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Oral vs intravenous tranexamic acid in total-knee arthroplasty and total hip arthroplasty

A systematic review and meta-analysis

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Abstract

Background: This study aimed to compare the efficacy and safety of oral tranexamic acid (TXA) with intravenous (IV) TXA in reducing perioperative blood loss in total-knee arthroplasty (TKA) and total-hip arthroplasty (THA).

Methods: PubMed, Web of Science, Embase, and Cochrane Library were fully searched for relevant studies. Studies comparing the efficacy and safety of oral TXA with IV TXA in TKA and THA were included in this research. Odds ratio (OR) or risk difference (RD) was applied to compare dichotomous variables, while mean difference (MD) was used to compare continues variables.

Results: A total of 7 studies (5 randomized controlled trials and 2 retrospective studies) were included into this study. As for patients undergoing TKA or THA, there were no obvious differences between oral TXA group and IV TXA group in hemoglobin (Hb) drop (MD = 0.06, 95% confidence interval [CI] = −0.01 to 0.13, P = .09), transfusion rate (OR = 0.78, 95% CI = 0.54–1.13, P = .19), total blood loss (MD = 16.31, 95% CI = −69.85 to 102.46, P = .71), total Hb loss (MD = 5.18, 95% CI = −12.65 to 23.02, P = .57), length of hospital stay (MD = -0.06, 95% CI = −0.30 to 0.18, P = .63), drain out (MD = 21.04, 95% CI = −15.81 to 57.88, P = .26), incidence of deep vein deep vein thrombosis (RD = 0.00, 95% CI = −0.01 to 0.01, P = .82) or pulmonary embolism (RD = 0.00, 95% CI = −0.01 to 0.01, P = .91). The sample size of this study was small and several included studies were with relatively low quality.

Conclusion: Oral TXA is equivalent to IV TXA in reducing perioperative blood loss and should be recommended in TKA and THA. More high-quality studies are needed to elucidate this issue.

Abbreviations: BMI = body mass index, CI = confidence interval, DVT = deep vein thrombosis, Hb = hemoglobin, IV = intravenous, MD = mean difference, NOS = Newcastle–Ottawa scale, OR = odds ratio, PE = pulmonary embolism, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, RD = risk difference, RST = retrospective study, THA = total-hip arthroplasty, TKA = total-knee arthroplasty, TXA = tranexamic acid.

Keywords: administration route, arthroplasty, blood loss, complications, tranexamic acid

1. Introduction

Patients with osteoarthritis, rheumatoid arthritis, or fractures of knee or hip often have to receive total-knee arthroplasty (TKA) and total-hip arthroplasty (THA).[1–6] Despite of satisfactory results of TKA and THA, patients must face the risks of postoperative anemia and transfusion for the perioperative blood loss, which is supposed to increase the mobility and costs.[7,8] Therefore, reducing the blood loss and minimizing the risk of

transfusions in TKA and THA have drew great attentions of orthopedic surgeons.[9–11]

Tranexamic acid (TXA), an antifibrinolytic agent, is conducive to reducing the perioperative blood loss and the risk of transfusions in TKA and THA.[12–14] TXA can be administered via intravenous (IV), topical, or oral routes.[15–17] Previous studies have suggested that IV TXA and topical TXA had comparable efficacy in TKA and THA.[10,17,18] However, the dispute on the comparison between oral TXA and IV TXA regarding reducing perioperative blood loss still remains.[19–25] Irwin et al retrospectively analyzed 3000 patients and observed less hemoglobin (Hb) drop in IV TXA group compared to oral TXA group,[21] similar results were found in Kayupov et al study.[20] Nevertheless, other studies showed there was no statistical difference between oral TXA group and IV TXA group in Hb drop.[22,25] Hence, this systematic review and meta-analysis aimed to compare the efficacy and safety of oral TXA with IV TXA in reducing perioperative blood loss in TKA and THA.

2. Materials and methods

This study was conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA).[26] The registration number is review registry 621 (https://www.researchregistry.com/).

2.1. Literature search and selection

PubMed, Web of Science, Embase, and Cochrane Library were fully searched up to April 19, 2018. The literature search strategy was as follows: ("intravenous" AND "oral") AND ("tranexamic acid" OR "TXA") AND ("total-knee arthroplasty" OR "total-knee replacement" OR "total-hip replacement" OR "total-hip arthroplasty"). There was no restriction on the language. The references of retrieved articles were also checked to avoid missing relevant studies. Literature search was completed by 2 authors independently.

2.2. Inclusion criteria and exclusion criteria

The included studies should meet following PICOS criteria (patients, intervention, comparator, outcome, and study design): Patients: patients undergoing TKA or THA; Intervention: oral TXA for TKA or THA; Comparator: IV TXA for TKA or THA; Outcomes: Hb drop, transfusion rate, total blood loss, total Hb loss, drain out, length of hospital stay, incidence of deep vein thrombosis (DVT), and pulmonary embolism (PE); Study design: randomized controlled trial (RCT) or retrospective study (RST). Reviews, comments, duplications, cell experiments, or animal experiments were excluded from this study.

2.3. Data extraction and quality assessment

Data extraction and quality assessment were completed by 2 authors independently. Any disagreement would be solved by discussing with the 3rd author. The following information was extracted: the 1st author, study design, sample size, gender, age, body mass index (BMI), transfusion rate, dosage of TXA, surgery, anesthesia, pneumatic tourniquet, and clinical outcomes. The main clinical outcomes included Hb drop, transfusion rate, total blood loss, total Hb loss, drain out, length of hospital stay, incidence of DVT and PE. Cochrane Collaboration's "risk of bias" was used to assess the quality of RCTs, and "risk of bias" was classified into three grades: "low risk, middle risk, and high risk."[27] Newcastle–Ottawa scale (NOS) was utilized to evaluate the study quality of RST.[28] In NOS scale, 3 domains, including selection, comparability, and outcome were assessed, with 4 categories in the selection domain, 1 category in the comparability domain, and 3 categories in the outcome domain. The total possible score was 9 points. The quality of studies with NOS > 5 was considered high.

2.4. Statistical analysis

All analyses were performed by Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 software (Stata, College Station, TX). Odds ratio (OR) or risk difference (RD) with corresponding 95% confidence interval (CI) was applied to compare dichotomous variables, such as gender, transfusion rate, and so on. Mean difference (MD) was used to compare continues variables, including length of hospital stay, total blood loss, Hb drop, and so on. Subgroup analyses for Hb drop and incidence of transfusion rate were performed. Hb drop and incidence of transfusion rate in each group were calculated using STATA 12.0. The inter-study heterogeneity was assessed by I^2 statistic. $I^2 \leq 50\%$ indicated there was no obvious heterogeneity among studies, and a fixed-effect model should be used. If not, a random-effect model should be applied. Publication bias was detected by funnel plots. All P values were

2 sides and the difference was considered to be significant when P values lowered than .05.

3. Results

3.1. Literature search and selection

As shown in Figure 1, a total of 167 articles were initially retrieved. After the removal of duplications, 98 remaining articles were further evaluated. Seventy-nine articles were directly excluded by scanning titles or abstracts. The full-texts of remaining 10 studies were carefully assessed and 3 articles were excluded for the following reasons: 1 was irrelevant to this topic and 2 reported the data from duplicated patients. Ultimately, 7 articles were included into this study.[19–25]

3.2. Characteristics of included studies

As shown in Table 1, a total of 7 studies containing 3924 patients were analyzed in this study.[19–25] All included studies were published in English. There were 5 RCTs[19,20,22,23,25] and 2 RSTs.[21,24] The mean age of patients ranged from 60 to 69 years in oral TXA group and 55 to 73 years in IV TXA group. Besides, 5 studies reported the BMI, which ranged from 22.69 to 33 kg/m^2 in oral TXA group and 22.64 to 32.3 kg/m^2 in IV TXA group.

The details of surgeries are summarized in Table 2. The transfusion trigger was Hb < 7.0 g/dL in 4 studies[19–21,25] and Hb < 8.0 g/dL in 1 study,[22] besides, 1 study regarded hematocrit < 28% as the transfusion trigger[23] and 1 study did not reported the transfusion trigger.[24] The dosage of TXA varied a lot in different studies. With respect to surgeries, 2 studies focused on THA,[20,25] 3 studies focused on TKA,[19,22,23] and 2 studies focused on both THA and TKA.[21,24] Spinal-epidural anesthesia, general anesthesia, adductor canal block, or spinal anesthesia were used. Pneumatic tourniquet was used in 5 studies.[19,21–24] The quality of included studies was evaluated by Cochrane Collaboration's "risk of bias" for RCTs (Table 3) and NOS for RSTs (Table 4). All RSTs included were with high quality; however, the quality of included RCTs was middle and even poor.

3.3. Meta-analysis for Hb drop

As show in Figure 2, the mean Hb drop was 2.85 (95% CI = 2.48–3.22) g/dL in oral TXA group and 2.81 (95% CI = 2.44–3.19) g/dL in IV TXA group. As shown in Figure 3, a fixed effect model was used because of mild heterogeneity ($I^2 = 39\%$), and no significant difference was observed (MD = 0.06, 95% CI = −0.01 to 0.13, $P = .09$). In the subgroup analysis, no obvious difference was observed between 2 groups when only analyzing RCTs (MD = −0.01, 95% CI = −0.10 to 0.08, $P = .81$; $I^2 = 0\%$). However, significantly more Hb drop was detected in oral TXA group compared to IV TXA group in the subgroup analysis of RSTs (MD = 0.18, 95% CI = 0.06–0.29, $P < .01$; $I^2 = 20\%$).

3.4. Meta-analysis for transfusion rate

As shown in Figure 4, the overall transfusion rate was 0.051 (95% CI = 0.036–0.067, $I^2 = 37.9\%$) in oral TXA group and 0.060 (95% CI = 0.032–0.088; $I^2 = 72.9\%$) in IV TXA group. There was no distinct difference between 2 groups regarding transfusion rate (OR = 0.78, 95% CI = 0.54–1.13, $P = .19$; $I^2 = 0\%$) (Fig. 5). In the subgroup analysis, comparable transfusion
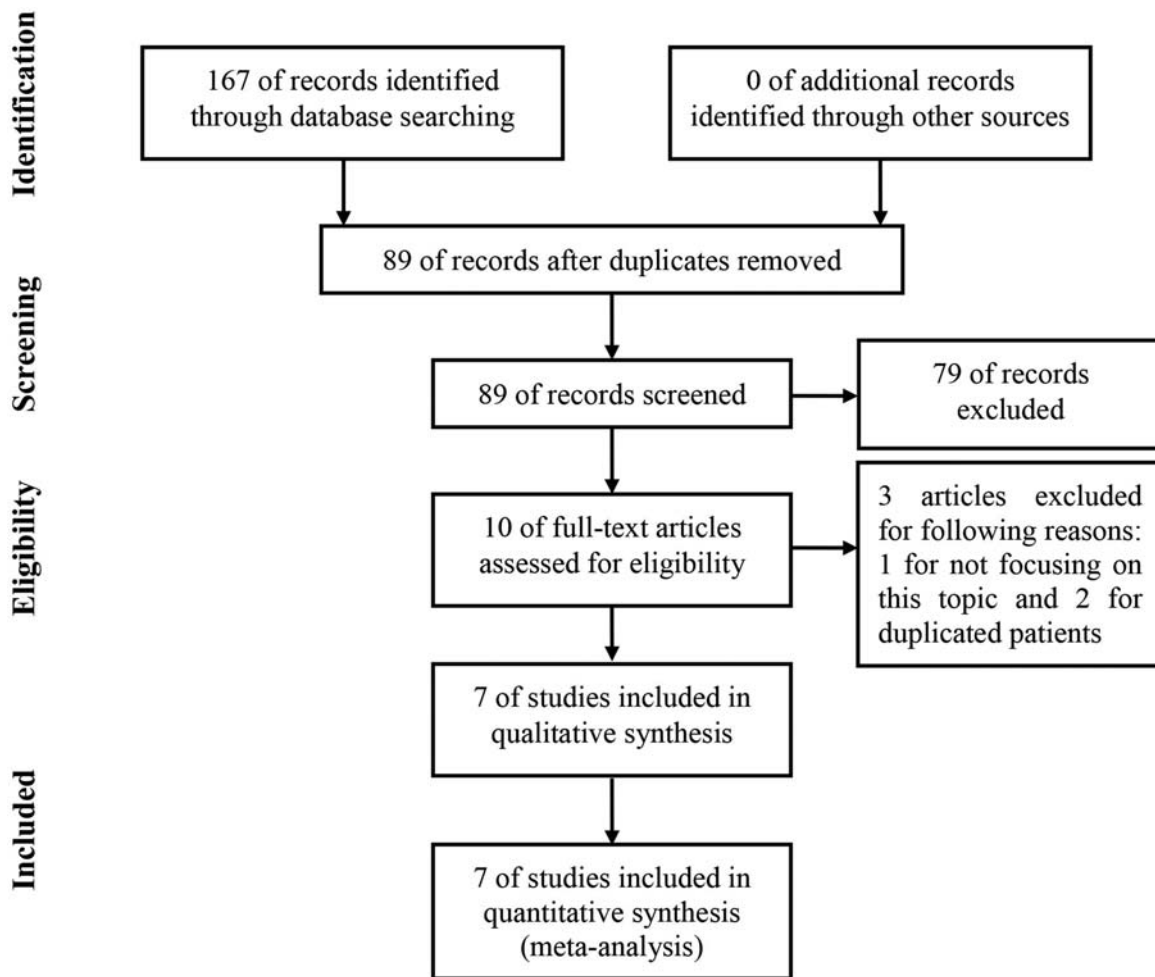
Figure 1. Flow chart of literature search.

rate between 2 groups was detected both for RCTs (OR = 1.10, 95% CI = 0.62–1.95, P = .74; I^2 = 0%) and RSTs (OR = 0.63, 95% CI = 0.38–1.03, P = .07; I^2 = 22%).

3.5. Meta-analysis for total blood loss

As showed in Figure 6A, a fixed-effect model was used for insignificant heterogeneity (I^2 = 0%). The results presented that patients in 2 groups had comparative total blood loss (MD = 16.31, 95% CI = −69.85 to 102.46, P = .71).

3.6. Meta-analysis for total Hb loss

There was no apparent difference between oral and IV TXA groups in total Hb loss (MD = 5.18, 95% CI = −12.65 to 23.02, P = .57; I^2 = 0%) (Fig. 6B).

3.7. Meta-analysis for length of hospital stay

There was no obvious difference between 2 groups regarding length of hospital stay (MD = −0.06, 95% CI = −0.30 to 0.18, P = .63; I^2 = 0%) (Fig. 6C).

Table 1

The demographics of included studies.

Study	Design	Patients (n)		Age (mean ± SD)		Gender (M/F)		BMI (kg/m^2)	
		Oral	IV	Oral	IV	Oral	IV	Oral	IV
Kayupov et al (2017)[20]	RCT	40	43	60.00 ± 10.00	55.00 ± 12.00	20/20	22/21	29 ± 5	31 ± 6
Yuan et al (2017)[22]	RCT	140	140	63.17 ± 6.81	63.74 ± 8.05	68/72	62/78	22.69 ± 1.54	22.64 ± 1.44
Fillingham et al (2016)[19]	RCT	34	37	62.00 ± 11.00	63.00 ± 10.00	13/21	11/26	33 ± 7	32 ± 7
Irwin et al (2013)[21]	RST	302	2698	67.60 (19–90)	68.20 (40–89)	134/168	1256/1442	NA	NA
Zohar et al (2004)[23]	RCT	20	20	69.00 ± 10.00	73.00 ± 8.00	8/12	6/14	NA	NA
Luo et al (2018)[25]	RCT	60	60	67.60 ± 10.38	66.98 ± 8.57	28/32	27/33	24.59 ± 3.09	24.51 ± 3.87
Gortemoller et al (2018)[24]	RST	165	165	67.00 (59–74)	68.00 (62–73)	55/110	64/101	32.0 (26.7–38.4)	32.3 (29.3–36.8)

BMI = body mass index, F = female, IV = intravenous, M = male, RCT = randomized controlled trial, RST = retrospective study, SD = standard deviation.

Table 2

The details of surgeries in include studies.

| Study | Transfusion trigger | The dosage of TXA | | Surgery | Anesthesia | Pneumatic tourniquet |
		Oral	IV			
Kayupov et al (2017)[20]	Hb < 7.0 g/dL	1950 mg/kg	1000 mg	THA	Combined spinal-epidural anesthesia	No
Yuan et al (2017)[22]	Hb < 8.0 g/dL	40 mg/kg	40 mg/kg	TKA	General anesthesia	Yes
Fillingham et al (2016)[19]	Hb < 7.0 g/dL	1950 mg	1000 mg	TKA	Combined spinal-epidural or adductor canal block with either a spinal or general anesthesia	Yes
Irwin et al (2013)[21]	Hb < 7.0 g/dL	25 mg/kg (maximum 2 g)	15 mg/kg (maximum 1.2 g)	TKA and THA	NA	Yes
Zohar et al (2004)[23]	Hematocrit < 28%	4000 mg	15 mg/kg and 10 mg/kg*12 h	TKA	General anesthesia	Yes
Luo et al (2018)[25]	Hb < 7.0 g/dL	2000 mg	20 mg/kg	THA	General anesthesia	No
Gortemoller et al (2018)[24]	NA	1950 mg	2000 mg	TKA and THA	NA	Yes

Hb = hemoglobin, IV = intravenous, NA = not available, THA = total-hip arthroplasty, TKA = total-knee arthroplasty, TXA = tranexamic acid.

Table 3

The quality assessment of included RCTs based on Cochrane Collaboration's "risk of bias.".

	Kayupov et al (2017)[20]	Yuan et al (2017)[22]	Fillingham et al (2016)[19]	Zohar et al (2004)[23]	Luo et al (2018)[25]
Random sequence generation (selection bias)	Low	Low	Low	Low	Low
Allocation concealment (selection bias)	Low	Low	Low	Low	Low
Blinding of participants and personnel (performance bias)	Low	Low	Low	Low	Low
Blinding of outcome assessment (detection bias)	Low	Low	Low	Low	Low
Incomplete outcome data (attrition bias)	Low	Low	Low	Unclear	Low
Selective reporting (reporting bias)	Unclear	Unclear	Unclear	Unclear	Unclear
Other bias	Unclear	Unclear	Unclear	Unclear	Unclear

RCT = randomized controlled trial.

3.8. Meta-analysis for drain out

As shown in Figure 6D, the meta-analysis showed there was no obvious difference between 2 groups (MD = 21.04, 95% CI = −15.81 to 57.88, $P = .26$; $I^2 = 69\%$).

3.9. Meta-analysis for the incidence of DVT

The incidence of PE was 0.4% (3/761) and 0.5% (15/3163) in oral TXA group and IV TXA group, respectively. No significant difference was observed between 2 groups (RD = 0.00, 95% CI = −0.01 to 0.01, $P = .82$; $I^2 = 0\%$) (Fig. 6E).

3.10. Meta-analysis for the incidence of PE

The incidence of PE was 0.4% (3/761) and 0.9% (29/3163) in oral TXA group and IV TXA group, respectively. No statistical difference was detected between 2 groups in the incidence of PE (RD = 0.00, 95% CI = −0.01 to 0.01, $P = .91$; $I^2 = 0\%$) (Fig. 6F).

Table 4

The quality assessment of included retrospective studies based on NOS.

	Irwin et al (2013)[21]	Gortemoller et al (2018)[24]
Selection of the study groups	****	****
Comparability of the groups	*	*
Outcome	**	***
Total score	*******	*******

NOS = Newcastle–Ottawa scale.

3.11. Publication bias

All funnel plots were symmetrical, and there was no obvious publication bias among included studies in Hb drop, transfusion rate, total blood loss, total Hb loss, length of hospital stay, drain out, incidence of DVT, or PE (Fig. 7).

4. Discussion

In our study, there were no obvious differences between oral TXA group and IV TXA group in Hb drop, transfusion rate, total blood loss, total Hb loss, length of hospital stay, drain out, or the incidence of DVT or PE in TKA and THA.

The Hb drop was the primary outcome in our study because it reflected the blood loss and has been regarded as the trigger for transfusion.[19,23,25] In our study, the average Hb drop was 2.81 g/dL in IV TXA group, which was similar to previous studies and indicated IV TXA had satisfactory efficacy in reducing blood loss in TKA and THA.[20,22–24] Other than IV TXA group, limited studies concerned on the effect of oral TXA in total joint arthroplasty. The mean Hb drop was 2.85 g/dL in oral TXA group in our study, which manifested that oral TXA had favorable effects on blood sparing. In an RCT conducted by Luo et al, 3.48 g/dL Hb drop was found in oral TXA group, which was larger than us.[25] Similarly, 3.0 g/dL Hb drop was detected in oral TXA group in Lee et al investigation.[29] This difference might be explained that their studies only focused on the patients undergoing THA, which generally caused more blood loss than TKA.[29] More importantly, we obtained comparable effects in Hb drop between oral TXA and IV TXA, which implied that oral TXA was equivalent to IV TXA in decreasing blood loss in TKA
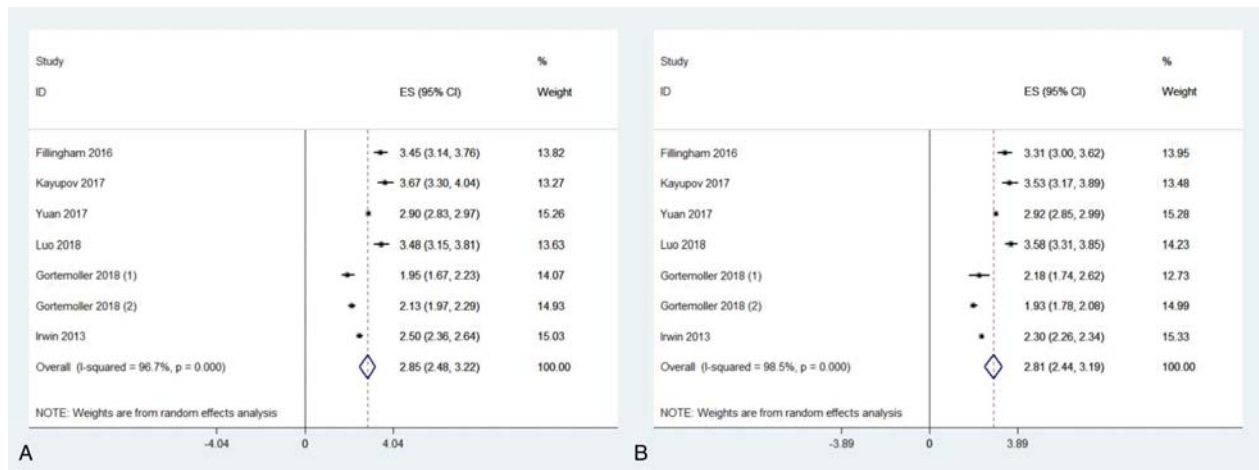
Figure 2. Meta-analyses for hemoglobin drop in oral tranexamic acid (TXA) and intravenous TXA group.
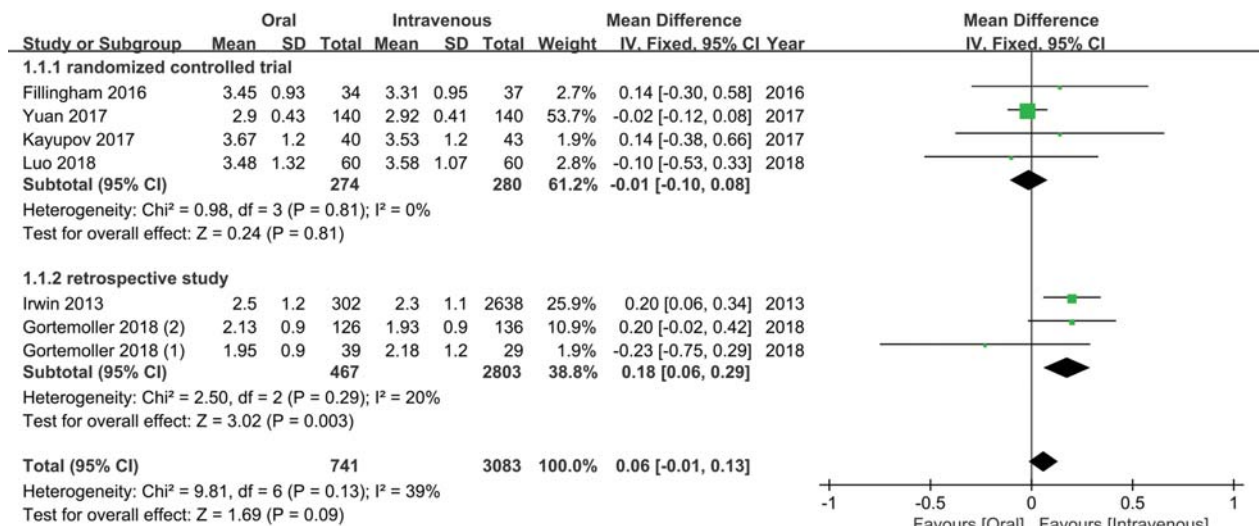

Figure 3. Meta-analysis for the comparison of hemoglobin drop between oral tranexamic acid (TXA) and intravenous TXA group.
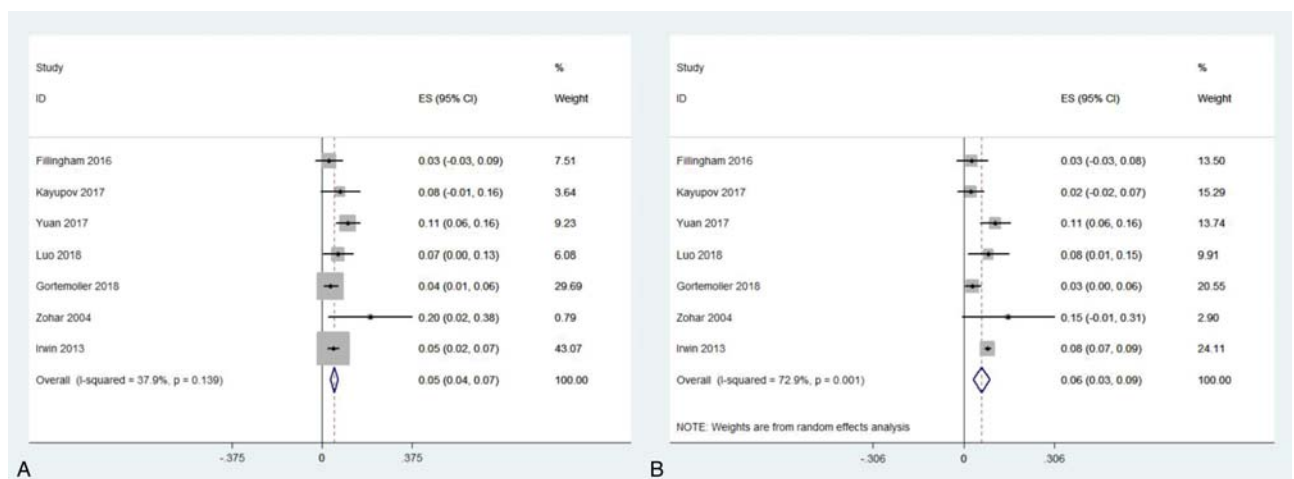

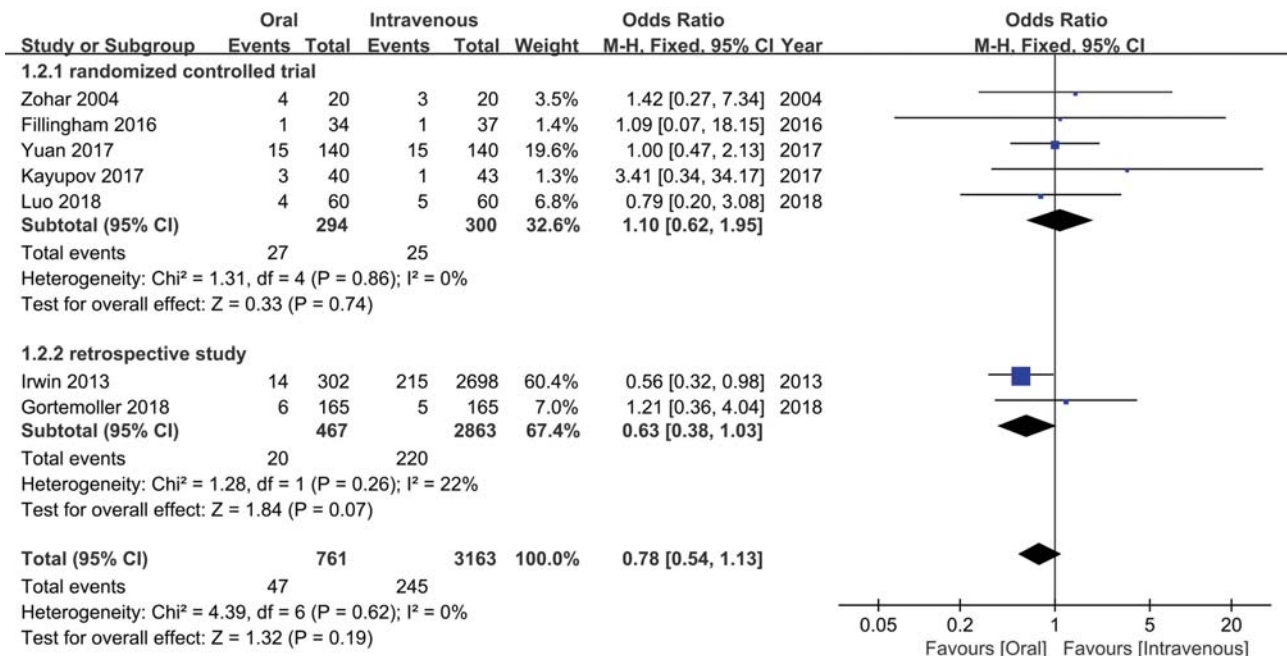**Figure 4.** Meta-analyses for transfusion rate in oral tranexamic acid (TXA) and intravenous TXA group.

Figure 5. Meta-analysis for the comparison of transfusion rate between oral tranexamic acid (TXA) and intravenous TXA group.

and THA. Several RCTs have also found alike effects between oral TXA and IV TXA in TKA and THA.[22,25] However, Irwin et al retrospectively evaluated 3000 patients and discovered oral TXA group (2.5 g/dL) had more Hb drop than IV TXA group (2.3 g/dL). It should be noted many factors might affect their results on account of the retrospective design.[21] Similarly, Hao et al performed a meta-analysis and also found IV TXA provided superior Hb drop in TKA or THA, but this difference might attribute to the high weight of Irwin et al study.[30] Therefore, to eliminate the influence of RSTs, we performed the subgroup analysis containing RCTs, and found oral TXA was equivalent to IV TXA in reducing blood loss in TKA and THA.

Transfusion rate was also compared between 2 groups in our study. Transfusion rate was 5.1% in oral TXA group and 6.0% in IV TXA group, which was similar to previous studies.[23–25] Our findings also suggested that oral TXA and IV TXA both could significantly reduce the risk of transfusions compared to control group reported in other studies.[15,22] Furthermore, there was no distinct difference regarding transfusion rate between oral TXA group and IV TXA group, which indicated these 2 administrations both could provide satisfactory blood-sparing efficacy in TKA and THA.

Complications were also major concerns for surgeons operating TKA or THA. The incidence of DVT was 0.4% in oral TXA group and 0.5% in IV TXA group. And 0.4% patients in oral TXA group and 0.9% patients in IV TXA group suffered from PE. Similar to previous studies,[23,25] there were no significant differences between 2 administrations regarding the incidences of DVT and PE in our study. Therefore, our work demonstrated oral TXA did not increase the risks of the occurrence of DVT or PE compared to IV TXA in TKA and THA.

Although the analysis for TXA costs was not performed in our study, 1 major advantage of oral TXA over IV TXA was less cost. Yuan et al conducted an RCT and observed less TXA cost in oral administration compared to IV administration in TKA (1936.6 vs

6062.4 ¥, $P < .01$).[22] Similarly, less TXA cost in oral TXA group was detected compared to IV TXA group (480 vs 3329.28 ¥, $P < .01$) in Luo et al study focusing on THA.[25] All these findings showed, compared to IV TXA in TKA and THA, oral TXA could decease the economic burdens of healthcare expenditures and patients' families.

Previous meta-analyses have compared the efficacy and safety between oral TXA and IV TXA in TKA and THA.[30,31] However, some highlights deserved to be mentioned in our study. First, 7 studies were included into this meta-analysis; therefore, larger sample size of our study could provide more forceful evidence. Second, subgroup analyses of Hb drop and transfusion rate were performed to eliminate the influence of Irwin et al study, which was an RST but with a large sample size.[21] Third, we observed comparable efficacy of 2 administrations in decreasing Hb drop, which was in contradiction with Hao et al meta-analysis where IV TXA was superior to oral TXA in Hb drop.[30] Fourth, Hb drop, incidence of DVT, and PE in each group were firstly calculated using STATA 12.0 in our study. Fifth, we performed the comparison of drain out between oral TXA group and IV TXA group, which offered new evidence on this topic. Nevertheless, several limitations should be considered when interrupting our results. First, the dosage and administration time of TXA varied a lot among included studies, which might affect the stringency of conclusions. Second, transfusion volume and TXA cost were not compared between 2 administrations for insufficient published data.

5. Conclusion

Oral TXA is equivalent to IV TXA in reducing perioperative blood loss in TKA and THA. Oral TXA should be advocated in TKA and THA in light of less cost and more convenience. Future studies should focus on the optimal dose of oral TXA in TKA and THA.
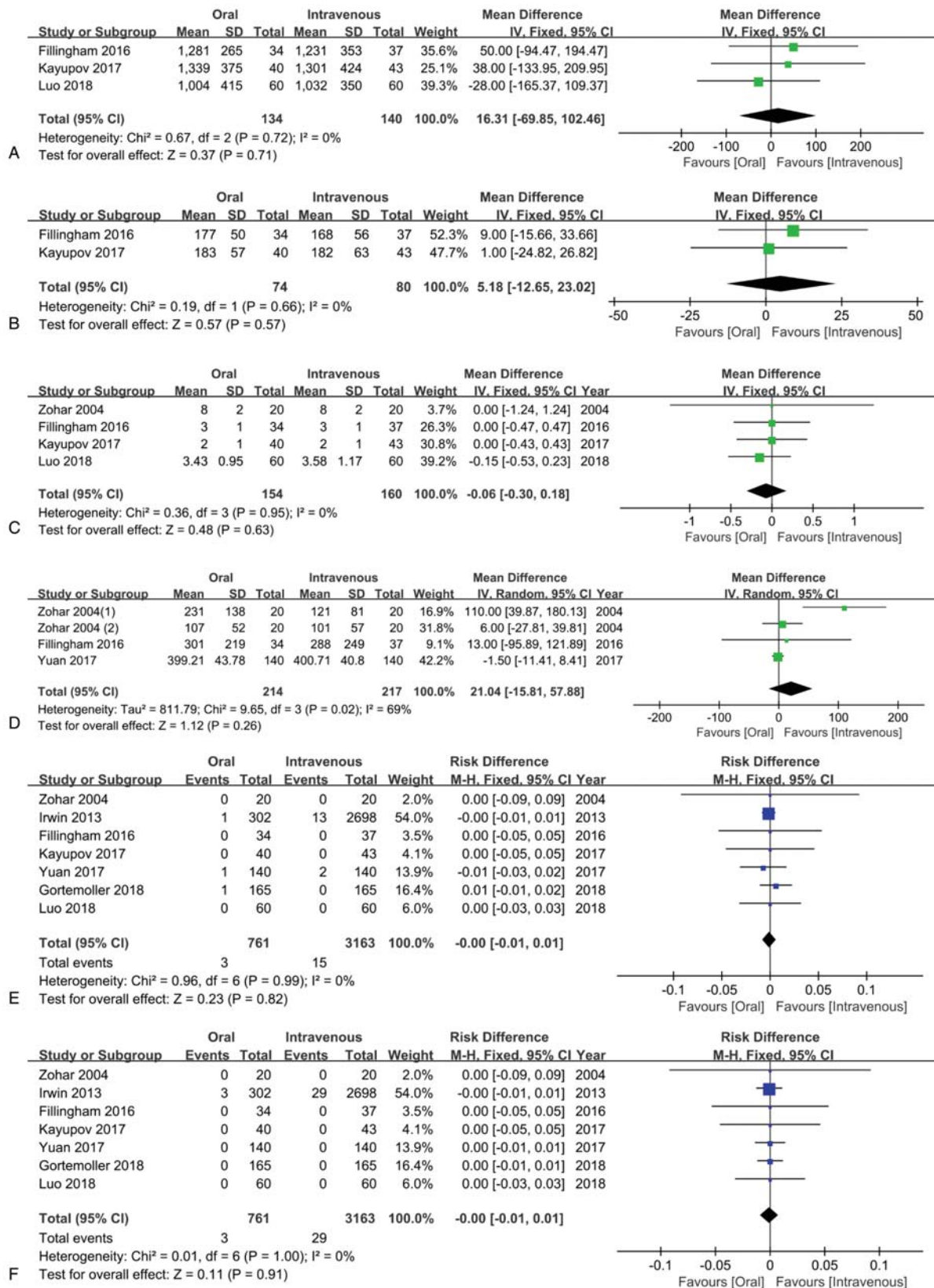
Figure 6. Meta-analyses for the comparisons of total blood loss (A), total hemoglobin loss (B), length of hospital stay (C), drain out (D), incidence of deep vein thrombosis (E) and PE (F).
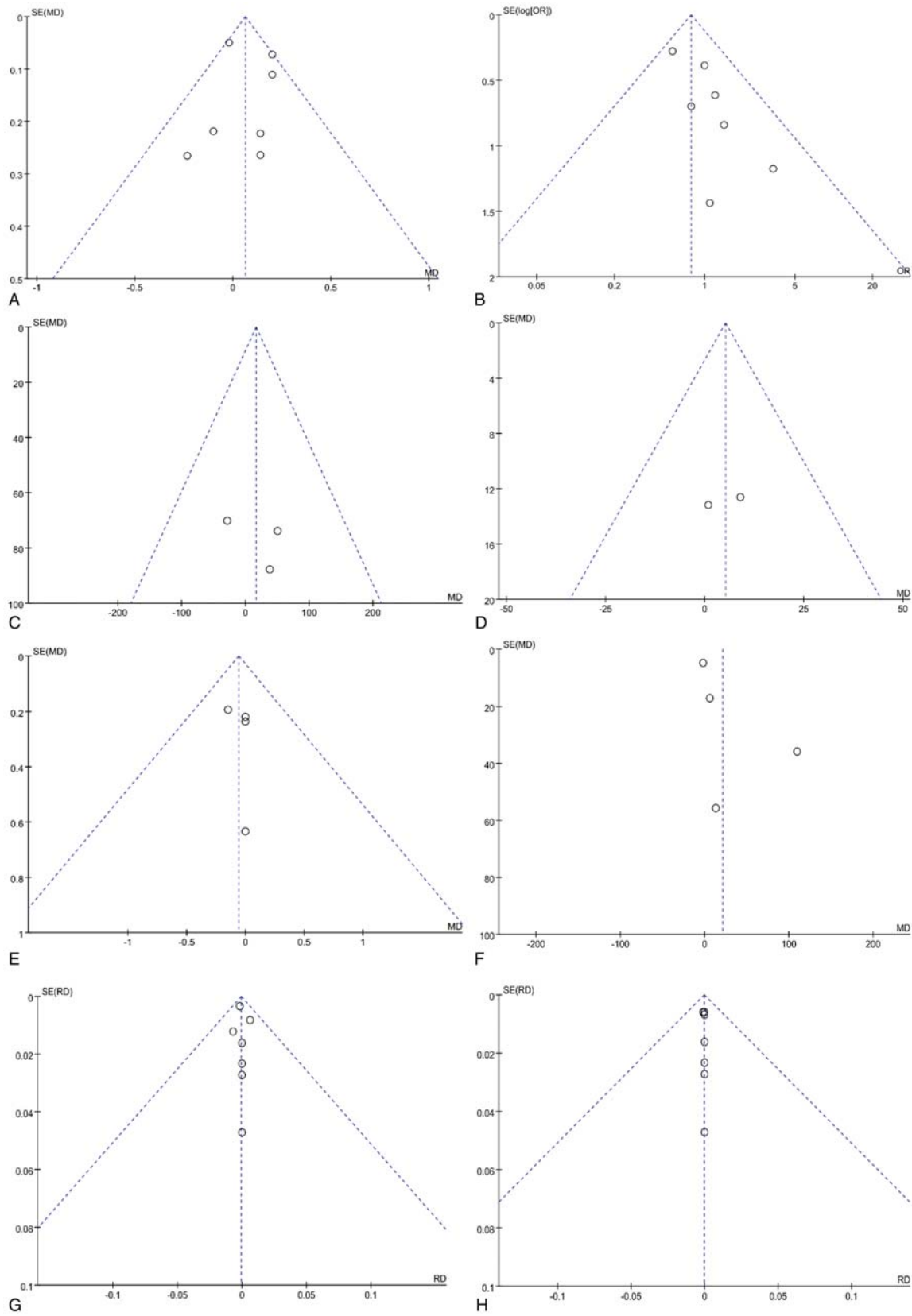
Figure 7. Funnel plots for hemoglobin drop (A), transfusion rate (B), total blood loss (C), total hemoglobin loss (D), length of hospital stay (E), drain out (F), incidence of deep vein thrombosis (G) and PE (H).

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