



Comparison of intravenous versus topical tranexamic acid in primary total hip arthroplasty: a systematic review and meta-analysis of ten randomized trials

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Aim: The optimal management approach for tranexamic acid (TXA) in primary total hip arthroplasty (THA) is still controversial. This meta-analysis aimed to evaluate the efficacy and safety of intravenous versus topical TXA during THA. **Materials & methods:** PubMed, Google Scholar, Embase and the Cochrane library were searched for all randomized controlled trials comparing topical and intravenous TXA (iTXA) following primary THA. The primary outcome consisted of blood loss including total blood loss, intraoperative blood loss and hidden blood loss (HBL), hemoglobin (Hb) level of postoperative day 1, maximum Hb drop and transfusion incidence. The second outcome included drainage volume, complications and length of stay. Extracted data were statistically analyzed with the Stata11.0. **Results:** A total of ten randomized controlled trials containing 1295 patients were included in the study. A similar effect of transfusion rate, total blood loss, Hb level of postoperative day 1, drainage volume, deep vein thrombosis events and wound complications appeared in the two routes. Intraoperative blood loss (weighted mean difference [WMD] = -12.687, 95% CI: -22.291, -3.083; $p = 0.010$), HBL (WMD = 14.276, 95% CI: 9.936, 19.459; $p < 0.001$) and maximum Hb drop (WMD = -0.400, 95% CI: -0.577, -0.222; $p < 0.001$) were significantly reduced in the intravenous group compared with topical group. **Conclusion:** The present result indicated comparable safety and transfusion rate for intravenous and topical TXA in primary THA, while the intravenous approach demonstrated a smaller intraoperative blood loss, HBL and maximum Hb drop.

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Total hip arthroplasty (THA) is currently recognized as the most successful surgical method to treat hip diseases such as end-stage inflammatory or degenerative arthritis, displaced fractured neck of the femur and end-stage avascular necrosis [1,2]. It was reported more than 1 million THAs were performed every year all over the world and the number in the USA alone was more than 500,000, while the number was steadily increasing with the aging of the population [3,4]. But perioperative blood loss and consequent anemia are common and serious complications for joint replacement surgery which increase systemic risks especially for elderly cases [5]. Although both autologous and allogeneic blood transfusion can rapidly and effectively supplement lost blood, the former only provides limited blood volumes and the re-infusion volumes of blood decrease with increasing age, while the latter might induce the risk of side effects such as surgical-site infections, virus infection, anaphylactic reactions and even increased mortality [6–8]. To decrease blood transfusion requirements, tranexamic acid (TXA) has been widely adopted in major orthopedic surgery with amazing efficacy and safety identified by various researches [7,9–11]. As an antifibrinolytic drug, TXA with intravenous injection exists a high risk of thrombotic events, such as deep vein thrombosis (DVT) and pulmonary embolism in theory and this has led to the emergence of other ‘safer’ routes of

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TXA administration including topical, oral and combined TXA, all of which demonstrated no statistical difference in controlling bleeding and risk of thrombosis compared with each other based on recent studies [12,13]. During the above-described routes, the intravenous and topical administration of TXA has been most often compared for their representative roles of efficiency and safety respectively [14–17]. A previous meta-analysis in 2014 concluded intravenous injection showed similar transfusion requirements and safety compared with topical TXA (tTXA) in total joint arthroplasty, while it seemed to be associated with the smaller maximum drop in hemoglobin (Hb) [14]. However, recent randomized controlled trials (RCTs) in 2019 reported topical application had superior therapeutic values compared with the intravenous application of TXA using same dose in THA [18]. Thus, the optimal administration route of TXA in THA has remained controversial. To obtain a comprehensive understanding of these two approaches, we performed this meta-analysis of RCTs to compare the efficacy and safety of intravenous versus topical administration of TXA during THA.

Materials & methods

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines [19,20].

Literature search

We searched all the related RCTs that comparing the approaches of TXA use in the treatment of THA through electronic databases including PubMed, Google Scholar, Embase, the Cochrane library with a full text in English. The retrieval was up until January 2021. The keyword including ‘tranexamic acid or TXA’, ‘intravenous topical (ivTXA) or intra-articular or local’ and ‘THA or total hip replacement’ with the Boolean operators was adopted as a search strategy. Furthermore, we manually screened the bibliography cited in the included studies for the potential eligible trials.

Inclusion & exclusion

The inclusion criterion was RCTs comparing intravenous with topical or local or intra-articular TXA for patients undergoing THA. The included studies should at least report the efficacy and safety of TXA between different administration routes for THA.

We excluded studies that were of low quality or not following inclusion criteria. To obtain comprehensive literature, follow-up time, patients’ age and presurgery status were not set as exclusion criteria.

Data extraction

All data were extracted by two separate reviewers, a third author was necessary when different opinions appeared. The following information from the included studies was extracted: the first author’s name, nationality, year of publication, sample number, mean age, gender, dose and route of TXA intervention, preoperative Hb, general surgical information and outcome parameters. Primary end points consist of blood loss including total blood loss (TBL), intraoperative blood loss (IBL), and hidden blood loss (HBL), Hb level including postoperative day 1 and maximum Hb drop and transfusion incidence. Second end points include drainage volume, complications (wound complications and DVT events) and length of stay (LOS).

Quality assessment

We conducted a quality assessment of RCTs by using the Cochrane Collaboration’s tool [21] and prepared a ‘risk of bias’ table including the following main factors to assess the risk of bias of each included publication: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. Three independent reviewers provided a score of high, unclear or low risk of bias for each bias domain. When there were different opinions, another leading author was involved until disagreements were resolved by consensus.

Statistical analysis

The extracted data were statistically analyzed with the Stata11.0 (T Stata Corp LP, TX, USA). When $I^2 > 50\%$, $p < 0.1$, the data were considered to be significant heterogeneity according to the Cochran’s Q statistic the I^2 statistics and random-effect model was conducted for meta-analysis. Otherwise, a fixed-effect model was performed. The results of dichotomous outcomes (transfusion rate, wound complication and DVT events) were expressed as

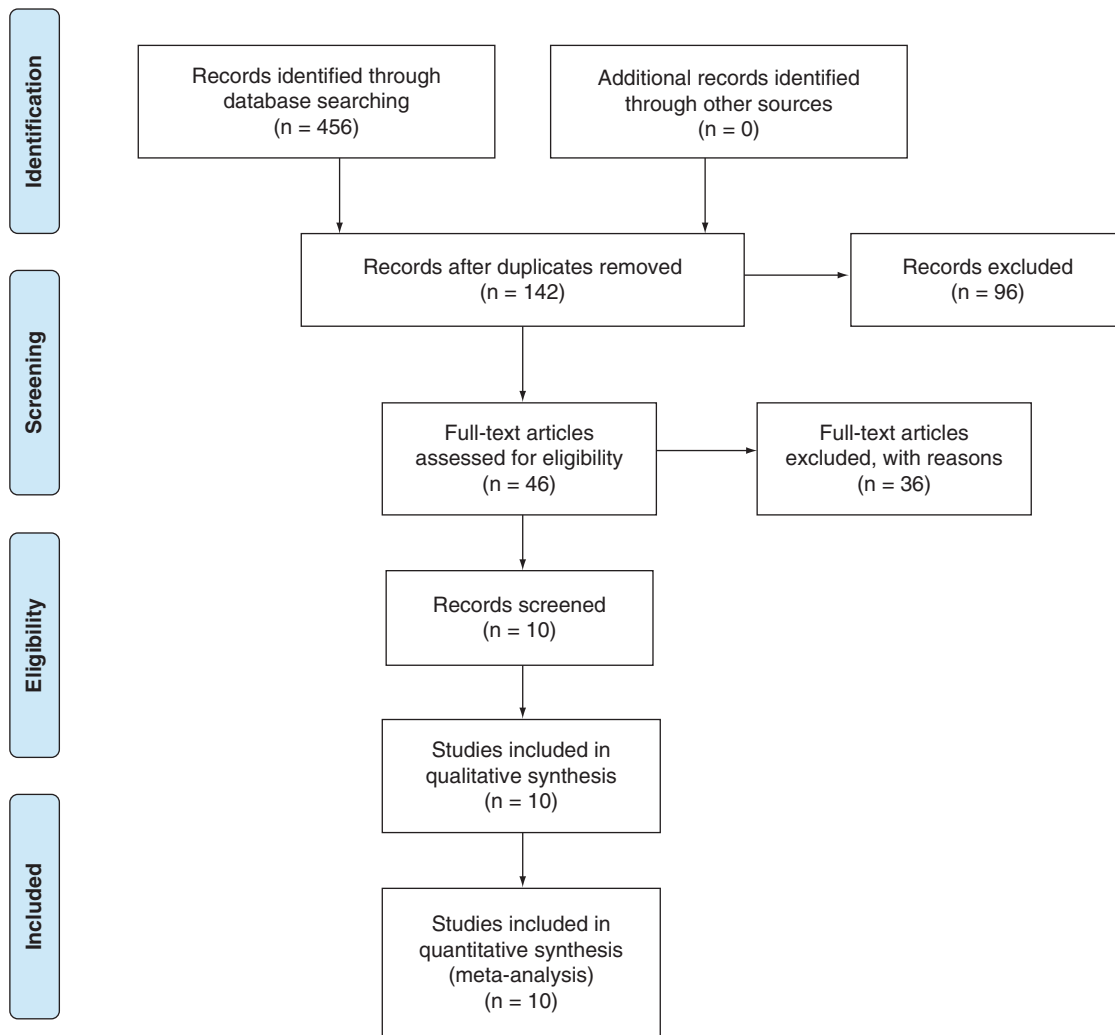


Figure 1. Schematic diagram of the study selection and exclusion procedure for the study.

relative risk with 95% CIs. For continuous various outcomes including blood loss, Hb level, drainage volume and LOS, weighted mean differences (WMD) with 95% CIs were applied for assessment. $p < 0.05$ was defined as the threshold of a statistically significant difference.

Results

Search results

As shown in Figure 1, we preliminarily identified 456 pieces of literature in the four selected databases. First, 314 records were removed owing to duplication or irrelevant studies. Then, we scanned the title and abstract, 96 reports were excluded according to the eligibility criteria. The left 46 pieces of literature were read by the full text and 36 reports were removed for the lack of necessary data. Finally, ten RCTs were included for the data extraction and meta-analysis.

Study characteristics

Eleven RCTs published between 2014 and 2020 were included in this study, all of which compared the effect of intravenous versus topical administration of TXA in patients receiving THA. A total of 1295 patients were involved, during which 656 participated in the intravenous group and 639 in the topical group. Other demographic characteristics and details such as mean age, sex ratio, BMI were shown in Table 1. All the included trials provided details about the methods and doses of TXA, transfusion criteria and DVT events prophylaxis during THA. One

Table 1. Characteristics of trials.

Study	Year	Country	Recruitment	Sample		Mean age (Y)		Gender (M/F)		BMI		Preoperative Hb (g/dl)	
				ivTXA	tTXA	ivTXA	tTXA	ivTXA	tTXA	ivTXA	tTXA	ivTXA	tTXA
Zhou <i>et al.</i>	2018	China	2014–2015	57	56	63.2 ± 10.0	65.8 ± 9.4	12/45	17/39	23.7 ± 3.2	23.2 ± 3.1	12.74 ± 1.4	12.96 ± 1.28
Xu <i>et al.</i>	2019	China	2016–2018	68	72	62.5 ± 6.6	61.9 ± 6.1	32/36	34/38	22.0 ± 2.3	22.3 ± 2.7	–	–
Luo <i>et al.</i>	2017	China	2016–2017	60	60	59.53 ± 11.50	62.24 ± 11.04	27/33	25/35	24.5 ± 3.87	25.27 ± 4.19	13.71 ± 0.75	14.07 ± 0.99
Xie <i>et al.</i>	2016	China	2014–2015	70	70	59.53 ± 11.50	62.24 ± 11.04	20/50	25/45	24.16 ± 3.08	24.47 ± 3.30	13.32 ± 1.26	13.22 ± 0.84
Zhang <i>et al.</i>	2020	China	2018–2019	36	36	66.98 ± 9.01	67.98 ± 8.87	15/21	16/20	23.4 ± 2.01	23.86 ± 2.38	–	–
Wei <i>et al.</i>	2014	China	2013–2014	101	102	63.6 ± 7.0	60.2 ± 6.5	39/62	35/67	24.2 ± 3.1	25.3 ± 3.0	–	–
Vles <i>et al.</i>	2020	Belgium	2014–2015	60	60	61.5 ± 11.8	64.0 ± 13.4	29/31	22/38	27.6 ± 4.4	26.3 ± 4.4	14.5 ± 1.23	13.9 ± 1.5
Gómez-Aparicio <i>et al.</i>	2020	Spain	2017–2019	110	85	63.94 ± 10.80	65.52 ± 10.92	48/62	45/40	28.43 ± 3.81	29.20 ± 5.26	14.21 ± 1.31	14.30 ± 2.21
North <i>et al.</i>	2015	USA	2013–2013	70	69	64.1 ± 12.0	65.7 ± 10.6	38/32	39/30	31.1 ± 5.4	31.1 ± 6.4	13.4 ± 1.3	13.2 ± 1.4
Zhang <i>et al.</i>	2016	China	2013–2014	25	25	44.5 ± 2.4	44.3 ± 3.7	14/11	13/12	24.3 ± 3.2	23.5 ± 3.4	126.5 ± 6.5	13.02 ± 0.58

F: Female; Hb: Hemoglobin; ivTXA: Intravenous tranexamic acid; M: Male; TXA: Topical tranexamic acid.

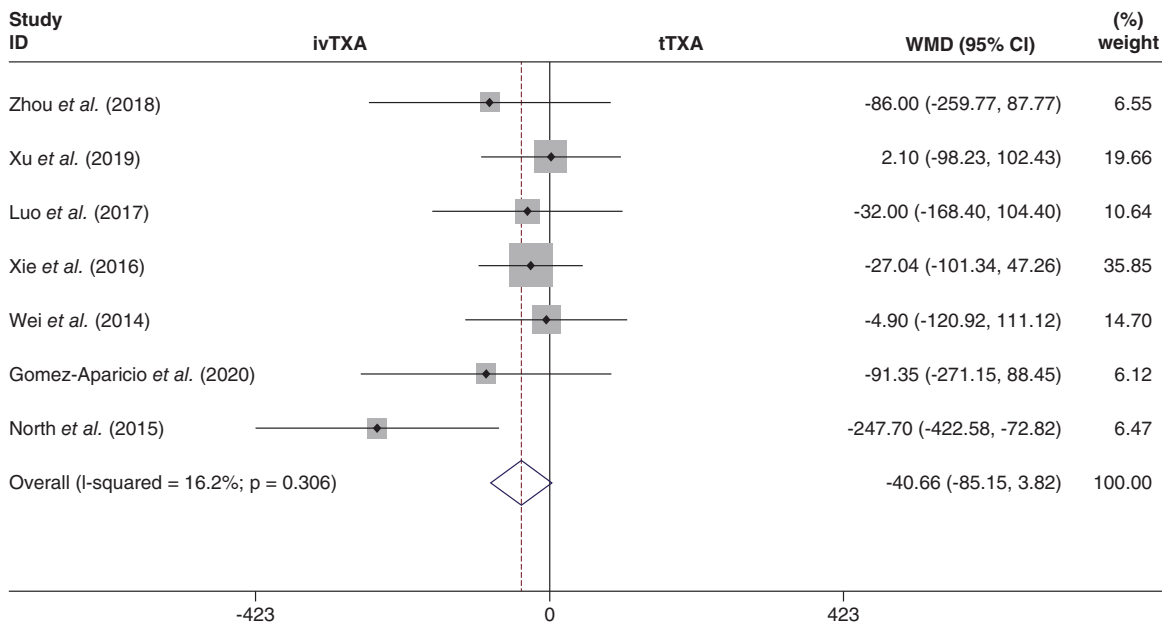


Figure 2. Forest plot diagram of the effect of intravenous versus tTXA on total blood loss.
ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid; WMD: Weighted mean difference.

RCT particularly recorded and analyzed the dynamic process of coagulation under the administration of TXA. Other surgical information was shown in [Table 2](#).

Risk of bias

The risk of bias of the included study was evaluated separately by two reviewers. Random sequence generation was illustrated in six studies. Allocation concealment and blinding of participants and personnel were considered as with a low risk of bias in five studies. Six studies were revealed to have a low risk of bias on the blinding of outcome assessment. As shown in [Table 3](#), all the ten RCTs did not make selective reports.

Outcomes of the meta-analysis

The effects of intravenous versus topical administration of TXA during THA was assessed via the evaluation indicators including blood loss (TBL, IBL and HBL), Hb level (postoperative day 1 and maximum Hb drop), transfusion incidence, drainage volume, complications (wound complications and DVT events) and LOS.

Blood loss

For a full comparison of blood loss between intravenous versus topical administration of TXA, a subgroup analysis was conducted based on the type of blood loss (TBL, IBL and HBL). Seven RCTs including 1050 patients in total provided data on TBL, during which 536 cases were in the intravenous group and 514 in the topical group and the data from different studies did not reveal significant heterogeneity ($p = 0.306$; $I^2 = 16.2\%$). As shown in [Figure 2](#), the effect of intravenous administration of TXA on TBL compared with the topical group during THA was not statistically significant (WMD = -40.665, 95% CI: -85.153, 3.823; $p = 0.073$). Four studies reported relevant data on IBL without statistical heterogeneity ($I^2 = 0.0$; $p = 0.763\%$), and the comparison illustrated statistical significance in the two groups (WMD = -12.687, 95% CI: -22.291, -3.083; $p = 0.010$; [Figure 3](#)). The present meta-analysis demonstrated ivTXA with a lower intraoperative blood loss than tTXA during THA. We further analyzed HBL which was mentioned in three studies involving 216 cases in the intravenous group and 191 in the topical group. A random-effect model was used due to significant heterogeneity among the RCTs ($I^2 = 20.6\%$; $p = 0.284$) and the result was statistically significant differences on HBL between the two groups (WMD = 14.276, 95% CI: 9.936, 19.459; $p < 0.001$). The result demonstrated ivTXA with a lower HBL than tTXA.

Table 2. Characteristics of included trials showing general surgical information.

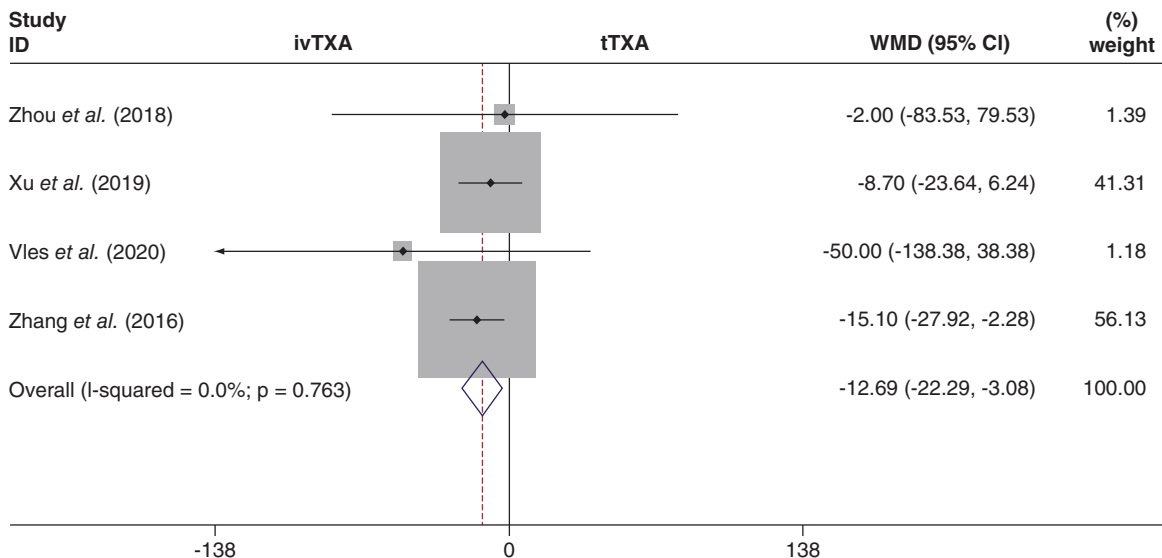
Study (year)	Surgical approach	Anesthesia	ivTXA	tTXA	Drainage	Transfusion criteria	VTE prophylaxis	Follow-up
Zhou <i>et al.</i> (2018)	Anterolateral approach	General anesthesia	First dose: 10 mg/kg 15 min before incision Second dose: 10 mg/kg 3 h after the first dose	3.0 g/60 ml irrigated 3 min before closure	Clamped for 2 h Removed on the 48 h postoperative	Hb <80 g/l or <100 g/l with anemic complications	Rivaroxaban for 15 days	6 weeks
Xu <i>et al.</i> (2019)	Posterolateral approach	Spinal anesthesia	Single dose: 20 mg/kg 5 min before incision	2.0 g/50 ml irrigated before closure	Clamped for 2 h Removed on the 48 h postoperative	(Hb) level <70 g/l or >70 g/l with anemic complications	Rivaroxaban for 35 days	6 months
Luo <i>et al.</i> (2017)	Posterolateral approach	General anesthesia	Single dose: 20 mg/kg 5 min before incision	2.0 g/150 ml dilution 50 ml irrigated the acetabulum 50 ml irrigated the femoral 50 ml injected after closure	No drains	Hb <70 g/l or >70 g/l with anemic complications	LMWH until discharge Rivaroxaban for another 15 days	3 months
Xie <i>et al.</i> (2016)	Posterolateral approach	General anesthesia	Single dose: 1.5 g 15 min before incision	3.0 g/150 ml dilution 50 ml irrigated the acetabulum 50 ml irrigated the femoral 50 ml injected after closure	Clamped for 30 min Removed on the 24 h postoperative	Hb <70 g/l or >70 g/l with anemic complications	LMWH until discharge Rivaroxaban for another 30 days	3 months
Zhang <i>et al.</i> (2020)	Posterolateral approach	General anesthesia	Single dose: 2.0 g/100 ml 30 min before incision	2.0 g/100 ml injected after closure	Clamped for 2 h Removed on the 24 h postoperative	Hb <70 g/l or <70 g/l with anemic complications	LMWH until discharge Rivaroxaban for another 10 days	NA
Wei <i>et al.</i> (2014)	Posterolateral approach	NA	Single dose: 3.0 g 10 min before incision	3.0 g/100 ml dilution 20 ml irrigated the acetabulum 20 ml irrigated the femoral 60 ml injected after closure	Clamped for 2 h Removed on the 24 h postoperative	Hb <90 g/l	LMWH	3 months
Vies <i>et al.</i> (2020)	Direct anterior approach	Spinal anesthesia	Single dose: 1.5 g/100 ml before closure	3.0 g/100 ml injected after closure	Clamped for 2 h	Hb <80 g/l or <85 g/l with anemic complications	LMWH until discharge Rivaroxaban for another 30 days	NA
Gómez-Aparicio <i>et al.</i> (2020)	NA	NA	Single dose: 15 mg/kg 15–20 min before incision	2.0 g/100 ml injected after closure	Clamped for 2 h Removed on the 48 h postoperative	Hb <80 g/l or <100 g/l with anemic complications	LMWH for 30 days	NA
North <i>et al.</i> (2015)	NA	NA	First dose: 1.0 g/50 ml 10 min before incision Second dose: 1.0 g/50 ml before fascial closure	2.0 g/100 ml irrigated before closure	No drains	Hb <70 g/l or <80 g/l with anemic complications	LMWH for 21 days or rivaroxaban for 35 days or aspirin for 21 days	NA
Zhang <i>et al.</i> (2016)	Anterior lateral approach	General or spinal anesthesia	Single dose: 1.0 g/250 ml 10 min before incision	1.0 g/100 ml injected after closure	Clamped for 3 h Removed on the 45 h postoperative	Hb <70 g/l or >80 g/l with anemic complications	LMWH for 2 weeks	1 year

Hb: Hemoglobin; ivTXA: Intravenous tranexamic acid; LMWH: Low molecular weight heparin; NA: Not available; tTXA: Topical tranexamic acid.

Table 3. Cochrane Collaboration's tool for quality assessment in trials comparing ivTXA to tTXA.

Study (year)	Sequence generation	Allocation concealment	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Others
Zhou <i>et al.</i> (2018)	Low	Low	Low	Low	Low	Low
Xu <i>et al.</i> (2019)	Low	Low	High	Low	Low	Unclear
Luo <i>et al.</i> (2017)	Low	Unclear	High	Low	Low	Low
Xie <i>et al.</i> (2016)	Unclear	Low	Low	Low	Low	Low
Zhang <i>et al.</i> (2020)	High	Unclear	High	Low	Low	Unclear
Wei <i>et al.</i> (2014)	Low	Low	Low	Low	Low	Low
Vles <i>et al.</i> (2020)	Low	Unclear	Low	Low	Low	Low
Gómez-Aparicio <i>et al.</i> (2020)	High	Unclear	Low	Low	Low	Unclear
North <i>et al.</i> (2015)	Unclear	Unclear	Low	Low	Low	Low
Zhang <i>et al.</i> (2016)	Low	Low	Unclear	Low	Low	Low

ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid.

**Figure 3. Forest plot diagram of the effect of intravenous versus tTXA on intraoperative blood loss.**
ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid; WMD: Weighted mean difference.

Hb level

Hb level was analyzed based on postoperative day 1 Hb (six studies) and maximum Hb drop (four studies). A random-effect model was adopted for these two indicators owing to the significant heterogeneity was illustrated among the studies ($I^2 > 50\%$; $p < 0.1$). There was no significant difference on postoperative day 1 Hb (WMD = -1.803, 95% CI: -5.269, 1.663; $p = 0.308$) between the two groups based on the results of the pooled analysis while the results demonstrated that ivTXA was related to a significantly smaller maximum Hb drop during THA (WMD = -0.400, 95% CI: -0.577, -0.222; $p < 0.001$; Figure 4).

Transfusion rate

All the ten RCTs reported direct information on the blood transfusion rate. Transfusions were needed in 63 of 639 cases (9.9%) in the topical group, compared with 79 of 656 cases (12.0%) in the intravenous group. Significant heterogeneity was not revealed ($I^2 = 0.0\%$; $p = 0.442$), so a fixed-effect model was adopted. The results showed that there was no significant difference between the two groups (OR: 1.274; 95% CI: 0.885, 1.835; $p = 0.193$; Figure 5).

A subgroup analysis was performed based on topical dose (≥ 2 g) or intravenous dose (single). Among the whole ten RCTs, nine studies (1247 patients) provided data on topical dose ≥ 2 g and eight studies (1043 patients)

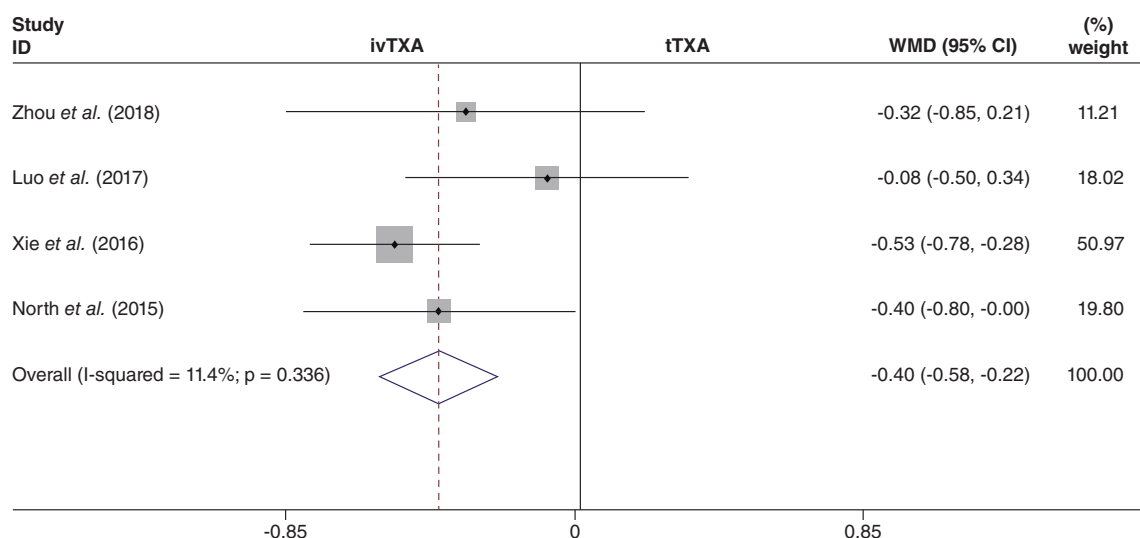


Figure 4. Forest plot diagram of the effect of intravenous versus tTXA on maximum hemoglobin drop. ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid; WMD: Weighted mean difference.

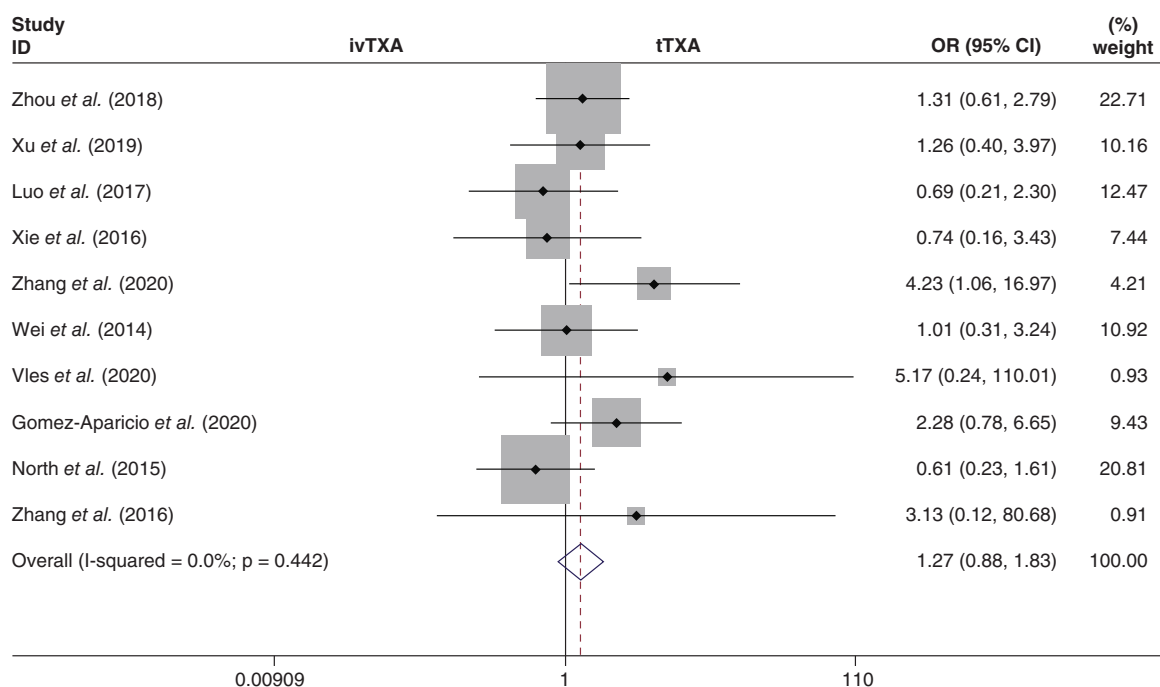


Figure 5. Forest plot diagram of the effect of intravenous versus tTXA on transfusion rate. ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid; WMD: Weighted mean difference.

provided data on a single intravenous dose. The fixed-effect model was adopted because significant heterogeneity was not found among the studies ($I^2 < 50\%$; $p > 0.1$). The subgroup analysis demonstrated that there was no significant difference observed in the transfusion rate between the topical route (dose ≥ 2 g) and the intravenous route (OR: 1.257; 95% CI: 0.870; 1.815; $p = 0.222$). Similarly, ivTXA in a single dose showed no significant difference in transfusion rate compared with the topical route (OR: 1.504; 95% CI: 0.942, 2.401; $p = 0.088$; Figure 6).

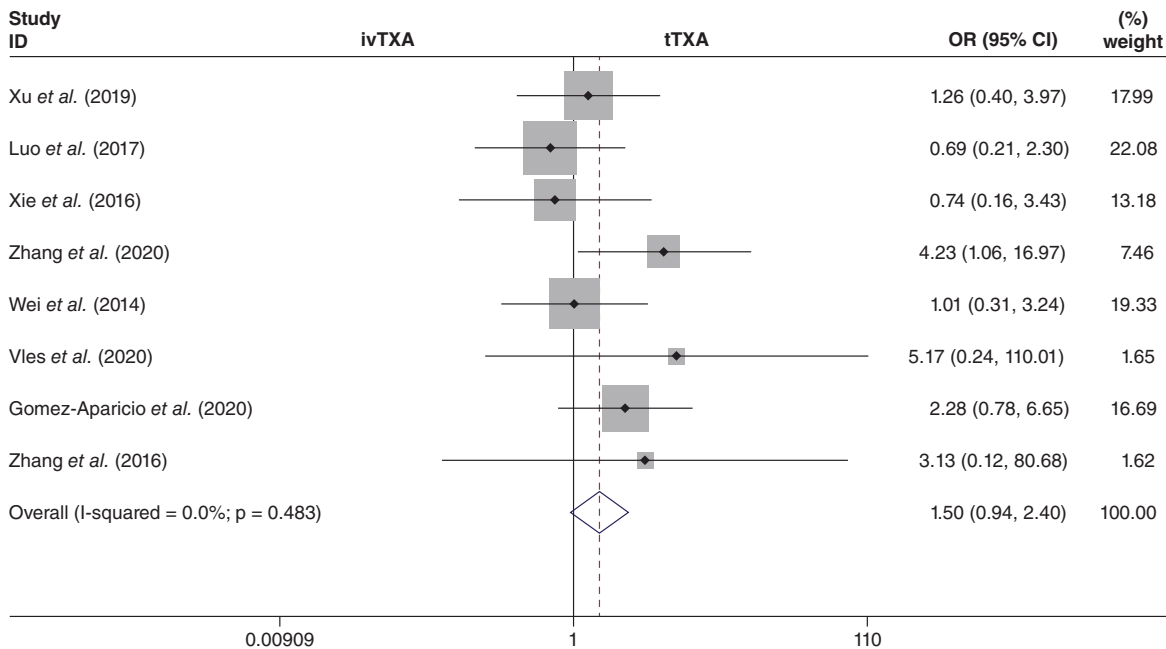


Figure 6. Forest plot diagram of the effect of the single-dose intravenous versus tTXA on transfusion rate.
ivTXA: Intravenous tranexamic acid; tTXA: Topical tranexamic acid.

Table 4. The postoperative outcomes of this systematic review and meta-analysis.

Outcomes	Studies numbers	Groups size		Overall effect			Heterogeneity	
		ivTXA	tTXA	Effect estimate	95% CI	p-value	I ² (%)	p-value
Transfusion rate	10	656	639	OR, 1.274	0.885, 1.835	0.193	0.0%	0.442
tTXA dose ≥ 2 g	9	632	615	OR, 1.257	0.870, 1.815	0.222	7.3%	0.374
ivTXA dose = single	8	529	514	OR, 1.504	0.942, 2.401	0.088	0.0%	0.483
Total blood loss	7	536	514	WMD, -40.665	-85.153, 3.823	0.073	16.2%	0.306
Intraoperative blood loss	4	210	213	WMD, -12.687	-22.291, -3.083	0.010	0.0%	0.763
Hidden blood loss	3	216	191	WMD, 14.276	9.936, 19.459	<0.001	20.6%	0.284
Postoperative 1st Hb	6	346	321	WMD, -1.803	-5.269, 1.663	0.308	74.3%	0.002
Drainage volume	4	295	273	WMD, 44.152	-84.118, 172.422	0.500	96.3%	0.000
Maximum Hb drop	4	257	255	WMD, -0.400	-0.577, -0.222	<0.001	11.4%	0.336
DVT	9	545	549	RD, 0.000	-0.014, 0.014	0.992	0.0%	0.906
Wound complications	5	409	389	RD, -0.003	-0.028, 0.022	0.816	0.0%	0.920
Length of stay	6	437	413	WMD, 0.283	-0.152, 0.718	0.202	88.0%	0.000

DVT: Deep vein thrombosis; Hb: Hemoglobin; ivTXA: Intravenous tranexamic acid; OR: Odds ratio; RD: Rate difference; tTXA: Topical tranexamic acid; WMD: Weighted mean difference.

Drainage volume

Four studies (568 patients) mentioned the data of drainage volume, and a random-effect model was used owing to significant heterogeneity among the studies ($I^2 = 96.3\%$; $p < 0.001$). The result showed there was no significant difference in drainage volume between the two groups (WMD = 44.152, 95% CI: -84.118, 172.422; $p = 0.500$). More details were shown in [Table 4](#).

Complications

A total of nine publications provided the patient's numbers of DVT events after THA and there was no significant heterogeneity ($I^2 = 0.0\%$; $p = 0.906$). Compared 545 patients treated with ivTXA to 549 patients treated with tTXA during THA, there was no statistical difference in DVT between the two groups (RD = 0.000; 95% CI:

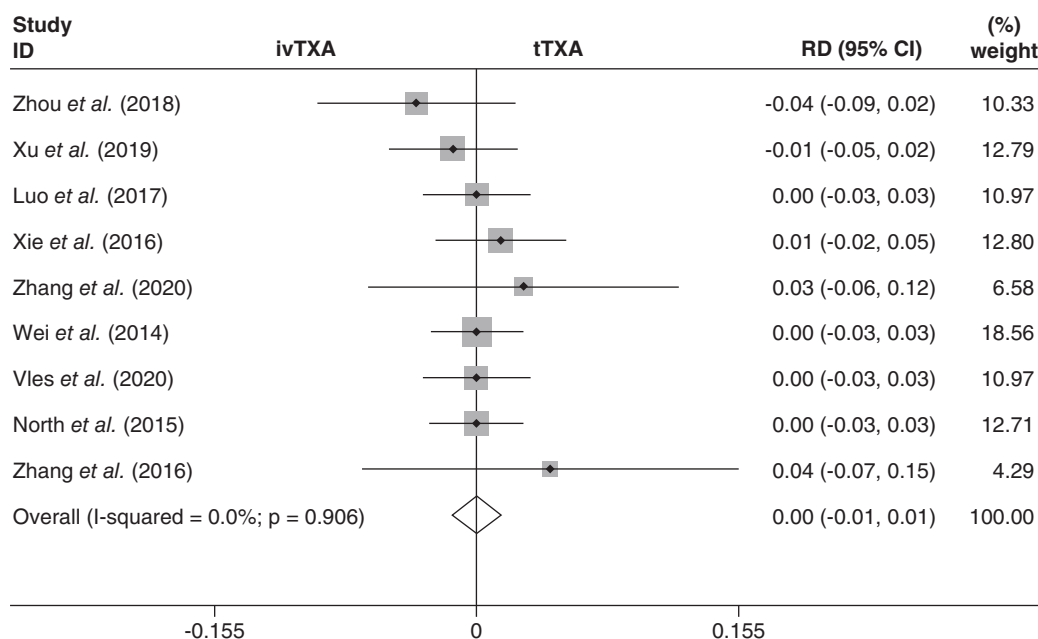


Figure 7. Forest plot diagram of the effect of intravenous versus topical tranexamic acid on deep vein thrombosis events.

ivTXA: Intravenous tranexamic acid; RD: Rate difference; tTXA: Topical tranexamic acid.

-0.014–0.014; $p = 0.992$, Figure 7). As for the wound complications, five studies reported related information without significant heterogeneity ($I^2 = 0.0\%$; $p = 0.920$) and no statistical difference was revealed between the two groups (OR: -0.003; 95% CI: -0.028, 0.022; $p = 0.816$).

Length of stay

Six studies (850 patients) in total reported the LOS. We adopted the random-effect model due to the significant heterogeneity ($I^2 = 88.0\%$; $p = 0.000$). Pooled results revealed no statistical difference in the two groups (OR: 0.283; 95% CI: -0.152, 0.718; $p = 0.202$).

Discussion

Perioperative blood-sparing management is an important component of enhanced recovery after surgery [22]. As an antifibrinolytic agent, TXA administrated in different routes including oral, intravenous, topical and combined routes have been adopted in the clinic to reduce perioperative blood loss and transfusion rate during total joint arthroplasty for decades with reliable efficiency and safety [12,13,23]. During the above management routes, intravenous and tTXA have been most commonly compared for a long-running controversy, simply, ivTXA might lead to a higher risk of thromboembolic events but a better hemostatic effect in theory, while the topical approach is just the opposite. Although, the previous meta-analysis has revealed no statistical differences between these two routes during total joint arthroplasty, optimal administration of TXA is elusive especially for THA because most clinical research focused on total knee arthroplasty (TKA) and only limited RCTs did that for THA up to date [12–17,24]. For example, the latest meta-analysis in 2019 compared intravenous and tTXA in total knee and hip arthroplasty based on 20 RCTs, during which only five studies adopted TXA in THA [13]. As far as we know, our study is the most comprehensive systematic review and meta-analysis including ten RCTs in total comparing the efficacy and safety of intravenous versus tTXA during THA, which would avoid the heterogeneity caused by totally different surgical management between THA and TKA [18,25–34].

In this study, we firstly analyzed blood loss-related items during THA. Although the results showed no statistical differences between the two routes on the TBL, which is consistent with the previous report [13,17], the average TBL in the intravenous group was smaller than the topical group. Similarly, in one meta-analysis, it was also concluded that ivTXA can lead to smaller TBL and the possible explanation is that intravenous administration of TXA might take effect earlier than the topical method whose hemostatic effect is restricted to postoperative bleeding [14]. Our result may support this view because IBL was significantly smaller in patients treated with ivTXA compared with the topical approach. Meanwhile, we further analyzed HBL which was reported to occupy approximately 50% of TBL and thus a key parameter to be considered [35]. A total of three RCTs indicated that averaged HBL was lower in the intravenous group, and the result was statistically significant. What's more, the result of lower HBL in the intravenous group was consistent with the previous report [14].

Hb level is the most important indicator to decide transfusion or not after surgery. A total of seven RCTs reported the Hb level of postoperative day 1, which demonstrated no statistical difference between the two routes in this study. However, the maximum Hb drop always appears on postoperative days 3–4 owing to HBL [36]. As a result, the maximum Hb drop was smaller in patients treated with ivTXA and this difference was statistically significant according to four RCTs. This lower maximum Hb drop induced by ivTXA may be especially significant for the rapid recovery of elderly patients receiving THA.

Although ivTXA is much more effective to reduce IBL, HBL and received less maximum Hb drop, the transfusion rate is similar in the present study, which may result from the similar TBL and different administrative doses of TXA among the included RCTs. Furthermore, the difference in maximum Hb drop may be compromised by different transfusion standards. To avoid the effects of different doses, we did a subgroup analysis for the ivTXA with a single dose and tTXA with a dose ≥ 2 g. Two doses of ivTXA will normally reduce the first dose of TXA, which in turn affecting the first-dose effect. At the same time, the fibrinolytic process might be repressed by the body and even be replaced by an antifibrinolytic reaction after surgery, which leads to less efficiency of the second dose of ivTXA in reducing blood loss [37]. The pooled result indicated ivTXA administrated in a single dose did not reduce transfusion rate compared with the topical route. The possible explanation is that although single-dose ivTXA enhances coagulation functions compared with tTXA during THA according to thrombosis-related parameters recorded by thromboelastography [32], the tTXA administration could reach a maximum and local dose in the shortest time at the surgical bleeding areas and; therefore, inhibit fibrinolytic and result in effective local microvascular hemostasis [38]. More importantly, the previous meta-analysis have reported the same effect on transfusion rate in the two routes during either THA or TKA [13,14,24].

Drainage volume after THA was similar in the study. Theoretically, tTXA will affect drainage volume because most of the fluid that dilutes TXA left in the joint will flow into the drainage pack in the end. Meanwhile, the time to clamp the drainage tube and remove the drainage tube can inevitably interfere with the final drainage volume [39]. Although TXA is always with a certain risk of thrombosis, this has not been reported before [40]. Some studies even reported a potential protective role of TXA on thrombogenesis [41]. Similarly, our meta-analysis found no statistical difference between these two routes. Routine postoperative anticoagulation measures such as low molecular weight heparin, rivaroxaban and intermittent pneumatic compression devices could have reduced the real difference of thrombotic events caused by different routes of TXA. Besides, differentiated anticoagulation management as shown in Table 2 might also affect the reliability of results. Wound infection leads to delayed wound healing and even revision surgery [42]. The result showed no significant difference between intravenous and tTXA. Although it was reported that topical irrigation with TXA increased wound tension which in turn increase the risk of wound complication, this most commonly occurs in the knee joint instead of the hip joint owing to different anatomical conditions [43].

There are some strengths in this study compared with the previous meta-analysis. First, we only included RCTs which increased the reliability of results. Meanwhile, the most comprehensive RCTs on the 'head-to-head' comparison of topical and intravenous routes during THA were included in the study. In addition, considering the different anatomy and surgical administration in the knee and hip, only THA was selected for our research. At the same time, this study also has several limitations. First of all, significant heterogeneity exists among the included trials because of differentiation in perioperative management. Additionally, methodological deficits appeared in several trials, and insufficient details affect quality assessment in trials. Moreover, the lack of effective long-term follow-up details inevitably results in the underestimation of postoperative complications.

Conclusion

This systematic review and meta-analysis indicated the comparable effect of intravenous administration of TXA on transfusion rate, TBL, Hb of postoperative day 1, drainage volume, DVT events and wound complications compared with the topical route. There were statistically significant differences in IBL, HBL and maximum Hb drop between the two routes. However, the heterogeneity between studies is higher than 50% with respect to Hb of postoperative day 1, drainage volume and LOS, which could influence the results. Given the amount of included RCTs is limited and differentiated perioperative management, the generality of our conclusions is relatively restricted. Therefore, more high-quality RCTs are essential to determine the optimal TXA administration method in the future to support the existing conclusion.

Summary points

- The optimal management approach for tranexamic acid (TXA) in primary total hip arthroplasty (THA) is still controversial.
- This meta-analysis aimed to evaluate the efficacy and safety of intravenous versus topical TXA (tTXA) during THA.
- The most comprehensive randomized controlled trials (RCTs) on the 'head-to-head' comparison of topical and intravenous routes during THA were included in the study.
- The present result indicated comparable safety and transfusion rate for intravenous and tTXA in primary THA.
- The intravenous TXA demonstrated a smaller intraoperative blood loss hidden blood loss and maximum hemoglobin drop compared with tTXA.
- Given the amount of included RCTs is limited, the generality of our conclusions is relatively restricted.
- More high-quality RCTs are essential to determine the optimal TXA administration method in the future to support the existing conclusion.
- This study is of great significance for the clinical management of TXA during THA.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data sharing statement

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

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