META-ANALYSIS

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Accepted: 2015.06.28 Accepted: 2015.09.20 Published: 2015.10.14		Safety and Efficacy Knee Arthroplasty	of Iranexamic Acid in Iotal
Authors' Contribution: Study Design A Data Collection B Statistical Analysis C Data Interpretation D Manuscript Preparation E Literature Search F Funds Collection G	BCDEF 1,2 EF 1,2 DEF 1,2 DEF 1,3	Xiao Yu* Weili Li* Pengchen Xu Jin Liu Yue Qiu Yuchang Zhu	 Department of Orthopaedics, Shanghai Tenth People's Hospital, Shanghai, P.R. China Nanjing Medical University, Shanghai, P.R. China School of Medicine, Suzhou University, Suzhou, Jiangsu, P.R. China School of Medicine, Tongji University, Shanghai, P.R. China
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Back Material/N	sground: Nethods:	orthopedic practice. To further investigated transfusion rate and blood loss in total kne This meta-analysis was conducted accordir well designed randomized controlled trials	g to the Cochrane methodology. Twenty-eight superior quality and (RCT) were collected to analyze for this study. Patients who had un-
	Results:	Finally, 28 RCTs were collected to analyze application of TA, by a mean of 420 ml [959 rate was also found in patients who receiv	n. The software, RevMan 5.2, was used to analyze collected data. For this study. Total blood loss was dramatically decreased via the 6 Cl: –514 to –327]. A significant reduction about blood transfusion ed TA. [RD: –0.26, 95%Cl: –0.33 to –0.19]. Moreover, no significant atrol groups in incidence of deep vein thrombosis (DVT) and pulmo-
Cond	lusions:	This meta-analysis demonstrates that the a sion rate. On the other hand, the application	pplication of TA in TKA could decrease total blood loss and transfu- of TA is not associated with high incidence of DVT or other adverse routine use in primary knee arthroplasty to benefit the patients.
MeSH Ke	ywords:	Arthroplasty, Replacement, Knee • Bloo	l Loss, Surgical • Meta-Analysis • Tranexamic Acid
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Safety and Efficacy of Tranexamic Acid in Total



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Background

The prevalence of total knee arthroplasty (TKA) is increasing, which is one of the most frequent operations in orthopedic practice [1]. However, the considerable intraoperative and postoperative blood loss may be a trigger increasing risk of allogeneic blood transfusion, which causes subsequent complications, such as infections, intravascular hemolysis, and cardiopulmonary events [1–3]. Moreover, patients who underwent TKA are mostly aged people (65.7 \pm 8.2) [4,5], whose ability to replace lost blood is insufficient to maintain health. Therefore, they are more vulnerable to series of transfusion reactions, and even death. Thus, an effective and safe way to decrease complications of blood transfusion is to suppress intraoperative and postoperative blood loss [4,5].

Several methods had been applied for suppressing perioperative blood loss, including tourniquet, intraoperative blood salvage, and the application of antifibrinolytic agents [6,7]. Antifibrinolytic agents are widely used and potentially interrupt the cascade of haemostatic abnormalities and enhance hemostasis [8]. As a result, they may potentially reduce blood loss, blood transfusion, and transfusion reaction.

Tranexamic acid is a kind of synthetical antifibrinolytic agent, which blocks the activation of plasminogen to plasmin and blocks the fibrinolytic action of plasmin on fibrin. With the administration of TA, activation of plasminogen and fibrinolysis are both suppressed [9,10]. TA can prevent clots and reduce blood loss. Topical and intravenous administration of TA has been applied in many surgical practices, including TKA, which not only could reduce topical blood loss but also inhibits plasmin-induced platelet activation to affect hemostasis of the cardiopulmonary system [9].

More and more researchers have reported positive outcomes of administration of TA in TKA. However, the TA treatment administration varied among countries and surgeons. Several researchers have found that the use of TA could increase the risk of deep vein thrombosis and question the effectiveness and safety of TA [11]. The goal of this analysis is to further investigate the safe and effective role of using tranexamic acid (TA) in reducing transfusion rate and blood loss in total knee arthroplasty.

Material and Methods

This study was conducted in accordance with the guidelines described in the Cochrane Handbook for meta-analysis and also based on the recommended PRISMA checklist guidelines [12].

Search strategy

We searched PubMed, Web of Science, and EMBASE from 1950 to June 2015 to identify relevant studies. The following selected Medical Subject Headings terms were used for the initial literature search: 'Anti-fibrinolytics' or 'Tranexamic acid' or 'Cyklokapron' and 'total knee replacement'or 'total knee arthroplasty'.

Criteria of eligibility

Studies were considered eligible if they met the following criteria: 1) patients underwent a primary TKA; 2) the experiment group was considered as the administration of intravenous TA and placebo or no treatment for control group; 3) outcome measures included total blood loss, blood transfusion rate, and incidence of thromboembolism complications; 4) randomized controlled trials and prospective comparative studies. Exclusion criteria: 1) allergy to TA; 2) bleeding disorders; 3) thromboembolic complications.

Data extraction

Eligible articles were reviewed independently by 2 investigators (Yu Xiao and Weili Li). The titles and abstracts of the references were read. Any disagreement on a controversial study was settled by discussion and consensus.

Quality assessment

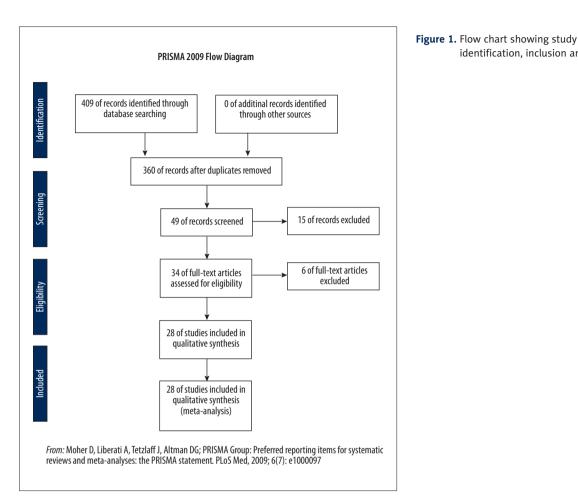
The methodological quality of included studies was evaluated with a generic evaluation tool [13]. The quality of each study was evaluated by a score from 0 to 24. Any disagreement on a controversial study was resolved by discussion and consensus.

Statistical analysis

Continuous variables were indicted as mean standard deviation, and the outcomes were analyzed by mean difference with 95% confidence interval. Dichotomous variables for each arm were indicted as risks, and the outcomes were analyzed by a risk difference with 95% CI.

Heterogeneity was conducted using Cochran's Q test and Higgins I-squared statistic. Heterogeneity was defined as p<0.10 or $l^2 >50\%$ [14]. The random-effects model was used if heterogeneity was observed (P<0.10), and the fixed-effects model was used in the absence of between-study heterogeneity (P>0.1). All of the above calculations were performed using RevMan 5.2 (Cochrane collaboration, Oxford, UK) software.

identification. inclusion and exclusion.



Results

Characteristics of the eligible studies

We initially found 409 studies in our search of PubMed, Web of Science, and EMBASE. With the review of these abstracts, 49 potentially relevant studies were identified as eligible for full-text review, and 34 RCTs met the inclusion criteria. Among them, 6 trials were further excluded because TA was administered through knee joint injection in 2 trials, and placebo or blank control group was not set in 2 trials. Finally, 28 studies [15-41] were identified according to the inclusion criteria of the meta-analysis (Figure 1) and detail information were displayed in Table 1.

Total blood loss

Total blood loss was reported in 24 studies [15-17,19,20, 22-29,30-33,35-42]. Total blood loss was dramatically decreased via the application of TA by a mean of 420 ml [95% Cl: -514 to -327, P<0.00001]. However, significant heterogeneity (I²=90%) among included studies was detected, so the random-effects model was used. Based on data (420 ml [95% CI: -514 to -327, P<0.00001]) displayed in Figure 2A, we

conclude that total blood loss volume decreased sharply with the use of TA in TKA.

Blood transfusion rate

Blood transfusions were recorded in 26 trials [15–26,28,30–42] including 2410 patients. Among them, there were 172 patients who took TA and 318 patients who took placebo who needed transfusion. TA significantly reduced the number of patients who needed transfusion [P<0.01, RD=-0.26, 95% CI -0.33 to -0.19]. Heterogeneity existed between trials [P<0.01, I²=80%]. As shown in Figure 2B ([P<0.01, RD=-0.26, 95% CI -0.33 to -0.19]), TA can also reduce the blood transfusion rate of patients who underwent TKA.

Postoperative drainage

Fifteen studies (997 patients) reported postoperative drainage [15,19,20,24–29,31,33,38,40–42]. The application of TA significantly decreased postoperative drainage [MD: -275.47 mL, 95% CI -362.64 to -188.30; P<0.00001]. There was significant heterogeneity [P<0.00001; I²=94%]. The TA group had less postoperative drainage compared to the control group (Figure 3).

McConnell 2012

Molloy 2007

Orpen 2006

Seo 2013

Shen 2015

Tanaka 2001

Veien 2002

Zhang 2007

Zohar 2004

Total (95% CI)

Total events

Α			TA		C	ontrol			Mean difference	Maan d	ifference	
	Study or subgroup	Mean		Total	Mean		Total	Weight		IV, random		
	Alvarez 2008	1,304	621	46	1,744	804	49	,	-443.00 [-730.89, -155.11]	1	,	
	Benoni 1996	730	280	43	1,410	480	43		-680.00 [-846.09, -513.91]			
	Camarasa 2006	1,095	473	35	1,784	660	60		-689.00 [-918.01, -459.99]			
	Chareoncholvanich 2011		234	50	1,208	421	50		-480.50 [-614.01, -346.99]			
	Dhillon 2011	274.62		52	809.64	227.3	56		-535.02 [-604.02, -466.02]	-		
	Engel 2001	800	315	12	865	388	12	3.5%	-65.00 [-347,77, 217.77]			
	Gautam 2011	427.6		20	911.5		20	4.6%	-483.90 [-611.64, -356.16]			
	Good 2003	1,045	368.7	27	1,426	620.9	24	3.4%	-381.00 [-665.69, -96.31]			
	Hippala 1995	847	356	15	1,549	574	13	2.9%-	-702.00 [-1,062.30, -341.70]	←		
	Hippala 1997	689	289	39	1,509	643	38		-820.00 [-1043.66, -596.34]	←		
	Ido 2000	276.9	153.1	21	518.5	213.6	22		-241.60 [-352.30, -130.90]			
	Jansen 1999	678	352	15	1,419	607	21		-741.00 [-1,055.85, -426.15]	←		
	Kakar 2009	225.52	514.77	25	452	195.48	25	4.0%	-226.48 [-442.33, -10.63]			
	Lin 2011	833	144	50	1,453	383	50	4.7%	-620.00 [-733.42, -506.58]			
	MacGillivray 2011	570	280	40	918	549	20	3.7%	-348.00 [-603.77, -92.23]			
	Maniar 2012	809	34.1	40	1,097	874.2	40	3.5%	-288.00 [-559.12, -16.88]			
	Molloy 2007	1,225	499	50	1,415	416	50	4.3%	-190.00 [-370.07, -9.93]			
	Orpen 2006	660	182	15	725	178	14	4.6%	-65.00 [-196.06, 66.06]		-	
	Seo 2013	528	227	50	833	412	50	4.6%	-305.00 [-435.38, -174.62]			
	Shen 2015	958	98.6	41	1,172	466	40	4.5%	-214.00 [-361.53, -66.47]			
	Tanaka 2001	896	187.2	22	1,470	264.8	26		-574.00 [-702.37, -445.63]			
	Veien 2002	409.7	174.9	15	761.7	313.1	15		-352.00 [-533.49, -170.51]			
	Zhang 2007	559	159	51	1,208	243	51	4.9%	-649.00 [-728.70, -569.30]	-		
	Zohar 2004	121	81	20	249	130	20	4.9%	–128.00 [–195.13, –60.87]			
	Total (95% CI) Heterogeneity: Tau ² =445 Test for overall effect: Z=				23 (P<0.0	0001);	809 ² =90%	100.0%	–420.76 [–514.25, –327.28]	-1000 -500 0 Favours [tranexamic acid]	500 Favours [control]	 1000
В					_							
		-	TA			ontrol			Risk difference	Risk dif		
	Study or subgroup	Eve	ents	Total	Even		otal	Weight	IV, random, 95% Cl	IV, random	, 95% CI	
	Alvarez 2008		1	46	6		49	4.7%	-0.10 [-0.20, 0.00]			
	Benoni 1996		8	43	24		43	3.8%	-0.37 [-0.56, -0.18]			
	Camarasa 2006		1	35	23		60	4.4%	-0.35 [-0.49, -0.22]			
	Chareoncholvanich 2012	3		60	53		60	4.3%	-0.32 [-0.47, -0.17]			
	Chareoncholvanich 2011	2		50	45		50	4.1%	-0.34 [-0.50, -0.18]			
	Dhillon 2011	2		52	56		56	4.4%	-0.48 [-0.62, -0.34]			
	Ellis 2001		1	10	7		10	2.4%	-0.60 [-0.94, -0.26]			
	Engel 2001		0	12	3		12	3.1%	-0.25 [-0.51, -0.01]			
	Gautam 2011		7	20	15		20	2.9%	-0.40 [-0.68, -0.12]			
	Good 2003		3	27	14		24	3.4%	-0.47 [-0.70, -0.24]			
	Hippala 1995	1		15	12		13	2.9%	-0.26 [-0.54, 0.02]			
	Hippala 1997	1		39 21	34		38	3.9%	-0.46 [-0.64, -0.28]			
	Jansen 1999 Lee 2012		2 4	21 36	13 15		21 36	3.3% 3.8%	-0.52 [-0.77, -0.28]			
	Lee 2012 Lin 2011		4 2	30 50	10		30 50	3.8% 4.5%	-0.31 [-0.50, -0.11] -0.16 [-0.28, -0.04]			
	MacGillivray 2011	1		40	10		20	4.3% 3.1%	-0.17 [-0.44, 0.09]		_	
	Maniar 2012		8	40	10		40	3.9%	-0.05 [-0.23, 0.13]		_	
	manul 2012		•	10	10			3.270	0.05 [0.25, 0.15]		_	

Figure 2. (A) Forest plot diagram showing the effect of TA on total blood loss. (B) Forest plot diagram showing the effect of TXA on blood transfusion rate.

4.9%

4.3%

3.2%

4.0%

4.4%

4.6%

3.7%

4.9%

3.2%

100.0%

0.00 [-0.08, 0.08]

-0.12 [-0.26, 0.02] -0.15 [-0.40, 0.10] -0.14 [-0.31, 0.03]

-0.03 [-0.16, -0.11]

-0.36 [-0.48, -0.24]

-0.13 [-0.33, -0.06]

-0.43 [-0.69, -0.18]

-0.26 [-0.33, -0.19]

-0.08 [-0.16, 0.00]

0

5 1

10

4

47

0

47

283 Heterogeneity: Tau²=0.03; Chi²=127.71, df=25 (P<0.00001); l²=80%

Test for overall effect: Z=7.05 (P<0.00001)

3

22

50

15

50

41

73

15

51

20

933

0

11

3 17

5

26 2

51

14

479

22

50 14

50

40

26

15

51

24

894

3098

0.5

Favours [control]

1

-0.5

Favours [tranexamic acid]

0

-1

Study or subgroup	Mea	TA n SD	Total	Mean	Control SD	Total	Weight	Mean difference IV, random, 95% Cl	Mean differ IV, random, 9	
Alvarez 2008	159	110	46	534	351	49	7.1%	-375.00 -478.29, -271.71	[
Chareoncholvanich 2011	727	234	50	1,208	431	50	6.6%	-481.00 -616.94, -345.06		
Dhillon 2011	274.62	128.34	52	809	227.3	52	7.5%	-534.38 -605.33, -463.43		
Good 2003	385	0	27	845	0	24		Not estimable		
Hippala 1995	128	76	39	641	320	38	7.0%	-513.00 -617.50, -408.50		
Hippala 1997	127	95	15	576	245	13	6.5%	-449.00 -590.59, -307.41		
Ido 2000	227.1	101.5	21	450.7	203.4	22	7.2%	-223.60 -319.04, -128.16		
Jansen 1999	122	96	21	200	125	21	7.5%	-78.00 -145.41, -10.59		
Kakar 2009	160	87	12	286	83	12	7.5%	-126.00 -194.03, -57.97		
Lin 2011	478	166	50	556	248	50	7.3%	-78.00 -160.72, 4.72		
Maniar 2012	385	186.2	40	500	184	40	7.3%	-115.00 -196.12, -33.88		
Shen 2015	195	98.6	41	341	118	40	7.7%	-146.00 -193.41, -98.59	-	
Veien 2002	409.7	174.9	15	761.7	313.1	15	5.9%	-352.00 -533.49, -170.51		
Zhang 2007	478	172	51	814	156	51	7.5%	-336.00 -399.73, -272.27		
Zohar 2004	121	81	20	249	130	20	7.5%	-128.00 -195.13, -60.87		
Total (95% CI)			500			497	100.0%	-275.47 [-362.64, -188.30]	•	
Heterogeneity: Tau ² =252 Test for overall effect: Z=				13 (P<0.0	00001);	l²=94%			-500 -250 0	250 500
									Favours [tranexamic acid]	Favours [control]

Figure 3. Forest plot diagram showing the effect of TA on postoperative drainage.

Incidence of DVT

In 26 trials [15–20,22–30,32–42], data on DVT were available. Studies included 919 and 877 patients in the TA group and control group, respectively. Among them, 22 patients in the TA group and 20 in the control group developed DVT. There was no statistically significant difference between TA and control groups (P=0.91) and no heterogeneity between trials (P=1.00, l^2 =0) (Figure 4A).

Incidence of PE

In 15 trials, data were available on patient outcomes [16–19, 23,25–27,30,32,33,35,37–39,42]. In the TA group, no PE was reported. In the control group, 3 patients out of 550 developed PE. There was no statistically significant difference in the risk of developing PE between TA and control groups (P=0.47). There was no heterogeneity between trials (P=1.00, l^2 =0) (Figure 4B).

Discussion

The results of the study demonstrate that the application of TA could significantly reduce total blood loss, allowing patients to benefit from it more. Moreover, the number of patients who needed to receive allogeneic transfusions in TKA was dramatically decreased with the application of TA. This study demonstrated that use of TA did not increase the incidence of DVT or PE. However, significant heterogeneity was detected between trials. Many factors may lead to the existence of heterogeneity, such as different types of anesthesia, surgical techniques, or TA use. The reasons for high heterogeneity may be that hidden bleeding was rarely measured or that different times of extraction of the drain tube were reported. Among all antifibrinolytic agents, TA is not the only agent used in TKA. Other antifibrinolytic agents include fibrin spray, epsilon aminocaproic acid, and aprotinin, which have been used to decrease surgical blood loss [43]. However, some defects had been detected via clinical observations. These antifibrinolytic agents had been shown to be more costly and less effective than TA [44]. TA could bring better penetration into major joints than fibrin spray and it is less expensive and safer than aprotinin and more effective than EACA. The binding of TA to plasminogen is 6 to 10 times more potent than that of EACA [45].

Because of activation of fibrinolysis and the exposed surface of cancellous bone, TKA could cause significant blood loss. Here, the most noteworthy result of this study was the efficiency of TA in reducing total blood loss and transfusion rates after TKA. Our study indicates that intravenous use of TA results in sparing at a mean of 420 ml of total blood loss and significantly reduced transfusion rates. At the same time, the use of TA could effectively reduce postoperative drainage volume. Because of occurrence of the occasional thromboembolism events, some physicians are reluctant to use TA in TKA. However, the safety of TA could further be confirmed with the help of our study. In our study, 22 patients in the TA group and 20 patients in the control group developed DVT, with no significant difference (P=0.91). Only 3 patients developed PE events and they all belonged to the control group. The difference between TA and control group was also not statistically significant (P=0.47). With the evidence collected, TA did not increase risks of DVT or PE. Tourniquet use is common in TKA, which activates the local fibrinolysis system and significantly increases blood loss after surgery. TA has antifibrinolytic potency via blocking the lysine-binding sites of plasminogen and is mostly used in bleeding caused by local accentuation of fibrinolysis. On this point, TA mainly resists the fibrinolysis effect

Study or subgroup	TA Events	Total	Cont Events	rol Total	Weight	Mean difference IV, random, 95% Cl	Mean difference IV, random, 95% Cl
, , ,					,		IV, random, 95% Ci
Alvarez 2008	0	46	0	49	5.4%	0.00 [-0.04, 0.04]	
Benoni 1996	4	43	3	43	4.9%	0.02 [-0.09, 0.14]	
Camarasa 2006	0	35	0	60	5.0%	0.00 [-0.04, 0.04]	Ť
Chareoncholvanich 2012	0	50	0	50	5.7%	0.00 [-0.04, 0.00]	+
Chareoncholvanich 2011	0	60	0	60	6.8%	0.00 [-0.03, 0.03]	+
Dhillon 2011	0	52	1	56	6.1%	-0.02 [-0.07, 0.03]	
Engel 2001	2	12	0	12	1.4%	0.17 [-0.07, 0.41]	
Gautam 2011	0	20	0	20	2.3%	0.00 [-0.09, 0.09]	
Good 2003	2	27	2	24	2.9%	-0.01 [-0.16, 0.14]	
Hippala 1995	0	15	2	13	1.6%	-0.15 [-0.37, 0.06]	
Hippala 1997	2	39	2	38	4.4%	0.00 [-0.10, 0.10]	
ldo 2000	0	21	0	22	2.4%	0.00 [-0.09, 0.09]	
Jansen 1999	0	21	2	21	2.4%	-0.10 [-0.24, 0.05]	
Kakar 2009	0	25	0	25	2.8%	0.00 [-0.07, 0.07]	
Lee 2012	3	36	4	36	4.1%	-0.03 [-0.16, 0.11]	.
MacGillivray 2011	2	40	0	20	3.0%	0.05 [-0.05, 0.15]	- +-
Maniar 2012	0	40	0	40	4.5%	0.00 [-0.05, 0.05]	- + -
McConnell 2012	Õ	22	Ő	22	2.5%	0.00 [-0.08, 0.08]	_
Molloy 2007	Õ	50	Ő	50	5.7%	0.00 [-0.04, 0.04]	+
Orpen 2006	Õ	15	Õ	14	1.6%	0.00 [-0.12, 0.12]	_
Seo 2013	3	50	Ő	50	5.7%	0.06 [-0.01, 0.13]	
Shen 2015	4	41	4	40	4.6%	0.00 [-0.13, 0.13]	
Tanaka 2001	0	73	0	26	4.4%	0.00 [-0.05, 0.05]	
Veien 2002	Ő	15	Ő	15	1.7%	0.00 [-0.12, 0.12]	
Zhang 2007	Ő	51	Ő	51	5.8%	0.00 [-0.04, 0.04]	
Zohar 2004	Ő	20	Ő	20	2.3%	0.00 [-0.09, 0.09]	
Total (95% CI) Total events		919		877	100.0%	0.00 [-0.02, 0.02]	T
Heterogeneity: Chi ² =9.75, c	22 df=25 (P=1.0	00); l ² =0%	20			-	
	df=25 (P=1.0	00); l ² =0%	20			-	-0.2 -0.1 0 0.1 0.2
Heterogeneity: Chi ² =9.75, o	df=25 (P=1.0	00); l ² =0%	20			-	-0.2 -0.1 0 0.1 0.2 Favours [tranexamic acid] Favours [control]
Heterogeneity: Chi ² =9.75, o	df=25 (P=1.0	00); l ² =0%	20			-	
Heterogeneity: Chi ² =9.75, o	df=25 (P=1.0 11 (P=0.91)			rol			Favours [tranexamic acid] Favours [control]
Heterogeneity: Chi ² =9.75, Test for overall effect: Z=0.1	df=25 (P=1.0 11 (P=0.91) TA		Cont		Weight	Risk difference IV. random. 95% CI	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Study or subgroup	df=25 (P=1.0 11 (P=0.91) TA Events	Total	Cont Events	Total	Weight	IV, random, 95% Cl	Favours [tranexamic acid] Favours [control]
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Study or subgroup Benoni 1996	df=25 (P=1.0 11 (P=0.91) TA <u>Events</u> 0	Total 43	Cont Events 1	Total 43	7.9%	IV, random, 95% Cl -0.02 [-0.09, 0.04]	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Study or subgroup Benoni 1996 Camarasa 2006	df=25 (P=1.0 11 (P=0.91) TA Events 0 0	Total 43 35	Cont Events 1 0	Total 43 60	7.9% 8.1%	IV, random, 95% CI -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04]	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Study or subgroup Benoni 1996 Camarasa 2006 Chareoncholvanich 2012	df=25 (P=1. 11 (P=0.91) TA Events 0 0 0	Total 43 35 60	Cont Events 1 0 0	Total 43 60 60	7.9% 8.1% 11.0%	IV, random, 95% CI -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.03, 0.03]	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Study or subgroup Benoni 1996 Camarasa 2006 Chareoncholvanich 2012 Chareoncholvanich 2011	df=25 (P=1. 11 (P=0.91) TA Events 0 0 0 0 0	Total 43 35 60 50	Cont Events 1 0 0 0	Total 43 60 60 50	7.9% 8.1% 11.0% 9.1%	IV, random, 95% Cl -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.03, 0.03] 0.00 [-0.04, 0.04]	Favours [tranexamic acid] Favours [control] Risk difference
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Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Benoni 1996 Camarasa 2006 Chareoncholvanich 2012 Chareoncholvanich 2011 Gautam 2011 Hippala 1995 Hippala 1997 Ido 2000 Lee 2012 MacGillivray 2011	df=25 (P=1.(11 (P=0.91) TA Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 35 60 50 20 15 39 21 36 40	Cont Events 1 0 0 0 1 1 1 0 0 0 0	Total 43 60 60 50 20 13 38 22 36 40	7.9% 8.1% 11.0% 9.1% 3.7% 2.5% 7.0% 3.9% 6.6% 7.3%	IV, random, 95% CI -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.03, 0.03] 0.00 [-0.04, 0.04] 0.00 [-0.09, 0.09] -0.08 [-0.26, 0.11] -0.03 [-0.10, 0.04] 0.00 [-0.09, 0.05] 0.00 [-0.05, 0.05]	Favours [tranexamic acid] Favours [control] Risk difference
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Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Benoni 1996 Camarasa 2006 Chareoncholvanich 2012 Chareoncholvanich 2011 Gautam 2011 Hippala 1995 Hippala 1995 Hippala 1997 Ido 2000 Lee 2012 MacGillivray 2011 Maniar 2012 Molloy 2007 Seo 2013 Tanaka 2001	df=25 (P=1.0 11 (P=0.91) TA Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 35 60 50 20 15 39 21 36 40 22 50 50 73	Cont Events 1 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0	Total 43 60 50 20 13 38 22 36 40 22 50 50 26	7.9% 8.1% 11.0% 9.1% 3.7% 2.5% 7.0% 3.9% 6.6% 7.3% 4.0% 9.1% 9.1% 7.0%	IV, random, 95% CI -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.09, 0.09] -0.08 [-0.26, 0.11] -0.03 [-0.10, 0.04] 0.00 [-0.09, 0.09] 0.00 [-0.05, 0.05] 0.00 [-0.05, 0.05] 0.00 [-0.04, 0.04] 0.00 [-0.05, 0.05]	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Benoni 1996 Camarasa 2006 Chareoncholvanich 2012 Chareoncholvanich 2011 Gautam 2011 Hippala 1995 Hippala 1995 Hippala 1995 Hippala 1997 Lido 2000 Lee 2012 MacGillivray 2011 Maniar 2012 Molloy 2007 Seo 2013	df=25 (P=1. 11 (P=0.91) TA Events 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 35 60 50 20 15 39 21 36 40 22 50 50	Cont Events 1 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 60 50 20 13 38 22 36 40 22 50 50	7.9% 8.1% 11.0% 9.1% 3.7% 2.5% 7.0% 3.9% 6.6% 7.3% 4.0% 9.1% 9.1%	IV, random, 95% CI -0.02 [-0.09, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.04, 0.04] 0.00 [-0.09, 0.09] -0.08 [-0.26, 0.11] -0.03 [-0.10, 0.04] 0.00 [-0.05, 0.05] 0.00 [-0.05, 0.05] 0.00 [-0.04, 0.04] 0.00 [-0.04, 0.04]	Favours [tranexamic acid] Favours [control] Risk difference
Heterogeneity: Chi ² =9.75, c Test for overall effect: Z=0.1 Benoni 1996 Camarasa 2006 Chareoncholvanich 2012 Chareoncholvanich 2011 Gautam 2011 Hippala 1995 Hippala 1995 Hippala 1997 Ido 2000 Lee 2012 MacGillivray 2011 Maniar 2012 Molloy 2007 Seo 2013 Tanaka 2001	df=25 (P=1. 11 (P=0.91) TA Events 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 35 60 50 20 15 39 21 36 40 22 50 50 73	Cont Events 1 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0	Total 43 60 50 20 13 38 22 36 40 22 50 50 26	7.9% 8.1% 11.0% 9.1% 3.7% 2.5% 7.0% 3.9% 6.6% 7.3% 4.0% 9.1% 9.1% 7.0%	$\begin{array}{c} \text{IV, random, 95\% Cl} \\ \hline -0.02 \ [-0.09, 0.04] \\ 0.00 \ [-0.04, 0.04] \\ 0.00 \ [-0.04, 0.04] \\ 0.00 \ [-0.09, 0.03] \\ 0.00 \ [-0.09, 0.09] \\ -0.08 \ [-0.26, 0.11] \\ -0.03 \ [-0.10, 0.04] \\ 0.00 \ [-0.09, 0.09] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.04, 0.04] \\ 0.00 \ [-0.04, 0.04] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.05, 0.05] \\ 0.00 \ [-0.09, 0.09] \\ \end{array}$	Favours [tranexamic acid] Favours [control] Risk difference
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Figure 4. (A) Forest plot diagram of TA on incidence of DVT. (B) Forest plot diagram of TA on incidence of PE.

caused by tourniquet and generally has little influence on the normal fibrinolysis system. These results are consistent with other meta-analyses [46,47]. The major contraindication to administering TA is allergy. Because high doses of TA might increase the incidence of thrombosis, it is not recommended in patients who have PE history or state. Poeran [48] reported that patients who received TA had lower rates of blood transfusion (7.7 vs. 20.1%) as well as combined complications (1.9 vs. 2.6%). With an increasing dose of TXA (0–1 g, 1–2 g and

>3 g), odds (OR: 0.31 to 0.38) of blood transfusion decreased and risk of complications did not increase significantly.

In our study, most of the trials were of high quality (QAS: 19–24), which makes the conclusions drawn from this metaanalysis more reliable, but there are still many limitations in our analysis: (I) Some uncontrolled factors among the studies may have accounted for the significant heterogeneity in total blood loss, transfusion requirements, and drain loss. (II) We

Table 1. Characteristics of included studies.

Author, year	Cases	Intervention	Control	DVT prophylaxis	Blood transfusion	DVT screening method	QAS
Alvarez 2008	95 (46)	10 mg/kg 30 min before tourniquet deflation, 1 mg/kg/h infusion for 6 h	S	Bemiparin	Hb <90 g/L	Clinical exam	23
Benoni 1996	86 (43)	10 mg/kg before tourniquet deflation, 10 mg/kg after 3 h	S	LMWH	Hb <85 g/L	Clinical exam	23
Camarasa 2006	95 (35)	10 mg/kg before tourniquet deflation, repeated 3 h later	S	Dalteparin sodium	Hb <80 g/L	Clinical exam/ ultrasound	23
Chareancholvanich 2012	120 (60)	10 mg/kg 10 min before tourniquet deflation, then 10 mg/kg 3 h postoperatively	NA	Ankle motion	Hb <100 g/L	Clinical exam	21
Charoencholvanich 2011	100 (50)	10 mg/kg 10 min before tourniquet deflation, repeated 3 h later	S	Ankle motion	Hb <100 g/L	Clinical exam	21
Dhillon 2011	108 (52)	10 mg/kg IV 10 min tourniquet deflation and after 3 h	NA	LMWH	Hb <90 g/L	Clinical exam	22
Ellis 2001	20 (10)	15 mg/kg 30 min before tourniquet deflation, 10 mg/kg/h infusion for 12h	S	Enoxaparin	Hct <27%	NA	24
Engel 2001	24 (12)	15 mg/kg before tourniquet deflation, 10 mg/kg after 3 h	NA	Certoparin	Hb <100 g/L	Clinical exam	21
Gautam 2011	40 (20)	10 mg/kg 0.5 h before tourniquet deflation, 2 mg/kg after 3 h	S	NA	Hb <80 g/L	Clinical exam	20
Good 2003	51 (27)	10 mg/kg before tourniquet deflation, repeated 3 h later	S	Fragmin	Hb <90 g/L	Clinical exam/ ultrasound	20
Hiippala 1995	28 (15)	15 mg/kg before tourniquet deflation	NS	LMWH	Hb <100 g/L	Clinical exam	23
Hiippala 1997	77 (39)	15 mg/kg before tourniquet deflation, additional doses of 10 mg/kg after 3h	S	Enoxaparin	Hb <100 g/L	Clinical exam	23
ldo 2000	43 (21)	1 g before tourniquet release,1 g 3 h after operation	NA	NA	NA	Clinical exam	19
Jansen 1999	42 (21)	15 mg/kg 30 min before tourniquet deflation,repeated every 8 h for 3 d	S	Fraxiparine	PCV <26%	Clinical exam	21
Kakar 2009	24 (12)	10 mg/kg before tourniquet deflation, 1 mg/kg/h until wound closure	NS	NA	Hb <80 g/L	NA	23

Author, year	Cases	Intervention	Control	DVT prophylaxis	Blood transfusion	DVT screening method	QAS
Lee 2012	72 (36)	10 mg/kg before tourniquet deflation, repeated 6 h later	NA	LMWH	Hb <80 g/L	Clinical exam/ ultrasound	20
Lin 2011	100 (50)	10 mg/kg IV before deflation of the tourniquet	S	LMWH	Hb <85 g/L	NA	18
MacGillivray 2011	60 (20)	10-15 mg/kg tourniquet deflation and after 3 h	NS	Warfarin	Hb <80 g/L	Clinical exam/CT	24
Maniar 2012	80 (40)	10 mg/kg IV before deflation of the tourniquet	S	LMWH	Hb <85 g/L	Clinical exam	22
McConnell 2012	44 (22)	10 mg/kg at induction of anesthesia	NA	Aspirin	NA	Clinical exam	20
Molloy 2007	100 (50)	500 mg 5 min before tourniquet deflation, repeated 3 h later	NA	Aspirin	Hct <25%	Clinical exam	23
Orpen 2006	29 (15)	15 mg/kg at cement mixing commenced	NS	Fragmin	Hb <90 g/L	ultrasound	23
Seo 2013	100 (50)	1.5g TXA/100mL NS	S	NA	Hb <80 g/L	NA	19
Shen 2015	96 (46)	100 mL,15 min before tourniquet deflation	S	LMWH	Hb <80 g/L	ultrasound	22
Tanaka 2001	99 (73)	10 mg/kg before surgery, 10 mg/kg 10 min before tourniquet deflation	S	NA	NA	Venography	19
Veien 2002	30 (15)	10 mg/kg before tourniquet deflation, repeated 3 h later	NS	Fraxiparine	Hct <28%	Clinical exam	22
Zhang 2007	102 (51)	1 g before tourniquet deflation, repeated 3 h later	S	LMWH	NA	Clinical exam	19
Zohar 2004	40 (20)	15 mg/kg 15 min before tourniquet deflation,10 mg/kg/h infusion for 12h	NA	Enoxaparin	Hct <28%	Clinical exam/ ultrasound	21

Table 1 continued. Characteristics of included studies.

NA - not available; S - saline; NS - normal saline; LMWH - low-molecular-weight heparin; QAS - quality assessment score.

selected studies that excluded high-risk patients, including patients with cardiovascular disorders, and DVT events. Thus, our results should be interpreted with caution.

Conclusions

This meta-analysis concludes that TA significantly reduces total blood loss and transfusion rate after TKA and does not apparently increase the risk of DVT or PE. Lager-scale prospective

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randomized controlled studies are needed and the optimal administration of TA in TKA still needs further investigation. Moreover, to better highlight the safety and efficacy of TA in TKA, studies that compare TA with other anti-fibrinolytics are needed.

Conflict of Interest

The authors have declared that no competing interests exist.

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