

Comparing efficacy and safety of 2 methods of tranexamic acid administration in reducing blood loss following total knee arthroplasty

A meta-analysis

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Abstract

Background: The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) were to gather data to evaluate the efficacy and safety of topical tranexamic acid (TXA) versus intravenous (IV) TXA for blood loss after a total knee arthroplasty (TKA).

Methods: Electronic databases: Pubmed, Web of Science, Cochrane library, and Embase from inception to June 2016 were searched. RCTs that comparing topical with IV TXA for blood loss control in patients prepared for TKA were included in this meta-analysis. The Cochrane risk of bias tool was used to appraise risk of bias. The primary outcomes were needed for transfusion, total blood loss, and blood loss in drainage. Secondary outcomes are hemoglobin (Hb) value at 24-hour post TKA and complication (deep venous thrombosis [DVT] and infection). The efficacy of blood loss was tested by total blood loss, drainage volume, Hb drop, and the Hb value at 24 hours after TKA. The safety was measured by the occurrence of DVT and infection. Continuous outcomes were expressed as the mean difference with the respective 95% confidence intervals (CIs). Discontinuous outcomes were expressed as the relative risk with 95% CIs. Stata 12.0 software (Stata Corp., College Station, TX) was used for the meta-analysis.

Results: A total of 14 articles involving 1390 patients were finally included for this meta-analysis. The pooled results revealed that there were no significant difference between the need for transfusion, total blood loss, blood loss in drainage, Hb value at 24-hour post TKA, the occurrence of complications (infection and DVT) between topical administration of TXA and IV TXA.

Conclusion: Topical TXA has similar efficacy for blood loss control to IV TXA without sacrificing safety in TKA. However, the dose of topical TXA and IV TXA is different, thus, optimal timing and dose of TXA are still needed to explore the maximum effect of TXA.

Abbreviations: CIs = confidence intervals, DVT = deep venous thrombosis, Hb = hemoglobin, IV = intravenous, MD = mean differences, Mesh = medical subject headings, RCTs = randomized controlled trials, RR = relative risk, TKA = total knee arthroplasty, TXA = tranexamic acid.

Keywords: blood loss, intravenous, meta-analysis, topical, tranexamic acid

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1. Introduction

Total knee arthroplasty (TKA) is the final alternative for patients who suffer from osteoarthritis pain. Indeed, the number of primary total knee replacement (TKR) procedures will be reached at 3.48 million in 2030 in the United States and the number will be as 8-fold to the year of 2005.^[1] Perioperative blood loss requiring blood transfusion has been reported during TKA, with the total blood loss varies between 800 and 1800 mL^[2] and the occurrence of need for transfusion ranging from 11% to 67%.^[3,4] The reason for massive blood loss during TKA is not only due to bone cut and soft tissue injury, but also fibrinolysis caused by surgical trauma. What's more, fibrinolysis is enhanced by the administration of tourniquet. Replacing blood loss by blood transfusions is considered undesirable alternative owing to associated risk of infection of HIV, other infectious disease, fluid overload, and graft-versus-host disease.^[5] Perioperative blood management including erythropoietin, fibrin sealant, and anti-fibrinolytic agents such as tranexamic acid (TXA). However, when taken into consideration the routine use of erythropoietin and fibrin sealant, it should balance its large costs.^[6-8] Compared with fibrin sealant, TXA performs equal hemostatic effects with less costs.^[8,9] Molloy et al^[10] conducted a randomized controlled trials (RCTs) comparing topical fibrin spray to intravenous (IV)

TXA demonstrated comparable blood loss control but also showed that the cost of topical fibrin spray was \$585.00 compared to \$6.00 with IV TXA. Thus, controlling of blood loss with antifibrinolytic agents such as TXA may be a preferable alternative.

Pharmacologically, TXA, a synthetic lysine analogous drug, inhibits fibrinolysis without increase of the plasma fibrin.^[11] Many studies demonstrated that IV TXA is effective and safe in reducing blood loss and subsequent blood transfusion in TKA. However, there are still concerns about risk of thromboembolic complications after systematic administration of TXA. Topical administration of TXA decreases systemic absorption; therefore, the occurrence of deep venous thrombosis (DVT) can be decreased. Previous meta-analysis was conducted on RCTs and prospective cohort trials, what's more, there are only 6 trials included.^[12] Recently, more clinical trials about topical versus IV TXA for blood loss control in TKA have been published. However, the efficacy and safety of topical administration of TXA versus IV TXA in preventing blood loss in patients prepared with primary TKA is still debated. Alshryda et al^[13] found that topical administration of TXA is superior to the IV route. Sarzaem et al^[14] indicated that IV TXA seems to be much more effective in terms of reducing hemoglobin (Hb) drop and transfused units than topical group. The purpose of this systematic review and meta-analysis of RCTs was to evaluate the optimal method of TXA (IV vs topical) for blood loss control in patients prepared for primary TKA.

2. Material and methods

The present study was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines^[15,16]. This review is registered in Protocol registration: PROSPERO 2016: CRD42016043515.

3. Search strategy

Electronic databases: Pubmed, Web of Science, Cochrane library, and Emabse were searched from inception to June 20, 2016 to identify any relevant studies that comparing topical TXA versus IV TXA for blood loss controlling after TKA. The search terms were as follows: "total knee replacement," "total knee arthroplasty," "TKA," "TKR," and "tranexamic acid". The medical subject headings (Mesh) for TKR are "Arthroplasty, Replacement, Knee "(Mesh)." The searches were limited to human subjects, and no restrictions were imposed on language. In addition to, reference lists of all the eligible studies and relevant reviews were searched for any additional studies. Since this is a meta-analysis, no ethics committee or institutional review board approval was necessary for the study.

4. Inclusion criteria and study selection

Inclusion criteria: Participants—participants, who had osteoarthritis or rheumatoid arthritis and prepared for TKA. Intervention and comparison—we included topical (including intra-articular, syringe spray, and intra-capsular) TXA as the intervention group and the IV TXA as the comparison group. Outcomes—primary outcomes: need for transfusion, total blood loss, and blood loss in drainage. Secondary outcomes included Hb drop, Hb value at 24-hour post TKA, and complication (DVT

and infection). Study—only RCTs were included in this study. Articles that must be published and reported at least 1 outcome were included. Quasi-RCT or non-RCT, letters, comments, editorials, and practice guidelines, studies with revision knee arthroplasty, or bilateral TKA were excluded for this meta-analysis.

5. Data abstraction and quality assessment

Two authors independently reviewed all the titles and abstracts of studies. Full texts of any potentially useful studies were reviewed, disagreements regarding which studies to include were resolved by discussion. Data regarding the patient characteristics (age, sex, and other baseline characteristics), intervention, outcomes, and follow-up were extracted and then checked by using another standardized form. Data in other forms (i.e., median, inter-quartile range, and mean \pm 95% confidence interval [CI]) were converted into mean \pm SD according to Cochrane Handbook.^[17] If the data were not reported numerically, we extracted them by manual measurements from the published figures. We contacted the author with Email or telephone for obtaining and confirming data from investigators if the article provide incomplete data for meta-analysis. The efficacy of TXA was measured by need for transfusion, total blood loss, blood loss in drainage, Hb drop, and Hb value at 24 hours after TKA. The safety of TXA was measured by the occurrence of DVT and infection.

Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) was used for assessing the risk of bias of the included studies by 2 authors independently. The content for the assessment including the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.^[17] Disagreement was resolved by the third author. Based on the information provided from included studies, each item was recorded by "Yes," "No," or "Unclear;" "Yes" indicates low risk of bias, "No" indicates high risk of bias, "Unclear" indicates lack of information or unknown risk of bias.

6. Statistical analysis

Continuous outcomes such as the total blood loss, blood loss in drainage, and Hb value at 24-hour post TKA were expressed as the mean difference (MD) with the respective 95% CIs. Discontinuous outcomes [i.e., the rate of transfusion and complication (DVT and infection)] were expressed as the relative risk (RR) with 95% CIs. Statistical heterogeneity was tested using the chi-squared test and I^2 statistic. A chi-squared test scoring $I^2 > 50\%$ was considered suggestive of statistical heterogeneity. When there was no statistical evidence of heterogeneity, a fixed effects model was adopted; otherwise, a random effects model was chosen. Publication bias was tested by funnel plot and quantitative analysis by Begg test. *P* value obtained in Begg test greater than 0.05 or funnel plot is symmetry indicating that there is no publication bias between the studies. Statistical significance was set at $P < 0.05$ to summarize the findings across trials. Stata, version 12.0 (Stata Corp., College Station, TX) was used for meta-analysis.

7. Search results and quality assessment

In the initial research, a total of 589 articles were identified, and 367 articles were reviewed after the removal of duplicates. When the records were reviewed, most of articles were excluded after

the title and abstracts were scanned. The reasons of removal were that most of the articles were case reports, irrelevant articles, meeting abstracts, and systematic reviews. Then, a total of 16 studies were assessed for eligibility, after carefully reading the papers; 2 studies were excluded. One study compared topical versus IV for bilateral TKA,^[18] and 1 was prospective comparable study.^[19] The flow diagram can be seen in Fig. 1. Finally, a total of 14 articles involving 1390 patients were included.^[2,14,20-31] All of the included studies were published from the year 2012, and mean age of topical and IV patients was ranging from 42 to 72. Only 1 study^[21] did not describe the diagnosis of the patients prepared for TKA; the rest studies included all patients with osteoarthritis. There were only 3 studies^[20-22] that did not state the type of prosthesis, and the rest 11 studies were all performed with cemented prosthesis. One study performed TKA with no administration tourniquet, and the remaining all included tourniquet. Two studies^[2,29] are with

computer-assisted TKA, and the rest are conventional TKA. Maniar et al^[2] performed different regimens (4 IV and 1 topical) during TKA, and thus we divided into 4 comparative studies. Seo et al^[29] performed different doses regimens for topical TXA (1.5 and 3.0 g), thus, it divided into 2 comparative studies. The general characteristic for the included studies can be seen in Table 1.

The quality of included studies and the potential sources of bias were outlined in Figs. 2 and 3. Only 5 trials were judged to be at a high risk of bias. All studies reported randomization; however, only 8^[2,14,20-24,30] studies reported an appropriate random sequence generation procedure, and 9^[2,14,20-24,26,30] studies described adequate concealment. Blinding of participants and assessment in 8 trials^[2,14,20,21,23-26] in all studies are with no bias of incomplete outcome data, reporting bias, and other bias. We rated 6 (42.9%) RCTs at unclear risk for random sequence generation, 2 (14.3%) RCTs were rated at unclear risk, and 3 (21.5%) RCTs were rated at high risk for allocation concealment.

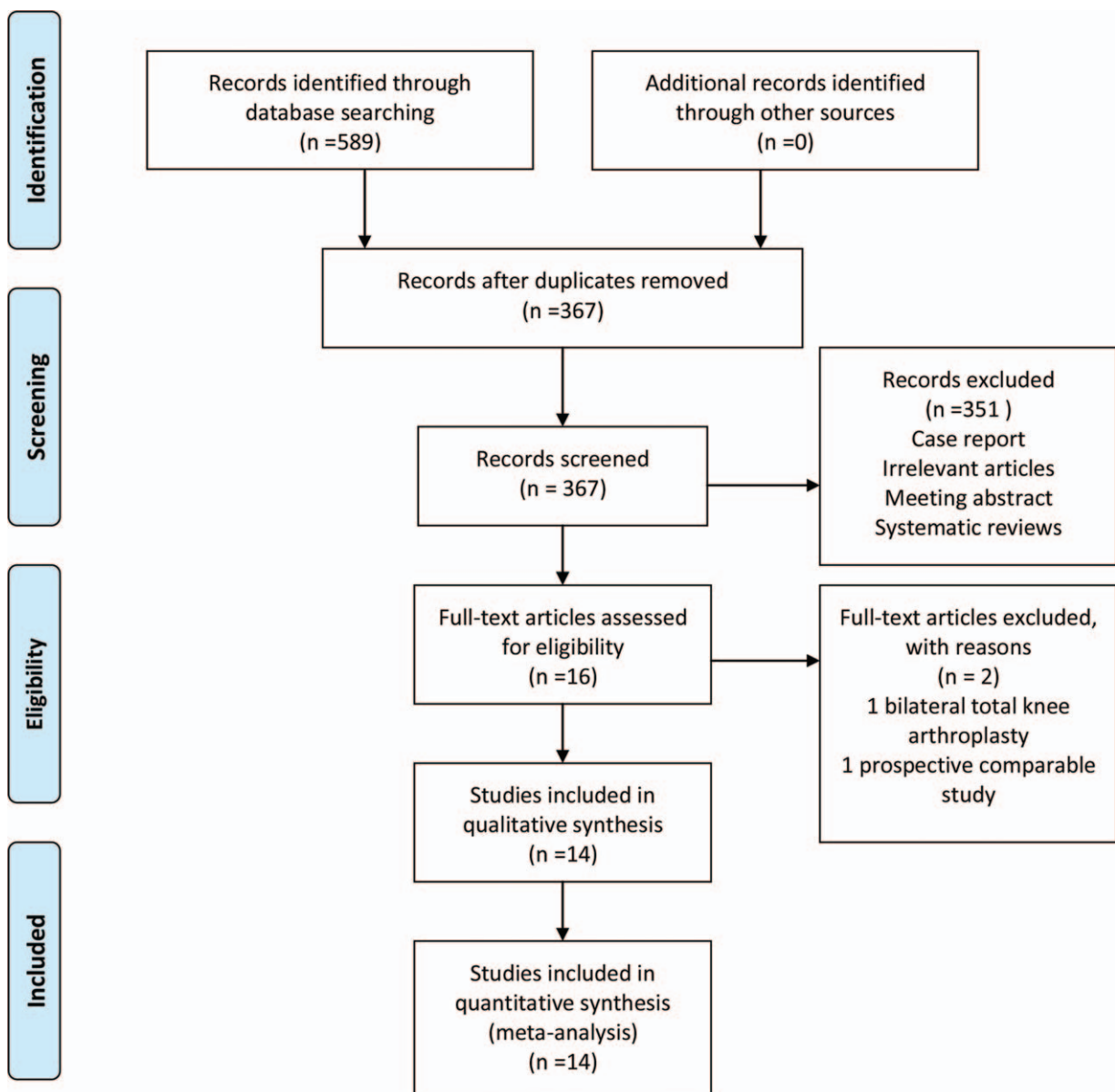


Figure 1. The flowchart of the included studies.

Table 1
The general characteristic of the included studies.

Reference	Study design	Intervention	Patients (T/I)	Age (mean year) (T/I)	Gender (F/M)	Outcomes	Follow-up
Gomez-Barrena et al ^[26]	RCT	IV TXA 15 mg/kg 2 dose 15–20 min before tourniquet release T TXA 3g/100 mL 1 dose before joint closure, the other after skin closure	39/39	70.1/71.8	51/27	1 2 3 4 5 7	1 mo
Patel et al ^[20]	RCT	IV TXA 10 mg/kg during operation T TXA 2 min before tourniquet release	47/42	42/64.9	23/66	1 2 3 4 7	14d
Maniar et al ^[2]	RCT	IV TXA 10 mg/kg 1, 2, and 3 dose during operation T TXA 3g/100 mL 5 min before tourniquet release	40/160	67.4/67.45	42/158	1 2 3 7	3 mo
Seo et al ^[29]	RCT	IV TXA 1.5g/100 mL postoperative T TXA 1.5g/100 mL when suturing	50/50	67.5/66.8	11/89	1 2 3 4 7	2 mo
Sarzaeem et al ^[4]	RCT	IV TXA 1.5g/100 mL postoperative T TXA 1.5g/100 mL or 3.0g/100 mL after closure	100/50	67.8/66.9	20/130	1 2 3 4 7	NS
Soni et al ^[30]	RCT	IV TXA 10 mg/kg 3 doses intraoperative and postoperative T TXA 3g/100 mL 5 min before tourniquet release	40/40	69.45/69.05	36/44	1 2 3 4 7	6 wk
Chen et al ^[24]	RCT	IV TXA 1.5g/100 mL 20 min after cemented the prosthesis T TXA 1.5g 20 min after cemented the prosthesis	50/50	65/65	75/25	2 3 5	4 d
Keyhani et al ^[27]	RCT	IV TXA 0.5g/100 mL at the end of surgery T TXA 3g/100 mL	40/40	68.4/67	31/49	1 2 3 5 7	2 wk
Aguilera et al ^[23]	RCT	IV TXA 1g 2 doses intraoperative T TXA 1g/100 mL after inserted prosthesis	50/50	72.53/72.49	70/30	1 2 3 5 6	2 mo
Digas et al ^[25]	RCT	IV TXA 15 mg/kg T TXA 2g	30/30	70/71	51/49	1 2 3 4 5 6 7	12 mo
May et al ^[21]	RCT	IV TXA 1g/100 mL before tourniquet deflation T TXA 2g/50 mL when capsular closure	62/69	65/63	102/29	5 6 7	1 mo
Uğurlu et al ^[22]	RCT	IV TXA 20 mg/kg 15 min before tourniquet release T TXA 3g/100 mL when suturing of the capsular	40/42	69.4/70.6	68/15	1 4 5 7	10d
Tzatzairis et al ^[31]	RCT	IV TXA 1g/100 mL 10 min before incision T TXA 1g/100 mL when joint capsule closure	40/40	69.55/69.10	64/16	1 6 7	14d
Oztaş et al ^[28]	RCT	IV TXA 15 mg/kg 1 h before deflation of tourniquet T TXA 2g before tourniquet deflation	30/30	68.56/67.06	9/51	1 2 3 6 7	3 mo

F = female, IV = intravenous, M = male, RCT = randomized controlled trial, T = topical, TXA = tranexamic acid, 1 need for transfusion 2 total blood loss 3 blood loss in drainage 4 Hb drop 5 Hb value at 24-hour post TKA 6 infection 7 DVT.

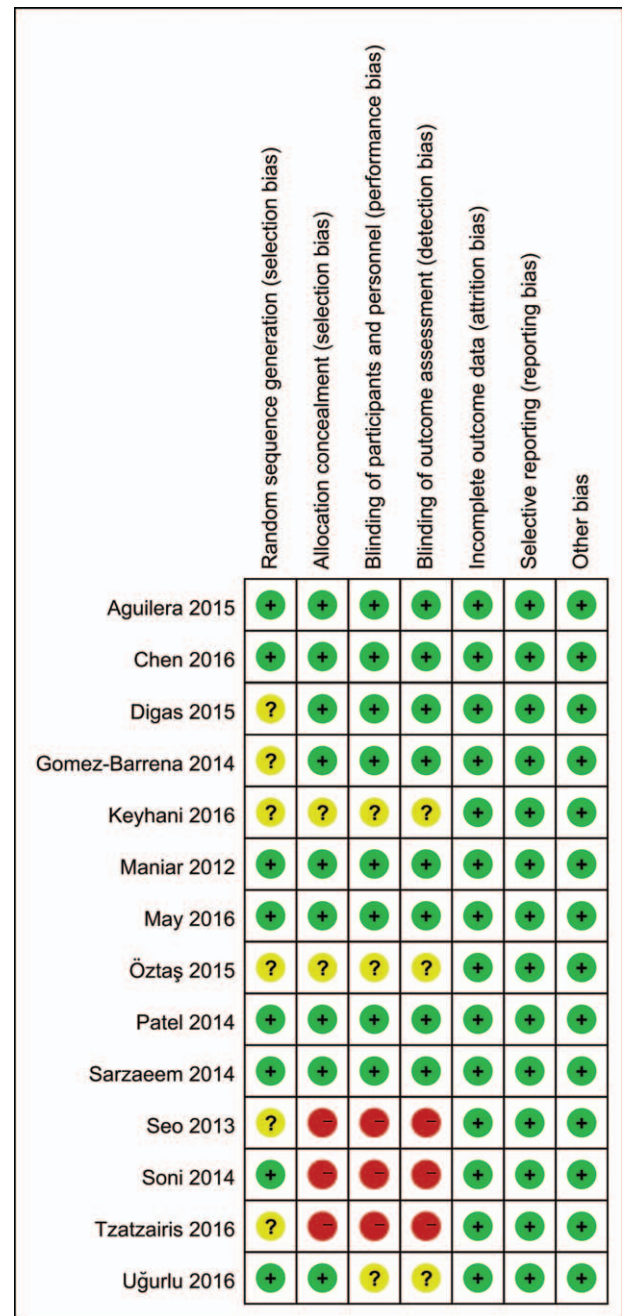


Figure 2. The risk of bias summary of the included studies.

We rated 3 (21.5%) RCTs at unclear risk and high risk for blinding of participants and personnel blinding of outcome assessment. The incomplete outcome data, selective reporting, and other bias are all with low bias.

8. Results

8.1. Need for transfusion

A total of 12 clinical trials^[2,14,20,22,23,25–31] performed the data of need for transfusion after TKA, and the pooled results indicated that there is no significant difference between need for transfusion between IV TXA and topical TXA group

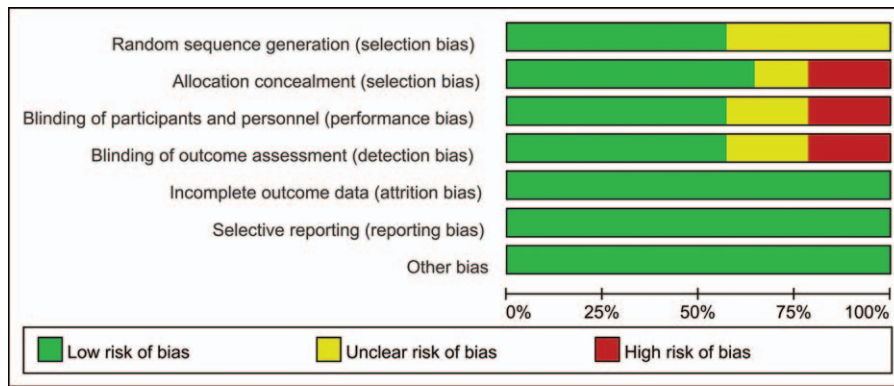


Figure 3. The risk of bias graph of the included studies.

(RR=0.91, 95% CI 0.66–1.26, $P=0.579$, Fig. 4) with low heterogeneity ($\chi^2=13.07$, $P=0.443$). The P value from Begg test is 0.070, indicated that there is no publication bias between the studies (Fig. 5). Funnel plot was also performed to verify the publication bias, results also indicated that the included studies are symmetrical, and thus there is no publication bias between the studies (Fig. 6).

8.2. Total blood loss

Figure 7 shows the effects of IV TXA versus topical TXA on total blood loss after TKA. There is no significant difference in total blood loss between the 2 groups (MD=14.75, 95% CI –54.41 to 83.91, $P=0.125$, Fig. 7), and substantial heterogeneity was observed ($P=0.001$, $I^2=68.0\%$). Thus, a random-model was performed to compile the data. To further explore the potential

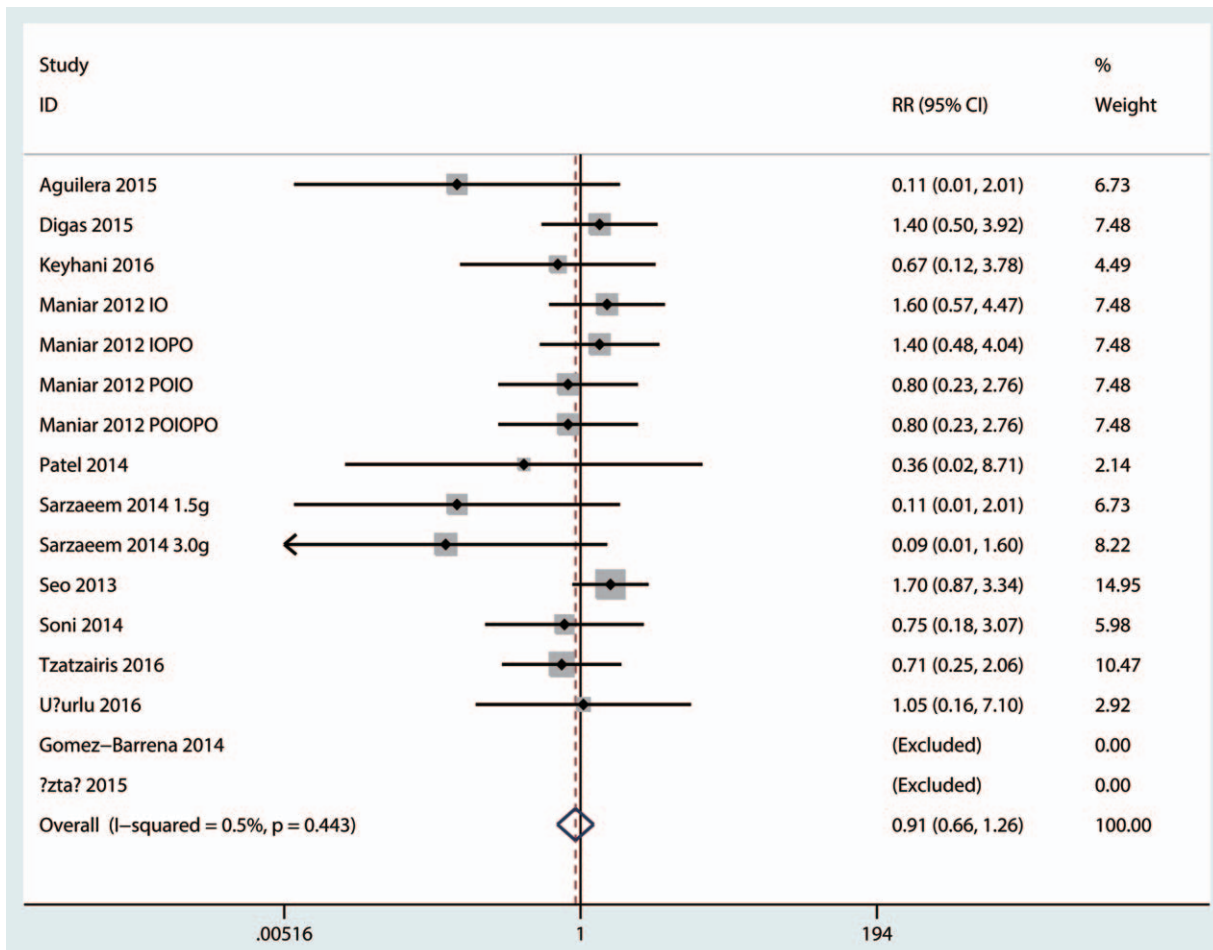


Figure 4. The funnel plot of the need for transfusion for intravenous tranexamic acid (TXA) versus topical TXA.

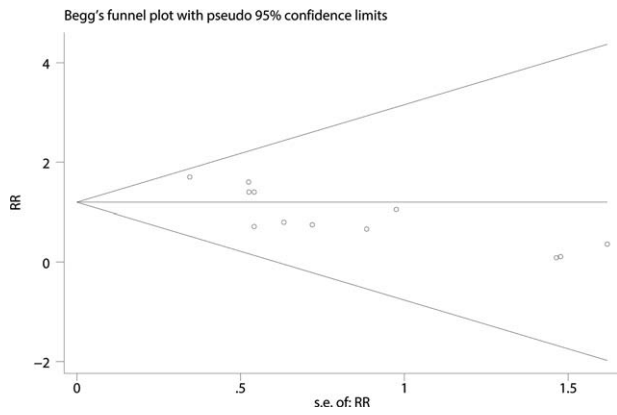


Figure 5. Begg test for need for transfusion.

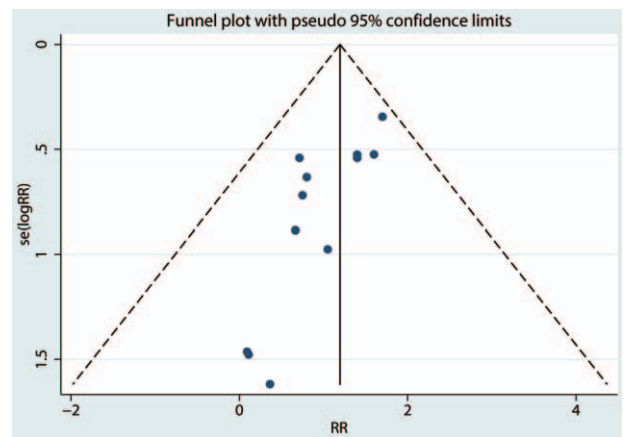


Figure 6. Sensitivity analysis of the need for transfusion.

source of heterogeneity across studies, we performed sensitivity analyses. The results indicated that no study affects the heterogeneity (Fig. 8).

8.3. Blood loss in drainage

A total of 12 studies^[2,14,20,23-30] with 1261 patients had reported the outcome of blood loss in drainage, and pooled results indicated that there is no significant difference between the blood loss in drainage between the 2 groups (MD=1.31, 95% CI -53.81 to 56.43, $P=0.963$, Fig. 9) in a random-model. There is large heterogeneity between the trials ($P=0.000$, $I^2=97.3\%$).

Sensitivity analysis was conducted to find out the source of heterogeneity. The results indicated that no study influences the final large heterogeneity (Fig. 10).

8.4. Hb drop

Seven studies^[14,20,22,25,26,29] involving 666 patients reported Hb drop between the 2 groups. Pooled results indicated that there is no significant difference between the 2 groups in terms of Hb drop after TKA (MD=-0.35, 95% CI -0.78 to 0.09, $P=0.119$, Fig. 11) with a large heterogeneity ($P=0.000$, $I^2=93.6\%$).

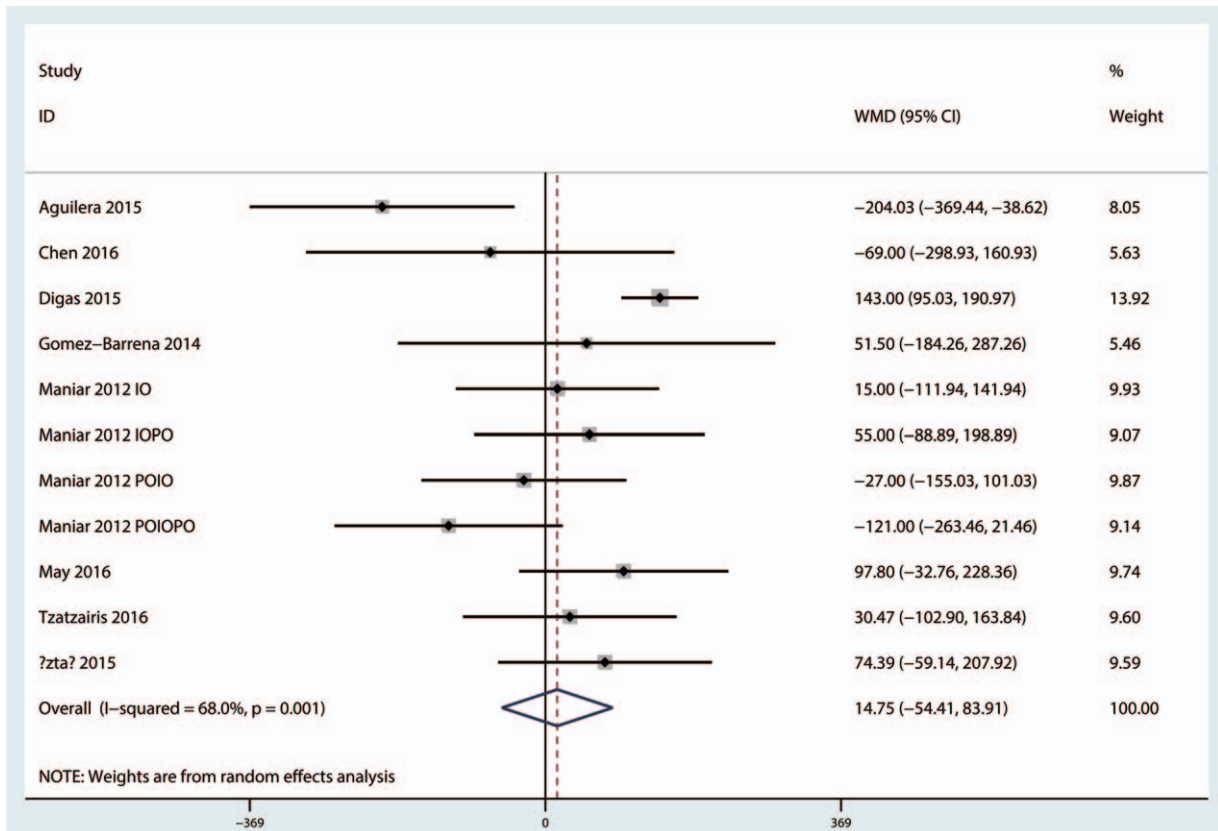


Figure 7. The funnel plot comparing total blood loss.

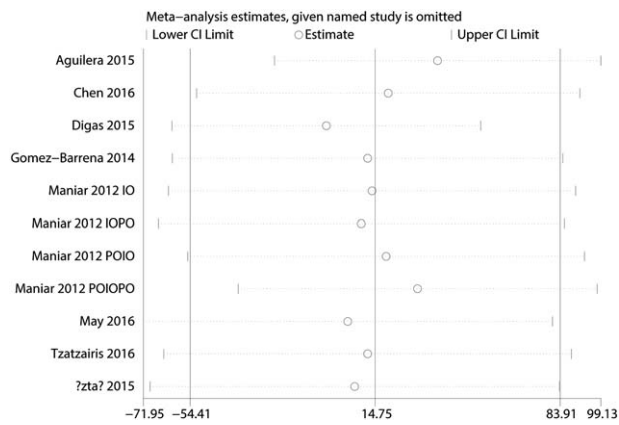


Figure 8. Sensitivity analysis for total blood loss.

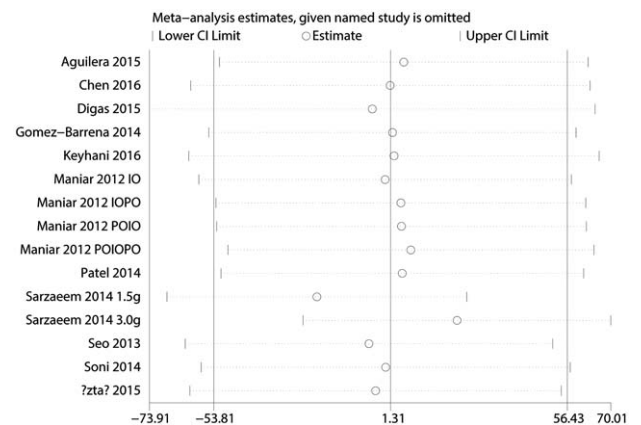


Figure 10. Sensitivity analysis for blood loss in drainage.

Sensitivity analysis was conducted to find out the source of heterogeneity. The results indicated that no study influences the final large heterogeneity (Fig. 12).

8.5. Hb value at 24-hour post TKA

Figure shows Hb value at 24-hour post TKA, and results indicated that there is no significant difference between the 2 groups in terms of Hb value at 24-hour post TKA (MD = -0.75,

95% CI -1.71 to 0.21, $P=0.126$, Fig. 13) with large heterogeneity ($P=0.000$, $I^2=91.5\%$).

8.6. Complications of DVT and infection

A total of 5 trials^[21,23,25,28,31] consisting of 431 patients reported the occurrence of infection, and pooled results indicated that there is no significant difference between the IV TXA with topical TXA (RR = 0.83, 95% CI 0.27–2.53, $P=0.746$, Fig. 14) with no

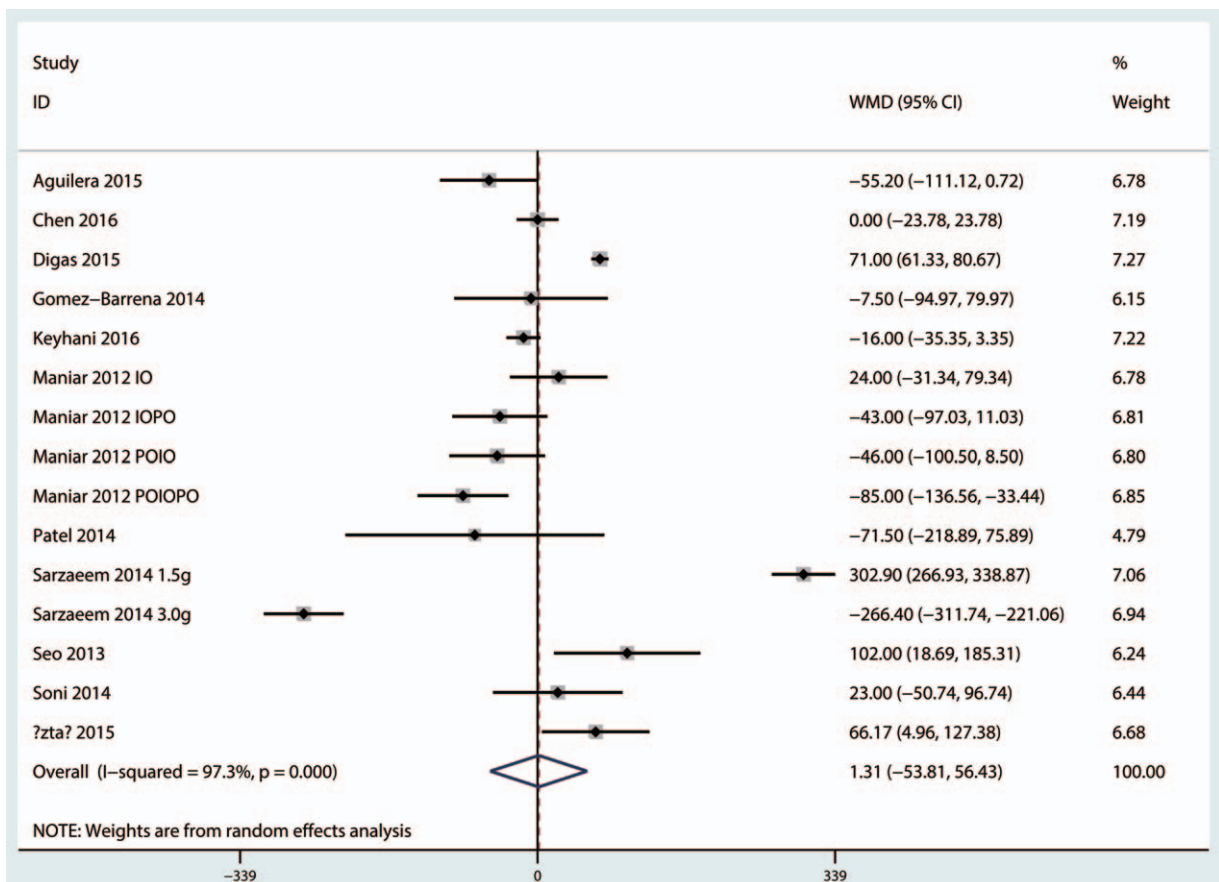


Figure 9. The funnel plot comparing blood loss in drainage.

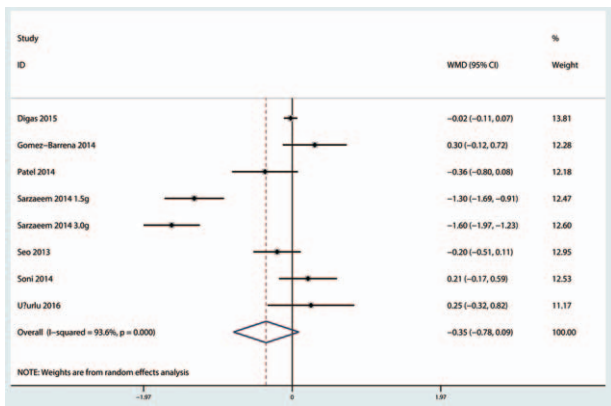


Figure 11. The funnel plot comparing hemoglobin drop.

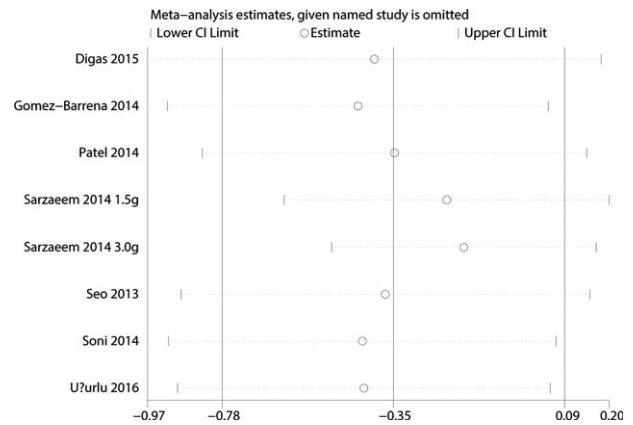


Figure 12. Sensitivity analysis for hemoglobin drop.

heterogeneity ($P=0.544$, $I^2=0.0\%$). A total of 12 studies^[2,14,20–22,25–31] with 1339 patients performed the data of postoperative DVT, pooled results indicated that there is no statistical difference between IV TXA with topical TXA (RR = 1.16, 95% CI 0.57–2.38, $P=0.684$, Fig. 15) with no heterogeneity ($P=0.750$, $I^2=0.0\%$).

9. Discussion

The present meta-analysis suggests that topical administration TXA, compared with IV TXA, has similar efficacy in blood transfusion, total blood loss, blood loss in drainage, Hb drop, and Hb value at 24 hour after TKA. What's more, there was no

significant difference between the occurrence of DVT and infection.

These results indicated that topical administration of TXA has comparable blood loss control with IV TXA. TXA, when given IV, widely distribute throughout the extracellular and intracellular compartment.^[32] Then, it can rapidly diffuse into the synovial fluid until the concentration of TXA reaches the equal level with serum.^[33] Based on this theory, TXA can reach faster hemostasis effect when given IV. Its biological half-life is 3 hours in the joint fluid, and 90% of TXA is eliminated within 24 hours by glomerular filtration.^[32,33] The advantage of topical TXA is easier to administrate, provides a maximum concentration at the bleeding site and minimal systemic absorption. Theoretically, it

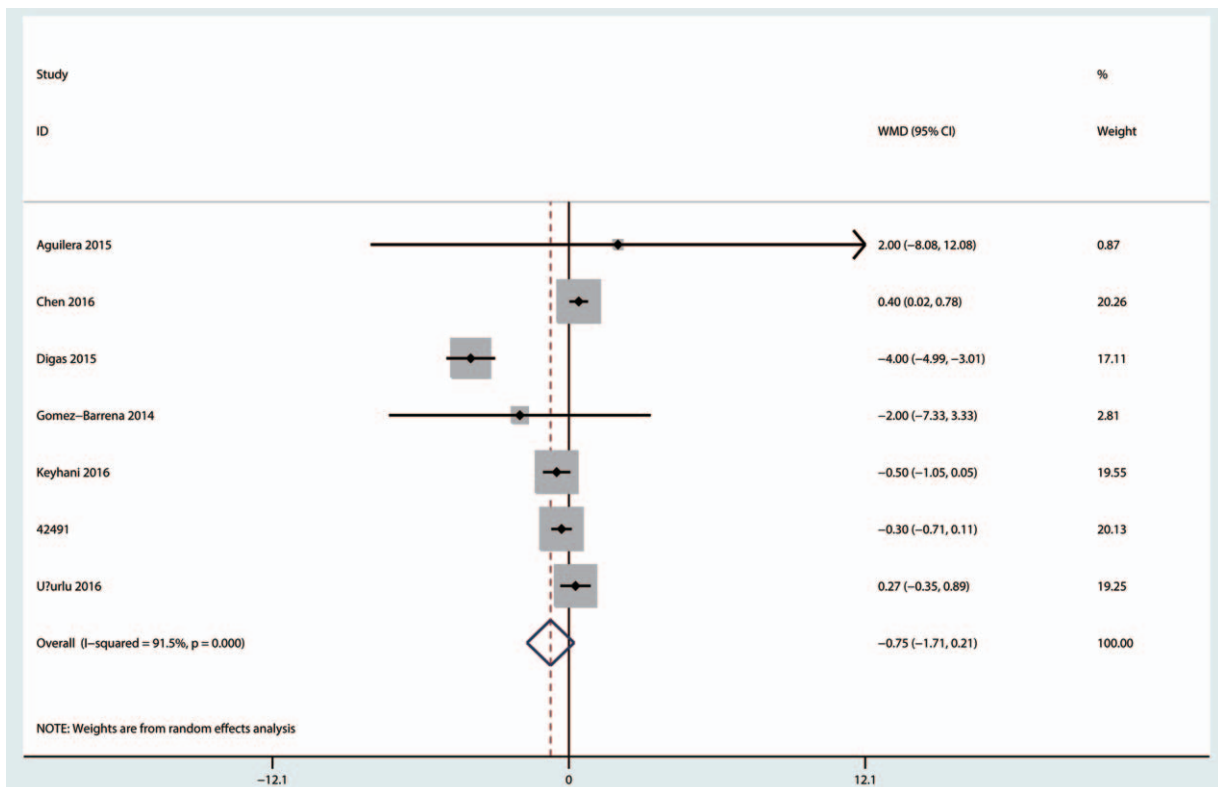


Figure 13. Funnel plot comparing hemoglobin value at 24-hour post total knee arthroplasty between the 2 groups.

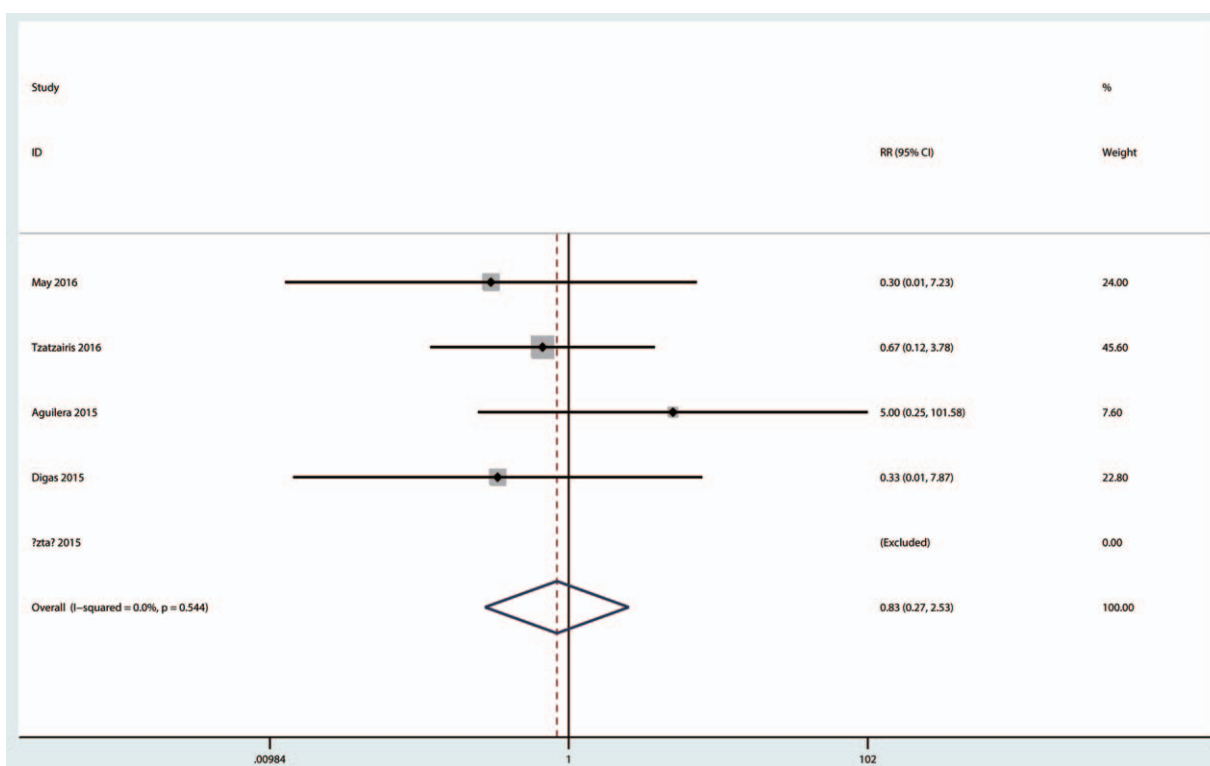


Figure 14. Funnel plot comparing the occurrence of infection.

may provide better blood loss control and less complications of DVT than IV administration. The results of this meta-analysis indicated that there is no statistically significant difference between the 2 groups in total blood loss (MD=14.75, 95% CI -54.41 to 83.91) and blood loss in drainage (MD=1.31, 95% CI -53.81 to 56.43, $P=0.963$). These results appear to support that TXA only works at active bleeding sites of the wound rather than in the normal blood vessels. This may be the main reason for considered hemostasis effect irrespective of the route of administration.

There is large heterogeneity between the studies in total blood loss and blood loss in drainage. Another important factor is the different dose of the 2 groups. The doses of IV TXA ranging from 10 to 30 mg/kg and the doses of topical TXA ranging from 1 to 3 g TXA dissolve in 50 to 100 mL saline. There is no consistent comparison between the different doses of TXA; subgroup was not performed in this meta-analysis to compare different doses of TXA in reducing blood loss after TKA. Sarzaem et al^[14] compared 1.5 versus 3.0 g TXA in reducing blood loss after TKA and found that the drainage in 1.5-g TXA injected through drain is less than 3.0 g TXA in reducing Hb drop. Maniar et al^[2] compared different doses of IV TXA for reducing blood loss after TKA and found that 3 doses of TXA (30 mg/kg) produced maximum effective reduction of drain loss.

As for Hb drop and Hb value at 24-hour post TKA, which represents the actual blood loss, Hb level after surgery is more important than need for transfusion and blood loss due to the race and transfusion volume. There is no significant difference between the IV TXA with topical TXA. Total blood loss contains blood loss in drainage and hidden blood loss. Only 1 included in the trial reported no significant difference between the 2 groups in terms of hidden blood loss. TXA could significantly reduce perioperative blood loss, thereby increasing nadir Hb value and

triggering less blood transfusion finally. Our results indicated that there is no statistically significant difference between the need for transfusion.

With the result of infection, results indicated that there is no significant difference between the occurrences of infection in the 2 groups. Meanwhile, there is no significant difference between the occurrences of DVT. Astedt et al^[34] reported that TXA did not suppress the fibrinolytic activity in the vessel walls. For the results of DVT, the long-terms follow up, and inspection method is as much important for the final results. The follow up in all the studies is not long enough to get the actual occurrence rates. What's more, all of the included studies excluded the patients with high risk of thrombosis and thus it is appropriate to administration of TXA topical when treated with patients with high risk of thrombosis.

There were several limitations in this meta-analysis: there was large heterogeneity among the included studies in total blood loss and blood loss in drainage, though sensitivity analysis was performed to seek out the heterogeneity source, the results was not significant; the duration of follow up these studies was relatively short and unclear; the occurrence of DVT may be underestimated; most exclusion criteria in the included studies excluded patients with high risk of thrombogenesis; thus, the occurrence of DVT should be cautious to treat; the dose, time, and interval to administration of TXA are different from each other, these will affect the final conclusion.

Further studies focusing on the following aspects are needed. The timing of IV TXA varied from each other according to the study protocols, and the optimal timing to administration with TXA remains unclear. Tanaka et al^[35] reported that the hemostatic effect of TXA was greatest when TXA was given preoperatively and on deflation of the tourniquet. What's more,

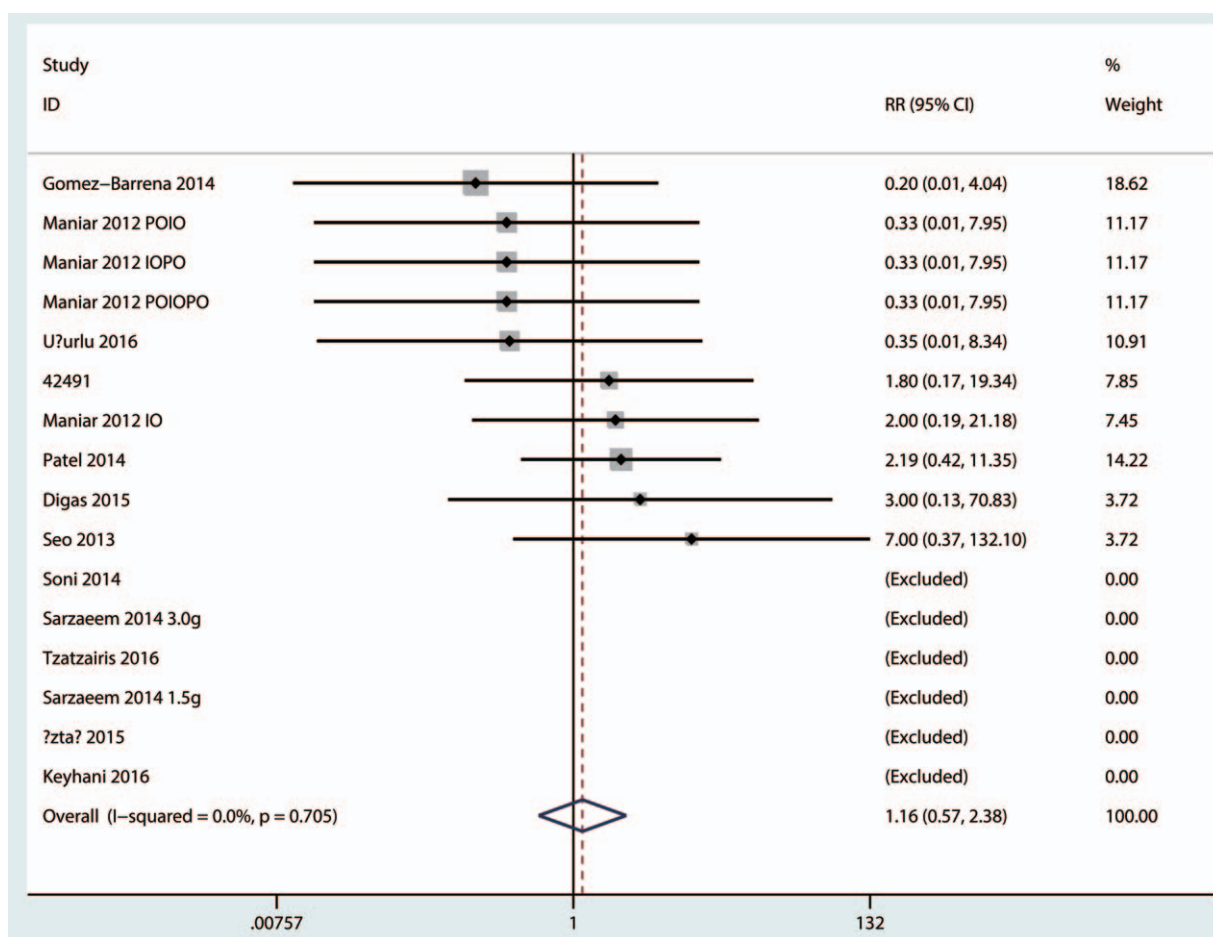


Figure 15. Funnel plot comparing the occurrence of deep venous thrombosis.

the dose of topical and IV TXA is different, and the optimal dose to administration with TXA remains further studies to identify. Multiple boluses of IV TXA cannot only reduce hidden blood loss, but also with less postoperative inflammatory response, less pain, less knee swelling, and better knee function.^[36] And, topical administration of TXA has a dose-response relationship with total blood loss after TKA.^[37]

10. Conclusion

Topical TXA has similar efficacy and safety to IV TXA in decreasing the blood transfusion, total blood loss, blood loss in drainage, Hb drop, and Hb value at 24-hour after TKA. What's more, there was no difference between the occurrence of DVT and infection after TKA.

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