible research based on the full text. When there was a disagreement, it can be resolved by discussion or by consulting a third reviewer.

2.3. Assessment of methodological quality

Following the criteria in the Cochrane Handbook for Systematic Reviews of methodological quality and the risk of bias, 2 reviewers independently assessed study quality, including assessment of sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias. Each study was judged as “Yes” (low risk of bias), “No” (high risk of bias), or “Unclear” (unclear risk of bias).[22]

2.4. Outcome measures

We compared oral TXA and IV TXA in terms of hemostatic effect and safety in THA. Primary outcomes were the total blood loss, maximum hemoglobin drop, transfusion requirements, and cost benefit. Secondary outcomes were length of stay, DVT, and/or PE.

2.5. Data extraction

The following data were extracted from the included trials: author, published date, age, gender, the number of participants, TXA interventions, DVT prophylaxis, DVT screening, and transfusion protocol. All data were independently extracted by reviewers from eligible studies in the predefined data fields.

2.6. Data synthesis

Statistical analysis was performed using RevMan 5 software (version 5.3, Cochrane Collaboration). Continuous data were calculated by mean difference (MD) and 95% confidence interval (CI), such as blood loss, maximum hemoglobin drop, and length of stay. Dichotomous data were calculated by risk ratio (RR) and 95% CI, such as transfusion requirements, wound complications, DVT, and PE. Chi-squared test and I² statistic was used to assess statistical heterogeneity. If the chi-squared test > 0.1 or the I² < 50%, the fixed-effects model was used. Otherwise, a random-effect model was chosen. Publication bias was tested using blood loss, and if the funnel plot was symmetric, there was a low potential for publication bias, or vice-versa.

3. Results

Figure 1 summarizes the identification of studies. A total of 226 studies were screened out through initial searches. After reading the titles, abstracts and full text, 4 independent RCTs[18,19,23,24] finally satisfied the predefined inclusion criteria in this meta-analysis. A total of 391 patients were included in the meta-analysis: 194 patients in the oral TXA group and 197 patients in the IV TXA group. All included studies were published in English between 2017 and 2018. The sample sizes included in these studies ranged from 34 to 60, and the average age ranged from 55.7 to 67.60 years. All studies reported DVT prophylaxis such as warfarin,[18] Low molecular weight heparin and rivaroxaban,[19,23,24] Doppler ultrasound was used screening for DVT. All studies have similar standards for blood transfusions (Hb < 7 g/dl or has symptoms of anemia). Tables 1 and 2 summarize the baseline characteristics of the included studies.

One study reported that the randomization method was performed using the random number algorithm,[18] and one study was conducted using sealed envelopes[23] and 2 studies were performed using computer-generated list.[19,24] There was a clear blind methodology in all studies. Figure 2 summarizes the methodological quality of the included studies. The plots of blood loss were symmetrical generally, suggesting considerable control of publication bias (Fig. 3).

3.1. Total blood loss

Three studies[18,19,24] reported data on total blood loss (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated that the blood loss was similar between the 2 groups (MD 0.31, 95% CI = −57.93–58.56, ? = .99). The fixed model was used (P = .84, I² = 0%) (Table 3).

3.2. Maximum hemoglobin drop

Three studies[18,19,24] reported data on maximum hemoglobin drop (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated no significant difference between the 2 groups (MD, 0.04; 95% CI, −0.17–0.24; ? = .73). The fixed model was used (P = .75, I² = 0%) (Table 3).

3.3. Transfusion requirements

Four studies[18,19,23,24] reported data on transfusion requirements. Transfusions requirements were reported in 8 of 194 patients (4.12%) in the oral TXA group, compared with 8 of 197 patients (4.06%) in the TXA group. Pooling the data demonstrated that the transfusion requirements were similar between the 2 groups (RR, 1.02; 95% CI, 0.39 to 2.63; ? = .97). The fixed model was used (P = .47, I² = 0%) (Table 3).
Table 1

| Authors       | Date   | Age, years | Participants | Gender (F/M) | BMI, kg/m² | Preoperative Hb, g/dL |
|---------------|--------|------------|--------------|--------------|------------|-----------------------|
| Kayupov et al[18] | 2017   | 60 ± 10    | 55 ± 12      | 40/20        | 29 ± 5     | 13.6 ± 1.3            |
| Luo et al[19]   | 2017   | 67.60 ± 10.38 | 66.98 ± 8.57 | 54/32        | 24.59 ± 3.09 | 13.85 ± 1.01        |
| Cao et al[23]   | 2018   | 55.7       | 55.7         | 50/30        | 22.24 ± 1.91 | 13.2 ± 1.1           |
| Zhao et al[24]  | 2018   | 60.47 ± 10.35 | 59.50 ± 1.42 | 40/20        | 22.46 ± 1.89 | 13.5 ± 1.8           |

BMI = body mass index, F = female, M = male, TXA = tranexamic acid.

Table 2

| Authors       | Surgical approach | Oral TXA | IV TXA | TXA interventions | DVT prophylaxis | DVT screening | Transfusion protocol |
|---------------|--------------------|----------|--------|-------------------|-----------------|---------------|----------------------|
| Kayupov et al[18] | Posterior approach | 1900 mg TXA approximately 2 h before the incision | 1 g TXA before wound closure | Warfarin | Doppler ultrasound | Hb < 7 g/dL or has symptoms of anemia |
| Luo et al[19]   | Posterior approach | 2 g TXA approximately 2 h before the incision | 20 mg/kg TXA 5 min before the skin incision | LMWH | Doppler ultrasound | Hb < 7 g/dL or 7–10 g/dL with symptoms of anemia |
| Cao et al[23]   | Posterior approach | 20 mg/kg IV TXA 5–10 min before skin incision, and received 2 g of oral TXA 4 h, 10 h, 16 h after surgery | LMWH | LMWH | Rivaroxaban |
| Zhao et al[24]  | Direct anterior approach | 20 mg/kg at 2 h before and 3 h after surgery | 15 mg/kg at 10 min before and 3 h after surgery | LMWH | Rivaroxaban |

DVT = deep venous thrombosis, Hb = hemoglobin, IV = intravenous, LMWH = low molecular weight heparin, TXA = tranexamic acid.
3.4. Length of stay
Three studies\cite{18,19,24} reported data on length of stay (140 and 143 patients in the oral TXA and IV TXA groups, respectively). Pooling the data demonstrated that the length of stay was similar between the 2 groups (MD, –0.00; 95% CI, –0.03–0.03; \( P = .95 \)). The fixed model was used (\( P = .74, I^2 = 0\% \)) (Table 3).

3.5. DVT and PE
Four studies\cite{18,19,23,24} reported data on DVT. DVT were reported in 0 of 194 patients (0%) in the oral TXA group, compared with 2 of 197 patients (1.02%) in the TXA group, no difference was found between the 2 groups (\( P = .30 \)). No PE was reported in all studies (Table 3).

3.6. Cost-benefits analysis
Two studies\cite{23,24} reported data on cost benefits. After all data were compiled for THA, the total average cost was US $75.41 in oral TXA and US $580.83 in IV TXA (see Table 4). Specifically, of the studies that provided specific data for oral TXA, the cost ranged from US $70.56 to $80.26, and the study providing specific data for IV TXA reported from US $489.4 to $672.26. Thus, patients in the oral TXA group had an average total cost savings of US $505.42 compared to patients in the IV TXA.

4. Discussion
In light of new healthcare policies, it is crucial to save medical costs without increasing the incidence of complications. Therefore, we hope to analyze the level I trial that have evaluated the use of oral TXA from the highest possible evidence in primary THA. This meta-analysis demonstrated that, based on the available evidence, the oral and IV routes of administration of TXA in primary THA were associated with similar total blood loss, maximum hemoglobin drop, transfusion requirements,
length of stay and incidence of DVT, and/or PE. However, the oral route is associated with a significantly smaller cost of TXA.

Similar studies evaluating the effectiveness of oral TXA have also been reported in another surgical field. Among these, a randomized rhinoplasty clinical trial demonstrated an average reduction in the bleeding volume of 50 mL in oral TXA group compared with control group, without any significant adverse events. Other studies in the obstetrics gynecology and urology literature have also evaluated the use of oral TXA or did not receive TXA, finding a difference in reducing blood loss and improving pain.

The use of tranexamic acid in total hip arthroplasty has been widely accepted as part of routine practice because it has been shown to provide clinical benefit. However, the optimal administration route of TXA was unclear. An updated meta-analysis included 18 RCTs comparing patients who received IV or topical TXA in primary THA or TKA indicated that both IV and topical TXA are similar benefits in reducing blood loss and transfusion rates. Zhao et al. reported that patients treated with oral or intravenous TXA showed similar efficacy for reducing hemoglobin drop, blood loss, and transfusion rate by the direct anterior approach. Similarly, Kayupov et al. prospectively evaluated 89 THAs randomized to receive orally 1.95 g TXA or intravenously 1 g TXA. They found that oral TXA provides equivalent reductions in blood loss compared with the IV formulation. In the current study, our results were also similar to those previously reported. The total blood loss, maximum hemoglobin drop, and transfusion requirements were not the significant difference between the oral TXA and IV TXA routes.

Our results suggest that oral TXA, the total average cost was the US $75.41, may be much more cost benefit than IV TXA, the total average cost was US $580.83, for achieving similar efficacy in reducing blood loss and transfusion requirements. Consequently, patients in the oral TXA group had an average cost savings of the US $505.42 compared to patients in the IV TXA group. Gillette et al. retrospectively reviewed 1018 patients, finding that a mean savings of $879 with TXA use when estimating total hospital cost for patients in total joint arthroplasty. As Luo et al. reported the lowest cost of TXA in oral TXA group ($70.56), compared with IV TXA group ($320.38). The use of oral was relatively more cost benefit compared with the additional cost associated with IV TXA without sacrificing efficacy or safety.

The effect of TXA on thromboembolic events in TKA is unclear. It is well known that TXA has been successfully used in clinical practice for the past decades, and it has not been clinically proven to increase the risk of DVT and/or PE.

### Table 3

| Clinical results | Participants | P | MD/RR | 95% CI | Heterogeneity P (I²) | Model |
|------------------|--------------|---|-------|--------|---------------------|-------|
| Total blood loss | 3 | 283 | 140 | 143 | .99 | 0.31 | –57.93 to 58.56 | .84 (0%) | Fixed |
| Transfusion requirements | 4 | 391 | 194 | 197 | .97 | 1.02 | 0.39 to 2.63 | .47 (0%) | Fixed |
| Length of stay | 3 | 283 | 140 | 143 | .95 | -0.00 | –0.03 to 0.03 | .74 (0%) | Fixed |
| DVT | 4 | 391 | 194 | 197 | .50 | 0.20 | 0.01 to 0.40 | .47 (0%) | Fixed |
| PE | 4 | 391 | 194 | 197 | n.s. | n.s. | n.s. | n.s. | Fixed |

CI = confidence interval, DVT = deep venous thrombosis, IV = intravenous, MD = mean difference, n.s. = not state, PE = pulmonary embolism, RR = risk ratio, TXA = tranexamic acid.

### Table 4

| Authors | Surgery | Total cost | Mean cost | Value |
|---------|---------|------------|-----------|-------|
| Luo et al.[19] | THA | $70.56 (¥ 480) | $418.84 | Positive |
| Zhao et al.[24] | THA | $80.26 (¥ 546) | $592 | Positive |

IV = intravenous, THA = total hip arthroplasty, TXA = tranexamic acid.

Costs were calculated in Chinese yuan (¥); 1¥ = 0.147 United States dollars (USD, $).
Third, more results have been analyzed, such as the benefits of TXA, and our study found that oral TXA is more likely to give patients optimal TXA costs.

Although the meta-analysis included well-designed RCTs, our study has some limitations. First, our selection criteria were used to choose only the studies with the best evidence, and then nonlevel I studies were excluded, which may potentially ignore other high-quality case series; Second, sample sizes of the most included studies were calculated by the reduction in hemoglobin, it may result in insufficient sample size to detect other outcomes, such as blood loss, transfusion requirements and thrombosis events. Third, publication bias may exist because of only English language publications. However, the plot of blood loss was symmetrical generally, suggesting considerable control of publication bias. Hence, we believe the factor would not affect our results.

5. Conclusions
The available evidence demonstrates that oral and IV of TXA administration shows similar benefits in total blood loss, maximum hemoglobin drop, transfusion requirements and, length of stay without sacrificing safety in the primary THA. However, oral TXA may be more cost-benefit than IV TXA.

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