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# The efficiency and safety of oral tranexamic acid in total hip arthroplasty

## A meta-analysis

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**Abstract**

**Background:** Intravenous (IV), topical and combination of both application of tranexamic acid (TXA) can reduce blood loss, hemoglobin drop, and transfusion rate in patients following total hip arthroplasty (THA). Lately, published articles reported that oral TXA had as similar blood-saving as IV and topical TXA in THA. The purpose of this meta-analysis is to investigate the efficiency and safety of oral TXA in THA.

**Methods:** We systematically searched articles about oral administration of TXA in THA from PubMed, Embase, Scopus, Web of Science, the Cochrane Library, and the Chinese Wanfang database. Study eligibility criteria:

1. Patients underwent primary THA;
2. The intervention was oral application of TXA in THA;
3. Outcomes included hemoglobin drop, total blood loss, transfusion rate, length of stay, and complications;
4. The studies were designed as randomized controlled trials (RCTs) or clinical comparative trial (CCT).

The outcomes were collected and analyzed by the Review Manager 5.3.

**Results:** Nine RCTs and 1 CCT, containing 1305 patients, were ultimately included according to the inclusion criteria and exclusion criteria in the meta-analysis. The effectiveness of oral TXA was as similar as the IV or topical TXA in regard to hemoglobin drop (SMD = −0.14; 95% CI, [−0.28, 0.01]; $P = .06$), total blood loss (SMD = 0.01; 95% CI, [−0.13, 0.16]; $P = .84$), transfusion rate (OR = 0.76; 95% CI, [0.38, 1.55]; $P = .37$). Compared with single oral TXA or blank group, multiple oral TXA effectively reduced hemoglobin drop (SMD = −1.06; 95% CI, [−1.36, −0.77]; $P < .05$), total blood loss (SMD = −1.30; 95% CI, [−1.66, −0.94]; $P < .05$), transfusion rate (OR = 0.53; 95% CI, [0.29, 0.95]; $P = .03$). There were no significant difference in terms of length of stay and complication among all of enrolled studies.

**Conclusion:** Oral TXA has favorable effect of blood-saving and do not increase risk of complication in patients following THA. Oral TXA may have no effect in the length of stay. More high quality RCTs are necessary.

**Abbreviations:** CCT = clinical comparative trial, IV = intravenous, RCTs = randomized controlled trials, THA = total hip arthroplasty, TKA = total knee arthroplasty, TXA = tranexamic acid.

**Keywords:** meta-analysis, oral, total hip arthroplasty, tranexamic acid

## 1. Introduction

Total hip arthroplasty (THA), which could relieve pain and promote physical function, has been generally recognized as the most efficient surgery for the treatment of end-stage hip disease.[1] THA was the mostly accompanied with the perioperative blood loss, postoperative anemia, and allogeneic blood transfusion, which delayed postoperative functional recovery.[2,3] Postoperative anemia and blood transfusion potentially result in increased morbidity and cost, immunologic reactions, transmission of disease, infection, and even mortality.[3,4] TXA, as an antifibrinolytic agent, which can promote clot stabilization via competitively inhibiting the activation of plasminogen, is able to reduce blood loss and transfusion incidence in THA.[5] Many studies have been demonstrated that several application forms of TXA were applied by surgeons, including intravenous, topical, or oral routes.[6–8] The majority of studies about administration form of TXA in THA have paid attention to IV, topical or combined intravenous and topical routes of administration,

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which have showed the efficiency and safety of IV, topical or combination form of TXA.[9,10] Currently, several studies have demonstrated that oral administration of TXA had similar effects of saving blood as IV or topical TXA in THA,[11–16] and other studies have reported that multiple oral TXA was efficient to reduce total blood loss and allogeneic blood transfusions compared with single oral TXA or blank group in THA.[13,17–19]

Several studies have reported that oral TXA effectively reduced blood loss in THA and total knee arthroplasty (TKA) through a meta-analysis.[20–23] We consider that THA is different from TKA. The reasons are as follows:

1. Patients are applied tourniquet intraoperatively in TKA;
2. THA are operated in deep tissue; recessive soft tissue cavity is large; perioperative blood loss volume is large.

So we implement a meta-analysis to analysis synthetically the effect of oral TXA in THA, which included oral vs IV or topical TXA, but also multiple oral TXA vs single oral TXA or blank group. And the meaning of multiple oral TXA is more than 1 dose of oral TXA.

## 2. Materials and methods

The meta-analysis was conducted and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. All analyses were based on previous published studies in the meta-analysis, thus no ethical institutional review board approval and patient consent were required.

### 2.1. Search strategies, inclusion criteria and exclusion criteria

We generally searched articles involving oral application of TXA in THA up to March 2019 from PubMed, Embase, Scopus, Web of Science, the Cochrane Library, and the Chinese Wanfang database. The following search keywords were used in all databases: "TXA" or "tranexamic acid", "oral", "total hip arthroplasty", or "total hip replacement", combined with Boolean operators "AND" or "OR". Two authors independently searched articles in databases and manually screened titles and abstracts to exclude completely irrelevant studies. Furthermore, we also manually searched the bibliographies of relevant articles and reviews for potentially eligible trials.

We enrolled trials must meeting the below inclusion criteria:

(1) The intervention was oral application of TXA in THA;
(2) The outcomes included hemoglobin drop, total blood loss, transfusion rate, length of stay, and complications;
(3) The trials are designed as RCTs or CCT;
(4) The English articles are enrolled only in this meta-analysis.

We did not enroll trials meeting the following exclusion criteria:

1. The patients had undergone revision THA, simultaneous or staged bilateral primary THA;
2. The type of trials is second source article, such as review article, systematic review, meta-analyze, expert opinion.

### 2.2. Data extraction

The full text of selected articles was read thoroughly. The available data were extracted from the articles by 2 authors independently, which included basic characteristics of studies (participants, age, gender, transfusion criteria, article type), interventions, and results (hemoglobin drop, total blood loss, transfusion rate, length of stay, complication). Different opinions between the 2 authors were resolved by discussion or the first author to reach consensus. If the data were other forms, such as median, interquartile range, and mean ± 95% confidence interval [CI], the data were converted to the mean ± standard deviation (SD) in accordance with Hozo.[24]

### 2.3. Quality assessment

Two authors evaluated the risk bias of the included articles for RCTs by using Jadad scales[25] independently. Jadad scales consisted of the below items: random sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and others.[26] If the Jadad scale of article was granter than 4 points, it was considered that the article was high quality. We assessed the risk of bias of included non-RCTS articles via applying Newcastle–Ottawa scale (NOS).[27] The high quality article should be at least 5 points.

### 2.4. Statistical analysis

All data analyses of the included articles were achieved by using Review Manager Software Windows 5.3 (RevMan5.3). We used mean difference (MD), standard mean difference (SMD) with 95% confidence intervals (CIs) to weigh the effect interval of continuous outcomes, and odds ratio (OR) with 95% CIs to weigh the effect interval of discontinuous outcomes. If unit of outcome was different, mean difference of outcome great, or measurement method of outcome different, we chose standard mean difference (SMD). Otherwise, mean difference (MD) was chosen. If there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .05$), we adopted a fixed-effects model for assessment. Otherwise, a random-effects model was adopted for assessment.[28] When $P$ value was less than 0.05, it was considered statistical significance.

## 3. Results

### 3.1. Search result and study characteristics

A total of 194 articles were retrieved initially via using the search strategy. Ninety three articles were obtained after removing duplicates. Eighty one articles were eliminated after reading the title and abstract. Two articles were excluded because they studied the oral vs IV application of TXA in total joint arthroplasty.[6,29] Finally, 10 articles were enrolled, which included 9 RCTs and 1 CCT. The search process was presented in Figure 1.

All of the enrolled articles were published in English from 2017 to 2019, which included 1465 patients. The mean age ranged from 55 to 69 years, the simple size ranged from 40 to 60 and the mean of body mass index (BMI) ranged from 22 to 31. Dosage of TXA and other more particular basic characteristics of the enrolled articles are presented in Table 1.

### 3.2. Meta analysis: hemoglobin drop

Six articles[11–16] including 665 patients reported the effectiveness of oral TXA compared to IV or topical TXA on hemoglobin drops in the THA. We did not discover significant difference between oral TXA and IV or topical TXA in hemoglobin drops

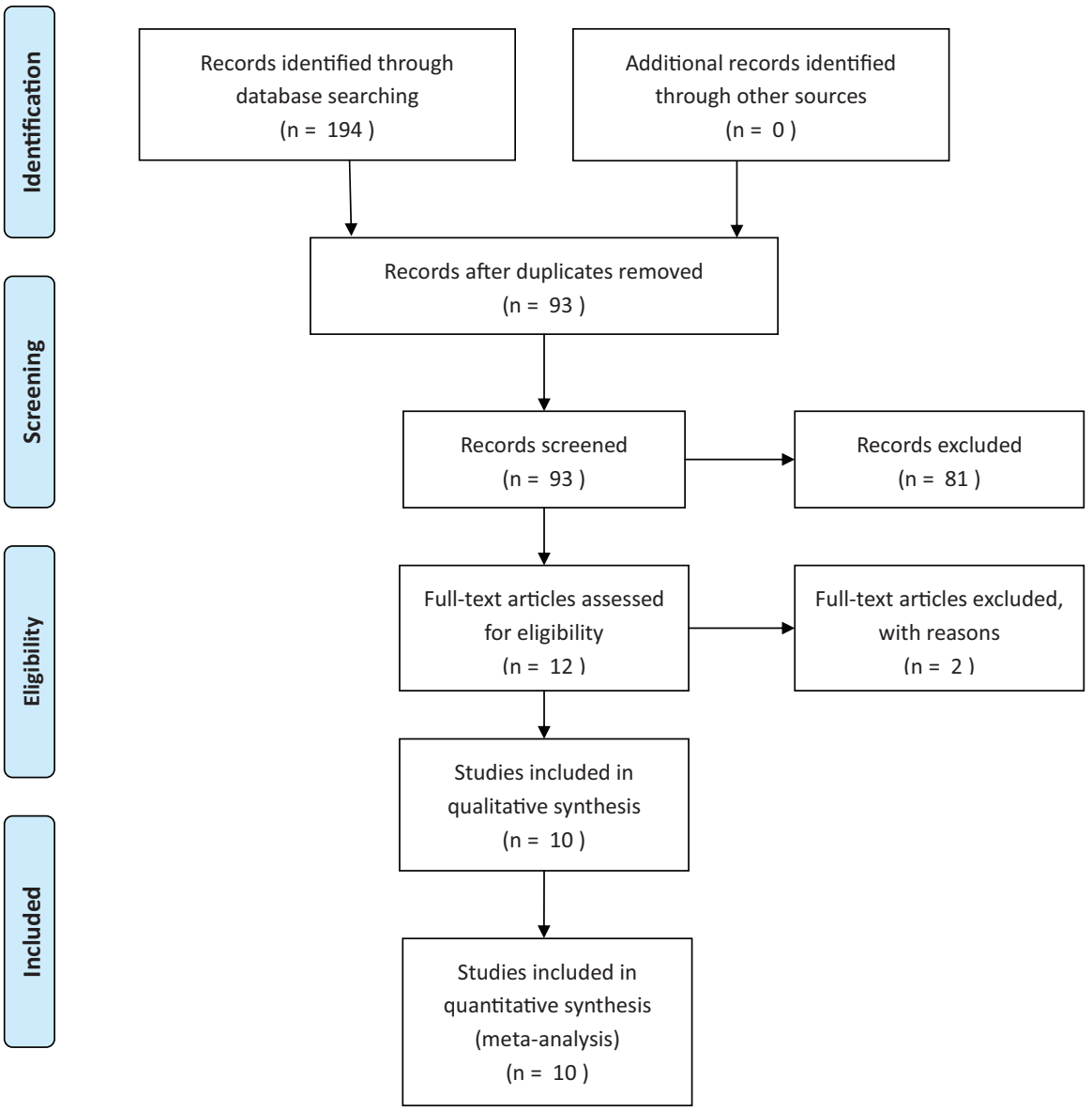


**Figure 1.** The search results and selection procedure.

(SMD = −0.14; 95% CI, [−0.28, 0.01]; $P = .06$). We did not find any statistical heterogeneity between the included articles, so a fixed-effect model was adopted ($I^2 = 25\%$, $P = .24$; Fig. 2).

Five articles[13,17–19,30] including 840 patients researched the effect of multiple oral TXA compared to single oral TXA or blank group on hemoglobin drops in the THA. There was statistical difference between multiple oral TXA and single oral TXA or blank group in hemoglobin drops (SMD = −1.06; 95% CI, [−1.36, −0.77]; $P < .05$). A random-effect model was adopted because there was significant heterogeneity between the included articles ($I^2 = 82\%$, $P < .05$; Fig. 3).

### 3.3. Meta analysis: total blood loss

Six articles[11–16] of 665 patients researched the effectiveness of oral TXA compared to IV or topical TXA on total blood loss in the THA. We did not find any significant difference between the oral TXA and IV or topical TXA in total blood loss (SMD = 0.01; 95% CI, [−0.13, 0.16]; $P = .84$). We did not discover significant heterogeneity between the included articles, and thus we adopted a fixed-effect model ($I^2 = 14\%$, $P = .32$; Fig. 4).

Five articles[13,17–19,30] of 840 patients studied the effect of multiple oral TXA compared to single oral TXA or blank group on total blood loss in the THA. There was significant difference between the multiple oral TXA and single oral TXA or blank group in total blood loss (SMD = −1.30; 95% CI, [−1.66, −0.94]; $P < .05$). A random-effect model was used as there was heterogeneity between the included articles ($I^2 = 87\%$, $P < .05$; Fig. 5).

### 3.4. Meta analysis: transfusion rate

Six articles[11–16] of 665 patients studied the effectiveness of oral TXA compared to IV or topical TXA on transfusion rate with no any heterogeneity ($I^2 = 0\%$, $P = .84$) in the THA. There was no significant difference between the oral TXA and IV or topical

**Table 1**

**The basic characteristic and invention of the included studies.**

| Studies (years) | Oral group | | | | | Control group | | | | | Transfusion trigger | Study type | QAS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | Age | Gender (M/F) | BMI ($Kg/m^2$) | Dosage of TXA | patients | Age | Gender (M/F) | BMI ($kg/m^2$) | Dosage of TXA | | | |
| Cao (2018) | 54 | 55.7 | 23/31 | 23.0 | 20 mg/kg IV pre- and 2g oral 4h, 10h, 16h post- | 54 | 55.7 | 20/34 | 23.6 | 20 mg/kg IV pre- and 1 g IV 6 h, 12 h, 18 h post- | Hb<70 g/L or Hb>70 g/L with symptoms | RCTs | 6 |
| Cao (2018) | 50 | 64.9 | 22/28 | 23.2 | 2 g oral 2 h pre- and 4 h, 10 h, 16 h post- | 51 | 64.6 | 27/24 | 23.8 | 2 g oral 2 h pre- | Hb<70 g/L or 70 g/L<Hb<100 g/L with symptoms | RCTs | 6 |
| | 51 | 64.26 | 20/31 | 24.7 | 2 g oral 2 h pre- and 4 h post- | | | | | | | | |
| Kayupov (2017) | 40 | 60 | 20/20 | 29 | 1.95 g oral 2 h pre- | 40 | 55 | 22/21 | 31 | 1 g IV before closing incision | Hb<70 g/L or symptoms | RCTs | 7 |
| Lee (2017) | 54 | 63 | 19/35 | 24.7±4.4 | 1 g oral 2 h pre-, and 6 h, 12 h post- | 54 | 61 | 21/33 | 24.5 | No TXA | Hb<80 g/L or symptoms | CCT | 7 |
| Luo (2018) | 60 | 67.6 | 28/32 | 24.59 | 2 g oral 2 h pre- | 60 | 66.98 | 27/33 | 24.51 | 20 mg/Kg IV pre- | Hb<70g/L or 70g/L<Hb<100g/L with symptoms | RCTs | 5 |
| | | | | | | 60 | 64.42 | 25/35 | 25.27 | 2 g topical | | | |
| Luo (2018) | 59 | 65.08 | 14/45 | 23.61 | 2 g oral 2 h pre and 1 g post- | 58 | 62.24 | 16/42 | 23.21 | 3 g topical | Hb<70 g/L or 70 g/L<Hb<100 g/L with symptoms | RCTs | 6 |
| Wu (2018) | 50 | 66.5 | 29/2 | 23.8 | 1 g oral 2 h pre- and 3 h, 6 h post- | 50 | 65.1 | 30/20 | 23.9 | 1 g IV pre- and 3 h, 6 h post- | Hb<70g/L or 70g/L<Hb<100g/L with symptoms | RCTs | 6 |
| Wang (2019) | 50 | 66.98 | 15/35 | 24.89 | 2 g oral 2 h pre- and 1 g oral 3 h post- | 50 | 64.41 | 13/37 | 25.11 | 2 g oral 2 h pre- | Hb<70g/L or 70 g/L<Hb<100g/L with symptoms | RCTs | 6 |
| | 50 | 66.76 | 17/33 | 24.44 | 2 g oral 2h pre- and 1 g oral 3 h, 9 h post- | | | | | | | | |
| | 50 | 63.94 | 14/36 | 25.51 | 2 g oral 2 h pre- and 1 g oral 3 h, 9 h, 15 h post- | | | | | | | | |
| Wang (2018) | 60 | 67.3 | 23/37 | 24.3 | 2 g oral 2 h pre- and 1 g oral 3 h post- | 60 | 68.7 | 22/38 | 24.6 | No TXA | Hb<70 g/L or symptoms | RCTs | 6 |
| | 60 | 68.9 | 22/38 | 24.4 | 2 g oral 2 h pre- and 1 g oral 3 h, 7 h post- | | | | | | | | |
| | 60 | 67.2 | 24/36 | 24.1 | 2 g oral 2 h pre- and 1 g oral 3 h, 7 h, 11 h post- | | | | | | | | |
| | 60 | 68.5 | 21/39 | 24.4 | 2 g oral 2 h pre- and 1 g oral 3 h, 7 h, 11 h, 15 h post- | | | | | | | | |
| Zhao (2017) | 40 | 60.47 | 22/18 | 22.24 | 20 mg/kg orally pre- and 3 h pos- | 40 | 59.50 | 23/17 | 22.46 | 15 mg/kg IV pre- and 3 h post- | Hb<70g/L or symptoms | RCTs | 7 |
| | | | | | | 40 | 59.86 | 25/15 | 22.52 | No TXA | | | |

BMI = body mass index, CCT = clinical comparative trial, Hb = hemoglobin, IV = intravenous, post- = post-operatively, Pre- = pre-operatively, QAS = quality assessment score, RCTs = randomized controlled trials, TXA = tranexamic acid.

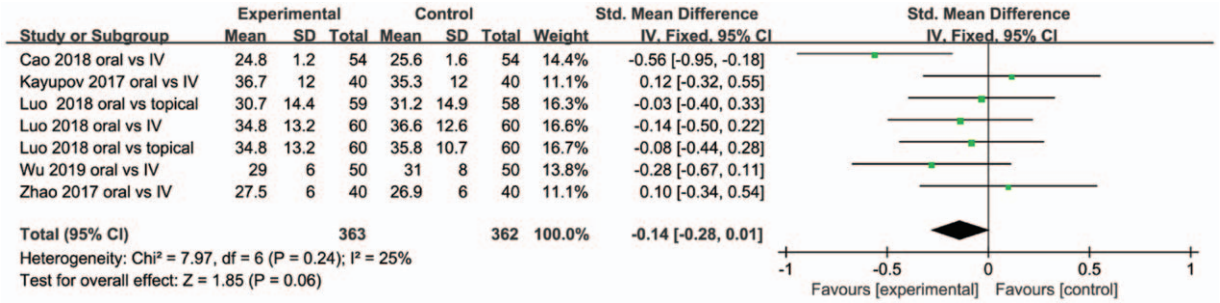


**Figure 2.** Forest plot showing hemoglobin drop comparing oral to IV or topical TXA.

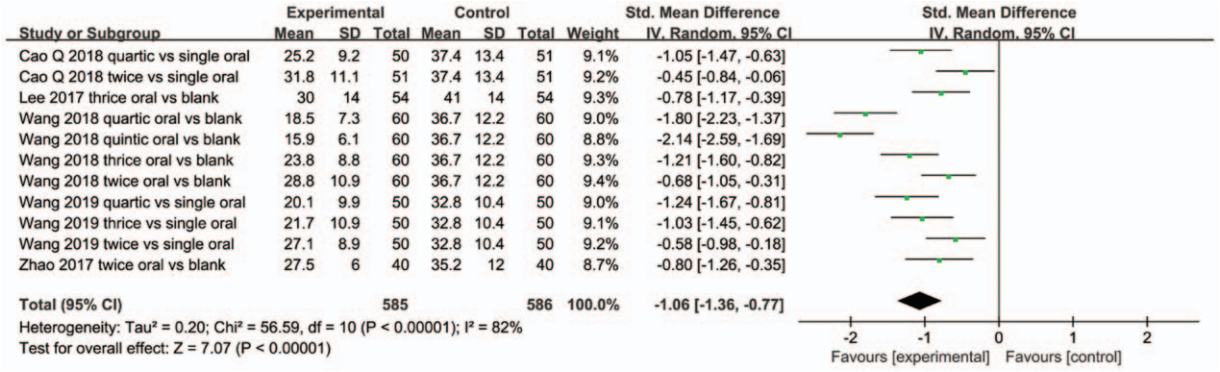


**Figure 3.** Forest plot showing hemoglobin drop comparing multiple oral to single oral TXA or blank group.

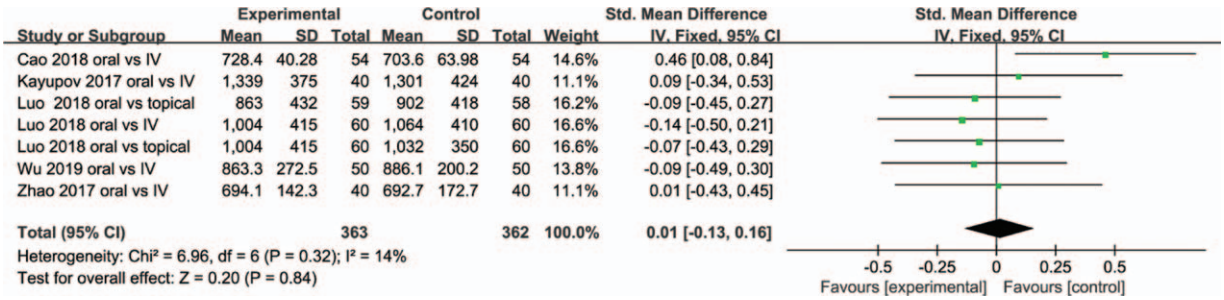


**Figure 4.** Forest plot showing total blood loss comparing oral to IV or topical TXA.

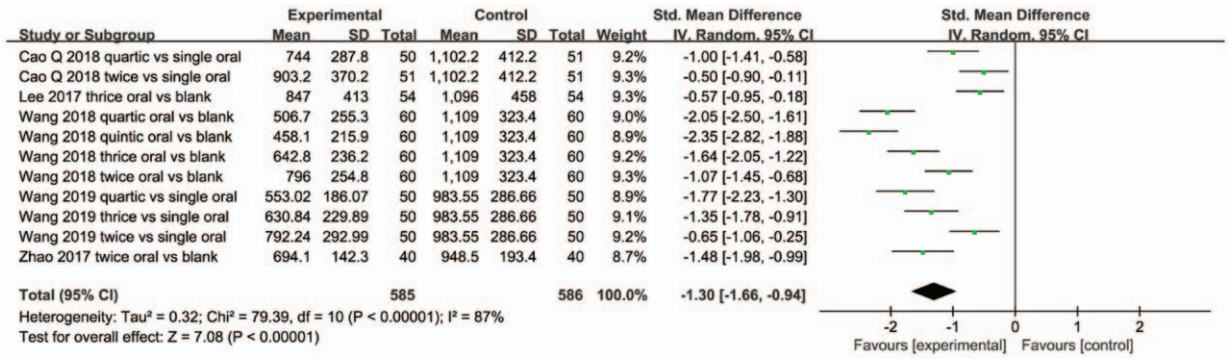


**Figure 5.** Forest plot showing total blood loss comparing oral to IV or topical TXA.

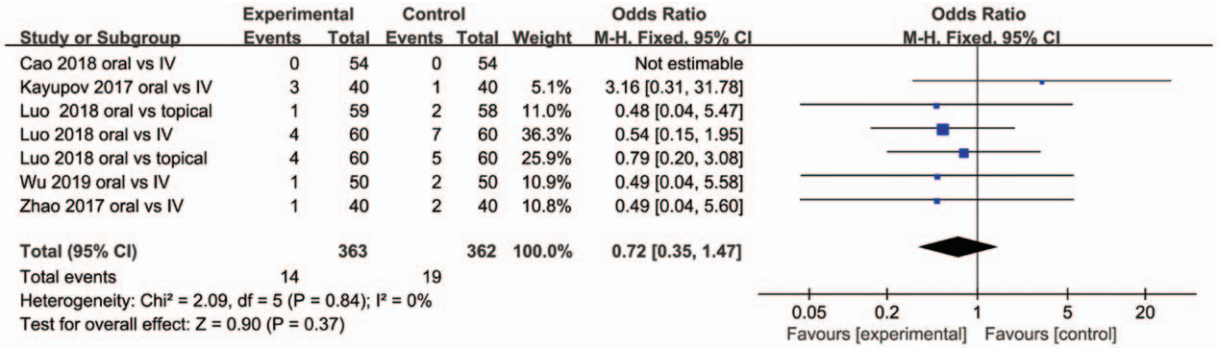


**Figure 6.** Forest plot showing transfusion rate comparing oral to IV or topical TXA.

TXA in transfusion rate under a fixed-effect model (OR = 0.72; 95% CI, [0.35, 1.47]; $P = .37$; Fig. 6).

Five articles[13,17–19,30] of 840 patients studied the effect of multiple oral TXA compared to single oral TXA or blank group on transfusion rate without significant heterogeneity ($I^2 = 0\%$, $P = .61$) in the THA. We found difference between the multiple oral TXA and single oral TXA or blank in transfusion rate under a fixed-effect model (OR = 0.53; 95% CI, [0.29, 0.95]; $P = .03$; Fig. 7).

### 3.5. Meta analysis: length of stay

Six articles[11–16] of 665 patients studied the length of stay of oral TXA compared to IV or topical TXA with no any heterogeneity ($I^2 = 0\%$, $P = .79$) in the THA. We did not find significant difference between the oral TXA and IV TXA or topical TXA in length of stay under a fixed-effect model (MD = −0.00; 95% CI, [−0.03, 0.03]; $P = .91$; Fig. 8).

Three articles[13,18,19] of 488 patients studied the length of stay of multiple oral TXA compared to single oral TXA or blank group with significant heterogeneity ($I^2 = 53\%$, $P = .06$) in the THA. We did not find any difference between the multiple oral TXA and single oral TXA or blank group in length of stay under a random-effect model (MD = −0.12; 95% CI, [−0.28, 0.04]; $P = .13$; Fig. 9).

### 3.6. Meta analysis: complication

Six articles[11–16] of 665 patients studied the complication of oral TXA compared to IV or topical TXA with no any heterogeneity

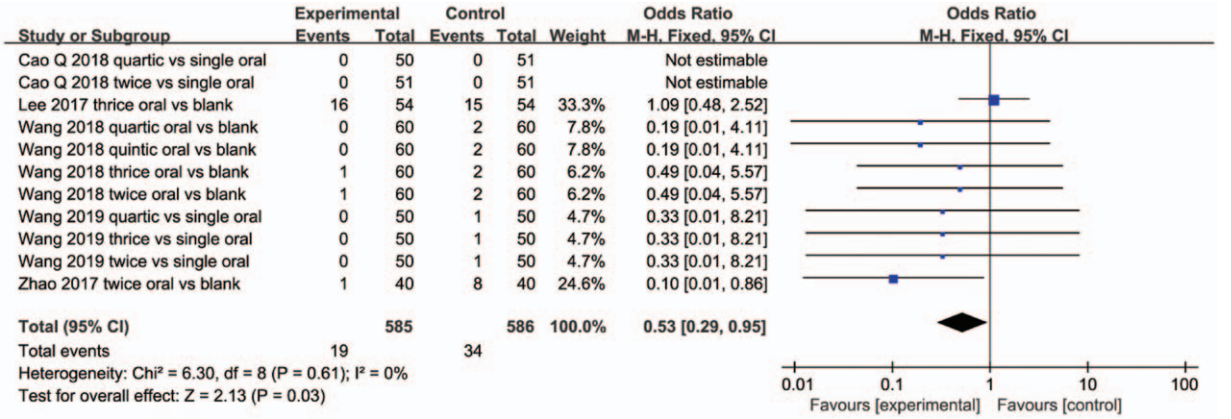


**Figure 7.** Forest plot showing transfusion rate comparing multiple oral TXA to single oral TXA or blank group.

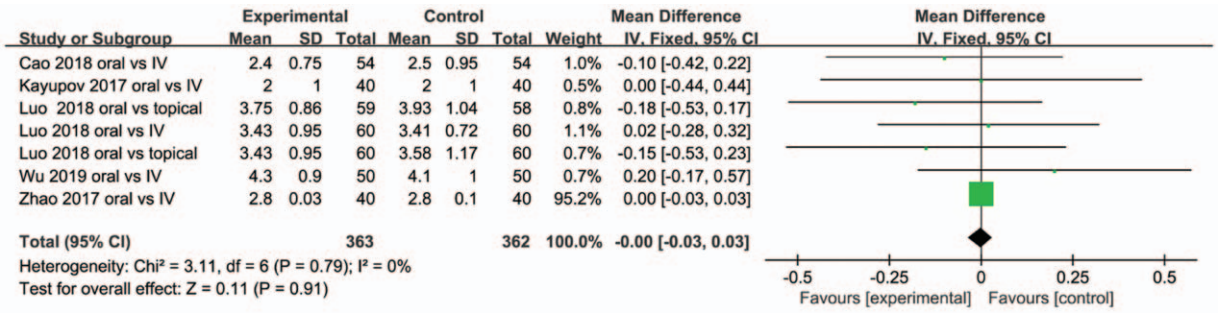


**Figure 8.** Forest plot showing length of stay comparing oral to IV or topical TXA.

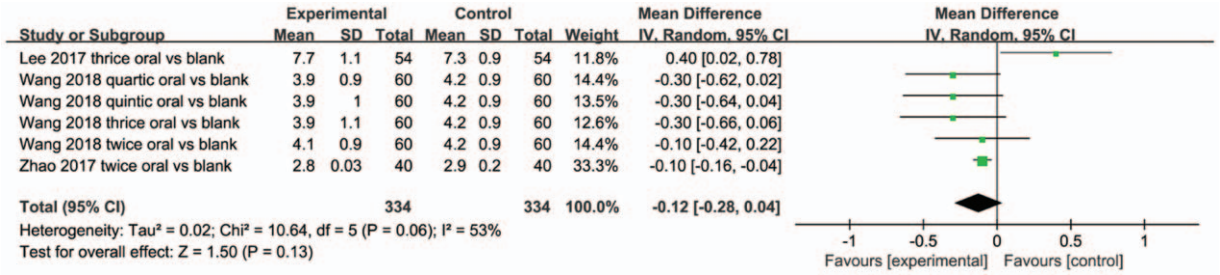


**Figure 9.** Forest plot showing length of stay comparing multiple oral to single oral TXA or blank group.

($I^2 = 0\%$, $P = .84$) in the THA. There was no significant difference between the oral TXA and IV or topical TXA in complication under a fixed-effect model (OR = 0.63; 95% CI, [0.32, 1.24]; $P = .18$; Fig. 10).

Five articles[13,17–19,30] of 840 patients studied the complication of multiple oral TXA compared single oral TXA or blank group without significant heterogeneity ($I^2 = 0\%$, $P = .93$) in the THA. We did not find any difference between the multiple oral TXA and single oral TXA or blank group in complication under a fixed-effect model (OR = 1.11; 95% CI, [0.71, 1.74]; $P = .64$; Fig. 11).

## 4. Discussion

THA frequently accompany with a large of perioperative blood loss, which delay postoperative functional recovery. As an antifibrinolytic agent, TXA has been applied widely to reduce perioperative blood loss and transfusion rate in THA. The application of TXA includes intravenous, topical, or oral routes. Previous clinical studies have demonstrated the efficacy of intravenous and topical TXA in decreasing blood loss in THA.[31,32] Recently, several studies have reported that oral TXA was another alternative option in decreasing blood loss in THA. However, whether oral TXA has comparable blood-saving effectiveness compared with IV or topical routes, and whether multiple oral TXA is superior to single oral TXA or blank group is still unknown. So we want to certify the effectiveness of oral TXA in THA through this meta-analysis.

The results of the meta-analysis demonstrated that multiple oral TXA could reduce effectively hemoglobin drop, total blood loss, transfusion rate compared with single oral TXA, or blank

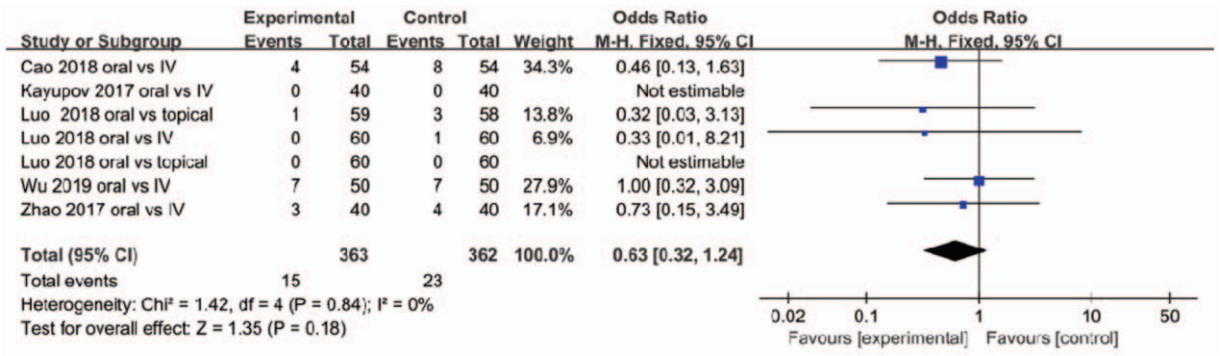


**Figure 10.** Forest plot showing complication oral to IV or topical TXA.

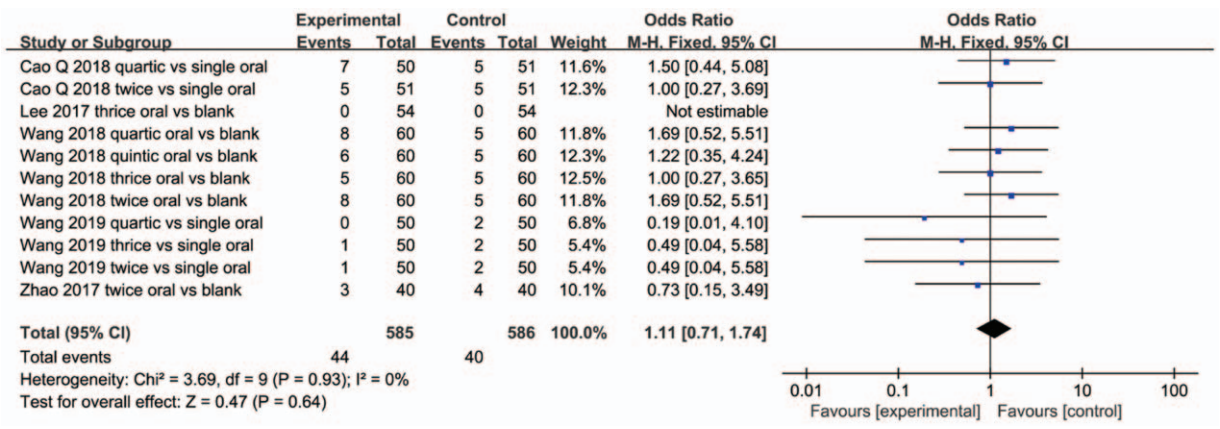


**Figure 11.** Forest plot showing complication multiple oral to single oral TXA or blank group.

group based on the available evidence in THA. And, oral TXA had similar effects on hemoglobin drop, total blood loss, transfusion rate compared with IV or topical TXA in THA. There was no statistical difference in length of stay, complication among all of the enrolled studies.

Not only RCTs article but non-RCTs were enrolled in this study. The score of the non-RCTs article was 7 via applying NOS, and the score of the RCTs articles ranged from 5 to 7 by using Jadad scale. The quality of all of the included articles was considerable high.

The hemoglobin drop and total blood loss reflected the degree of the blood loss and as the transfusion trigger (70 g/L). Previous studies have already reported that IV and topical TXA can effectively reduce blood loss in THA.[33,34] In recent years, several studies have demonstrated that multiple oral TXA can effectively reduce hemoglobin drop and total blood loss compared to single oral TXA or blank in THA,[13,17–19,30] and oral TXA had similar effect on decreasing hemoglobin drop and total blood loss compared with IV TXA or topical TXA in THA.[11–16] Han et al[20] reported that oral TXA had similar efficacy on blood-sparing compared with IV TXA in TKA and THA. Li et al[35] considered that oral TXA significantly decreased blood loss, hemoglobin drop in TKA. Above results were consistent with our comprehensive meta-analysis results. In addition, we just analyzed the effect of oral TXA in THA, which was different from above study. After generalized analysis, we considered that oral TXA effectively reduce hemoglobin drop and total blood loss in THA.

Massive perioperative blood loss results in postoperative anemia and potentially increases the risk of blood transfusion in THA. Thus, blood transfusion rate was another important result of evaluation of blood-saving in this meta-analysis. The effect of reducing the blood transfusion rate via IV and topical TXA in THA have been reported by published studies.[8,32] Several studies reported that oral TXA can reduce blood transfusion rate in THA.[11–14,16,17,19] Zhang et al[22] reported that there was no statistical difference compared oral TXA to IV TXA in total knee and hip arthroplasty. This was also consistent with our results analyzing alone the effect of oral TXA in THA. Thus, we considered that oral TXA could decrease the rate of blood transfusion in THA.

The length of stay is another important outcome in this meta-analysis. Wang et al[21] considered that there was no difference of length of hospital stay compared oral TXA to IV TXA in TKA and THA through meta-analysis. Our results of meta-analysis showed that oral TXA had no influence on length of hospital stay in THA. Our result was consistent with obvious result.

The complication of this meta-analysis included deep vein thrombosis, pulmonary embolism, wound complications, cardiac infarction, and acute renal failure. TXA was suspected whether increased the potential risk of thrombotic complications through IV application, and whether increased the risk of wound complications through topical application. Previous studies have reported that neither IV TXA nor topical TXA increased the risk of thrombotic complications, wound complications and other complications in THA. Han et al[20] considered that oral TXA did not increase the incidence of thromboembolic diseases compared with IV TXA in THA and TKA. Our outcome was consistent with obvious result. The results of this meta-analysis showed that there was no significant difference whether compared oral TXA to IV or topical TXA, or multiple oral TXA to single oral TXA or blank group in THA.

This meta-analysis existed some limitations:

1. This meta-analysis enrolled 10 studies, included 9 RCTs studies and 1 CCT study. Not all of articles were RCTs, and this might impact the final meta-analysis result.
2. Patients of control group were applied different forms of TXA, various doses of TXA, it might enlarge the heterogeneity of included studies.
3. As some outcomes of studies enrolled this meta-analysis, such as hematocrit dorp, intraoperative blood loss, TXA cost, were insufficient, these outcomes were failed to analyzed.
4. Single oral TXA showed similar effect as IV or topical TXA treatment, but blank group did not. The combination of the single oral TXA and blank group might possibly bring bias for the final conclusion of comparison between multiple oral TXA and single oral TXA.

## 5. Conclusion

Oral TXA had comparable efficacy and safety compared with IV or topical TXA in patients following THA, which could effectively reduce blood loss, hemoglobin drop, and transfusion rate, and did not increase the incidence of complication. In addition, multiple oral TXA was much better effect of blood-saving than single oral TXA or blank group. Due to limitations of this meta-analysis, much more higher quality and large simple size RCTs are necessary.

## Author contributions

**Data curation:** Shaoting Sun, Ming Guo.
**Formal analysis:** Shaoting Sun, Qing Feng.
**Methodology:** Yi-Peng Xu.
**Project administration:** Bin Dong.
**Resources:** Bin Dong.
**Software:** Qing Feng, Bin Dong, Ming Guo.
**Validation:** Guanfeng Zhang.
**Visualization:** Guanfeng Zhang.
**Writing – original draft:** Yi-Peng Xu.
**Writing – review & editing:** Shaoting Sun, Guanfeng Zhang, Xiaoyan Wang.

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