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KNEE ARTHROPLASTY

Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials

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Abstract
Background The purpose of this meta-analysis was to compare the blood loss and complications of intra-articular (IA) with intravenous (IV) tranexamic acid (TXA) for total knee arthroplasty (TKA).
Methods A comprehensive search of studies was conducted to identify related articles in Pubmed, Embase, Cochrane central Register of Controlled Trials, springerLink, OVID and the Research published from January 1980 to September 2016. All studies that compared IA TXA with IV TXA application on TKA were included. Main outcomes of the two methods were collected and analyzed by using Review Manager 5.3.
Results There were 16 randomized controlled trials with 1308 cases met the criteria. Compared with IV TXA, IA TXA had similar blood volume of drainage, hidden blood loss, transfusion rate and complications ($P > 0.05$). IA TXA had lower total blood loss than IV TXA, and there was significant difference ($P < 0.05$). Subgroup analysis of total blood loss based on times of IV TXA administration showed that repeat dose of IV TXA had a higher total blood loss and postoperative hemoglobin drop ($P < 0.05$) than IA TXA. However, single dose of IV TXA had a similar efficacy on total blood loss and postoperative hemoglobin drop ($P > 0.05$) when compared with IA TXA.
Conclusions Both IA TXA and single dose of IV TXA are effective in reducing total blood loss and postoperative hemoglobin drop without increasing complications of DVT or PE. The current meta-analysis suggests that 1.5 g TXA by IA administration or 1 g TXA by IV administration 10 min before tourniquet deflation is effective and safe in patients undergoing TKA.

Keywords Total knee arthroplasty · Tranexamic acid · Intra-articular · Intravenous · Meta-analysis

Introduction

Total knee arthroplasty (TKA) has been the common procedure used to treat osteoarthritis, and the surgical volume is increasing along with the elders increased. Despite the dramatic reduction in complications, TKA is associated with a substantial postoperative blood loss. The estimated blood loss during TKA varies from 500 to 1500 mL, and the blood transfusion rate is ranging between 11 and 50%. Blood transfusion has many potential risks including infections, disease transmission, immunologic reaction and even death [1, 2].

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent which stabilizes fibrin clots, resulting in more stable hemostasis by reducing the effects of plasmin, and as a consequence decreases the rate of fibrinolysis [3]. It can be administrated by IA or IV route. Previous studies reported that TXA takes about 30 min for IA administration and 5–15 min for IV administration to take effect. IV TXA has been recommended by some studies and meta-analysis as preferred method for patients undergoing TKA [4, 5]. However, there is no consensus on the doses and times of IV TXA. Even when to use IV TXA is under debate.

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Pharmacokinetic studies reported that an 20 mg/kg dose of IV TXA is suitable for TKA because therapeutic levels can be maintained for approximately 8 h after operation, which covers the period of postoperative hyperfibrinolysis [6]. Hourlier [7] reported that single-dose IV TXA was effective as continuous infusion in TKA. A study reported by Iwai [8] suggested that repeat-dose IV TXA reduced total blood loss in TKA. Maniar [9] reported that giving TXA preoperatively would deactivate the fibrinolysis as soon as it starts. Akgul [10] reported that a high, single dose of TXA intravenously given to the patient prior to the TKA significantly reduces the bleeding during the operation and within the postoperative 24 h. Sun [11] reported that the preoperative dose and an additional dose of IV TXA were superior to a single preoperative dose of TXA in reducing blood loss in TKA. Recently, studies reported that IA TXA has many advantages, such as easy administration, inhibits local activation of fibrinolysis and less systemic absorption [12, 13]. The current doses of IA TXA vary from 1 to 3 g and used before tourniquet deflation (when used) or before wound close. Previous study reported that there was no difference in the efficacy of 1.5 versus 3.0 g of IA TXA in reducing perioperative blood loss during TKA [14]. Several clinical studies [15–17] and meta-analysis [18, 19] have shown that both IA and IV TXA could effectively reduce blood loss and transfusion in TKA without increasing the complications.

Considering effectiveness of both IA and IV TXA, studies were performed to compare IA TXA with IV TXA for patients undergoing TKA. Tzatzairis [20] reported that 1 g IA TXA has a similar efficacy with 1 g IV TXA in the treatment of patients undergoing TKA. Seo [21] reported that 1.5 g IA TXA was more effective than 1.5 g IV TXA in terms of reducing total blood loss and transfusion rate. Aggarwal [22] reported that IA TXA was better than IV TXA in reducing blood loss. Despite the evidences from these studies that compared IA TXA with IV TXA, there is still no consistent conclusion on which route, IA or IV is the preferred treatment for TKA [20, 23]. Therefore, a meta-analysis was conducted to investigate the total blood loss, blood transfusion and complications of IA TXA and IV TXA in TKA.

Materials and methods

Search strategy

Studies were indentified through a computerized search in Pubmed, Embase, Cochrane central Register of Controlled Trials, SpringerLink, OVID and the Research using the following terms: total ankle arthroplasty OR total arthroplasty replacement OR TKA OR TKR and tranexamic acid or TXA from January 1980 to September 2016.

Inclusion and exclusion criteria

Studies should be to meet the following inclusion criteria: (1) randomized controlled trials; (2) comparison of IA and IV TXA in patients undergoing total knee arthroplasty; (3) patients older than 18 years; (4) the clinical outcomes included blood loss or postoperative complications; (5) the articles were restricted to English language.

Exclusion criteria: (1) type of studies as "case report," "review," "letters," "talk" and "commentary"; (2) data were duplicated or overlapped.

Literature search result

Figure 1 shows details of the identification of studies, their inclusion and exclusion. Three hundred and thirty-two articles were identified through the search, and abstract screen of these 332 articles resulted in exclusion of 76 duplicates and 235 other articles that did not fit the inclusion criteria, leaving 21 articles for full text. Three articles were not RCT, and two articles were not written in English. This eventually resulted in 16 studies included.

Risk of bias assessment

Two authors independently performed the initial screening and data extraction. Any disagreements were resolved by discussion among the authors. Information retrieved from the studies included study design, patient characteristics, sample size, geographical and complications. Literature quality assessment was performed by two researchers. A third researcher was the adjudicator when there was debate between the two researchers. The quality assessment was risk of bias in all included studies. And the evaluation criteria and methods followed the Cochrane Collaboration's proposal and used their tool RevMan 5.3 to assess risk of bias. The methodological quality of the RCTs was assessed by using the modified Jadad scale, which includes randomization, allocation concealment, blinding, withdrawals and dropouts. High-quality studies were reflected by scores of 4–7.

Statistical analysis

We performed statistical analysis with the RevMan 5.3 provided by Cochrane Collaboration. The assessment for statistics heterogeneity was calculated through χ^2 and I^2 test, with values of 25, 50 and 75% considered low, moderate and high heterogeneity. A random effect model was used when $I^2 > 50\%$. For continuous data, means and standard

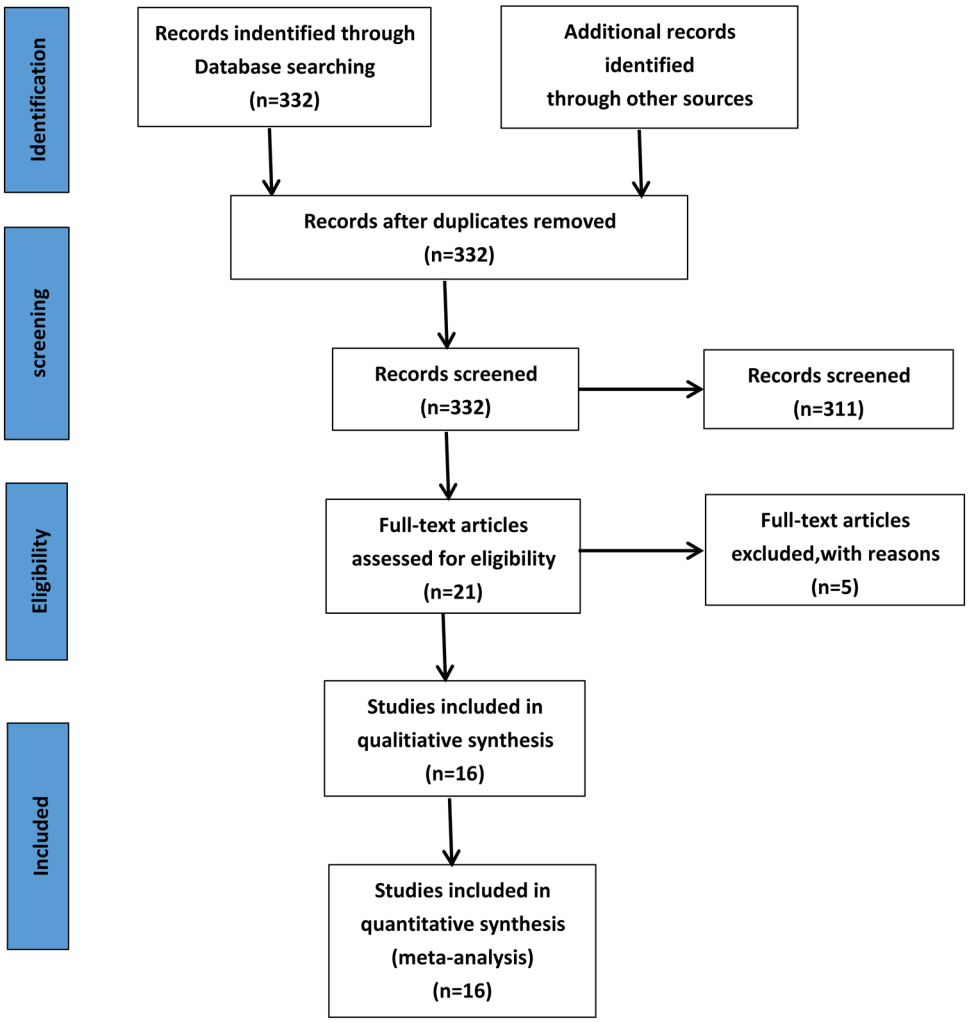

Fig. 1 Flow chart showing study identification, inclusion and exclusion

deviations were pooled to a mean difference (MD) and 95% confidence internal (CI) in the meta-analysis. For binary data, risk ratios (RR) and 95% confidence interval (CI) were assessed ($a=0.05$ for the inspection standards). Subgroup analysis based on times of IV TXA administration was performed for total blood loss and postoperative hemoglobin drop to explore a potential source of heterogeneity.

Results

Demographic characteristics

A total of 1308 patients from 16 studies were included. The demographic characteristics were summarized in Table 1. There were 653 patients treated with IA TXA, and 655 patients treated with IV TXA. Two studies were from the USA [24, 25], two from Spain [26, 27], three from Greece [20, 23, 28], three from India [22, 29, 30], two from Iran [8, 31], one from Singapore [32], one from Thailand [33], one from Korea [21] and one from Brazil [34]. The interventions of IA and IV group were collected in Table 2.

Risk of bias

The summary of bias is summarized in Fig. 2. All trials reported random sequence generation, but only six trials reported allocation concealment [24, 26–28, 32, 33], and six trials reported blinding [21, 22, 25, 27, 32, 35]. Two trials had patients lost to follow-up [9, 26].

Results of meta-analysis

Total blood loss

A total of nine studies provided data of total blood loss (Fig. 3). There was significant difference between the groups with respect to total blood loss (MD −66.12 mL, 95% CI −118.10 to 14.14, $I^2=76\%$, $P<0.05$). Four studies

Table 1 The characteristics of included studies

Study	Year	Country	Patients (*n*)		Age (*Y*)		Gender				Study design	Quality score
							Topical		IV			
			IA	IV	IA	IV	*M*	*F*	*M*	*F*		
Aggarwal	2016	India	35	35	55.66 ± 8.71	58.77 ± 10.14	23	12	22	13	RCT	5
Aguilera	2015	Spain	50	50	72.53 ± 6.6	72.49 ± 7.68	18	32	38	12	RCT	5
Gomez-Barrena	2014	Spain	39	39	70.1 ± 9.1	71.8 ± 10.3	26	13	25	14	RCT	6
Chen	2016	Singapore	50	50	65 ± 8	65 ± 8	10	40	15	35	RCT	7
Digas	2015	Greece	30	30	71 ± 7	70 ± 6.5	7	23	2	28	RCT	5
Drosos	2016	Greece	30	30	71.1 ± 6.32	69.27 ± 7.21	6	24	6	24	RCT	3
Keyhani	2015	Iran	40	40	67 ± 11.9	68.4 ± 10.4	23	17	26	14	RCT	2
Maniar	2012	India	40	40	67 ± 7.96	67.3 ± 9.1	6	34	10	30	RCT	4
May	2016	USA	62	69	63 ± 10.6	65.0 ± 9.6	18	44	11	58	RCT	6
Patel	2014	USA	47	42	64.8 ± 9.7	64.9 ± 7.8	13	34	10	32	RCT	5
Pinsornsak	2016	Thailand	30	30	67.63 ± 7.96	69.97 ± 7.55	5	25	7	23	RCT	3
Sarzaeem	2014	Iran	50	50	67.5 ± 7.6	66.9 ± 7.2	6	44	7	43	RCT	4
Seo	2013	Korea	50	50	67.5 ± 6.6	66.8 ± 6.3	5	45	6	44	RCT	2
Soni	2014	India	30	30	69.4 ± 4.71	69.05 ± 4.10	17	23	19	21	RCT	3
Tzatzairis	2016	Greece	40	40	69.1 ± 8.68	69.55 ± 6.61	7	33	9	31	RCT	3
Zekcer	2016	Brazil	30	30	65.7 (48 − 88)	65.7 (48 − 88)	9	21	6	24	RCT	5

IA intra-articular, *IV* intravenous, *M* man, *F* female, *RCT* random control trial

were assigned to the repeat dose of IV TXA subgroup, and five studies were assigned to the single dose of IV TXA subgroup. The repeat dose of IV TXA subgroup showed a higher total blood loss as compared with the IA group, and there was significant difference (MD −98.57 mL, 95% CI −182.11 to −15.02, $I^2 = 90\%$, $P < 0.05$). The single dose of IV TXA subgroup showed a higher total blood loss as compared with the IA group, although there was no significant difference (MD −45.62 mL, 95% CI −112.02 to 20.78, $I^2 = 0\%$, $P > 0.05$) (Fig. 3).

Blood volume of drainage

A total of 11 studies provided data of blood volume of drainage. The heterogeneity test indicated moderate statistical evidence of heterogeneity ($\chi^2 = 36.87$, $P < 0.01$, $I^2 = 73\%$). There was no significant difference between the groups in terms of blood volume of drainage (MD −29.89 mL, 95% CI −68.99 to 9.2, $P > 0.05$) (Fig. 4).

Hidden blood loss

A total of three studies provided data of hidden blood loss. The heterogeneity test indicated low statistical evidence of heterogeneity ($\chi^2 = 3.34$, $P > 0.05$, $I^2 = 40\%$). There was no significant difference between the groups with respect to hidden blood loss (MD 48.57 mL, 95% CI −20.5 to 117.64, $P > 0.05$) (Fig. 5).

Postoperative hemoglobin drop

A total of ten studies provided data of postoperative hemoglobin drop. The pooled standard mean difference in postoperative hemoglobin drop was −0.01 mL (95% CI −0.38 to 0.35), indicating that there was 0.01 mL less postoperative hemoglobin drop in the IA group as compared to the IV group, but this difference was no statistically significant ($\chi^2 = 75.47$, $I^2 = 88\%$, $P > 0.05$). Four studies were assigned to the repeat dose of IV TXA subgroup, and six studies were assigned to the single dose of IV TXA subgroup. The repeat dose of IV TXA group showed a greater postoperative hemoglobin drop as compared with the IA group, and there was significant difference (MD −0.43 mL, 95% CI −0.8 to −0.05, $P < 0.05$). The single dose of IV TXA group showed a lower postoperative hemoglobin drop as compared with the IA group, although there was no significant difference (MD −0.51,95% CI −1.02 to 0.01, $P = 0.05$) (MD 0.29 mL, 95% CI −0.16 to 0.74, $P > 0.05$) (Fig. 6).

Blood transfusion rate

A total of 13 studies provided data of blood transfusion rate. The heterogeneity test indicated low statistical evidence of heterogeneity ($\chi^2 = 5.78$, $P > 0.01$, $I^2 = 14\%$). There was no statistically significant difference between the groups with respect to the blood transfusion rate (RR: 1.17, 95% CI: 0.84–1.93, $\chi^2 = 14, 15$, $I^2 = 15\%$, $P > 0.05$) (Fig. 7).

Table 2 Characteristics of the 16 trials selected showing general surgical information

Study	Dose and time		Transfusion criteria	Tourniquet	Thromboprophylaxis	DVT screening method
	IA	IV				
Aggarwal	15 mg/kg TXA/100 mL NS after meticulous suturing	(1) 15 mg/kg TXA 30 min before tourniquet deflation (2) 15 mg/kg TXA after 2 h	Hb < 8.0 g/dL postoperative blood loss >20%	Yes	DVT stockings; Ankle pumps; early mobilization	Clinical symptoms
Aguilera	1 g TXA/10 mL NS	(1) 1 g TXA 15–30 min before tourniquet inflation (2) 1 g TXA when tourniquet deflation	Hb < 8.0 g/dL Hb < 8.5 g/dL + heart disease or >70 years 8.5 g/dL < Hb < 9.0 g/dL + low orthostatic tolerance	Yes	LMWH	N/S
Gomez-Barrena	3.0 g TXA/100 mL NS (1) Half of the volume: irrigation before joint closure (2) Other half: intra-articularly after skin closure	(1) 15 mg/kg TXA, 15–20 min before tourniquet deflation (2) 15 mg/kg TXA 3 h after surgery	Hb < 8.0 g/dL Hb < 10.0 g dL + symptoms	Yes	LMWH	Clinical exam + Doppler ultrasound
Chen	1.5 g TXA//100 mL NS after cementing the prostheses	1.5 g TXA/100 mL NS 20 min after cementing the prostheses	Hb < 8.0 g/dL Hb < 10.0 g dL + symptoms Hb < 8.5 g/dL Hb < 9.5 g/dL + heart disease	Yes	LMWH	N/S
Digas	2 g TXA after skin closure	15 mg/kg TXA before tourniquet deflation	Physiological signs of inadequate oxygenation symptoms of myocardial ischemia occur	Yes	Tinzaparin sodium	Clinical exam
Drosos	1 g TXA/30 mL NS at the start of the wound suturing	1 g TXA at the start of the wound suturing	Hb < 10.0 g/dL symptoms or any anemia-related organ dysfunctions	Yes	N/S	N/S
Keyhani	(1) 1.5 g TXA/50 mL NS before joint closure (2) 1.5 g TXA/50 mL NS after wound closure by a portovac drain	500 mg TXA/100 mL NS at the end of the surgery	Hb < 8.0 g/dL	Yes	LMWH	Clinical exam + Doppler ultrasound
Maniar	3.0 g TXA/100 mL NS 5 min before tourniquet deflation	10 mg/kg TXA 15 min before tourniquet deflation	Hb < 8.5 g/dL Hb < 10.0 g/dL + heart disease 8.5 g/dl < Hb < 10.0 g/dL + symptoms	Yes	LMWH	Clinical exam + Doppler ultrasound
May	2 g TXA/50 min after capsular closure	(1) 1 g TXA before tourniquet inflation, (2) 1 g TXA after capsular closure	HB < 7.0 g/dL Hb < 10.0 g dL + symptoms	Yes	LMWH	N/S
Patel	2 g TXA/100 mL NS, 2 min before tourniquet deflation	10 mg/kg, 10 min before tourniquet deflation	Hb < 8.0 g/dL + symptoms	Yes	LMWH	Doppler ultrasound + Chest CT + V/Q scans

Table 2 (continued)

Study	Dose and time		Transfusion criteria	Tourniquet	Thromboprophylaxis	DVT screening method
	IA	IV				
Pinsornsak	750 mg TXA before tourniquet deflation	750 mg TXA before tourniquet deflation	Hb < 10.0 g/dL or symptoms of anemia	Yes	Foot pump exercise and early ambulation	Clinical exam
Sarzaeem	1.5 g TXA/100 mL NS, after closing the wound immediately	1.5 g TXA/100 mL NS after closing the wound immediately injected through the portovac drain	Hb < 8.0 g/dL Hb < 10 g/dL + symptoms	Yes	N/S	N/S
Seo	1.5 g TXA/100 mL NS before tourniquet deflation	1.5 g TXA/100 mL NS before tourniquet deflation (1) 10 mg/kg TXA 20 min before Tourniquet application	Hb < 8.0 g/dL Hb < 10 g/dL + symptoms	Yes	N/S	N/S
Soni	3 g TXA/100 mL NS after cementing the implant and before tourniquet deflation	(2) 10 mg/kg TXA 15 min before deflation of the tourniquet (3) 10 mg/kg TXA 3 hours after intraoperative dose	Hb < 8.0 g/dL	Yes	LMWH	N/S
Tzatzairis	1 g TXA/100 mL NS intra-articulary after joint capsule closure	1 g TXA/100 mL NS 10 min before incision	Hb level < 10 g/dL symptoms or anemia-related organ dysfunction	No	LMWH	Doppler ultrasound, D-dimers test, spiral computed tomography
Zekcer	1.5 g TXA/50 mL NS sprayed over the area operated before tourniquet deflation	20 mg/kg TXA/100 mL NS, given at the same time as anesthesia	N/S	Yes	Elastic stockings, sodium enoxaparin	Duplex ultrasound examinations

IA intra-articular, *IV* intravenous, *TXA* tranexamic acid, *NS* normal saline, *N/S* not stated, *Hb* hemoglobin, *LMWH* low molecular weight heparin

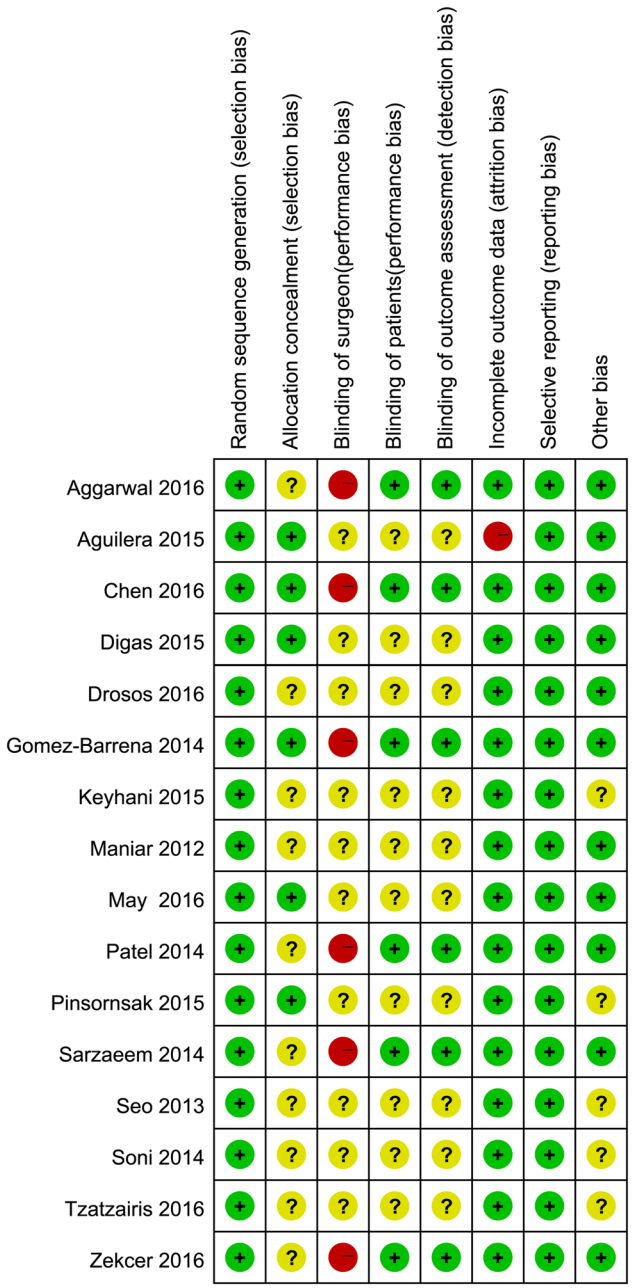

Fig. 2 Risk of bias summary

Blood units transfused per patient

A total of five studies provided data of blood units transfused per patient. The heterogeneity test indicated low statistical evidence of heterogeneity ($\chi^2 = 1.434$, $P > 0.05$, $I^2 = 25\%$). There was no significant difference between the two groups in terms of blood units transfused per patient (MD −0.1, 95% CI −0.23 to 0.04, $P > 0.05$) (Fig. 8).

Superficial or deep infection of wound

All studies provided data of superficial or deep infection. Digas [28] reported one case of superficial infection in IA group. Drosos [23] reported one case of superficial infection in IV group. One case of superficial infection and one case of deep infection in IA group while four cases of superficial infection in the IV group reported by May [24]. Tzatzairis [20] reported three cases of superficial infection in the IA group and two cases of superficial infection and one case of deep infection in the IV group. There was no statistically difference between the groups in terms of superficial and deep infection (RR 0.81, $\chi^2 = 1.23$, $I^2 = 0\%$, $P > 0.05$) (Fig. 9).

Thromboembolic complications

All studies provided data of thromboembolic complications. One study reported by Digas [28] documented one DVT case of the IA group. May [24] reported one case of DVT and one case of PE in IA group, while two PE cases and two DVT cases in IV group. Seo [21] reported three cases of DVT in IA group. Another study reported by Zekcer [35] documented one case of DVT in IA group. Patel [25] reported one case in the IA group and two cases in the IV group have clinical suspicion of DVT and the duplex Doppler study of each of these patients was negative. There was no significant difference between the groups with respect to thromboembolic complications (RR = 0.50, $\chi^2 = 2.01$, $I^2 = 0\%$, $P > 0.05$) (Fig. 10).

Discussion

The purpose of this meta-analysis was to compare the outcome of IA and IV TXA in the treatment of TKA. There was no significant differences in blood volume of drainage, hidden blood loss, blood transfusion rate, blood units transfused per patient, superficial and deep infection and thromboembolic complications such as DVT or PE when compared IA TXA with IV TXA in primary TKA. Subgroup analysis showed that repeat dose of IV TXA had a higher total blood loss and a higher postoperative hemoglobin drop as compared with the IA group. In addition, IA TXA had a similar efficacy with single dose of IV TXA in terms of reducing total blood loss and postoperative hemoglobin drop.

Application of tourniquet during TKA may avoid massive blood loss, however, when it is released at the end of the surgery, fibrinolytic activity and bleeding increase [34, 36]. In order to avoid anemia, blood transfusion may be required depending on the amount of blood lost. As blood transfusion increases the risk of postoperative

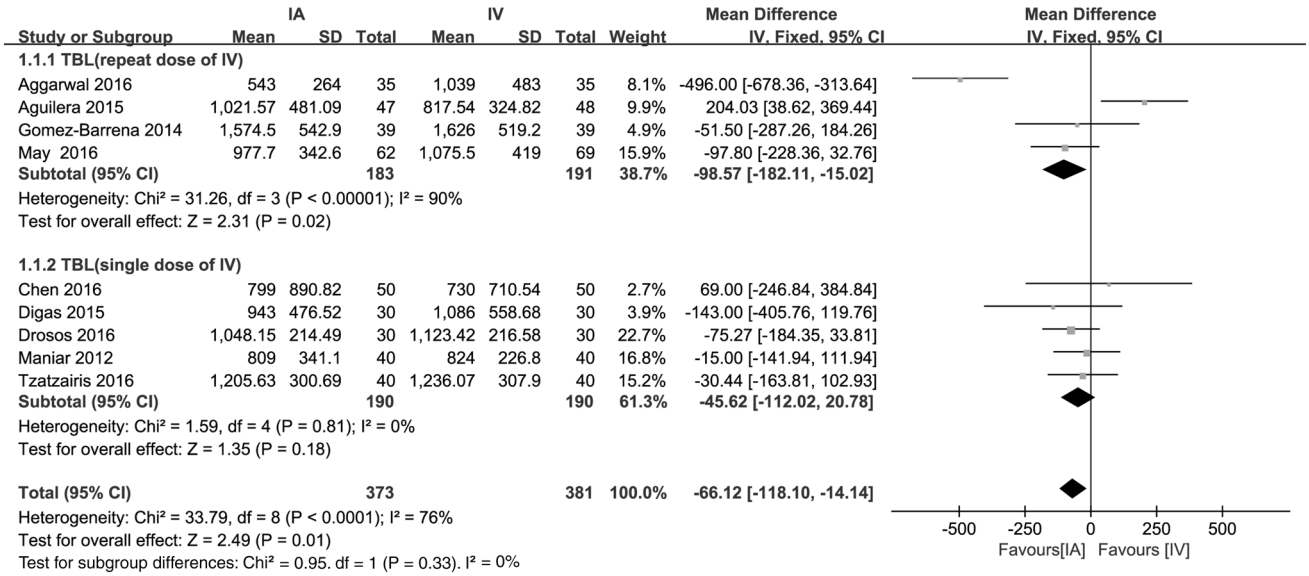

Fig. 3 Forest plot of total blood loss showed that there was significant difference between IA TXA group and IV TXA group. Subgroup analysis based on times of IV TXA administration showed that there was significant difference between IA TXA group and repeat dose of IV TXA group. There was no significant difference between IA TXA group and single dose of IV TXA group

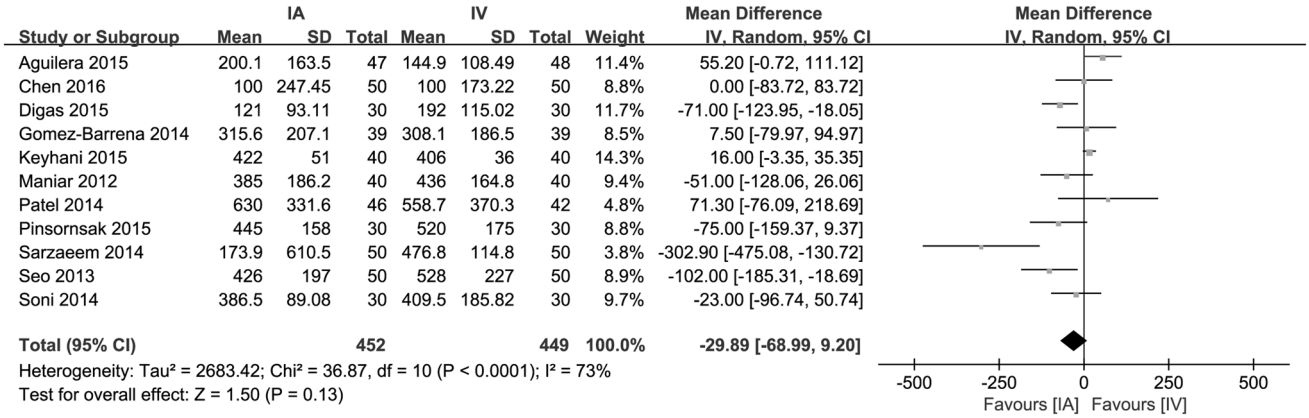

Fig. 4 Forest plot of blood volume of drainage showed that there was no significant difference between IA TXA group and IV TXA group

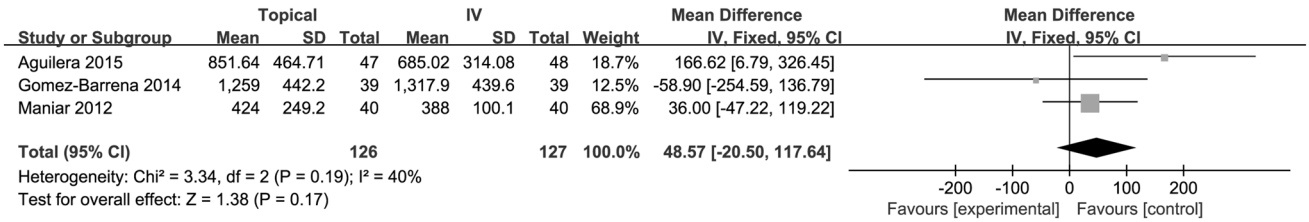

Fig. 5 Forest plot of hidden blood loss showed that there was no significant difference between IA TXA group and IV TXA group

infections, costs, the length of hospital stay and morbidity, pharmacological strategies are recommended to reduce bleeding [37, 38].

Pharmacologic agents such as TXA, an antifibrinolytic drug, have been employed to reduce bleeding and prevent the need for transfusion. Despite the concern about the

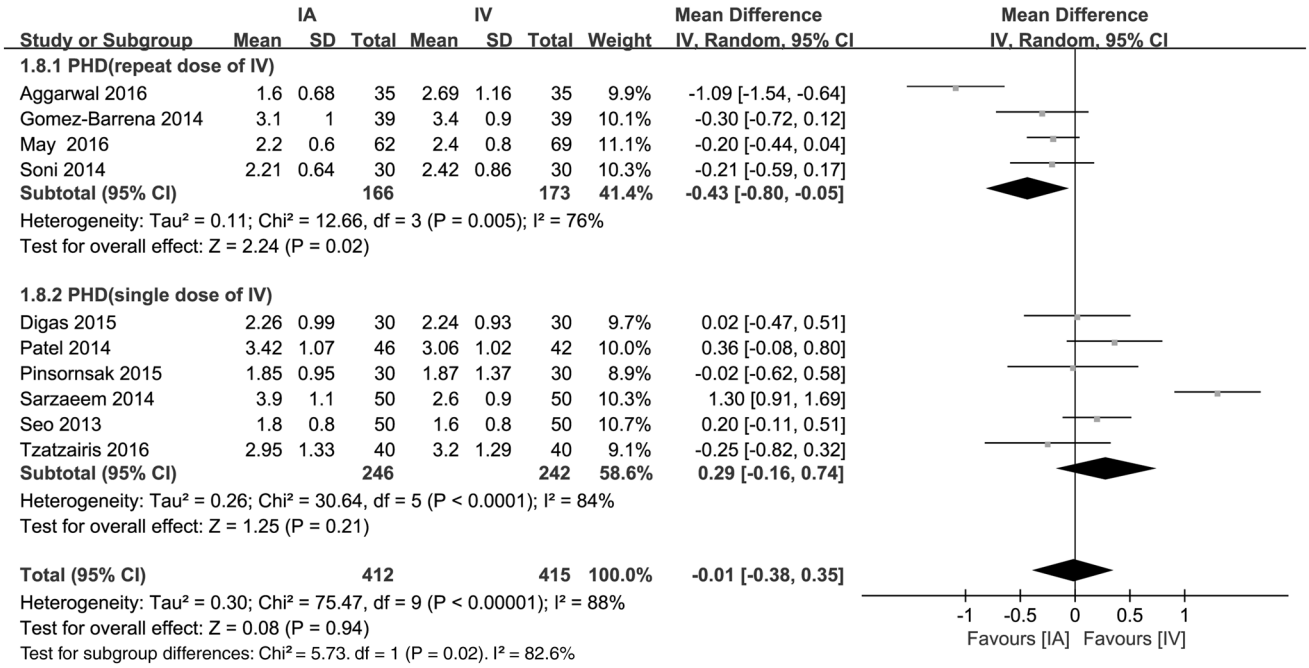

Fig. 6 Forest plot of postoperative hemoglobin showed that there was no significant difference between IA TXA group and IV TXA group. Subgroup analysis based on times of IV TXA administration showed that there was statistical significance between IA TXA group and repeat dose of IV TXA group. There was no significant difference between IA TXA group and single dose of IV TXA group

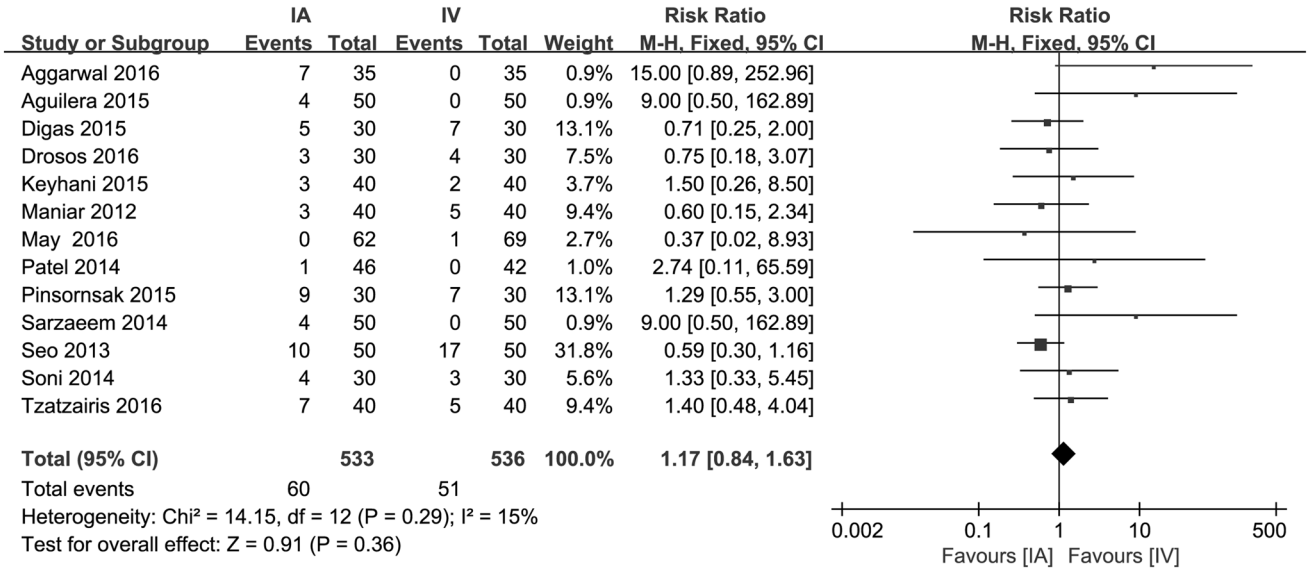

Fig. 7 Forest plot of blood transfusion rate showed that there was no significant difference between IA TXA group and IV TXA group.

greater risk of venous thromboembolism, a significant risk in the orthopedic surgeries population was not reported by studies [21, 39]. Many studies have reported that by administrating TXA in TKA, no matter by IA or by IV route, the thromboembolic episodes are not increasing [9, 20, 31]. However, the route of application of TXA in TKA varies across clinical trials [40] and consensus on the most appropriate route is lacking. Then, this meta-analysis of comparing IA TXA with IV TXA in TKA was considered.

Some studies consider that TXA application through IA route can avoid local activation of fibrinolysis and increase local thrombus formation, resulting in less bleeding and less systemic absorption as compared with TXA application through IV route [25, 41]. Our meta-analysis showed

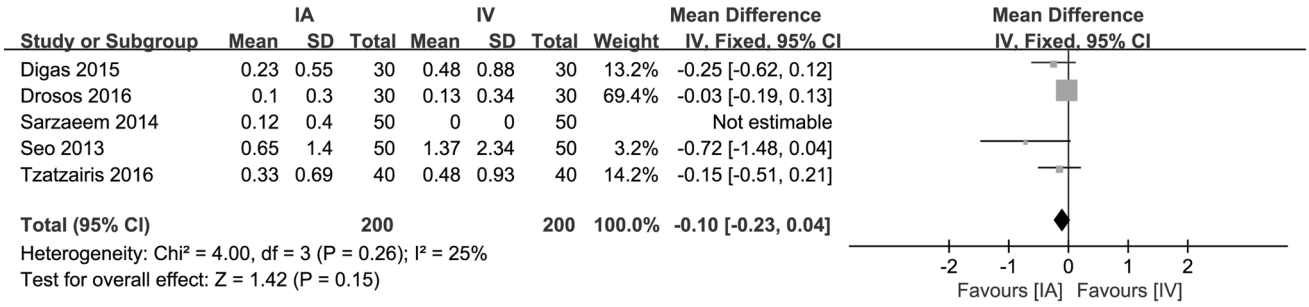

Fig. 8 Forest plot of blood units transfused per patient showed that there was no significant difference between IA TXA group and IV TXA group

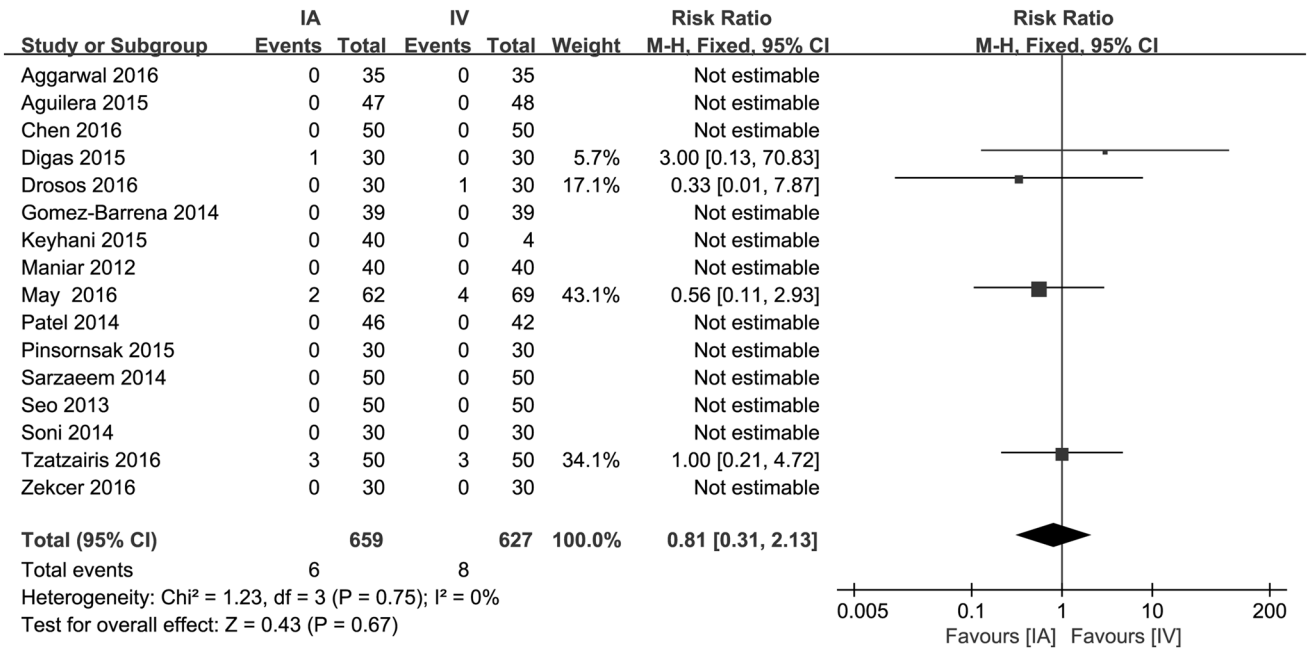

Fig. 9 Forest plot of wound infection showed that there was no significant difference between IA TXA group and IV TXA group

that IA TXA reduced the total blood loss by a mean volume of −66.12 mL when compared with IV TXA and this result had significant difference ($P > 0.05$). From Table 2, we noticed that some studies used repeat dose of IV TXA and the others used single dose of IV TXA. In order to observe which route, repeat dose of IV TXA or single dose of IV TXA, caused the higher total blood loss, subgroup analysis was performed. Subgroup analysis showed that repeat dose of IV TXA had a higher total blood loss than IA TXA and there was significant difference ($P < 0.05$). This result was inconsistent with previous studies that repeat dose IV TXA further decreases blood loss in TKA [8, 21]. Combined with the result of subgroup analysis that repeat dose of IV TXA has a higher postoperative hemoglobin drop (MD −0.43, $P < 0.05$) than IA group, our meta-analysis suggested that IA TXA was superior to repeat dose of IV TXA in terms of reducing total blood loss and decreasing postoperative hemoglobin drop. In addition, our subgroup analysis also suggested that IA TXA and single dose of IV TXA have a similar effect on total blood loss and postoperative hemoglobin drop and just be efficient for patients undergoing TKA. Previous studies reported that TXA can effectively reduce the blood volume of drainage by about 50%, and it has no effect on reducing hidden blood loss, which is not mediated by fibrinolysis in the initial phase [42]. Our meta-analysis results suggested that IA TXA and IV TXA have no significant difference in reducing blood volume of drainage and hidden blood loss. Although IV TXA group has a higher total blood loss, there was no significant difference in reducing blood units transfused per patient and transfusion rate when compared with IA group. These results may be attributed to the fact that the transfusion

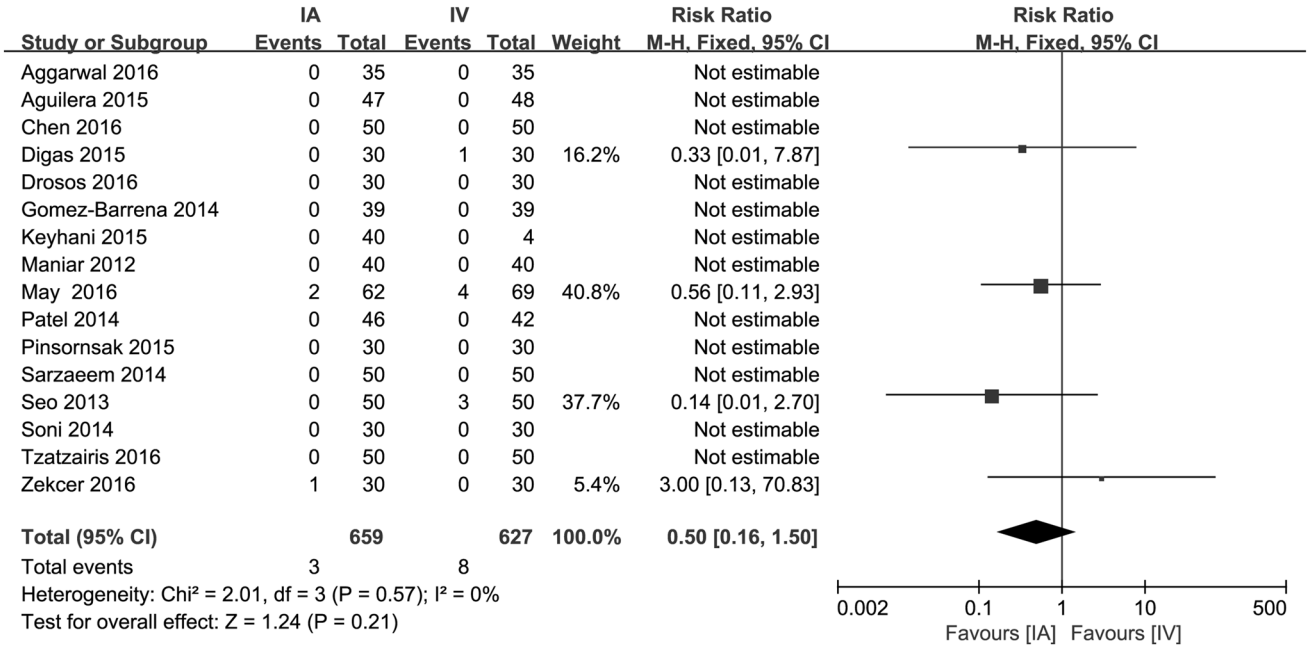

Fig. 10 Forest plot of thromboembolic complications showed that there was no statistical significance between IA TXA group and IV TXA group.

criteria were inconsistent among the studies. Many studies suggested that TXA has anti-inflammatory effects and IA application of TXA in TKA did not increase the infection [43, 44]. Our analysis showed that 6 of 659 patients (0.91%) in the IA group and 8 of 627 patients (1.28%) in the IV group had superficial or deep infection, suggested that IA TXA did not increase the risk of infection compared with IV TXA group.

The fatal complication of anastaltic was thrombosis and pulmonary embolism. Theoretically, TXA administration through the IV route carries a higher risk of DVT and PE. And a growing number of studies recommend IA TXA to minimize the adverse effects [27, 29]. Our meta-analysis did not show an increased risk of DVT or PE either by using IV or IA TXA. In our meta-analysis, one study reported by Digas [28] documented one DVT case of the IA group. May [24] reported one case of DVT and one case of PE in IA group, while two PE cases and two DVT cases in IV group. Seo [21] reported three cases of DVT in IA group. Another study reported by Zekcer [35] documented one case of DVT in IA group. Patel [25] reported that one case in the IA group and two cases in the IV group have clinical suspicion of DVT and the duplex Doppler study of these patients was negative. Nonetheless, uncertainty still remains because of the different methods of DVT and PE screening and seven included studies failed to report the method of DVT screen. In addition, the small numbers of patients involved and high-risk patients such as those with a history of PTE or DVT and those with cerebrovascular or heart disease excluded also prevented us from drawing an accurate conclusion. Considering the above factors, the conclusion of DVT and PE requires further confirmation. The current meta-analysis suggested that 1.5 g TXA by IA administration or 1 g IV TXA 10 min before tourniquet inflation is effective and safe in patients undergoing TKA.

This study has some limitations. Firstly, all trials included in our analysis excluded high-risk patients, such as patients with previous DVT events, cardiovascular disease and renal dysfunction. Secondly, the dose and timing administration of TXA application in TKA were different. Finally, there was significant heterogeneity among studies when total blood loss and postoperative hemoglobin drop were evaluated.

In conclusion, IA TXA has similar clinically effectiveness compared to IV TXA in blood volume of drainage, hidden blood loss, transfusion rate, blood units transfused per patient and wound infection. In addition, results from subgroup analysis evaluating effect of the times of TXA administration through the IV route suggested that single dose of IV TXA is effective than repeat dose of IV TXA with respect to total blood loss and postoperative hemoglobin drop. Both IA TXA and single dose of IV TXA are effective in reducing total blood loss and postoperative hemoglobin drop without increasing complications of DVT or PE. Further studies with high quality are required to confirm the effectiveness and safety of IA and IV TXA for primary TKA.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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