HIP ARTHROPLASTY

Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials

Xin-die Zhou · Li-jiang Tao · Jin Li · Li-dong Wu

Abstract

Background Studies have shown that tranexamic acid reduces blood loss and transfusion need in patients undergoing total hip arthroplasty. However, no to date, no study has been large enough to determine definitively whether the drug is safe and effective. We examined whether intravenous tranexamic acid, when compared with placebo, was safe and effective in total hip arthroplasty.

Methods The literature search was conducted using the PubMed, Cochrane Library, MEDLINE, EMBASE, and China National Knowledge Infrastructure (CNKI) databases. Data were evaluated using the generic evaluation tool designed by the Cochrane Bone, Joint and Muscle Trauma Group. Ultimately, 19 randomized controlled trials involving 1,030 patients were included.

Results The use of tranexamic acid significantly reduced total blood loss by a mean of 305.27 mL [95 % confidence interval (CI) −397.66 to −212.89, $p < 0.001$], intraoperative blood loss by a mean of 86.33 mL(95 % CI −152.29 to −20.37, $p = 0.01$), postoperative blood loss by a mean of 176.79 mL (95 % CI −236.78 to −116.39, $p < 0.001$), and "hidden" blood loss by a mean of 152.70 mL (95 % CI −187.98 to −117.42, $p < 0.001$), resulting in a meaningful reduction in the proportion of patients requiring blood transfusion (odds ratio 0.28, 95 % CI 0.19 to 0.42, $p < 0.001$). There was no significant difference in occurrence of deep vein thrombosis, pulmonary embolism, or other complications among the study groups, or cost or hospitalization duration.

Conclusions The data from this meta-analysis indicate that intravenous tranexamic acid may reduce blood loss and transfusion need in patients undergoing total hip arthroplasty without increasing the risk of complications. However, high-quality randomized controlled trials are required to validate the results.

Keywords Tranexamic acid · Total hip arthroplasty · Blood loss · Transfusion · Meta-analysis

Introduction

Total hip arthroplasty (THA) has long been considered the treatment of choice for osteoarthritis of the hip, developmental dysplasia of the hip, and osteonecrosis of the femoral head in older patients. In association with our aging society, the number of patients who will need THA may increase significantly in the next few years [1]. However, in THA, considerable blood loss remains a major problem, which can lead to a need for allogeneic blood transfusion. Such transfusion of allogeneic erythrocytes is not free of adverse events and has been associated with transmission of infectious diseases, increased postoperative bacterial infection, immune sensitization, transfusion-related acute lung injury, intravascular hemolysis, transfusion-induced coagulopathy, renal failure, admission to intensive care, and even death [2–4].

Several effective interventions have been developed to reduce blood loss and postoperative transfusion rates, such as preoperative autologous donation, cell salvage, controlled hypotension, regional anesthesia, and the use of erythropoietin and antifibrinolytics [5–7].

The antifibrinolytics include aprotinin, tranexamic acid (TXA), and ε-aminocaproic acid, which have different

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mechanisms of action [8]. TXA is a synthetic derivative of the amino acid lysine and a competitive inhibitor of plasminogen activation, and thus interferes with fibrinolysis. Compared with other antifibrinolytic drugs, TXA is cheaper and safer than aprotinin and more potent than the others. Numerous studies have evaluated the use of antifibrinolytics in orthopedic surgery and have shown them to be effective in reducing blood loss [9–24]. However, the available clinical trials and meta-analyses lack sufficient statistical power to determine the effectiveness of antifibrinolytic agents in total hip arthroplasty. Consequently, we performed a meta-analysis of randomized controlled trials from 1966 to November 2012 to investigate the evidence for the effectiveness and safety of intravenous TXA in relation to reducing blood loss and transfusion requirement in total hip arthroplasty.

Materials and methods

We performed our review according to the standards described in 'Preferred reporting items for systematic reviews and meta-analyses' statement [25].

Inclusion criteria

In this meta-analysis, we evaluated randomized controlled trials (RCTs) comparing TXA with control (placebo or nothing) in terms of hemorrhage and blood transfusion need during perioperative period. Studies for which full texts could not be obtained were excluded, as were articles that were not formally published or published only in abstract form in connection with meetings. Trials that compared TXA with another active intervention were excluded, except those with both a placebo group and the other intervention. Subgroup analyses of patients with different hemoglobin and hematocrit levels were performed. The subjects were adults who had undergone THA, regardless of the type or size of prosthesis or bone cement used. Studies that involved oral, injection of the articular cavity, or intramuscular treatment were excluded.

The intervention considered was the administration of intravenous TXA. Primary outcomes were estimated intraoperative, postoperative, total, and "hidden" blood loss, as well as allogeneic blood transfusion and changes in postoperative hemoglobin and hematocrit. "Hidden" blood loss, which is calculated as the total blood loss minus the measurable blood loss, usually includes blood extravasating into the tissues, remaining in the joint cavities, and lost via hemolysis. It is considered to be the main reason why the postoperative hemoglobin is lower than anticipated in joint replacement patients [26]. Secondary outcomes were the proportion of patients who had postoperative

complications, especially deep vein thrombosis and pulmonary embolisms, as well as myocardial infarction and cerebrovascular accident. The economic effectiveness of TXA and hospitalization duration were also considered if data were available. When the data allowed, we also examined the dose–effect relationship between the dosage of TXA and the total blood loss, to explore the trends in the change in the relationship between TXA and blood loss.

Search strategy

For the review, we retrieved articles that were included in the MEDLINE, PubMed, EMBASE, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases, which describe trials of TXA and THR and were published before November 2012, with no date restriction. Languages other than English and Chinese were excluded. For the electronic database search, the following exploded Medical Subject Headings (MeSH) terms were used: "Antifibrinolytics," "Tranexamic acid," "Cyklokapron," "hip arthroplasty," "hip replacement," and "joint replacement." The reference lists of related reviews and original articles identified were also reviewed for relevant trials, including clinical trials and randomized controlled trials, in adult humans.

Review methods

To select suitable references, three independent reviewers first applied the search strategy to scan the titles and abstracts from the databases to confirm that they fulfilled the inclusion criteria. When there was uncertainty about any of the vital information, the full article was retrieved for further scrutiny, or the authors of individual trials were contacted directly to provide further information, when necessary. To assess the methodological quality of the studies included, we used a modified version of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group [27] (Table 1). The methodological quality of each trial was scored from 0 to 24, where higher scores indicated better quality. Disagreements were resolved by consensus or consultation with the senior reviewer. Data extracted from the included studies were entered independently by three reviewers. Any disagreement was resolved by the senior reviewer, LW. When this was not possible or data were missing through loss to follow-up, intention-to-treat principles were used.

Statistical analysis

Data were checked and entered into Review Manager 5.0 by the three reviewers independently and the results were cross-checked. Continuous data were entered as means

Table 1 Quality assessment items and possible scores

A. Was the assigned treatment adequately concealed prior to allocation?

  2 = Method did not allow disclosure of assignment

  1 = Small but possible chance of disclosure of assignment or unclear

  0 = Quasi-randomized or open list/tables

B. Were the outcomes of participants who withdrew described and included in the analysis (intention-to-treat)?

  2 = Withdrawals well described and accounted for in analysis

  1 = Withdrawals described and analysis not possible

  0 = No mention, inadequate mention, or obvious differences and no adjustment

C. *Were the outcome assessors blinded to treatment status?*

  2 = Effective action taken to blind assessors

  1 = Small or moderate chance of unblinding of assessors

  0 = Not mentioned or not possible

D. *Were the treatment and control group comparable at entry?*

  2 = Good comparability of groups, or confounding adjusted for in analysis

  1 = Confounding small; mentioned but not adjusted for

  0 = Large potential for confounding, or not discussed

E. *Were the participants blind to assignment status after allocation?*

  2 = Effective action taken to blind participants

  1 = Small or moderate chance of unblinding of participants

  0 = Not possible, or not mentioned (unless double-blind), or possible but not done

F. *Were the treatment providers blind to assignment status?*

  2 = Effective action taken to blind treatment providers

  1 = Small or moderate chance of unblinding of treatment providers

  0 = Not possible, or not mentioned (unless double-blind), or possible but not done

G. *Were care programmes, other than the trial options, identical?*

  2 = Care programmes clearly identical

  1 = Clear but trivial differences

  0 = Not mentioned or clear and important differences in care programmes

H. *Were the inclusion and exclusion criteria clearly defined?*

  2 = Clearly defined 1 = inadequately defined 0 = not defined

I. *Were the interventions clearly defined?*

  2 = Clearly defined 1 = inadequately defined 0 = not defined

J. *Were the outcome measures used clearly defined? (by outcome)*

  2 = Clearly defined 1 = inadequately defined 0 = not defined

K. *Were diagnostic tests used in outcome assessment clinically useful? (by outcome)*

  2 = Optimal 1 = adequate 0 = not defined, not adequate

L. *Was the surveillance active, and of clinically appropriate duration? (by outcome)*

  2 = Optimal 1 = adequate 0 = not defined, not adequate

and standard deviations (SDs), while dichotomous data were entered as number of events. The presence of heterogeneity was explored by Chi squared test with a significance set at a *p* value of 0.1, and the degree of heterogeneity was measured using the I^2 value [28]. The origins of heterogeneity, if present, were analyzed according to differences in methodological quality, characteristics of participants, and interventions. A non-significant Chi squared test result (a *p* value ≥0.1 and an I^2 value ≤50 %) suggested only a lack of evidence of heterogeneity; it did not necessarily indicate homogeneity, because the statistical power may have been insufficient to detect heterogeneity

[29]. A fixed-effect model analysis was used to compare trials not showing heterogeneity, while a random-effects model analysis was used for those that did. For each study, the odds ratios (OR) and 95 % confidence intervals were calculated for dichotomous outcomes, and mean differences and 95 % confidence intervals for continuous outcomes. The relationship between TXA dosage and the total blood loss was explored using the SPSS software. The correlation coefficient (*r*) was used to evaluate the relationship between the dosage of TXA and total blood loss. *p* values less than 0.05 were considered to indicate significance.
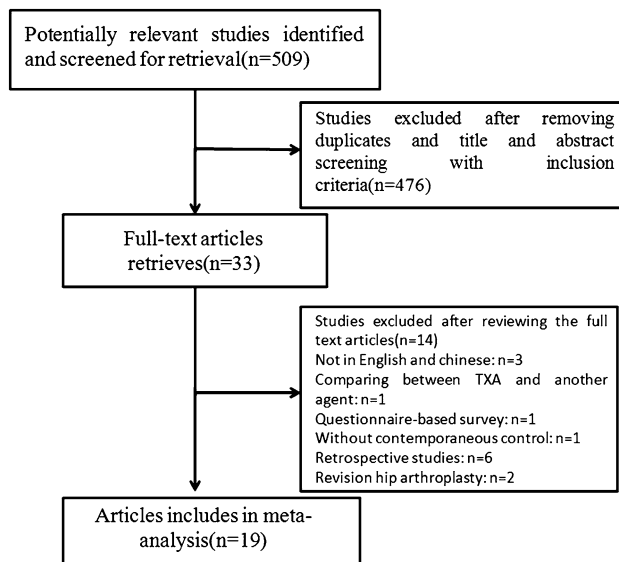
Fig. 1 Flow chart of included and excluded studies

Results

Results and patients' characteristics

Following application and refinement of the literature search strategy, 19 independent randomized controlled trials [9–24, 30–32], containing 1,030 patients, were eligible for data extraction and meta-analysis (Fig. 1) (Table 2). Most were relatively well-designed and the quality assessment score of most was high, with a mode of 24, the highest possible score; a median value of 22; and a range of 14–24. The trials included were all of THA, and osteoarthritis was the most common diagnosis. Preoperative autologous blood donation or intraoperative clean blood collection were used in four studies [9, 13, 14, 22], and the amount of autotransfusion was not included in the postoperative blood transfusion statistics. Postoperative drainage was quantified between 24 and 48 h, when drains were in most cases removed. The study by Jamie [20], reported in 2011, included a group that received fibrin spray as well as TXA and control groups, was also included. The last study [24] 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 research (Table 3). Two studies compared the economic costs of blood products and TXA [11, 15] and favored the use of TXA. In addition to the key outcome measure below, some other adverse events are worth mentioning, which have been listed in Table 4.

Blood loss

Blood loss data were provided by all 19 studies. Seven studies [9, 13–15, 17, 31, 32] of a total of 382 patients, used an outcome of total blood loss. TXA significantly reduced total blood loss in the TXA group compared with the placebo group, by a mean of 305.27 mL (95 % CI −397.66 to −212.89 mL; $p < 0.001$; Fig. 2). Intraoperative blood loss volume was measured by weighing sponges and suction drainage at the end of surgery in nine studies [9, 13–15, 17–19, 22, 32]. The blood loss volume per patient was significantly less in the TXA group (weighted mean difference −86.33 mL (95 % CI −152.29 to −20.37 mL; $p = 0.01$; Fig. 3). Eight studies [9, 10, 13–15, 17, 22, 31], including 419 patients, provided postoperative blood loss data. The use of TXA significantly reduced postoperative blood loss, as measured by drainage volume, by a mean of 176.79 mL (95 % CI −236.78 to −116.79 mL; $p < 0.001$; Fig. 4). Two studies [15, 23], including 140 patients, had "hidden" blood loss data. The use of TXA significantly reduced "hidden" blood loss in the TXA group compared with the placebo group (weighted mean difference −152.70 mL (95 % CI −187.98 to −117.42 mL; $p < 0.001$; Fig. 5).

Changes in hemoglobin and hematocrit

Changes in postoperative hemoglobin (Hb) and hematocrit (Hct) were mentioned in nine studies [9, 13–15, 17–19, 30, 32]. However, data on changes in Hb and Hct with standard deviations were reported in only five [9, 13, 14, 17, 18]. The use of TXA significantly ameliorated the postoperative hemoglobin decrease, by 6.03 g/L in total (95 % CI 3.90 to 8.15 g/L; $p < 0.001$; Fig. 6) and the hematocrit decrease, by 2.29 % in total (95 % CI 1.42 to 3.16 %; $p < 0.001$; Fig. 7). We also conducted a subgroup analysis in chronological order, with 6-h, and 1- and 7-day changes in postoperative hemoglobin and 1- and 7-day changes in hematocrit. The Hct results of days 1 and 7 postoperatively were both significantly higher in the TXA group compared with the placebo group, and identical to the outcome for the total change in Hct; while the Hb results at 6 h and day-1 were significant, and identical to the outcome of the total change in Hb.

Allogeneic blood transfusion

Allogeneic blood transfusion data were provided by 18 studies [9–17, 19–24, 30–32]. The number of patients who required transfusion was significantly (28 %) less in the TXA group than the placebo group (95 % CI 0.19 to 0.42; $p < 0.001$; Fig. 8). Blood units transfused per patient data

Table 2 Characteristics of included studies

Trials	Years	Cases (Tx/C)	TXA dose	Bone cement	Control
Benoni	2000	40 (20/20)	10 mg/kg IV at end of operation and 3 h later	Cemented	Saline
Ekbäck	2000	40 (20/20)	10 mg/kg IV just before operation then 1 mg/kg/h infusion over 10 h + 10 mg/kg further dose after 3 h from operation	Cemented	Saline
Ido	2000	40 (20/20)	1 g IV just before operation and 3 h after operation	Cemented	None
Benoni	2001	40 (20/20)	10 mg/kg IV before the operation started	Cemented	Saline
Hust	2003	40 (20/20)	10 mg/kg IV just before operation then 1 mg/kg/h infusion over 10 h	Cementless or hybrid	Saline
Lemay	2003	39 (20/19)	10 mg/kg IV followed by an infusion of 1 mg/kg/h infusion until skin closure	Cemented or cementless	NS
Garneti	2004	50 (25/25)	10 mg/kg IV at induction of anesthesia	Cemented	NS
Yamasaki	2004	40 (20/20)	1 g IV just before operation	Cementless	None
Johansson	2005	100 (47/53)	15 mg/kg IV just before surgery	Cemented	Saline
Niskanen	2005	39 (19/20)	10 mg/kg IV just before the operation then 8 and 16 h later	Cemented	Saline
Claeys	2007	40 (20/20)	15 mg/kg IV in a slow infusion 15 min before surgery	Hybrid	Saline
Rajesparan	2009	73 (36/37)	1 g IV before the skin incision.	Cemented, cementless or Hybrid	None
Kazemi	2010	64 (32/32)	15 mg/kg, IV 5 min prior to operation	Cementless	NS
Singh	2010	42 (21/21)	10 mg/kg IV prior to incision	Cemented or cementless	None
Jamie	2011	66 (22/22)	10 mg/kg IV accompanying with the beginning of the operation	Cemented	None
Malhotra	2011	50 (25/25)	15 mg/kg IV 15 min before the incision	Cementless	NS
Clave	2012	70 (37/33)	1 g IV preoperatively (at incision);1 g IV at H3, H7 and H12.	Cementless	None
Fu	2012	40 (20/20)	20 mg/kg IV accompanying with the beginning of the operation	Cementless	NS
Norio	2012	117 (95/22)	(1) 1 g IV 10 min before skin closure; (2) 1 g IV 10 min before skin closure and again 6 H later; (3) 1 g IV 10 min before surgery; (4) 1 g IV 10 min before surgery and again at 6 H later.	Cementless	None

DVT prophylaxis	DVT screen	Anesthesia	Blood transfusion protocol	D-b study	QAS
LMWH	Clinical	Regional or general	None	Yes	24
LMWH	Ultrasound	Regional	Hct < 27 %	Yes	22
Not mentioned	Clinical	Not mentioned	None	No	14
LMWH and Mechanical	Clinical	Regional or general	None	Yes	24
LMWH	Clinical	Regional	Reduction in Hb > 25 % and clinical symptoms	Yes	24
LMWH and Mechanical	Clinical and ultrasound	Regional	Hb < 70 g/l (fit patient) Hb < 90 g/l (elderly patient with comorbidity) and clinical symptoms	Yes	23
Mechanical only	Ultrasound or venography	Regional	None	Yes	24
Not mentioned	Clinical	Regional	None	Yes	24
LMWH	Clinical	Regional	Hb < 90 g/l	Yes	24
LMWH and mechanical	Clinical	Regional or general	Hct 0.28 to 0.30	Yes	24
LMWH	Clinical and ultrasound	Regional	Hb < 8.5 g/dl or Hct < 27 %	Yes	22
LMWH	Venogram	Regional & general	Clinical	No	14

Table 2 continued

DVT prophylaxis	DVT screen	Anesthesia	Blood transfusion protocol	D-b study	QAS
LMWH	Clinical	Regional	Hct < 30 %	Yes	22
LMWH	Clinical and ultrasound	Regional	Clinical	No	17
Aspirin	Clinical	Regional or general	None	No	22
LMWH and mechanical	Ultrasonic	Regional	Reduction in Hb > 25 % and clinical symptoms	Yes	22
Rivaroxaban	Clinical	Regional	(SFAR) guidelines	No	21
Not mentioned	Clinical	Not mentioned	None	Yes	16
LMWH and mechanical	Computed tomography	Regional or general	None	No	17

TXA tranexamic acid, *DVT* deep vein thrombosis, *LMWH* low-molecular-weight heparin, *QAS* quality assessment score, *IV* intravenous, *NS* normal saline, *None* data not available, *Hb* hemoglobin, *Hct* hematocrit, *Tx* treatment group, *C* control group, *D-b study* double-blind study

Table 3 Characteristics of the study of Norio

Trials	Cases(Tx/C)	TXA dose	Bone cement
Norio 2012.1	24/22	1 g IV 10 min before skin closure	Cementless
Norio 2012.2	20/22	1 g IV 10 min before skin closure and again 6 H later	Cementless
Norio 2012.3	25/22	1 g IV 10 min before surgery	Cementless
Norio 2012.4	26/22	1 g IV 10 min before surgery and again at 6 H later	Cementless

Control	DVT prophylaxis	DVT screen	Anesthesia
None	LMWH and mechanical	Computed tomography	Regional or general
None	LMWH and mechanical	Computed tomography	Regional or general
None	LMWH and mechanical	Computed tomography	Regional or general
None	LMWH and mechanical	Computed tomography	Regional or general

Table 4 Other adverse events

Trials and year	The tranexamic acid group	The Placebo group
Benoni_2001	One developed chest pain, One developed slight hemiparesis due to infarctions in the right hemisphere, One patient had continuous secretions and was re-operated.	One developed nausea when the drug was injected.
Lemay_2003	NA	One suffered from a brief respiratory arrest, One was reintubated for delirium from unrecognized alcohol withdrawal.
Johansson_2005	NA	Three developed superficial wound infections but healed.
Niskanen_2005	One developed superficial wound infection, One developed transient dyspnea, One developed pyelonephritis.	One developed dysuresia, One suffered from acute gluteal eczema.
Rajesparan_2009	Two had low oxygen saturation, Thirteen developed hypotension, Six had low urine output.	One experienced low oxygen saturation, Seventeen performed hypotension, Four experienced low urine output.
Clave_2012	Two exhibited nausea.	NA

were available in only nine studies [9, 10, 14, 19, 20, 22–24, 31]. No significant evidence was available on reducing the average number of allogeneic red blood cell (RBC) transfusions per patient when the TXA group was compared with the placebo group. (weighted mean difference 0.3 units; 95 % CI −0.49 to 1.09 units; $p = 0.45$).
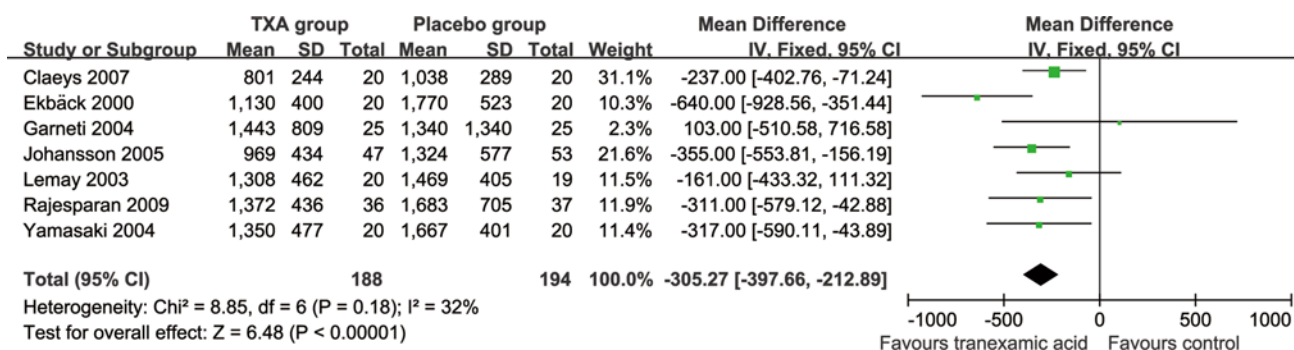
| Study or Subgroup | TXA group | | | Placebo group | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Claeys 2007	801	244	20	1,038	289	20	31.1%	-237.00 [-402.76, -71.24]	
Ekbäck 2000	1,130	400	20	1,770	523	20	10.3%	-640.00 [-928.56, -351.44]	
Garneti 2004	1,443	809	25	1,340	1,340	25	2.3%	103.00 [-510.58, 716.58]	
Johansson 2005	969	434	47	1,324	577	53	21.6%	-355.00 [-553.81, -156.19]	
Lemay 2003	1,308	462	20	1,469	405	19	11.5%	-161.00 [-433.32, 111.32]	
Rajesparan 2009	1,372	436	36	1,683	705	37	11.9%	-311.00 [-579.12, -42.88]	
Yamasaki 2004	1,350	477	20	1,667	401	20	11.4%	-317.00 [-590.11, -43.89]	
Total (95% CI)			188			194	100.0%	-305.27 [-397.66, -212.89]	

Heterogeneity: Chi² = 8.85, df = 6 (P = 0.18); I² = 32%
Test for overall effect: Z = 6.48 (P < 0.00001)

-1000 -500 0 500 1000
Favours tranexamic acid   Favours control

Fig. 2 Forest plot diagram showing the effect of tranexamic acid (TXA) on total blood loss. *TXA* tranexamic acid, *CI* confidence interval, *SD* standard deviation, *IV* inverse variance, and *df* degrees of freedom, *M–H* Mantel–Haenszel
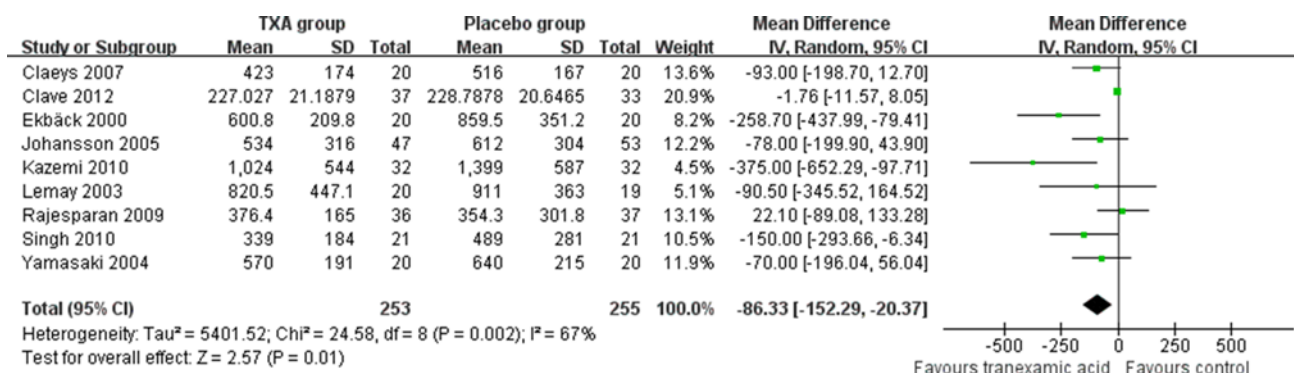
| Study or Subgroup | TXA group | | | Placebo group | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Claeys 2007	423	174	20	516	167	20	13.6%	-93.00 [-198.70, 12.70]	
Clave 2012	227.027	21.1879	37	228.7878	20.6465	33	20.9%	-1.76 [-11.57, 8.05]	
Ekbäck 2000	600.8	209.8	20	859.5	351.2	20	8.2%	-258.70 [-437.99, -79.41]	
Johansson 2005	534	316	47	612	304	53	12.2%	-78.00 [-199.90, 43.90]	
Kazemi 2010	1,024	544	32	1,399	587	32	4.5%	-375.00 [-652.29, -97.71]	
Lemay 2003	820.5	447.1	20	911	363	19	5.1%	-90.50 [-345.52, 164.52]	
Rajesparan 2009	376.4	165	36	354.3	301.8	37	13.1%	22.10 [-89.08, 133.28]	
Singh 2010	339	184	21	489	281	21	10.5%	-150.00 [-293.66, -6.34]	
Yamasaki 2004	570	191	20	640	215	20	11.9%	-70.00 [-196.04, 56.04]	
Total (95% CI)			253			255	100.0%	-86.33 [-152.29, -20.37]	

Heterogeneity: Tau² = 5401.52; Chi² = 24.58, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 2.57 (P = 0.01)

-500 -250 0 250 500
Favours tranexamic acid   Favours control

Fig. 3 Forest plot diagram showing the effect of TXA on intraoperative blood loss

| Study or Subgroup | TXA group | | | Placebo group | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Claeys 2007	352	152	20	524	255	20	12.1%	-172.00 [-302.10, -41.90]	
Clave 2012	440.5	22.9135	37	641.8	48.0583	33	27.5%	-201.30 [-219.28, -183.32]	
Ekbäck 2000	529.2	319.5	20	910.3	360.4	20	6.3%	-381.10 [-592.18, -170.02]	
Garneti 2004	411	220	25	353	311	25	10.3%	58.00 [-91.33, 207.33]	
Ido 2000	581.3	224.4	20	867.3	319.2	20	8.6%	-286.00 [-457.00, -115.00]	
Johansson 2005	350	114	47	528	211	53	21.1%	-178.00 [-243.49, -112.51]	
Lemay 2003	487	234	20	580	290	19	8.9%	-93.00 [-258.89, 72.89]	
Yamasaki 2004	655	418	20	890	353	20	5.1%	-235.00 [-474.78, 4.78]	
Total (95% CI)			209			210	100.0%	-176.79 [-236.78, -116.79]	

Heterogeneity: Tau² = 3317.29; Chi² = 17.46, df = 7 (P = 0.01); I² = 60%
Test for overall effect: Z = 5.78 (P < 0.00001)

-500 -250 0 250 500
Favours tranexamic acid   Favours control

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

| Study or Subgroup | TXA group | | | Placebo group | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fu 2012	169.89	58.5	20	322.37	57.69	20	96.0%	-152.48 [-188.49, -116.47]	
Johansson 2005	287	410	47	445	489	53	4.0%	-158.00 [-334.27, 18.27]	
Total (95% CI)			67			73	100.0%	-152.70 [-187.98, -117.42]	

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 8.48 (P < 0.00001)
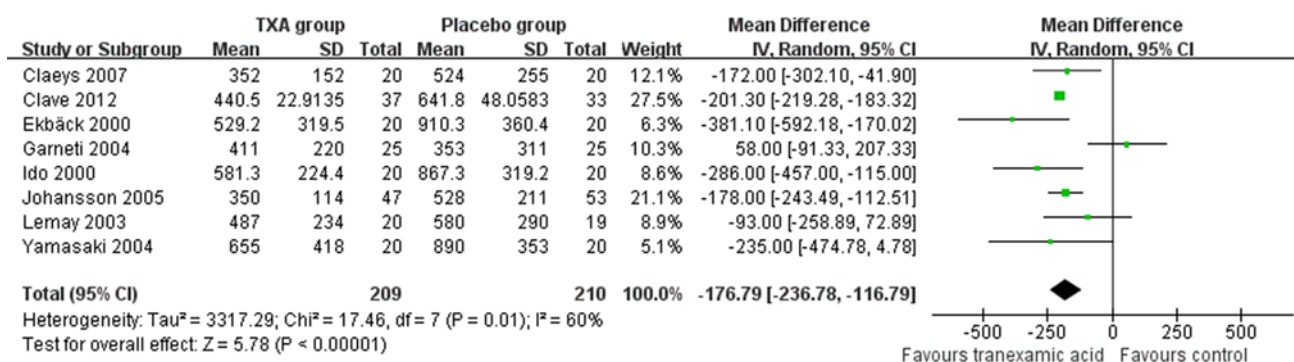
-500 -250 0 250 500
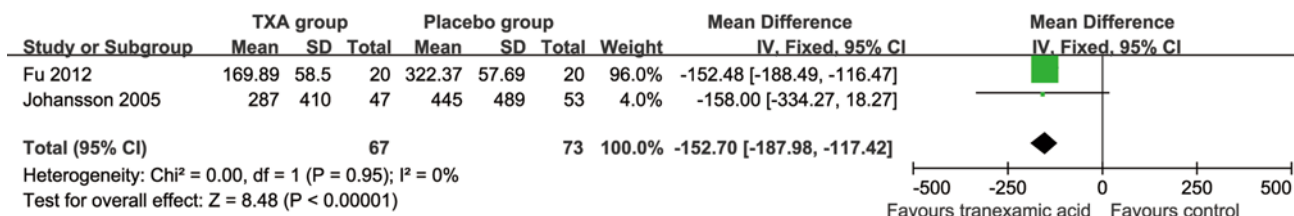Favours tranexamic acid   Favours control

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

Fig. 6 Forest plot diagram showing the effect of TXA on postoperative hemoglobin (Hb)
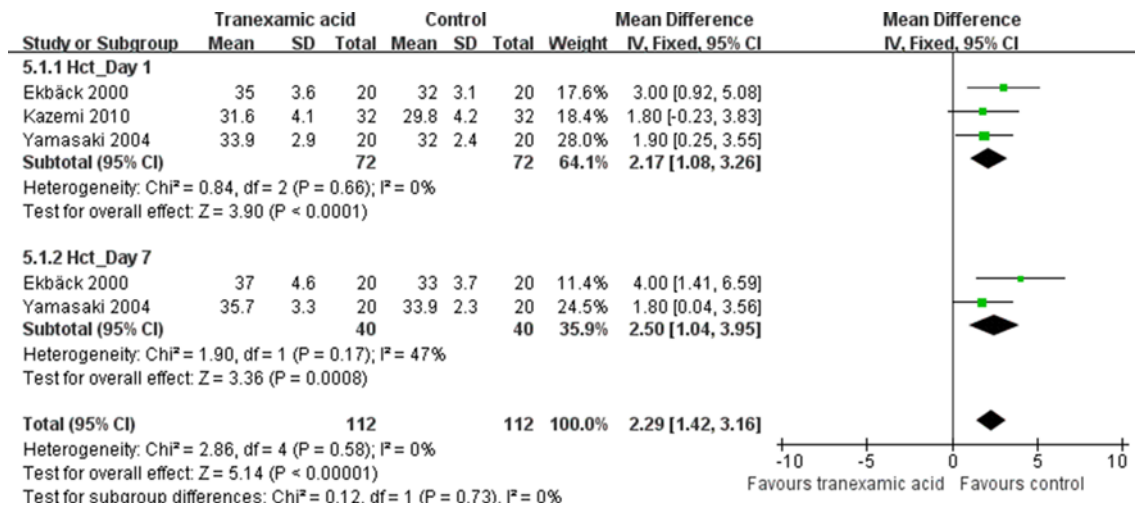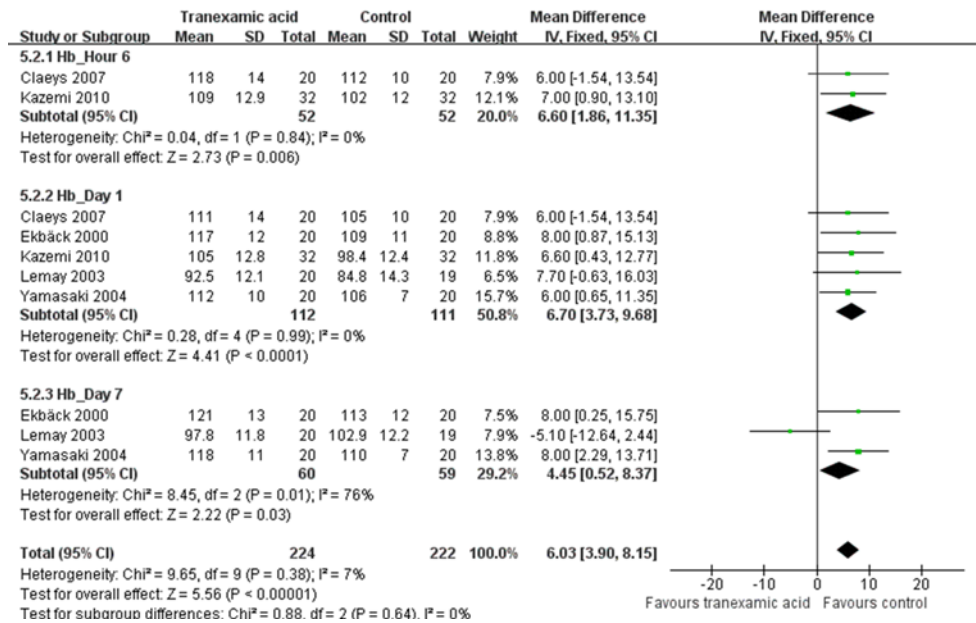

Fig. 7 Forest plot diagram showing the effect of TXA on postoperative hematocrit (Hct)

Thromboembolic complications

All 19 studies reported DVT complication data. Patients receiving TXA (539 patients) had 15 episodes of DVT, while the 535 patients who did not receive TXA had a total of 19 episodes. Thus, based on these numbers, DVT was not affected by the use of TXA (OR 0.73, 95 % CI 0.36–1.49, $p = 0.39$). Three trials [11, 24, 31] reported four pulmonary embolism events, three of 539 in the TXA group and one of 535 in the control group. However, there was no statistically significant difference in the risk of developing pulmonary embolism based on these data [OR 1.95; (95 % CI 0.34–11.06); $p = 0.45$].

Hospitalization duration

This outcome measure was reported in two studies [18, 19]. Hospitalization duration was not affected by the use of TXA when the TXA group was compared with the placebo group [weighted mean difference −0.58 days (95 % CI −1.6 to 0.43 days); $p = 0.26$].

Dose–effect relationship

This outcome was available in 11 studies [9, 10, 13–17, 22, 24, 30, 32], in which various doses of TXA were used. We plotted the TXA dose on the abscissa, and the

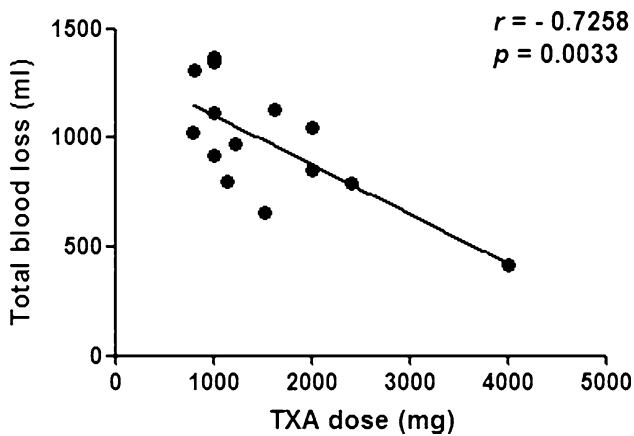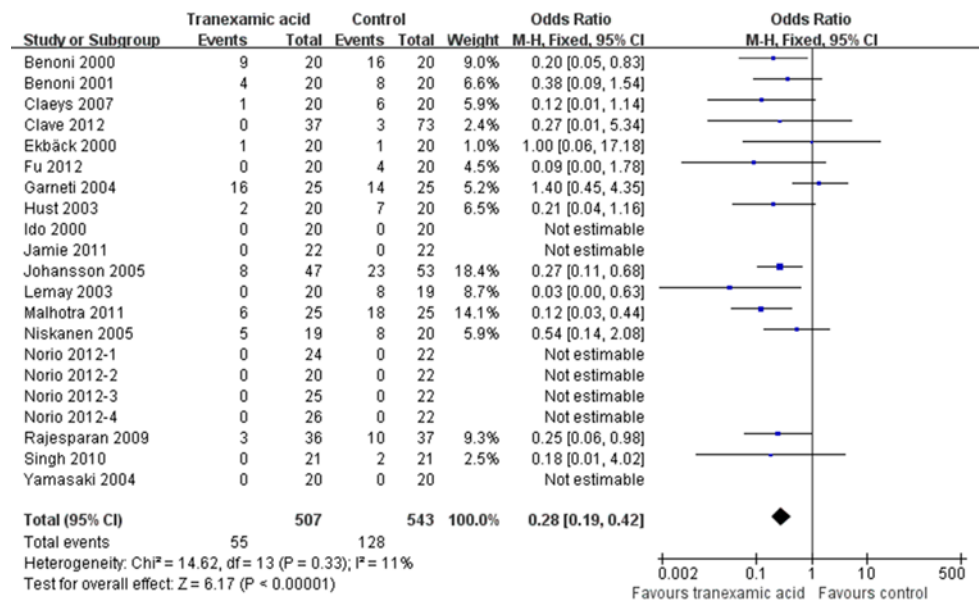**Fig. 8** Forest plot diagram showing the effect of TXA on the number of patients who needed homologous transfusion

Study or Subgroup	Tranexamic acid Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Benoni 2000	9	20	16	20	9.0%	0.20 [0.05, 0.83]
Benoni 2001	4	20	8	20	6.6%	0.38 [0.09, 1.54]
Claeys 2007	1	20	6	20	5.9%	0.12 [0.01, 1.14]
Clave 2012	0	37	3	73	2.4%	0.27 [0.01, 5.34]
Ekbäck 2000	1	20	1	20	1.0%	1.00 [0.06, 17.18]
Fu 2012	0	20	4	20	4.5%	0.09 [0.00, 1.78]
Garneti 2004	16	25	14	25	5.2%	1.40 [0.45, 4.35]
Hust 2003	2	20	7	20	6.5%	0.21 [0.04, 1.16]
Ido 2000	0	20	0	20		Not estimable
Jamie 2011	0	22	0	22		Not estimable
Johansson 2005	8	47	23	53	18.4%	0.27 [0.11, 0.68]
Lemay 2003	0	20	8	19	8.7%	0.03 [0.00, 0.63]
Malhotra 2011	6	25	18	25	14.1%	0.12 [0.03, 0.44]
Niskanen 2005	5	19	8	20	5.9%	0.54 [0.14, 2.08]
Norio 2012-1	0	24	0	22		Not estimable
Norio 2012-2	0	20	0	22		Not estimable
Norio 2012-3	0	25	0	22		Not estimable
Norio 2012-4	0	26	0	22		Not estimable
Rajesparan 2009	3	36	10	37	9.3%	0.25 [0.06, 0.98]
Singh 2010	0	21	2	21	2.5%	0.18 [0.01, 4.02]
Yamasaki 2004	0	20	0	20		Not estimable
Total (95% CI)		507		543	100.0%	0.28 [0.19, 0.42]
Total events	55		128			

Heterogeneity: Chi² = 14.62, df = 13 (P = 0.33); I² = 11%
Test for overall effect: Z = 6.17 (P < 0.00001)

Fig. 9 Scatter plot showing the relationship between the changing of TXA dose and the amount of total blood loss

corresponding total blood loss as the ordinate, to generate a scatterplot. In addition, the linear correlation coefficient (*r*) was also calculated. A significantly positive correlation between the dosage of TXA and total blood loss was found ($r = -0.7258$, $p = 0.0033$; Fig. 9). The total blood loss tended to decrease as the TXA dose increased.

Discussion

To minimize the possibility of bias, we performed a primary analysis including only RCTs, although some of them were not double-blinded. Our results showed that the use of TXA could significantly reduce total, postoperative, and "hidden" blood loss, as well as the number of patients

who needed allogeneic transfusions. Comparing the data of total blood loss and dominant blood loss, it can be seen that "hidden" blood loss is an important issue in total hip arthroplasty. However, only two studies reported hidden blood loss measurement methods and results.

TXA also played a positive role in lowering the decrease of the postoperative hemoglobin and hematocrit. Furthermore, TXA did not increase the prevalence of deep vein thrombosis, pulmonary embolism, or hospitalization duration. These results are similar to the meta-analyses by Sukeik [29], although their studies differed from ours. However, the strength and reliability of the rate of adverse events is limited by the lack of a systematic investigation and the relatively short duration of postoperative observation.

Tranexamic acid, a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent that acts by binding to plasminogen and blocking the interaction of plasmin (ogen) with fibrin, thereby preventing dissolution of the fibrin clot [33]. As a result, it contributes to reduced blood loss, as well as the number of blood transfusions per patient and the number of patients requiring transfusions when the tranexamic acid group was compared with the placebo group.

From this, one issue that must be addressed is whether TXA influences the fibrinolytic system in THA after the operation. The effects of TXA on the fibrinolytic system may means that it also affects prothrombin time, activated partial thromboplastin time, international normalized ratio, and platelets. However, only one trial [9] refers to changes in these postoperative indexes. During the perioperative period (up to day 1 postoperatively), prothrombin time, activated partial thromboplastin time, fibrinogen,

and plasminogen-activator inhibitor showed no significant differences in the TXA group compared with the placebo group. Also, TXA may reduce blood loss by reducing induced fibrinolysis, as shown by a decreased D-dimer and increased PAP [9]. This also raises the issue as to whether TXA interacts with thromboprophylaxis agents. However, data are insufficient to investigate this further. Patients who received TXA did not have a higher risk of deep vein thrombosis or pulmonary embolism, compared with those who received placebo, based on the meta-analysis data. Nevertheless, randomized controlled trials with larger numbers of patients are needed to confirm the results of our meta-analysis.

In addition, the 19 studies included in our meta-analysis used various doses. When the effect estimates for a reduction in the total blood loss were plotted against the total amount of TXA administered, the best-fitting line showed a direct relationship between the amount of TXA given and the effect estimate. However, more data are needed to validate a relationship between dose and effect. From these results, the intravenous administration of 10–20 mg/kg (or 1 g) of TXA before the operation, followed or not, by 10–20 mg/kg 3–12 h afterwards, appears to be safe and effective. Benoni [30] and Norio [24] reported that intravenous administration of TXA only after the operation or before skin closure may weaken its effect in terms of reducing blood loss and allogeneic blood transfusion volume. Of course, this finding should also be confirmed by more data.

Our meta-analysis demonstrated the economic effectiveness and lack of an effect on hospitalization duration of TXA [11, 15, 18, 19]. Due to the high cost of allogeneic blood, TXA appears to have an advantage compared to transfusions. However, there was no significant effect on hospitalization duration in the TXA group compared with the placebo group.

The limitations of our study included insufficient data to support the analysis of functional outcome scores or quality of life outcome measures. In addition, the autotransfusion protocol, allogenic blood transfusion, different time periods of intravenous administration, surgical techniques, and measurement of blood loss likely contributed to the differences observed among studies. Furthermore, the trials included in our study were designed to assess the efficacy and safety of TXA in THA, after excluding high-risk factors such as patients with a history of cardiovascular disease, including angiocardiopathy, thromboembolic events, bleeding diathesis, allergy to TXA, renal failure, and bleeding diathesis, and those who were pregnant, or on warfarin or a therapeutic dose of low-molecular-weight heparin. In addition, with the exception of the total blood loss, our findings do not support the assumption that a higher dose of TXA necessarily reduces the intraoperative and postoperative blood loss or blood transfusion rates. Therefore, no definite conclusions regarding the safety and effectiveness of TXA can be derived from our meta-analysis regarding high-risk patients.

Conclusions

In conclusion, our analysis suggests that the use of TXA in THA significantly reduced the risk of bleeding and the need for allogeneic transfusion. However, data are insufficient to evaluate safety and cost-effectiveness. Thus, no definite conclusions regarding the clinical risk:benefit ratio of the use of tranexamic acid in THA can be drawn at this stage. Larger, high-quality prospective trials are required to strengthen our conclusions, define the optimal regimen, and assess the safety and cost-effectiveness of TXA before recommending its use in THA.

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

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