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ORIGINAL ARTICLE

Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials

Qiang Wu · Hong-An Zhang · Shi-Long Liu · Tao Meng · Xin Zhou · Ping Wang

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Abstract
Background Tranexamic acid (TXA) is well established as a versatile intraarticular and intravenous (IV) antifibrinolytic agent that has been successfully used to control bleeding after total knee arthroplasty (TKA). The present meta-analysis aimed at assessing the effectiveness and safety of TXA in reducing blood loss and transfusion in TKA.
Methods We searched the PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases from 1966 to December 2013. Only randomized controlled trials (RCTs) were included in the present study. Two independent reviewers identified the eligible studies, assessed their methodological quality, and extracted data. The data were using fixed-effects or random-effects models with standard mean differences and risk ratios for continuous and dichotomous variables, respectively. Subgroup analysis was performed according to the IV or intraarticular administration of TXA.
Results Thirty-four RCTs encompassing 2,594 patients met the inclusion criteria for our meta-analysis. Our meta-analysis indicated that when compared with the control group, the IV or intraarticular use of TXA significantly reduced total blood loss, postoperative blood loss, Hb loss, and transfusion rate as well as blood units transfused per patient after primary TKA, but did not reduce intraoperative blood loss. No significant difference in deep vein thrombosis (DVT), pulmonary embolism, or other adverse events among the study groups.
Conclusions IV or intraarticular use of TXA for patients undergoing TKA is effective and safe for the reduction blood loss and blood transfusion requirements, yet does not increase the risk of postoperative DVT.
Level of evidence Level II.

Keywords Tranexamic acid · TKA · Meta-analysis · Blood loss · Transfusion

Q. Wu · H.-A. Zhang · S.-L. Liu · T. Meng · X. Zhou · P. Wang (✉)
Department of Orthopaedics, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300000, People's Republic of China
e-mail: wangping22110@163.com

Introduction

Total knee arthroplasty (TKA) is widely acknowledged to be one of the effective treatments for severe osteoarthritis of the knee. However, this surgery is particularly prone to significant intraoperative and postoperative blood loss with long operation times and large wound surfaces. Estimated blood loss reported for TKA varies between 500 and 1,500 mL [1]. Despite the advances in techniques and perioperative management, however, TKA is associated with substantial bleeding [2]. Therefore, considerable blood loss after TKA is still problem, which can increase morbidity [3]. Postoperative blood transfusion may be a life-saving measure in those with hemorrhage, but it carries a substantial risk of transmitting infections (viral and bacterial), hemolytic transfusion reactions, transfusion-related diseases and increases hospital costs [4, 5]. Thus, it is very important to control perioperative bleeding for maintaining hemodynamic stability.

A variety of effective blood-conservation interventions have been used to reduce blood loss and the need for postoperative transfusion, including controlled hypotension,

autologous blood transfusion, intraoperative blood salvage, navigation, minimally invasive surgery (MIS), use of tourniquet, and intravenous (IV)I or intraarticular administration of tranexamic acid (TXA) [6–8]. TXA is a synthetic antifibrinolytic drug that competitively blocks the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator, thereby delaying fibrinolysis and blood clot degradation [9]. Currently, IV administration of TXA has been widely used in different settings and reduced the need for transfusion in cardiac, orthopedic, cranial and orthognathic, hepatic, and urological surgery [10, 11].

With respect to the IV administration of TXA in TKA patients, it has been reported to reduce blood loss and be safe [12]. However, TXA may be administered intravenously or topically in the surgical wound and different surgeons have their individual plans. Therefore, the optimal TXA treatment protocol in such conditions is still unknown. Besides, a number of clinical studies are conflicting on the effectiveness and safety of TXA [6, 13–21]. Because individual studies might have been underpowered to detect the overall effects and some studies are limited by their sample size and subsequently suffer from too low power to detect effects that may exist, and meta-analysis combining data from many randomized controlled trials (RCTs) is generally considered to provide the strongest evidence of clinical interventions, we deemed it important to perform a quantitative synthesis of the evidence. Therefore, we carried out this meta-analysis to evaluate the safety and efficacy of TXA in the reduction of blood loss in TKA.

Methods

Literature search

We identified RCTs from the previously published systematic review. We updated the list of studies by searching the PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases. Two authors independently searched for relevant studies from 1966 to December 2013. The search strategy was created with the assistance of a librarian using a combination of terms including antifibrinolytics, tranexamic acid, cyklokapron, total knee arthroplasty, total knee replacement, TKA, TKR, RCT, prospective, meta, review, and random. We limited searches to randomized controlled trials, systematic reviews, and meta-analyses and imposed no language or other limitations. Reference lists of all the selected articles were hand-searched for any additional trials. Authors were contacted when possible to obtain missing information.

Inclusion and exclusion criteria

Studies were included if they met the following three inclusion criteria: (1) The patients underwent unilateral TKA; (2) the study involved the comparison of a TXA treatment group to a control group who received either a placebo or no treatment at all; and (3) the trial was RCT. Exclusion criteria included: (1) RCTs of low quality; (2) simultaneous bilateral primary TKA or revision TKA; (3) the procedure involved was described as minimally invasive or less invasive. Two authors independently assessed the articles for compliance with the inclusion criteria, and disagreement was followed by discussion until consensus was reached.

Selection of the literature

Two authors according to inclusion criteria independently reviewed the title and abstract and excluded the studies that did not meet the inclusion criteria obviously. A full text of any published article that potentially met the inclusion criteria was obtained to confirm. Any disagreements during the selection course were resolved by discussion with a third reviewer.

Methodological quality assessment

Two reviewers assessed the quality of the studies independently; revised Jadad Scale was used to perform the quality assessment. This scale includes the random sequence production (2 points), allocation concealment (2 points), appropriateness of blinding (2 points), and description of dropouts and withdrawals (1 point). The total score is 7 points, 0–3 points means poor quality and 4–7 points means high quality, and consolidated standards on reporting trials (CONSORT) checklist and scoring system were used to evaluate the quality of included trials: Scores of 18–22 are considered excellent study quality, 13–17 good, 8–12 fair, and <7 poor.

Data extraction

All data were extracted independently by two reviewers. The following data were extracted: postoperative venous thromboembolism (VTE), postoperative drainage loss, total blood loss, intraoperative blood loss, rate of patients who had allogeneic blood transfusion, units of transfusion, incidence of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) complications and other adverse events. A consensus method was used to resolve disagreements, and a third reviewer was consulted if disagreements persisted. In order to understand the baseline of each included study, we extracted from trials included the following

Table 1 Description of included trials

References	Study design	Mean age (year)	Male/female	VTE prophylaxis	BT protocol	Intervention	Number of cases	
							TA	C
Georgiadis [16]	RCT	C: 64.5 ± 8.2 TXA: 67.0 ± 9.0	41/70	LMWH	Symptomatic anemia with Hb of 8.0 g/dL or any Hgb <7.0 g/dL	TXA 2.0 g in 75 mL normal saline and applied to the wound	50	51
Martin [30]	RCT	TXA: 67.16 ± 10.55 C: 64.28 ± 9.68	25/25	Mechanical foot compression	Symptomatic hypotension, or Hb <7 g/dL	TXA 2 g in 100 mL of normal saline into the joint space prior to surgical closure	25	25
Pachauri [36]	RCT	NT	18/81	NT	NT	TXA 1 g IV 1 h before surgery, the second dose 6 h after the first dose	50	49
Aguilera [3]	RCT	TXA: 72.4 ± 6.6 C: 74.9 ± 7.0	11/76	LMWH	HB <8 g/dL, or HB <8.5 g/dL in patients with heart disease or older than 70 years, or HB between 8.5 and 9 g/dL in patients who had low orthostatic tolerance	TXA 1 g IV 15–30 min before inflation of pneumatic tourniquet, and the second 1 g dose IV when the tourniquet was removed	44	43
Seo [42]	RCT	IA: 67.5 ± 6.6 IV: 66.8 ± 6.3 C: 67.8 ± 6.1	16/134	NT	HB <8.0 gdL or HB <10.0 g/dL with concomitant intolerable anemic symptoms or any anemia-related organ dysfunctions	(1) TXA 1.5 g IV immediately after closing surgical sites (2) TXA 1.5 g into the knee joint cavity while suturing	Intraarticular: 50 IV: 50	50
Lee [28]	RCT	TXA: 69.7 ± 7.9 C: 69.2 ± 7.7	10/62	Fondaparinux	HB <8.0 g/dL or clinical symptoms of anemia any time during the postoperative period	TXA 10 mg/kg IV before tourniquet release and the second infusion 6 h after the first	36	36
Alshryda [4]	RCY	C: 67.1 ± 10.2 TXA: 65.5 ± 9.6	74/83	LMWH	HB <7 g/dL, Hb <8 g/dL in a patient who tolerated anemia poorly; Hb between 7 and 10 g/dL in a patient who developed fatigue, palpitation, pallor, tachycardia, and tachypnea due to anemia	TXA 1 g in 50 mL saline solution sprayed into the wound at the end of the TKA	79	78
Kim [27]	RCT	TXA: 73.5 ± 5.5 C: 71.9 ± 5.9	23/157	LMWH	Hb <7.0 mg/dL or if anemic symptoms such as dyspnea or tachycardia persisted even after volume replacement in patients with an Hb level between 7.0 and 8.0 mg/dL	TXA 10 mg/kg IV 30 min before tourniquet deflation, and repeated 3 h after the commencement of the first injection	90	90
Chareancholvanich [9]	RCT	C: 69.8 ± 6.3 TXA: 69.4 ± 6.3	17/103	Mechanical ankle pumping exercise	Hb <10 g/dL or compromised clinical criteria (tachycardia, hypo tension, or symptoms of anemia)	TXA 10 mg /kg IV 10 min before inflating the tourniquet and 10 mg/kg at 3 h postoperatively, then, 1,500 mg per day of oralformed TXA for 5 days after operation	60	60
Roy [39]	RCT	TXA: 66.04 ± 7.15 C: 66.56 ± 8.03	19/31	Compression stockinet and early mobilization, and LMWH	(1) Hematocrit ≤28 %, (2) drain collection ≥500 ml in first 8–10 h along with a Hb loss ≥4 gm/dL and, (3) patient develops subjective symptoms of anemia (breathlessness, tachycardia and hypotension)	TXA 500 mg in the operated intraarticular space	25	25

Table 1 continued

References	Study design	Mean age (year)	Male/female	VTE prophylaxis	BT protocol	Intervention	Number of cases	
							TA	C
Maniar [29]	RCT	C: 66.2 ± 7.2 IV: 67.3 ± 9.1 IA: 67.4 ± 7.9	20/100	Ankle and foot movement exercises, LMWH and below-knee stockings	HB <8.5 g/dL; cardiac disorders with HB <10 g/dL; hemoglobin between 8.5 and 10 g/dL with symptoms related to anemia develop, such as tachycardia, tachypnea, or decreased exercise tolerance	(1) TXA 10 mg/kg 15 min before deflation of the tourniquet (2) 3 g diluted in 100 mL normal saline applied locally after cementing the implant and before tourniquet release	IV 40 IA 40	40
McConnell [32]	RCT	NT	25/19	Compression stockings and oral aspirin	NT	TXA 10 mg/kg IV at induction of anesthesia	22	22
Onodera [34]	RCT	TXA: 70.4 ± 10.1 C: 70.5 ± 8.3	17/83	NT	NT	1 g TXA + 50 mg carbazochrome/50 ml NS Intraarticular administration after wound closure	50	50
Charoencholvanich [11]	RCT	TXA: 69.20 ± 6.13 C: 68.80 ± 6.12	15/85	Mechanical ankle pumping exercise regimen	NT	TXA 10 mg/kg IV 10 min before tourniquet inflation and again 3 h postoperatively, and then an oral form of the drug (250 mg/capsule; two capsules three times daily) for 5 days	50	50
Ishida [21]	RCT	TXA: 73.3 (5.0) C: 73.5 (6.1)	12/88	LMWH	NT	TXA 2,000 mg/20 mL Intraarticular administration	50	50
Gautam [15]	RCT	TXA: 65.65 ± 6.2 C7 64.65 ± 9.75	16/24	NT	Hb <8 g/dL or Hct <30 %	TXA 10 mg/kg 0.5 h before tourniquet deflation, then 2 mg/kg after 3 h	20	20
Wong [43]	RCT	C: 68.4 ± 10.4 TXA: 67 ± 11.9	19/47	LMWH	HB <8.0 g/dL or HB <10.0 g/dL if the patient developed intolerable symptoms of anemia or any organ dysfunction that may have been related to anemia and was not attributable to another cause (such as myocardial ischemia or hypoxemia) or if ongoing blood loss was occurring	TXA 1.5 g applied into the joint at the end of surgery	31	35
Abrishami [2]	RCT	TNA67 ± 9 C69 ± 11	3/13	NT	NT	TXA 1.5 g local application for 3 min at the conclusion of the operation	7	9
Kakar [24]	RCT	TXA: 62.4 ± 9.4 C: 66.2 ± 4.8	7/17	NT	Patients over 60 and associated cardiopulmonary disease, HB <10 g /dL other patients,HB <8 g /dL	TXA 10 mg/kg IV before tourniquet deflation, then 1 mg/kg/h until wound closure	12	12
Alvarez [6]	RCT	TXA: 71 ± 9 C: 72 ± 7	17/78	Bemiparin	Hb <8 g /dL or patients presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnea, or syncope	TXA 10 mg/kg IV 30 min before deflation of the tourniquet and then 1 mg/kg/h infusion for 6 h	46	49
Molloy [33]	RCT	NT	NT	Aspirin	Hct <25 %	TXA 500 mg 5 min IV before tourniquet deflation, repeated 3 h later	50	50
Zhang [44]	RCT	TXA: 68.14 ± 9.0 C: 67.64 ± 8.3	43/59	LMWH	Hb <100 g/L	TXA 1 g IV before tourniquet deflation, repeated 3 h later	51	51

Table 1 continued

References	Study design	Mean age (year)	Male/female	VTE prophylaxis	BT protocol	Intervention	Number of cases	
							TA	C
Orpen [35]	RCT	C: 69 (63–74) TXA: 73 (70–78)	11/18	LMWH	Hb <90 g/L	TXA 15 mg/kg IV at time cement mixing commenced	15	14
Camarasa [10]	RCT	C: 72 (52–85) TXA 73 (61–84)	21/74	NT	Hb <80 g/L	TXA 10 mg/kg IV before deflation of the tourniquet and 10 mg/kg IV 3 h after the first IV	35	60
Zohar [45]		C: 73 ± 7 TXA: 73 ± 8	13/27	LMWH	Hct <28 %	TXA 15 mg/kg 15 min IV before tourniquet deflation, then 10 mg/kg/h infusion for 12 h	20	20
Good [17]	RCT	C: 72 (50–84) TXA: 72 (46–83)	15/36	LMWH	Hb <90 g/L	TXA 10 mg/kg IV before deflation of the tourniquet and 10 mg/kg IV 3 h after the first IV	27	24
Veien [46]	RCT	TXA: 70.5 ± 9.5 C: 69.5 ± 9.0	5/25	LMWH	Hct <28 %	TXA 10 mg/kg IV before deflation of the tourniquet and 10 mg/kg IV 3 h after the first IV	15	15
Tanaka [43]	RCT	C: 65 (59–70) Preop TA: 65 (60–71) Intraop TA: 65 (59–69) Pre- and intraop TA: 65 (58–70)	31/68	NT	NT	(1) TXA 20 mg/kg IV 10 min before surgery and saline 10 min before deflation of the tourniquet (preop TNA group) (2) saline 10 min before surgery and TXA 20 mg/kg 10 min before deflation of the tourniquet (intraop TNA group) (3) TXA 10 mg/kg 10 min before surgery and again 10 min before deflation of the tourniquet (pre- and intraop TNA group)	73	26
Engel [13]	RCT	C: 66 ± 11 TXA: 71 ±9	8/16	LMWH	HB <10 g/dL	TXA 15 mg/kg iv before deflation of the tourniquet and 10 mg/kg after 3 h	12	12
Ellis [12]	RCT	C: 72 ± 8 TXA: 71 ± 5	7/13	LMWH	Hct <27 %	TXA 15 mg/kg 30 min IV before tourniquet deflation, then 10 mg/kg/h infusion for 12 h	10	10
Jansen [22]	RCT	C: 71 (64–84) TXA: 70.7 (62–80)	8/34	LMWH	Packed cell volume <26 %	TXA 15 mg/kg IV before inflation of the tourniquet and repeated every 8 h for 3 days	21	21
Hiippala [19]	RCT	TXA: 70 ± 7 C: 69 ± 5	12/65	LMWH	HB <10 g/dL	TXA 15 mg/kg IV before deflation of the tourniquet and 2 additional doses of 10 mg/kg after 3–4 h and 6–7 h	39	38
Benoni [8]	RCT	TXA: 76 ± 7 C: 74 ± 7	23/63	LMWH	Hb <85 g/L	TXA 10 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h	43	43

Table 1 continued

References	Study design	Mean age (year)	Male/female	VTE prophylaxis	BT protocol	Intervention	Number of cases	
							TA	C
Hiippala [20]	RCT	TXA: 70 (56–82) C: 70 (63–78)	5/23	LMWH	Hb <100 g/L	TXA 15 mg/kg IV before tourniquet deflation	15	13

LMWH low molecular weight heparin, *C* control group, *IV* intravenous groyp, *IA* Intraarticular group, *NT* not mentioned, *BT* blood transfusion

information: Number of patients enrolled, characteristics of participants, male/female ratio, dose of TXA, method of TXA administration, and transfusion criteria.

Data analysis

For each study, relative risks and 95 % confidence intervals were calculated for dichotomous outcomes, and standard mean differences (SMD) and 95 % confidence intervals were calculated for continuous outcomes. We assessed statistical heterogeneity for each study with the use of a standard Chi-square test with a significance set at a p value of 0.1, and the quantity of heterogeneity was measured by I^2 statistic. An I^2 statistic value of 50 % was considered to indicate substantial heterogeneity. We performed the meta-analysis using a fixed-effect model if no significant heterogeneity was present ($I^2 < 50$ %; $p > 0.1$). Otherwise, we adopted the random-effects model. The clinical heterogeneity prevented a direct quantitative meta-analysis; the data would be pooled by subgroup analysis according to the different (IV or topical) administration of tranexamic acid. To investigate whether publication bias might affect the validity of the estimates, funnel plot for transfusion rate (as this was the outcome that most studies included in meta-analysis) was generated to evaluate potential publication bias. Data analyses were performed using STATA version 11.0. A p value of <0.05 was considered statistically significant.

Results

Literature search

A search of the PubMed, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases retrieved 658 articles. By screening the title, reading the abstract, 472 articles were excluded. Then, of the remaining 40 studies, two were excluded for bilateral TKA, two revision TKAs and one computer-assisted TKA. Therefore, a total of 34 studies were included by reading the whole paper.

Study characteristics

These 34 studies [4, 13–45] included a total population of 1,351 participants in the TXA group and 1,241 in control group. Thirty-three studies were published in English, and one study was Chinese. All included trials had compared the baseline preoperatively, and each had similar baseline. More characteristics of the 34 studies are described in Table 1. All the studies were RCT. TXA was administered intravenously in 25 studies [13, 14, 16, 17, 19, 20, 23–32,

Table 2 Quality assessment of included randomized controlled trials with revised Jadad scale and CONSORT statement

References	Random equence production	Allocation concealment	Blind method	Withdrawal	Revised Jadad's scale score	CONSORT statement
Georgiadis [16]	1	2	2	1	6	17
Martin [30]	1	1	2	1	5	19
Pachauri [36]	2	1	2	1	6	11
Aguilera [3]	2	2	0	1	5	19
Seo [42]	1	1	2	1	5	16
Lee [28]	2	2	2	1	7	19
Alshryda [4]	2	2	2	1	7	19
Kim [27]	2	1	2	1	6	18
Cchareancholvanich [9]	2	2	1	1	6	17
Roy [39]	2	2	2	1	7	18
Maniar [29]	1	2	2	1	6	20
McConnell [32]	1	2	1	1	5	15
Onodera [34]	1	1	2	1	5	14
Charoencholvanich [11]	2	2	2	1	7	19
Ishida [21]	1	0	2	1	4	14
Gautam [15]	2	2	2	1	7	17
Wong [43]	2	2	2	1	7	20
Abrishami [2]	1	1	2	1	5	17
Kakar [24]	1	1	2	1	5	12
Alvarez [6]	2	2	2	1	7	19
Molloy [33]	2	2	2	1	7	17
Zhang [44]	1	1	2	1	6	14
Orpen [35]	1	1	2	1	5	17
Camarasa [10]	2	2	2	1	7	20
Zohar [45]	2	1	2	1	6	16
Good [17]	2	1	2	1	6	16
Veien 2002 [46]	2	2	2	1	7	18
Tanaka [43]	1	2	2	1	6	15
Engel [13]	1	1	2	1	5	13
Ellis [12]	1	1	2	1	5	13
Jansen [22]	2	1	2	1	6	15
Hiippala [19]	1	2	2	1	6	15
Benoni [8]	1	2	2	1	6	17
Hiippala [20]	1	2	2	1	6	16

34, 35, 37, 38, 40–42, 44, 45], intraarticularly in seven studies [4, 15, 17, 22, 33, 39, 43]. Two studies [21, 36] reported the results on both IV and intraarticular use of TXA. To prevent DVT, seventeen trials used low molecular weight heparin [4, 13, 15, 16, 24, 27, 28, 30–34, 40, 42–45], three performed a mechanical ankle pump exercise regimen [13, 18, 26], two used aspirin [37, 38], two used compression stockinet and low molecular weight heparin [20, 36], one used bemiparin [23], one used fondaparinux [17] and eight did not mention any preventative measures [19, 21, 22, 25, 29, 35, 39, 41]. Postoperative drainage was quantified between 24 and 48 h, when drains were in most cases removed. The study by Onodera et al. [39], used TXA containing 50 mg of carbazochrome, was also included. The study by McConnell et al. [37], reported in 2012, included a group that received fibrin as well as TXA and control groups, was also included. The study [41] compared four IV bolus methods. Since there were five randomized controlled groups in this study, we regarded it as four independent studies in the following comparative

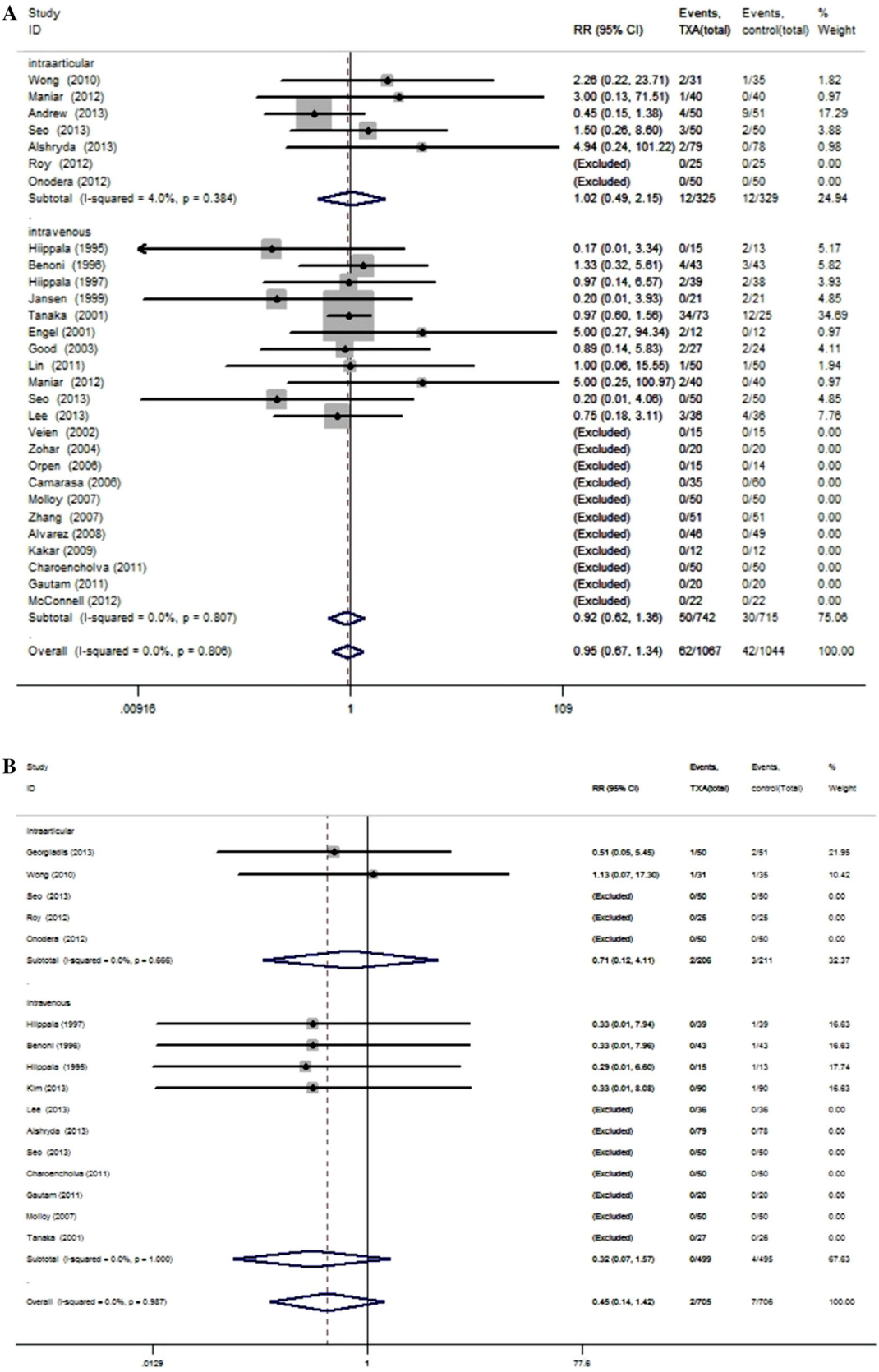

Fig. 1 Forest plot diagram showing the effect of TXA on incidence of: **a** DVT, **b** PE, **c** other adverse events

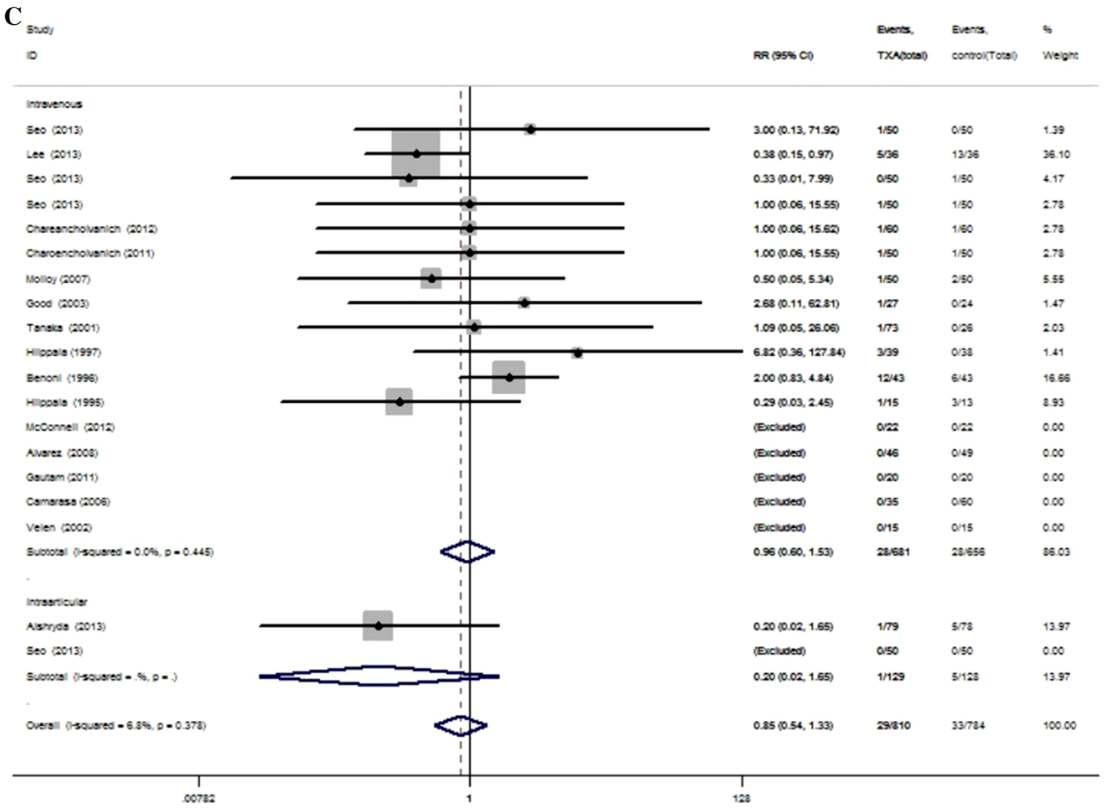

Fig. 1 continued

research. Two studies [21, 39] compared efficacies of intraarticular and IV tranexamic acid, which had three independent randomized controlled groups, so we included them and regarded them as two independent studies in this review (Table 1).

Methodological quality

These 34 studies [4, 13–45] were relatively well designed, and the quality assessment score of most was high. For the revised Jadad Scale, no studies were 1–3 points with a poor quality; 34 studies were 4–7 points with a high quality. 35 RCTs were evaluated by the CONSORT checklist and scoring system; four studies were 8–12 scores; 19 studies were 13–17 scores; and 11 studies were 18–22 scores, all the RCTs had satisfied quality. The details are described in Table 2.

Publication bias

The funnel plot based on the studies with data on transfusion rate (as this was the outcome that most studies included in their meta-analysis) demonstrates only minimal asymmetry and a few outliers, indicating minimal publication bias.

Safety of TXA

Twenty-seven of the trials [4, 13, 15–17, 20, 21, 23, 25, 26, 28–32, 34–45] reported on the DVT. Among them, 61 patients in TXA group and 41 in control group developed DVT. The IV subgroup was proved to present higher DVT incidence (6.3 %) compared with the control group (3.8 %), although the difference did not reach levels of statistical significance, (RR = 0.92, $p = 0.678$, 95 CI 0.62, 1.38). The DVT incidence for the intraarticular subgroup was 3.8 % (12/325) and for the control was 3.6 % (12/329) (RR 1.02, 95 % CI 0.49, 2.15; $p = 0.953$) with no evidence of heterogeneity ($I^2 = 4$ %, $p = 0.384$) (Fig. 1a).

For PE, 15 trials [4, 15–17, 20, 21, 24, 26, 29, 31, 32, 38, 39, 41, 43] including 1,411 patients provided useful data on PE. The incidences of PE in the TXA and control groups were 2 of 705 and 7 of 706 patients, respectively. The rate of PE was not affected by the use of TXA when the TXA group was compared with the control group and evidence showed no heterogeneity (Fig. 1b).

Besides thromboembolic complications, other adverse events including hematoma, ecchymosis, infection and pneumonia et al were found in 16 studies [4, 14, 17, 21, 23–26, 29–32, 37, 38, 41, 42]. The IV subgroup was proved to present lower adverse events incidence (4.1%) compared with the control group (4.3 %), although the difference did not reach levels of statistical significance (RR = 0.96, $p = 0.849$, 95 CI 0.60, 1.53). Evidence showed no heterogeneity ($I^2 = 0$ %, $p = 0.445$). The adverse events incidence for the intraarticular subgroup was 0.78 % (1/129) and for the control was 3.9 % (5/128) (RR 0.2, 95 % CI 0.02, 1.65; $p = 0.134$) (Fig. 1c).

Transfusion rate

The 27 eligible studies [4, 13–17, 20, 21, 23–32, 34, 36, 38–45] that reported a total of 2,235 patients provided information on transfusion requirements. The transfusion rates for the intraarticular was 7.4 % (24/325) and for the control was 26.4 % (87/329) (RR = 0.35, 95 % CI 0.18, 0.67; $p = 0.002$) with evidence of heterogeneity ($I^2 = 42.3$ %, $p = 0.109$), showing that there was significant difference between the two groups. In the IV subgroup, the pooled analysis also found significant difference in transfusion rates between two groups (RR = 0.40, 95 % CI 0.31, 0.52; $p = 0.00$). Evidence showed substantial heterogeneity ($I^2 = 1.5$ %, $p = 0.000$) (Fig. 2).

Blood units transfused per patient

The units of blood transfused to patients were recorded in 14 trials [14, 15, 23, 25–28, 30–32, 34, 38, 41, 42], including 503 patients in TXA group and 479 patients in control group. In the intraarticular group, there was only one studies reported the data of blood units transfused per patient [15]. This study documented the mean number of transfused units was lower in patients receiving TXA (0 U) than in the control group (0.14 U). In the IV subgroup, the combined SMD for patients undergoing IV administration was found to be −1.14 ($p = 0.000$; 95 % CI −1.53, −0.76). The pooled analysis indicates that blood units

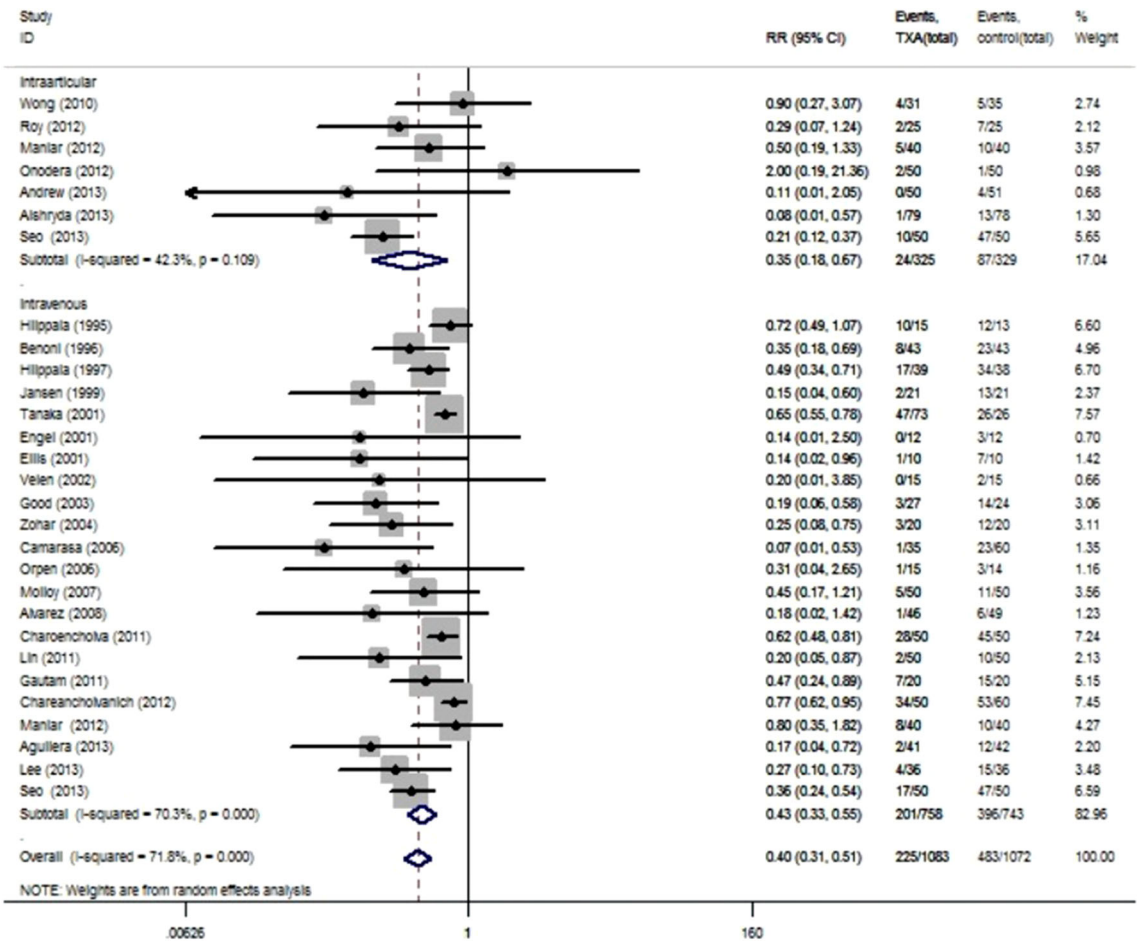

Fig. 2 Forest plot diagram showing the effect of TXA on transfusion rate

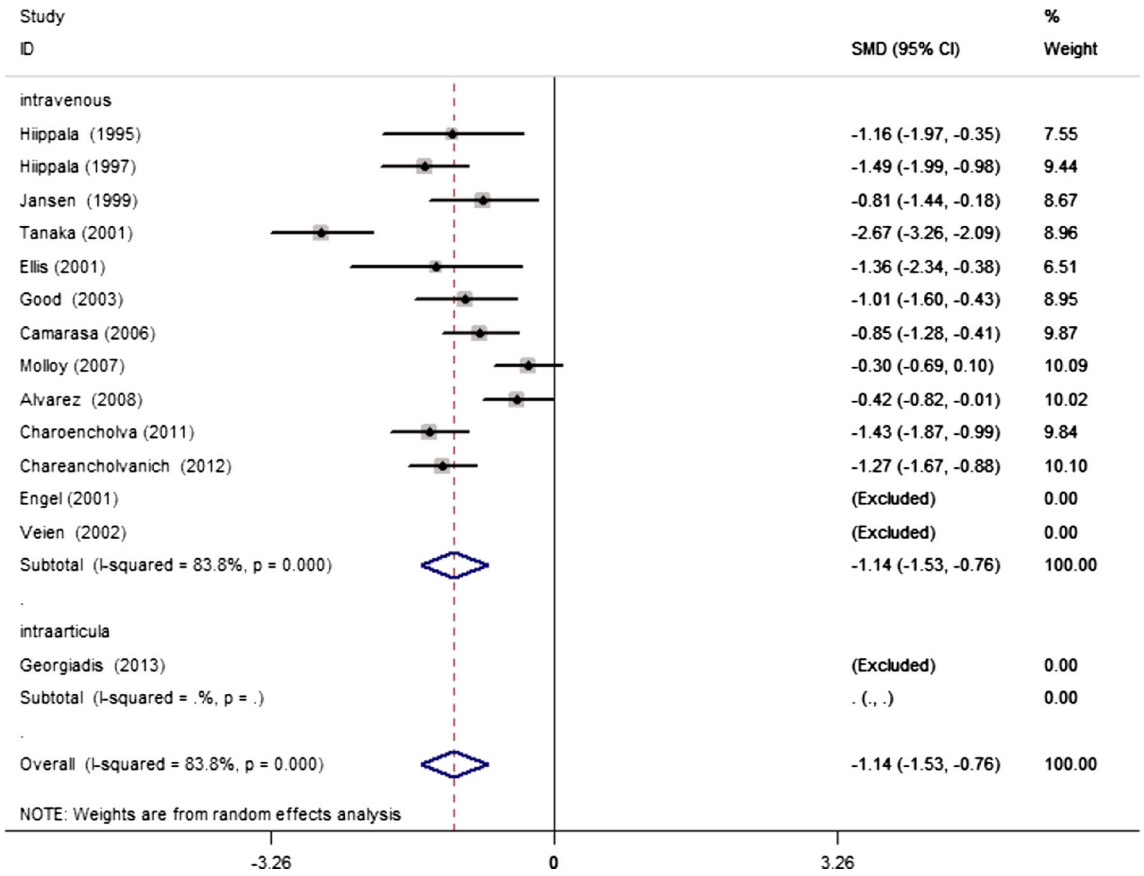

Fig. 3 Forest plot diagram showing the effect of TXA on blood units transfused per patient

transfused per patient was less in the IV TXA groups in comparison with the control group at a statistically significant level. There was significant heterogeneity between studies ($p = 0.000$, $I^2 = 83.8$ %) (Fig. 3).

Total blood loss

Eighteen trials [4, 13, 15, 16, 22–26, 29, 31, 32, 34–36, 38, 39, 44] described total blood loss, including 756 patients in TXA group and 780 patients in control group. In TXA group, five studies [4, 15, 22, 36, 39] provided data on transfusion rate in intraarticular application of TXA and 14 studies [13, 16, 23–26, 29, 31, 32, 34, 35, 38, 39, 44] were IV administration. The combined SMD for patients undergoing intraarticular application was found to be −0.86 ($p = 0.000$; 95 % CI −1.14, −0.59). This indicates that total blood loss was less in the intraarticular TXA groups in comparison with the control group at a statistically significant level. In the IV subgroup, the use of TXA significantly reduced total blood loss (SMD = −1.01, 95 % CI −1.43, −0.60; $p = 0.00$). There was a high level of statistical heterogeneity between studies ($p = 0.000$, $I^2 = 92.7$ %) (Fig. 4).

Postoperative blood loss

Sixteen trials [4, 13, 14, 17, 20, 21, 23–25, 29, 31–33, 36, 44, 45] involving 1,420 patients described postoperative blood loss. Four studies [4, 20, 21, 36] provided data on postoperative blood loss in intraarticular application of TXA and 14 [13, 14, 17, 20, 21, 23–25, 29, 31–33, 44, 45] were in IV administration. The combined SMD for patients undergoing intraarticular application was found to be −1.32 ($p = 0.001$; 95 % CI −2.08, −0.55). This indicates that postoperative blood loss was less in the intraarticular TXA groups in comparison with the control group at a statistically significant level. There was heterogeneity between studies ($p = 0.000$, $I^2 = 90.4$ %). In the IV subgroup, the use of TXA significantly reduced postoperative blood loss (SMD = −1.11, 95 % CI −1.61, −0.61; $p = 0.000$). There was a high level of statistical heterogeneity between studies ($p = 0.000$, $I^2 = 92.6$ %) (Fig. 5).

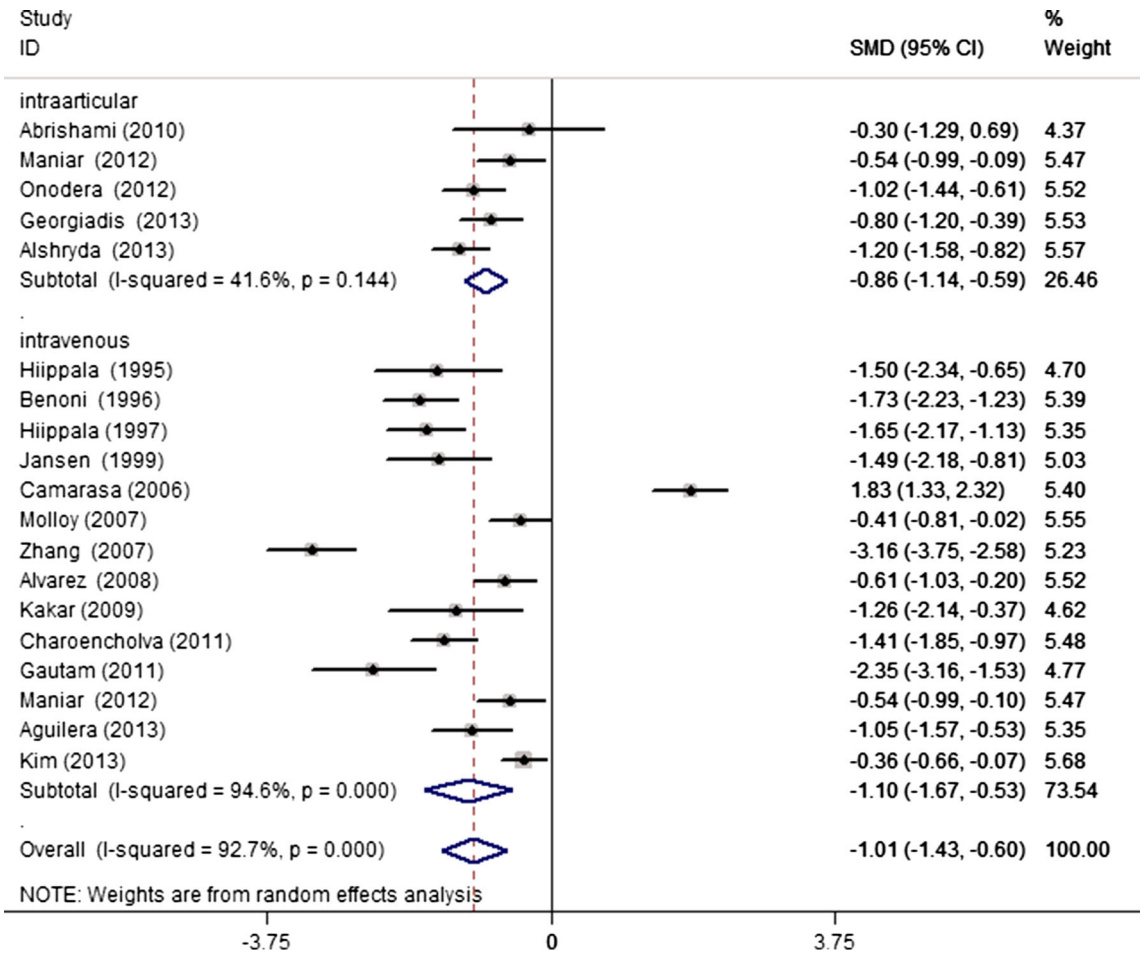

Fig. 4 Forest plot diagram showing the effect of TXA on total blood loss

Intraoperative blood loss

Intraoperative blood loss was recorded in six trials [15, 20, 24, 31, 32, 44] which included 223 patients in TXA group and 221 patients in control group. In intraarticular subgroup, the combined SMD for patients undergoing intraarticular application was found to be −0.67 ($p = 0.098$; 95 % CI −1.47, 0.12). This indicates that intraarticular TXA did not significantly reduce intraoperative blood loss. In the IV subgroup, there was no decrease intraoperative blood loss associated with the use of TXA compared with the control group (SMD = −0.14, $p = 0.244$, 95 CI −0.37, 0.09) (Fig. 6).

Hb loss

Eleven trials [14–17, 20, 21, 25, 26, 29, 38, 39] reported postoperative reduction of Hb level. In intraarticular subgroup, the combined SMD for patients undergoing intraarticular application was found to be −0.65 ($p = 0.000$; 95 % CI −0.96, −0.35). This indicates that postoperative reduction of Hb level was lower in intraarticular group in comparison with the control group at a statistically significant level. In the IV subgroup, postoperative reduction of Hb level was lower compared with the control group (SMD = −0.85, $p = 0.000$, 95 CI −1.26, −0.44) (Fig. 7).

Discussion

In this meta-analysis, we assessed the evidence from RCTs that compared outcomes with TXA or not in TKA. The most important findings of our meta-analysis demonstrate a statistically significant benefit for TXA in reducing total blood loss, postoperative blood loss, Hb loss, blood units transfused per patient, and the number of patients receiving allogeneic transfusions in TKA. Only for the intraoperative blood loss, TXA has a trend of reduced intraoperative blood loss, but not statistically significant between TXA and control groups. At the same time, TXA did not appear to increase the risk of thromboembolic complications and

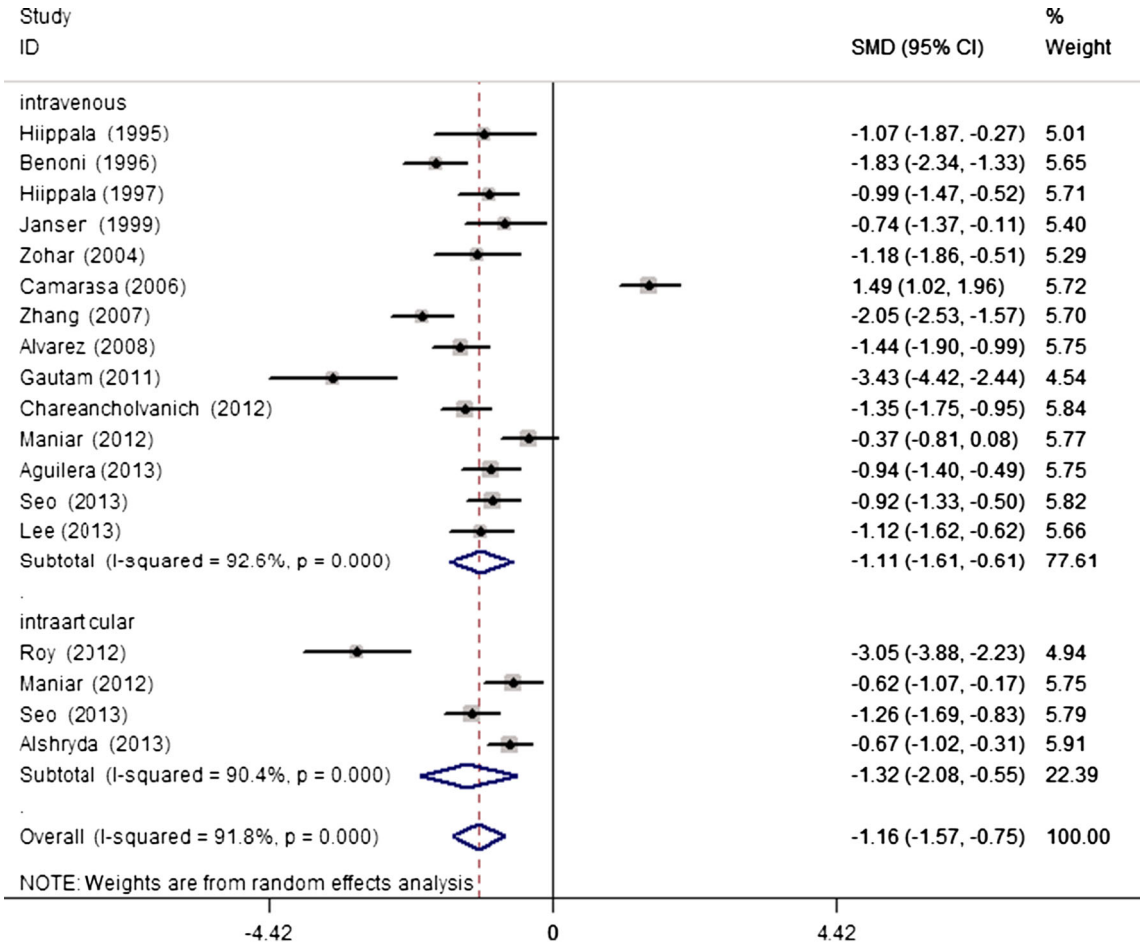

Fig. 5 Forest plot diagram showing the effect of TXA on postoperative blood loss

other adverse events. We found the effect was even greater or patients in our review.

Our findings were basically consistent with the recent meta-analysis by Tan et al. [46] which included 19 trials, and another systematic review by Zhang et al. [12], which included 15 trials; however, more studies with higher amount cases were included in this analysis. This study was a complete meta-analysis about clinical results in the topical or IV use of TXA for prevention of bleeding associated with TKA procedures. More comprehensive evaluating indicators were discussed in this study which included total blood loss, postoperative blood loss, Hb loss, intraoperative blood loss, and blood units transfused per patient, the number of patients receiving allogeneic transfusions, DVT, PE, and other adverse events. What is more, previous meta-analysis only included 19 RCTs, which intervention was the administration of IV TXA, while our review included 34 RCTs. There had been a growing interest in the intra-articular use of TXA for prevention of bleeding in TKA. So, this study provided a more credible and stable evidence in comparing the effectiveness and safety of TXA in reducing blood loss and transfusion in TKA.

The methodological quality assessment identified some limitations of the current evidence bases. The quality assessment score for most of the studies included was high, which contributes to the strength of point estimates. The majority of included trials were of good methodological quality, they were relatively well designed, and the quality assessment score was high in most of them. There are several issues related to quality control in conducting a meta-analysis, in particular study selection and the homogeneity of the studies. Hence, our study focused on the use of TXA and the data would be pooled by subgroup analysis according to the IV or intraarticular use of TXA. Accordingly, this review of meta-analysis should be considered as appropriate.

Heterogeneity is a potential problem when interpreting the results of the present meta-analysis. In this meta-analysis, notable heterogeneity was observed in some comparisons. Although the overall methodological quality of

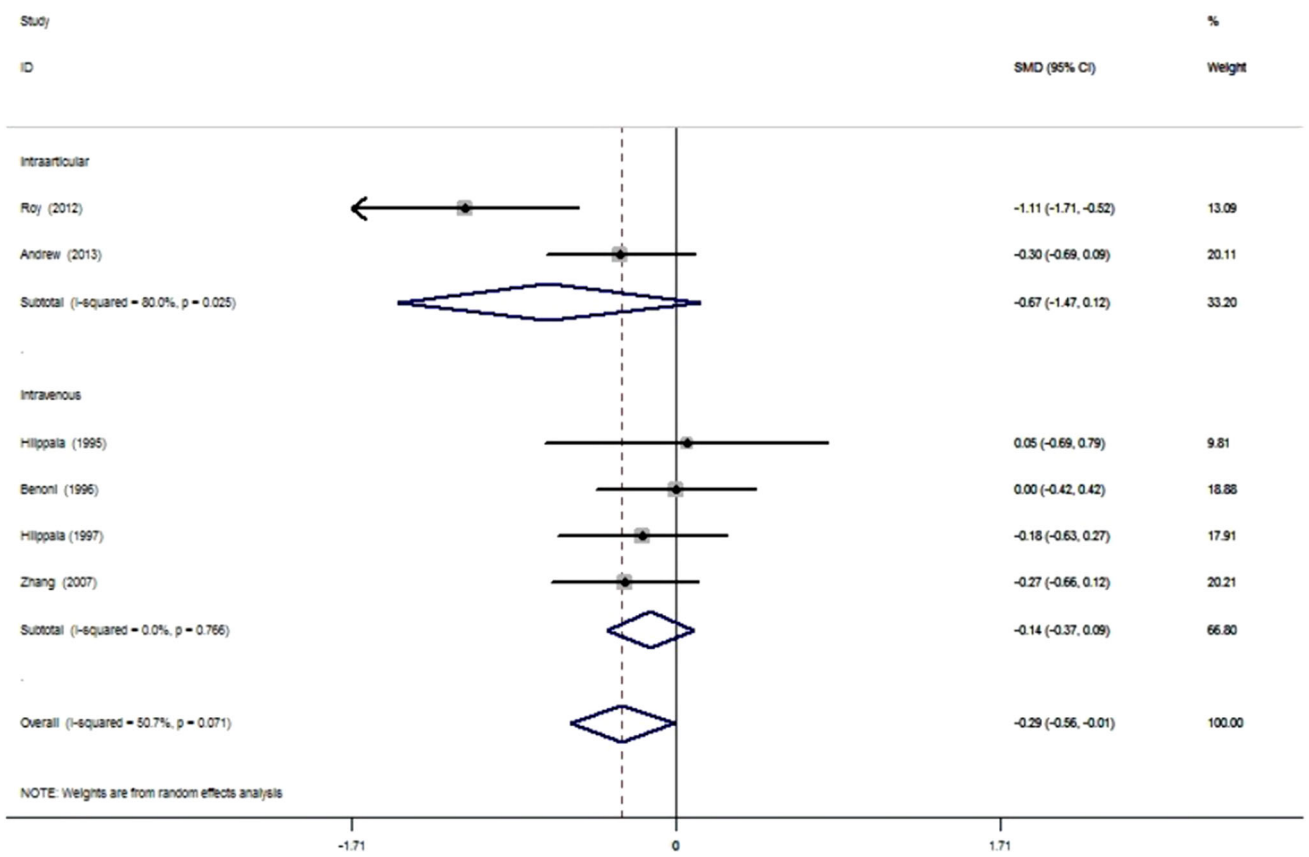

Fig. 6 Forest plot diagram showing the effect of TXA on intraoperative blood loss

the included studies was high relatively, some degree of clinical heterogeneity was induced by the following factors: first, clinical heterogeneity may be caused by blood transfusion protocol, surgical technologies of different centers, and the type of surgical hemostasis (i.e., gauzes packing, electrical cauterization). Second, the total blood loss and the amount of transfused blood per person may be affected by the operation time, type of surgery procedure, dose regimen of TXA, different follow-ups etc. Finally, the baseline of patients of individual studies, such as age, preexisting comorbidities, and economic condition, may also be confounding factors, which may exert influence on the stability of the pooled results.

There were several strengths of our review and meta-analysis. First, we performed exhaustive searches of the English and non-English languages literature to limit publication bias and pooled data from 34 manuscripts, including only RCTs. Second, all included studies were assessed rigorously by revised Jadad Scale and CONSORT checklist and scoring system, which indicated that most articles were of high quality. When came to heterogeneity, a random-effects model and sensitivity analysis were performed to control the veracity and stability of pooled results.

Although this study was believed to be the most comprehensive meta-analysis of RCT-based evidence for the safety and efficacy of TXA in the reduction of blood loss in TKA, we acknowledged that this study has some limitations. First, the general lack of random sequence production and allocation concealment methods in the included RCTs made it difficult to assess their methodological quality; thereby, the risk of bias and potential to overestimate the effect may be existent. Second, we did not limit the language in the process of the literature retrieval, but only Chinese- and English-language trials were included in the meta-analysis, publication and potential English language biases may have occurred. Third, the results of the other outcome measures (functional outcome scores, quality of life, length of stay, and cost effective) could not be pooled, either because too few data were available or because the methods varied too much; therefore, no definite conclusions can be drawn from these data.

Conclusion

This meta-analysis demonstrated that intraarticular or intraoperative application of TXA significantly reduced

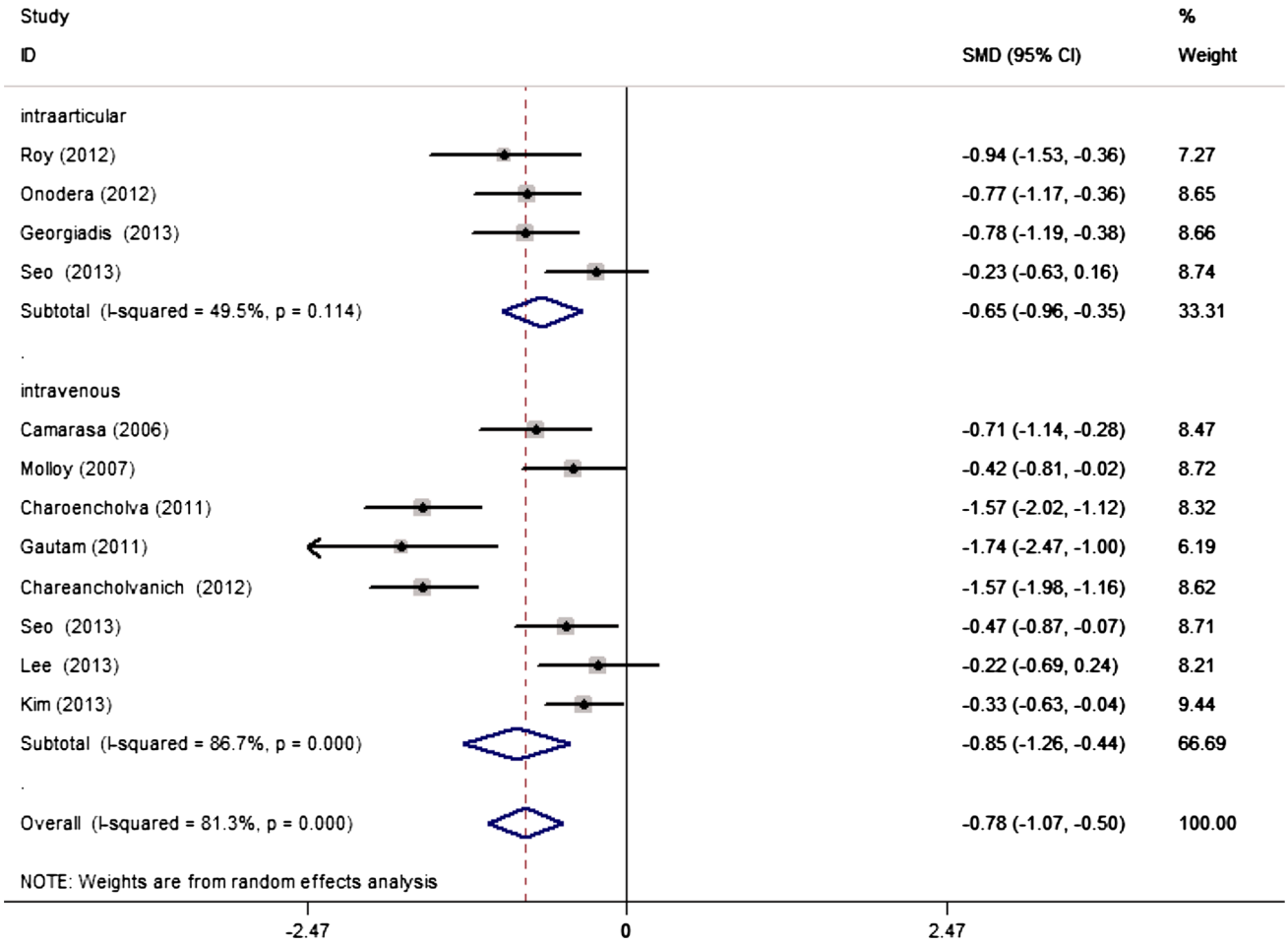

Fig. 7 Forest plot diagram showing the effect of TXA on Hb loss

total blood loss, postoperative blood loss, Hb loss and transfusion rate as well as blood units transfused per patient after primary TKA. However, there were no statistically significant differences in reducing intraoperative blood loss. Patients receiving TXA had no significant increase in the risk of thromboembolic complications or other adverse events. For exploring the cost effective and optimal dose, well-designed RCTs are still needed to be run.

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

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