Efficacy of tranexamic acid plus drain-clamping to reduce blood loss in total knee arthroplasty
A meta-analysis
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Abstract
Background: Perioperative blood loss is still an unsolved problem in total knee arthroplasty (TKA). The efficacy of the preoperative use of tranexamic acid (TXA) plus drain-clamping to reduce blood loss in TKA has been debated. This meta-analysis aimed to illustrate the efficacy of TXA plus drain-clamping to reduce blood loss in patients who underwent a TKA.

Methods: In February 2017, a systematic computer-based search was conducted in PubMed, EMBASE, Web of Science, the Cochrane Database of Systematic Reviews, and Google Scholar. Data from patients prepared for TKA in studies that compared TXA plus drain-clamping versus TXA alone, drain-clamping alone, or controls were retrieved. The primary endpoint was the need for transfusion. The secondary outcomes were total blood loss, blood loss in drainage, the decrease in hemoglobin, and the occurrence of deep venous thrombosis. After testing for publication bias and heterogeneity between studies, data were aggregated for random-effects models when necessary.

Results: Ultimately, 5 clinical studies with 618 patients (TXA plus drain-clamping group = 249, control group = 130, TXA-alone group = 60, and drain-clamping group = 179) were included. TXA plus drain-clamping could decrease the need for transfusion, total blood loss, blood loss in drainage, and the decrease in hemoglobin than could the control group, the TXA-alone group, and the drain-clamping group (P < .05). There was no significant difference between the occurrence of deep venous thrombosis between the included groups (P > .05).

Conclusions: TXA plus drain-clamping can achieve the maximum effects of hemostasis in patients prepared for primary TKA. Because the number and the quality of the included studies were limited, more high-quality randomized controlled trials are needed to identify the optimal dose of TXA and the clamping hours in patients prepared for TKA.

Abbreviations: CI = confidence interval, DVT = deep venous thrombosis, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomized controlled trials, RR = relative risk, SD = standard deviation, TKA = total knee arthroplasty, TXA = tranexamic acid, WMD = weight mean difference.

Keywords: drain-clamping, meta-analysis, total knee arthroplasty, tranexamic acid

1. Introduction
Total knee arthroplasty (TKA) is 1 of the effective alternative treatments for severe knee osteoarthritis or osteoarthritis.[1] It is reported that the number of primary TKA procedures will reach 3.48 million in the United States by the year of 2030, which would be an 8-fold increase from the year 2005.[2] However, considerable blood loss is a problematic complication after TKA. It has been reported that patients who underwent TKA may have a resultant blood loss that ranges from 1450 to 1790 mL.[3,4]

Several methods including fibrin sealant, tranexamic acid (TXA), and drain-clamping have been reported to reduce postoperative blood loss and avoid homologous blood transfusion.[3–4] Various protocols for drain-clamping with antibiotics, epinephrine, or TXA have been reported.[9–11] All the above studies proved that drain-clamping can decrease the early period of blood loss in TKA. However, some studies reported that drain-clamping has no benefit in primary TKA.[12]

Tranexamic acid is a synthetic antifibrinolytic agent that is routinely used to prevent bleeding after TKA. The optimal procedure and dose of TXA remain unclear. In the previous references, researchers recommended that TXA combined with drain-clamping can be more effective than drain-clamping alone.

Nevertheless, the evidence is low and included number is limited. Thus, we conducted a meta-analysis to compare the efficacy of TXA plus drain-clamping versus TXA alone, drain-clamping alone, or a control group regarding blood loss in TKA patients.

2. Materials and methods
This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses...
2.1. Search strategies
The following databases were searched in September 2016 without restrictions on location or publication type: PubMed (1950–February 2017), EMBASE (1974–February 2017), the Cochrane Library (February 2017 Issue 3), and the Google database (1950–February 2017). The Mesh terms and their combinations used in the search were as follows: “blood loss” OR “blood” OR “tranexamic acid” OR “drain” OR “drain tube” OR “clamping” AND “total knee arthroplasty” [Mesh terms]. The reference lists of related reviews and original articles were searched for any relevant studies, including randomized controlled trials (RCTs) involving adult humans. Moreover, gray literature and relevant books were manually searched to identify any omitted studies. No language was restricted. When multiple reports describing the same sample were published, the most recent or complete report was used. Since this is a meta-analysis, no ethic approval was need for this meta-analysis.

2.2. Inclusion criteria
2.2.1. Patients. We included adults who have undergone unilateral TKA surgery (no restriction on the sex, disease severity, or comorbidities).

2.2.2. Intervention. Perioperative intra-articularly or intravenous TXA plus drain-clamping was chosen as an intervention group, and there was no restriction on the dose of TXA and timing of clamp.

2.2.3. Comparison. Placebo, TXA only, or drain-clamping only was identified as a comparison group.

2.2.4. Outcomes. Primary outcomes were the need for transfusion, total blood loss, blood loss in drainage, and a decrease in hemoglobin. Secondary outcome was the occurrence of deep venous thrombosis (DVT).

2.2.5. Study design. Randomized controlled trials and non-RCTs were included in this meta-analysis. When multiple reports describing the same sample were published, the most recent or complete report was used.

2.3. Study selection
Two independent reviewers (Y.Z. and J.-W.Z.) screened the titles and abstracts of the identified studies after removing duplicates from the search results. Any disagreements about the inclusion or exclusion of a study were mitigated by discussion or consultation with an expert. The reliability of the study selection was determined by Cohen kappa test, and the acceptable threshold value was set at 0.61.

2.4. Data abstraction
A specific extraction was conducted to collect data in a pregenerated standard Microsoft Excel (Microsoft Corporation, Redmond, Washington, D.C.) file. The items extracted from relevant studies were as follows: first author and publication year, country, sample size of the intervention and control groups, transfusion criteria, study type, and follow-up. Outcomes such as the need for transfusion, total blood loss, blood loss in drainage, a decrease in hemoglobin, and the occurrence of DVT were abstracted and recorded in the spreadsheet. Data in other forms (ie, median, interquartile range, and mean ± 95% confidence interval [CI]) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook. If the data were not reported numerically, we extracted these data from the published figures using “ GetData Graph Digitizer” software. All the data were extracted by 2 independent reviewers, and disagreements were mitigated by discussion.

2.5. Quality assessment
The quality of all included trials was independently assessed by 2 reviewers based on the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://www.cochrane-handbook.org/). A total of 7 domains were used to assess the overall quality: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was measured as low bias, unclear bias, or high bias. The methodologic quality of the RCTs was evaluated using the modified Jadad scale, which is a numeric scale that evaluates the quality of the randomization, double blinding, and withdraws and dropouts. Studies scoring 4 or more out of a total possible of 8 were considered to be of high quality. The Newcastle–Ottawa quality assessment scale (NOS) was used to assess the quality of the included non-RCTs. The NOS scale assigns 9 points for non-RCTs. Validity scores of NOS scale were evaluated as follows: 8 to 9, high quality; 6 to 7, medium quality; 5, low quality.

2.6. Outcome measures and statistical analysis
Continuous outcomes (total blood loss, blood loss in drainage, and the decrease in hemoglobin) were expressed as the weighted mean differences (WMDs) with 95% CI. Dichotomous outcomes (the need for transfusion and the occurrence of DVT) were expressed as a risk ratio (RR) with a 95% CI. Statistical significance was set at P < .05 to summarize the findings across the trials. Variables in the meta-analysis were calculated using Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was evaluated using the chi-square test and the I² statistic. A random-effects model was applied to estimate the pooled outcomes without regarding heterogeneity. Publication bias was visually assessed using funnel plots and was quantitatively assessed using Begg test. If there was a large heterogeneity, we perform sensitivity analysis to find out the source of heterogeneity.

3. Results
3.1. Search results
The process of study selection can be seen in Figure 1. In the initial search, a total of 203 studies were identified from the electronic databases (PubMed = 65, EMBASE = 74, Web of Science = 32, Cochrane Library = 30, and Google database = 2). A total of 189 papers were reviewed, and 184 papers were removed according to the inclusion criteria at the abstract and title levels. One study compared drain-clamping alone versus nonclamping after TKA and was excluded. Ultimately, 5 clinical studies with 618 patients (TXA plus drain-clamping group = 249, control group = 130, TXA alone group = 60, and drain-clamping group = 179)
were included in the meta-analysis.\textsuperscript{11,18–21} The clamping hours ranged from 1 to 3 hours. The dose of TXA ranged from 250 to 1000mg. Detailed information on the general characteristics of the studies can be seen in Table 1.

### 3.2. Quality assessment
Details regarding the Jadad scores of the included studies can be seen in Table 2. The total Jadad score of the included studies ranged from 5 to 7. The risk of bias summary and risk of bias graph can be seen in Figures 2 and 3, respectively. Random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors are appropriate in 4 studies.\textsuperscript{11,19–21} Three studies did not report incomplete outcomes data.\textsuperscript{11,20,21} The NOS was used to assess the quality of the non-RCTs, and the results can be seen in Table 3. Mutsuzaki and Ikeda\textsuperscript{18} reported 8 scores (high quality). The Kappa value between the reviewers was 0.796, which indicated that there was good consistency between the included studies.

### 3.3. Results of the meta-analysis

#### 3.3.1. Need for transfusion
Pooled results indicated that preoperative TXA plus drain-clamping can decrease the need for transfusion (RR = 0.30, 95% CI 0.22, 0.42, \( P = .000 \); Fig. 4) compared with the control group. Compared with the group that included drain-clamping only, TXA plus drain-clamping group was associated with a lower transfusion need (RR = 0.41, 95% CI 0.30, 0.57, \( P = .000 \); Fig. 4). Compared with the TXA group, the
TXA plus drain-clamping group was associated with a lower transfusion need (RR = 0.68, 95% CI 0.46, 1.00, P = .049; Fig. 4).

### 3.3.2. Total blood loss.

Total blood loss was presented in 6 studies. The pooled results indicated that TXA plus drain-clamping can reduce total blood loss when compared with the control group (WMD = −642.20, 95% CI −748.94, −535.46, P = .000; Fig. 5). Compared with drain-clamping, TXA plus drain-clamping was associated with less total blood loss (WMD = −130.96, 95% CI −230.91, −31.00, P = .010; Fig. 5).

### 3.3.3. Blood loss in drainage.

Total blood loss was presented in 2 studies. The pooled results indicated that TXA plus drain-clamping could reduce the blood loss in drainage when compared with the control group (WMD = −443.14, 95% CI −855.39, 30.89, P = .035; Fig. 6). Compared with drain-clamping, TXA plus drain-clamping was associated with less total blood loss (WMD = −176.12, 95% CI −286.15, −66.09, P = .002; Fig. 6). Compared with the TXA group, the TXA plus drain-clamping group was associated with a lower transfusion need (WMD = −198.00, 95% CI −281.66, −114.34, P = .000; Fig. 6).

### 3.3.4. Decrease of hemoglobin.

The decrease of hemoglobin was presented in 1 study. The pooled results indicated that TXA plus drain-clamping can reduce the decrease in hemoglobin when compared with the control group (WMD = −1.50, 95% CI −1.79, −1.21, P = .000; Fig. 7). Compared with drain-clamping, TXA plus drain-clamping was associated with less of a decrease in hemoglobin (WMD = −0.87, 95% CI −1.04, −0.70, P = .000; Fig. 7). Compared with the TXA group, TXA plus drain-clamping was associated with a lower transfusion need (WMD = −0.30, 95% CI −0.53, −0.07, P = .012; Fig. 7).

### 3.3.5. The occurrence of DVT.

Pooled results indicated that there was no significant difference between TXA plus drain-clamping than with drain-clamping alone (RR = 2.33, 95% CI 0.35, 15.46, P = .380; Fig. 8).

### 3.4. Publication bias

Funnel plot and Begg test of the need for transfusion can be seen in Figures 9 and 10, respectively. Results indicated that effect size
was symmetrical and thus no publication bias existed. The $P$ value drawn from Begg test was 0.844 and indicated that there was no publication bias.

4. Discussion

This is the first systematic review and meta-analysis that compares the efficacy of TXA plus drain-clamping to reduce blood loss in TKA patients. A total of 5 studies were ultimately included in this meta-analysis. Pooled results indicated that TXA plus drain-clamping could reach the maximum effects of hemostasis than could TXA alone, drain-clamping alone, or control groups. Meanwhile, the occurrence of DVT was not statistically significant between the groups. The major strengths of the current meta-analysis were the comprehensive search and the rigorous statistical calculation. The databases of PubMed, EMBASE, the Cochrane Library, and the Google scholar were searched from inception to February 2017.

Pooled results indicated that compared with drain-clamping, TXA and controls alone, TXA plus drain-clamping could decrease the need for transfusion, total blood loss, and blood loss in drainage to an extreme. The differences between the groups were clinically important. When compared with controls, TXA plus drain-clamping was associated with a reduction of need for transfusion by 53.1% ($RR = 0.30$, $95\% CI 0.22, 0.42$, $P = .000$). The blood-saving effects of TXA are certain and have been identified in several previous studies and meta-analyses.\textsuperscript{[22,23]} The effects of drain-clamping for blood loss has been dubiously reported in previous studies.\textsuperscript{[12]} Previous studies have reported that most of the blood loss in TKA occurs during the first postoperative day\textsuperscript{[24,25]}; thus, it seems reasonable to clamp the drain in the early postoperative period to control blood loss.

### Table 3

| Quality assessment of included non-RCTs according to NOS. |
|----------------------------------------------------------|
| **Quality assessment for non-RCTs**                     |
| Election point                                            |
| Companiability point                                      |
| Outcome point                                             |
| Total score                                               |
| **Mutsuzaki and Ikeda, 2012**                            |
| 3                                                        |
| 2                                                        |
| 3                                                        |
| 8                                                        |

NOS = Newcastle–Ottawa quality assessment scale, RCT = randomized controlled trial.

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Figure 3. Risk of bias graph.

Figure 4. Forest plot comparing the need for transfusion between the 2 groups.
Single administration with drain-clamping is not sufficient to control the blood loss as reported by a previous study.[7,26] Another issue that should be addressed is the clamping hours for the drain. Yamada et al.[27] reported that one-hour clamping is preferable to 24-hour clamping when using the drain-clamping method for minimizing complications.
### Figure 7. Forest plot comparing the decrease in hemoglobin between the 2 groups.

| Study                  | ID             | WMD (95% CI)   | Weight |
|------------------------|----------------|----------------|--------|
| TXA+clamp versus control | Chareanchohanich 2012 | -1.50 (-1.79, -1.21) | 15.21 |
|                        | Subtotal (I² = %, p = .) | -1.50 (-1.79, -1.21) | 15.21 |
|                        | . P=0.000      |                 |        |
| TXA+clamp versus clamp | Onodera 2012 | -0.91 (-1.38, -0.44) | 12.97 |
|                        | Sa–Ngasoongsong 2011 | -0.90 (-1.36, -0.44) | 13.09 |
|                        | Sa–Ngasoongsong (250 mg) 2013 | -0.70 (-1.11, -0.29) | 13.76 |
|                        | Sa–Ngasoongsong (500 mg) 2013 | -0.70 (-1.11, -0.29) | 13.76 |
|                        | Chareanchohanich 2012 | -1.00 (-1.27, -0.73) | 15.42 |
|                        | Subtotal (I² = %, p = 0.683) | -0.87 (-1.04, -0.70) | 69.00 |
|                        | . P=0.000      |                 |        |
| TXA+clamp versus TXA   | Chareanchohanich 2012 | -0.30 (-0.53, -0.07) | 15.80 |
|                        | Subtotal (I² = %, p = .) | -0.30 (-0.53, -0.07) | 15.80 |
|                        | . P=0.012      |                 |        |

### Figure 8. Forest plot comparing the occurrence of deep venous thrombosis (DVT) between the 2 groups.

| Study                  | ID             | RR (95% CI)        | Weight |
|------------------------|----------------|-------------------|--------|
| TXA+clamp versus control | Chareanchohanich 2012 | (Excluded) 0.00 |        |
|                        | Subtotal (I² = %, p = .) | (Excluded) 0.00 |        |
| TXA+clamp versus clamp | Onodera 2012 | 2.00 (0.19, 21.36) | 66.67 |
|                        | Sa–Ngasoongsong (250 mg) 2013 | 3.00 (0.13, 71.74) | 33.33 |
|                        | Sa–Ngasoongsong (500 mg) 2013 | (Excluded) 0.00 |        |
|                        | Chareanchohanich 2012 | (Excluded) 0.00 |        |
|                        | Subtotal (I² = %, p = 0.84) | 2.33 (0.35, 15.46) | 100.00 |
|                        | . P=0.380      |                  |        |
| TXA+clamp versus TXA   | Chareanchohanich 2012 | (Excluded) 0.00 |        |
|                        | Subtotal (I² = %, p = .) | (Excluded) 0.00 |        |
|                        | . P=0.000      |                  |        |
The most concerning complication regarding drain-clamping is ecchymosis. Chareancholvanich et al. reported that TXA plus drain-clamping did not increase the incidence of ecchymosis when compared with the control group or to a group of patients without drain-clamping. Another complication is the incidence of DVT when compared with the control group or to a group of patients drain-clamping did not increase the incidence of ecchymosis. Chareancholvanich et al. reported that TXA plus drain-clamping for the control of blood loss after primary TKA. Some blood-saving effects were observed with the administration of TXA plus drain-clamping that did not increase complications. Due to the sample size and the limited number of included studies, a multicenter RCT is needed to identify the effects of TXA plus drain-clamping for the reduction of blood loss after primary TKA.

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