Comparison between epsilon-aminocaproic acid and tranexamic acid for total hip and knee arthroplasty: A meta-analysis

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Abstract
Background: The aim was to compare the efficacy and safety of epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) in total hip arthroplasty (THA) and total knee arthroplasty (TKA). Methods: Potential academic articles were identified from the Cochrane Library, Springer, PubMed, and ScienceDirect databases from inception to December 2019. Randomized controlled trials (RCTs) and non-RCTs involving EACA and TXA in THA or TKA were included. Pooled data were analyzed using RevMan 5.1. Results: Three RCTs and three non-RCTs met the inclusion criteria. The present meta-analysis reveals that EACA is associated with significantly more blood loss than TXA. No significant differences were identified in terms of blood transfusion rate, transfusion units, hemoglobin (Hb) level at discharge, operation time, length of hospital stay, deep venous thrombosis (DVT), or 30-day readmission. Conclusions: Compared with TXA, EACA led to more blood loss in patients undergoing THA or TKA. However, there was no significant difference in the blood transfusion rate, transfusion units, Hb level at discharge, operation time, length of hospital stay, DVT, or 30-day readmission between groups.

Keywords
aminocaproic acid, arthroplasty, blood loss, meta-analysis, tranexamic acid

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Introduction
Epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic amino acid derivatives that promote hemostasis by competitively blocking the lysine-binding site of plasminogen.1,2 Both drugs are widely used to reduce blood loss and transfusion requirements in orthopedic, hepatic, and cardiac surgery.2–4 To date, the intravenous administration of TXA in total hip arthroplasty (THA) and total knee arthroplasty (TKA) has been well established in the literature.5,6 Recently, several published studies have compared EACA with TXA in patients treated with THA and TKA.7–10 However, their results are not consistent. Moreover, some limitations exist in these previous studies, such as small sample sizes, inconclusive results, and inaccurate evaluations. Therefore, we conducted a large sample meta-analysis of randomized controlled trials (RCTs) and non-RCTs to compare the efficacy and safety of EACA and TXA in patients undergoing THA or TKA.

Methods

Search strategy
Potentially relevant published academic literature was identified from the PubMed, MEDLINE, Cochrane Library, Embase, and ScienceDirect databases from inception to December 2019. Secondary sources were identified from the...
references of the included studies. No studies were excluded on the basis of the language used. The keywords used for the search were “replacement OR arthroplasty,” “tranexamic acid,” and “aminocaproic acid” in combination with the Boolean operators AND or OR.

**Selection criteria and quality assessment**

The present meta-analysis included published RCTs and non-RCTs that compared EACA with TXA in patients undergoing primary THA or TKA. Two independent reviewers determined the suitability of the studies. A third reviewer resolved any disagreements. A quality assessment of the RCTs was conducted according to a modified generic evaluation tool described in the *Cochrane Handbook for Systematic Review of Interventions*. The Methodological Index for Nonrandomized Studies (MINORS) form was used to assess non-RCTs.

**Data extraction**

The data were extracted from the included literature by two independent researchers. For incomplete data, additional details were obtained by writing to the corresponding author of the included study. The following information were extracted: the first author’s name, publication year, intervening measures, outcome measures, sample size, and comparable baselines. Other relevant parameters were also extracted from individual studies.

**Data analysis and statistical methods**

RevMan 5.1 (The Cochrane Collaboration, Oxford, UK) was used to analyze the pooled data. The values of $p$ were used to estimate the heterogeneity, and $I^2$ depended on the standard $\chi^2$ test. When $I^2 > 50\%$, $p < 0.1$ was considered to indicate significant heterogeneity, which indicated that a
A random-effects model should be used for the data analysis. When $I^2 < 50\%, p > 0.1$ was considered to indicate no significant heterogeneity. Then, a fixed-effects model was used for the data analysis. When significant heterogeneity was found, a subgroup analysis was performed to identify the sources. The mean differences (MDs) and 95% confidence intervals (CIs) were determined for continuous outcomes. Dichotomous data were analyzed by the risk differences (RDs) and 95% CIs.

**Results**

**Search results**

A total of 196 studies were identified as potentially relevant literature reports. By scanning the titles and abstracts, 190 reports were excluded according to the eligibility criteria. No additional studies were obtained after reviewing the references. Ultimately, three RCTs and three non-RCTs were eligible for data extraction and the meta-analysis. The search process is shown in Figure 1.

**Risk of bias assessment**

RCT quality was assessed based on the *Cochrane Handbook for Systematic Review of Interventions* (Figure 2). The RCTs stated clear inclusion and exclusion criteria. The included RCTs included adequate methodology of randomization, concealment of allocation, blinding, and intent-to-treatment analysis. No unclear bias was reported due to incomplete outcome data or selective outcomes. For the non-RCTs, the MINORS score was 20 for the retrospective controlled trials. The methodological quality assessment is illustrated in Table 1.

**Study characteristics**

Demographic characteristics and details concerning the literature type of the included studies are summarized in Table 2. Statistically similar baseline characteristics were observed between both groups.

**Outcomes of the meta-analysis**

It was possible to perform a meta-analysis with eight outcomes (Table 3). EACA was associated with significantly more blood loss than TXA (RD = 136.11, $p = 0.004$). There were no statistically significant differences between the EACA and TXA groups regarding blood transfusion rate (RD = 0.00, $p = 0.94$), transfusion units per patient (MD = −0.01, $p = 0.71$), hemoglobin (Hb) level at discharge (MD = 0.14, $p = 0.26$), operation time (MD = −1.02, $p = 0.68$), length of hospital stay (MD = 0.05, $p = 0.60$), deep venous thrombosis (DVT; RD = −0.00, $p = 0.94$), or 30-day readmission (RD = 0.00, $p = 0.79$).

**Discussion**

The application of TXA has been confirmed to effectively reduce blood loss and transfusion rates in TKA and THA. EACA has a similar mechanism of action to TXA, and several studies have assessed the efficacy of EACA in TKA and THA. However, it is controversial whether EACA is as effective for preventing blood loss as TXA in TKA and THA. Our meta-analysis was more systematic, comprehensive, and novel than the previous meta-analysis.
Studies have shown that the total calculated blood loss ranges from 1000 ml to 2000 ml in primary TKA and THA, and 10–38% of patients require transfusions.16 There is a risk of transfusion-associated complications, such as induced infectious disease, hemolysis, and anaphylactic reactions, and blood transfusions also increase the economic burden.17 Our study showed greater blood loss in the EACA group than in the TXA group. These results are consistent with previous studies.13,14 The pooled results indicated that the Hb levels at discharge in the EACA group were similar to those in the TXA group. The indications for blood transfusion were based on postoperative Hb levels and clinical symptoms of anemia. Although the transfusion indicators varied among the included studies, the present meta-analysis showed that the blood transfusion rate and the average transfusion units were not significantly different between the EACA and TXA groups.

The length of hospital stay is another element in determining the effectiveness of THA and TKA. Alshryda et al.18 reported that TXA decreased the length of hospital stay after TKA by 24%. Churchill et al.8,9 compared the length of hospital stay between the EACA and TXA groups of patients who underwent THA and TKA. Their outcomes showed that the length of hospital stay was shorter in the EACA group. Recently, Boese et al.7 performed an RCT, and the results showed no statistically significant differences in the length of hospital stay between groups. Their results were consistent with the present meta-analysis. Moreover, the pooled results indicated that the 30-day all-cause readmission rate was similar for both the EACA and TXA groups. Taking these findings together, we concluded that EACA may be an acceptable alternative to TXA for preventing blood loss following TKA.

Postoperative DVT is a common complication in TKA and THA. DVT may develop into pulmonary embolism (PE) and result in death. Theoretically, TXA and EACA inhibit fibrinolytic activity and may increase the risk of DVT.19 Astedt et al.20 found that intravenous TXA does not suppress fibrinolytic activity in the normal vein wall. Numerous studies21,22 have confirmed the safety of TXA, without increases in the incidence of either DVT or PE. All included studies reported the use of postoperative anticoagulant therapy. In total, 8 of 1679 patients in the EACA

### Table 2. Characteristics of included studies.

| Study          | Operation | Intervention | Cases | Mean age | Female | Dosage | Prophylactic antithrombotic |
|----------------|-----------|--------------|-------|----------|--------|--------|-----------------------------|
| Boese et al.7  | TKA       | EACA         | 96    | 66.12    | 71     | 2 g    | Warfarin                    |
|                |           | TXA          | 98    | 64.97    | 69     | 14 g   |                             |
| Bradley et al.13| THA       | EACA         | 44    | 59.2     | 21     | 5 g    | Aspirin                     |
|                |           | TXA          | 46    | 61.3     | 27     | 1 g    |                             |
| Camarasa et al.10| EACA      | 32            | 73    | 28       | 10 mg/kg | LMWH |
|                |           | TXA          | 35    | 73       | 26     | 3 g    |                             |
| Churchill et al.9| THA       | EACA         | 711   | 64.7     | 392    | 1 g    | Surgeon’s discretion        |
|                |           | TXA          | 445   | 65.1     | 263    | 1 g    |                             |
| Churchill et al.8| TKA       | EACA         | 820   | 63.9     | 527    | 1 g    | Surgeon’s discretion        |
|                |           | TXA          | 610   | 65.8     | 392    | 1 g    |                             |
| Lum et al.14   | THA       | EACA         | 183   | 62.7     | 105    | 1 g    | Aspirin/warfarin            |
|                |           | TXA          | 204   | 65       | 100    | 1 g    |                             |

THA: total hip arthroplasty; TKA: total knee arthroplasty; EACA: epsilon-aminocaproic acid; TXA: tranexamic acid; LMWH: low-molecular-weight heparin.

### Table 3. Meta-analysis results.

| Outcome                  | Studies | Groups (EACA/TXA) | Overall effect | Heterogeneity |
|--------------------------|---------|-------------------|----------------|---------------|
| Total blood loss         | 4       | 244/252           | 136.11         | 41            |
| Discharge Hb level       | 4       | 1647/1174         | 0.14           | 76            |
| Blood transfusion rate   | 4       | 1958/1511         | 0.00           | 67            |
| Transfusion units per patient | 3 | 1563/1090 | -0.01         | 56            |
| Operation time           | 2       | 128/133           | -1.02          | 45            |
| Length of hospital stay  | 5       | 1743/1272         | 0.05           | 79            |
| Deep venous thrombosis   | 5       | 1679/1209         | -0.00          | 0             |
| 30-day readmission       | 2       | 1531/1055         | 0.00           | 0             |

Hb: hemoglobin; CI: confidence interval; EACA: epsilon-aminocaproic acid; TXA: tranexamic acid.
group and 6 of 1209 patients in the TXA group reported clinical complications of DVT. The present meta-analysis showed that the use of EACA did not increase the risk of DVT compared with TXA.

Previous studies indicated that the routine use of TXA was associated with lower mean total direct hospital costs after primary THA and TKA. Churchill et al. reported that the medication acquisition cost for EACA was $2.70 per surgery compared with $39.58 per surgery for TXA. EACA is more economical than TXA and has a similar efficacy. Therefore, there is an advantage for patients undergoing TKA or THA to use an intravenous application of EACA.

Several potential limitations should be noted: (1) Only six studies were included, all of which had a relatively small sample size; (2) methodological weaknesses existed in studies, and some outcome parameters were not fully described, so we failed to perform a meta-analysis for those parameters; and (3) subgroup analysis was not performed because of the limited number of included studies, so we could not determine the source of heterogeneity.

Conclusion
Compared with TXA, EACA led to more blood loss in patients undergoing THA or TKA. However, there was no significant difference in blood transfusion rate, transfusion units, Hb level at discharge, operation time, length of hospital stay, DVT, or 30-day readmission between groups. More high-quality RCTs are required due to the limited quality of the evidence and amount of data currently available.

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Author contributions
Wen-bin Liu and Gui-Shi Li contributed equally to this work.

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