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Research Article

Intra-Articular Versus Intravenous Tranexamic Acid Application in Total Knee Arthroplasty

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Abstract

Objectives: Tranexamic acid (TXA) has been reported to decrease bleeding in total knee arthroplasty (TKA) with different administration routes of different efficacies. We aim to review intra-articular (IA) versus intravenous (IV) TXA injection in TKA.

Methods: A systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA). The search strategy included the following databases: (1) PubMed, (2) Google Scholar, (3) Scopus, (4) Web of Science (ISI), (5) Embase, (6) Cochrane central and (7) CINHAL where we searched for relevant randomised controlled trials that compared the effictiveness of IA TXA with IV injection in TKA.

Results: Out of 16 studies that met the inclusion criteria, three reported that IA was better than IV TXA injection, two reported the opposite while the rest reported equal efficacies of both routes. In addition, only four studies reported a significant difference between IA and IV groups in reducing post-operative hemoglobin and five in reducing total blood loss while three in decreasing the need to blood transfusion. Thromboembolic complications and wound infections were reported by four studies each, and for that, throbmboprophylactics (mostly low-molecular-weight-heparin) and antibiotics were prescribed.

Conclusion: It was found that both IA and IV routes are effective. However, the frequency and dosage of injection may affect this efficacy. Moreover, many factors should be considered to increase the quality of the studies that compare these two routes.

Keywords: *Intra-Articular; Intravenous; Total Knee Arthroplasty; Tranexamic Acid; Systematic Review*

Introduction

Total knee arthroplasty (TKA) is a surgical procedure that is widely used in the orthopedic unit especially with elder patients. It has been proven as a cost-effective and beneficial procedure that is mainly used to treat severe osteoarthritic knees. It enhances the quality of life together with other various benefits which will enable patients, especially the elderly, to pursue their daily normal activities and can end their suffering [1]. Although the procedure has very few complications, it has been associated with postoperative blood loss in patients that need a pre-operative allogeneic blood transfusion (ABT) which may impact patients' recovery [2,3]. This will increase the risk of developing anemia and other complications as syncope, fatigue, breathlessness, cardiac abnormality, delayed wound healing, hypovolemic shock, renal failure, delayed healing of wounds, and increased financial burdens [1].

The reported amount of blood loss is variable, however, an average estimate of 1500 ml has been commonly associated with this procedure [4-6]. Surgical trauma has been reported to be the major cause for postoperative blood loss which consequently leads to the activation of fibrinolysis and coagulation cascades [7]. Moreover, as it is widely used in such procedures to decrease the blood loss, a tourniquet will lead to further activation of the fibrinolytic system leading to more blood loss [8,9]. In addition, transfusion practices are risky and have many concerns including the occurrence of infections, and immunologic abnormal reactions that can lead to several complications that may eventually end up with death [10,11]. Therefore, blood conservative procedures have been developed to reduce the risks and costs of blood loss and subsequent transfusion [12-14].

Medical treatments such as tranexamic acid (TXA) and aminocaproic acid have been reported in this field [4]. TXA, which is a synthetic antifibrinolytic agent that leads to the stabilization of fibrin clots [15], has been previously reported to effectively decrease postoperative blood loss in other non-orthopedic approaches as cardiac [16] and dental [17] procedures. It acts by decreasing the effects of plasmin which will lead to an increased state of hemostasis and therefore reduce the fibrinolytic events [18-20]. However, its effectiveness with TKA surgeries has been reported by a minimal number of studies with a lot of concerns regarding the safety of intravenous (IV) injection and the high risk to develop thrombotic events as deep venous thrombosis (DVT) and pulmonary thromboembolism. Therefore, different routes of administration as intra-articular (IA) applications of TXA have been approached to decrease the risk of these complications [21-24]. The advantages of IA injection include fewer systematic side effects, local inhibition of the fibrinolytic system, and easy administration [25,26]. Favoring IA over IV administration and vice versa, however, is controversial as both routes have shown several advantages in reducing postoperative blood loss after TKA procedures [27-31]. Moreover, various studies have reported different indications and doses for both routes [32-35].

Aim of the Study

Therefore, in this study, the aim is to systematically review the effectiveness of IATXA injection in reducing TKA postoperative hemorrhages and the need to perform blood transfusions. Moreover, summarizing the results of previously published randomized controlled trials (RCTs) that compared other TXA administration routes with IA injection.

Methods

Search strategy

In this systematic review, the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) in conducting the study was followed. The search strategy for the relevant studies was on July 2020 on the following databases: (1) PubMed, (2) Google Scholar, (3) Scopus, (4) Web of Science (ISI), (5) Embase, (6) Cochrane central and (7) CINHAL databases with the following search term: (total ankle arthroplasty OR total arthroplasty replacement OR TKA OR TKR) AND (tranexamic acid or TXA). All relevant articles were included and exported using Endnote X9 program for removing all potential duplicates. Afterward, the results were exported to an excel sheet for screening according to the inclusion and exclusion criteria.

Inclusion and exclusion criteria for screening

All of the following criteria should be achieved by a study to be included in the review: (1) A randomized controlled trial, (2) that compares the effectiveness of IA and IV TXA administration in TKA procedures, (3) in patients that are older than 18 years, (4) in terms of blood loss or postoperative hemoglobin levels, (5) and were written in English. The excluded studies was: (1) had different study designs than RCTs, (2) were not human trials, (3) had overlapping or duplicated data and (4) were not written in English.

Screening for studies

At first, title and abstract screening was done to include the relevant studies and exclude the irrelevant ones. After that, full-texts screening was done to finally include all the studies that met all of the inclusion criteria. Any disagreement was solved by a proper discus-

sion and consensus with a supervisor/librarian. Extracted information includes basic information as study year and first author names, study design, sample size, patient's characteristics, study outcomes including the primary and secondary ones.

Quality assessment of the included papers

This step aims to assess the risk of bias in the included studies. For this, the Cochrane Collaboration's proposal was used with RevMan 5.3 for the risk of bias assessment of the included RCTs. A scale of randomization, allocation concealment, blinding, withdrawals, and dropouts were used and studies were sorted as high, low, or unclear according to their scale scores.

Results

Search results

A summary of the search strategy and results is presented in the PRISMA flow chart in figure 1. The search resulted in the aforementioned databases resulted in a total of 3125 search results. By using Endnote, 780 articles were removed, and after title and abstract screening, another 2312 articles were removed. After full-text screening, 130 results were excluded according to the inclusion and exclusion criteria. The final list included 16 RCT studies that met the inclusion criteria.

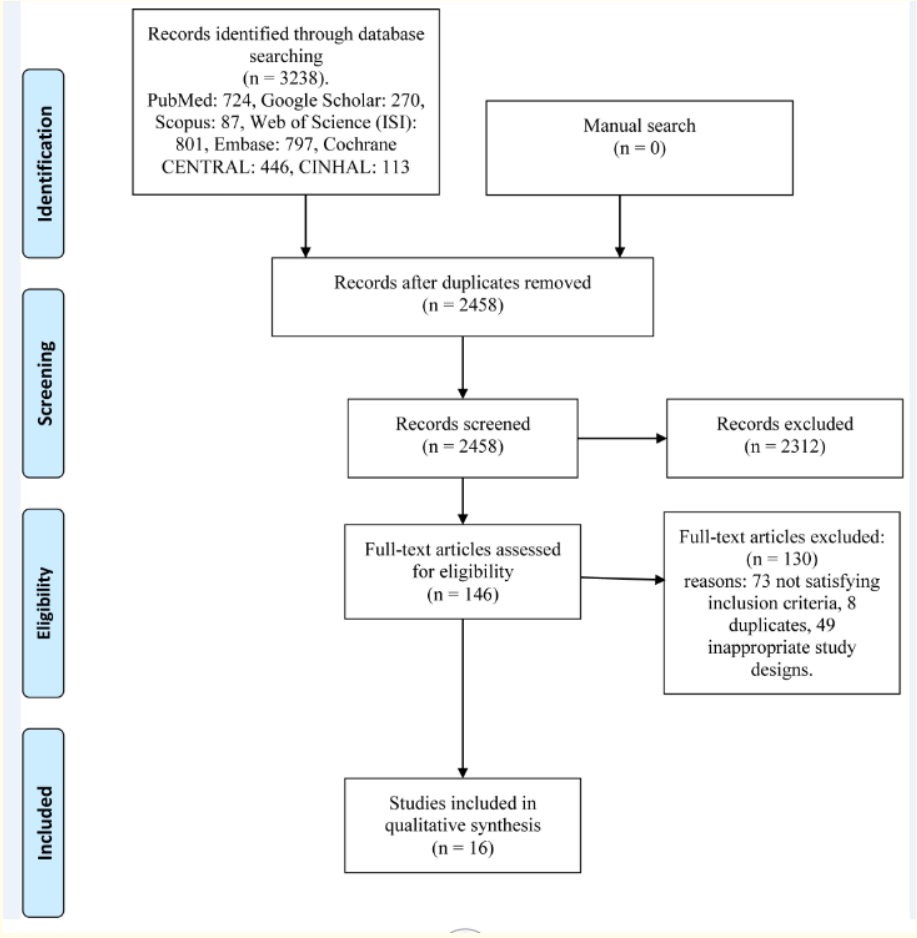
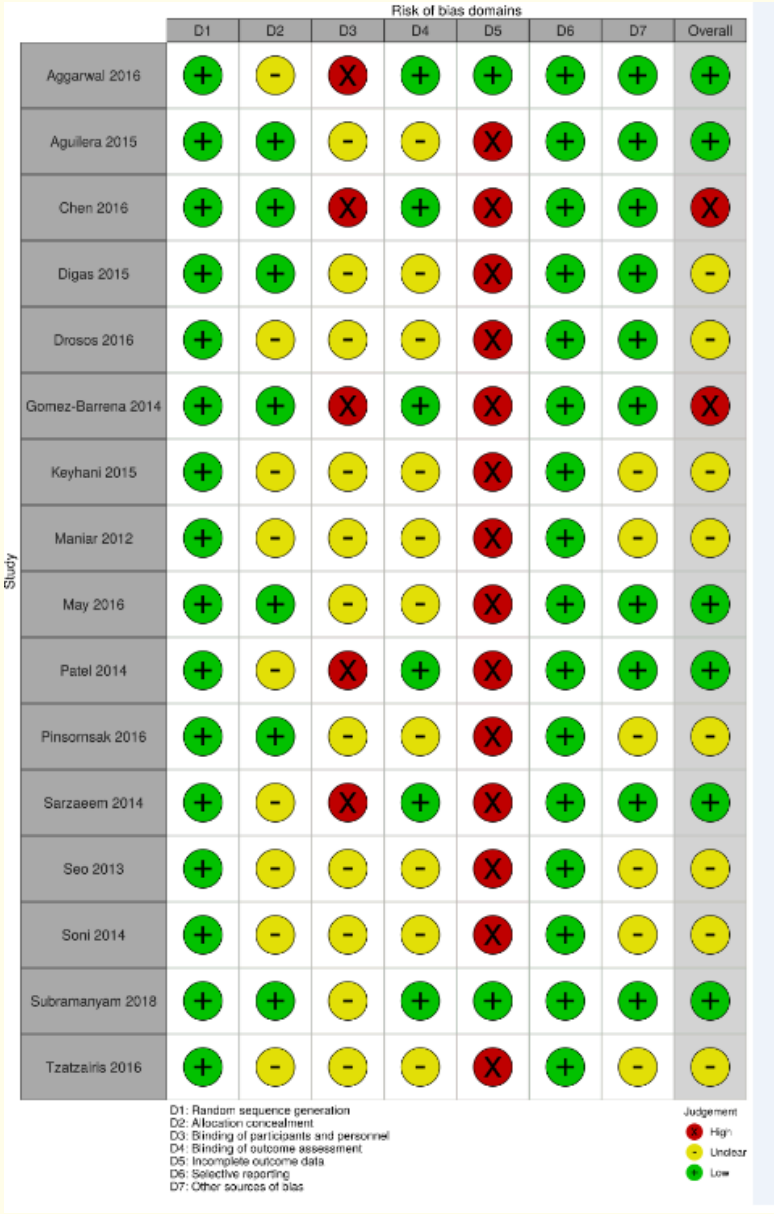


Figure 1: *PRISMA flow diagram showing the process of the review.*

Risk of bias

Quality assessment of the included studies showed that only six studies [29,36-40] had a low risk of bias while two [41,42] had high and eight [33,43-49] had an unclear risk of bias. All studies had random sequence generation and selective reporting, but seven of them [37,38,40-43,46] reported allocation concealment, and the other six [36,39,40-42,50] reported blinding. A summary of the quality assessment results is presented in figure 2A. Overall, all studies (100%) showed a low risk of bias in random sequence generation and selective reporting. On the other hand, a high risk of bias was found in incomplete outcome in the majority of the assessed studies. Assessment of blinding in both participants and outcome assessment was unclear in many studies as shown in figure 2B.



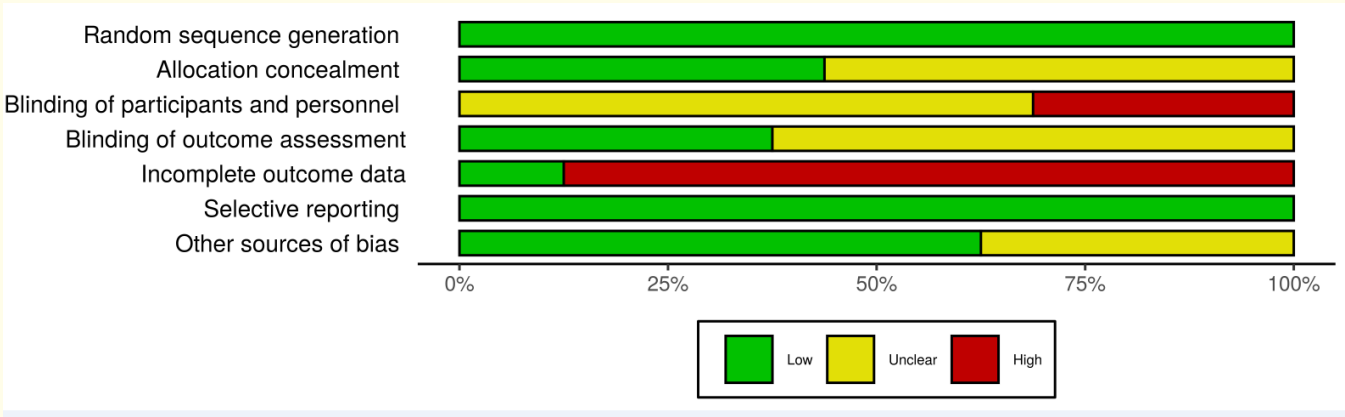


Figure 2: *Quality of the included studies. A: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. B: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.*

Study characteristics

A total of 16 eligible RCT studies with a total of 1430 patients, of whom 714, and 716 in the IA and IV groups, respectively. Moreover, four studies were held in India [33,36,40,48], three in Greece [43,44,49], two in Spain [37,42], two in Iran [45,50], two in the USA [38,39], one in Singapore [41], one in Thailand [46], and one in Korea [47]. Other characteristics of the included studies are presented in table 1.

Study	Year	Country	Patients (n)		Age (y), mean (SD)	
			IA	IV	IA	IV
Aggarwal	2016	India	35	35	55.66 ± 8.71	58.77 ± 10.14
Aguilera	2015	Spain	50	50	72.53 ± 6.6	72.49 ± 7.68
Chen	2016	Singapore	50	50	65 ± 8	65 ± 8
Digas	2015	Greece	30	30	71 ± 7	70 ± 6.5
Drosos	2016	Greece	30	30	71.1 ± 6.32	69.27 ± 7.21
Gomez-Barrena	2014	Spain	39	39	70.1 ± 9.1	71.8 ± 10.3
Keyhani	2015	Iran	40	40	67 ± 11.9	68.4 ± 10.4
Maniar	2012	India	40	40	67 ± 7.96	67.3 ± 9.1
May	2016	USA	62	69	63 ± 10.6	65.0 ± 9.6
Patel	2014	USA	47	42	64.8 ± 9.7	64.9 ± 7.8
Pinsornsak	2016	Thailand	30	30	67.63 ± 7.96	69.97 ± 7.55
Sarzaeem	2014	Iran	50	50	67.5 ± 7.6	66.9 ± 7.2
Seo	2013	Korea	50	50	67.5 ± 6.6	66.8 ± 6.3
Soni	2014	India	30	30	69.4 ± 4.71	69.05 ± 4.10
Subramanyam	2018	India	91	91	63 (57 to 68)	63 (58 to 69)
Tzatzairis	2016	Greece	40	40	69.1 ± 8.68	69.55 ± 6.61

Table 1: *Baseline characteristics of the included studies and their populations.*

Outcomes and Discussion

Among these studies, three of them [36,43,47] reported that IA administration of TXA was better than IV, while two of them [33,50] reported the opposite and the rest [37-42,45,46,48,49] reported no superiority of one route over the other. The results are similar to these of similarly recently published meta-analysis [51-56], however, because of the heterogeneity of the included studies, their quality is considered to be moderate to low [52]. This heterogeneity is due to the following factors: study design, patients selection, doses and timing of injections, route of administration, the use of a tourniquet, surgical approaches, DVT prophylaxis, drains use, methods of blood loss calculations, rehabilitation, and prioritizing outcomes. Another factor is the misunderstanding of the literature by clinicians and therefore, results should be interpreted cautiously as Subramanyam., *et al.* [40] said that being unable to prove that one route is superior over the other does not mean that both routes have equal efficacies. Moreover, only Pinsornsak., *et al.* [46] reported the use of periarticular TXA administration rather than IA like other studies did.

Regarding the number of doses applied by the included studies, a variety of doses have been identified. Aggarwal., *et al*. [36], Aguilera., *et al.* [37], Drosos., *et al.* [44], and Tzatzairis., *et al.* [49] used 1g of both IA and IV TXA injections. However, Aggarwal., *et al.* [36] repeated the dose with IV injection before and at tourniquet deflation. Other doses include 3.0g in five studies [33,42,45,48,50], 2.0g in another three [38,39,43] while 1.5g was applied by another two [54,47]. Moreover, Pinsornsak *et al.* [46] reported the lowest used dose (750 mg) in both IA and IV routes. Maniar., *et al.* [33] found that IV administration became better only after the application of more than one dose. However, Sarzaeem., *et al.* [50], reported that a single dose of 500 mg IV TXA was enough to be superior to 3g of IA administration. On the other hand, among the studies that reported the superiority of IA over IV routes, despite using double doses of IV by Aggarwal., *et al.* [36] and similar, equal doses by Seo., *et al* [47].

The main outcomes of the included studies are comprised of postoperative hemoglobin (Table 2), total blood loss (Table 3), blood volume of drainage (Table 4) and blood transfusion rate (Table 5). Postoperative hemoglobin was reported in eleven of the included studies [31,36,38,40,42,43,46-50]. Its value was statistically significant between the two IA and IV groups in four studies only [36,47,49,50]. Previously published studies reported that IA TXA injection can lead to local thrombus formation, and therefore can prevent bleeding unlike IV administration [39,57]. In addition, total blood loss was reported in eleven studies [33,36-38,40-45,49]. Gomez-Barrena *et al.* [42] recorded the highest average amount of lost blood in both the IA and IV groups among all other included studies, however, no significance was found between the two groups. On the other hand, Subramanyam *et al.* results showed the lowest total volume of blood loss in both the IA and IV groups despite recruiting the largest population of patients (Table 3). Moreover, five studies showed statistical significance in total blood loss between the IA, IV, and control groups [36,37,44,45,49]. A heterogeneity, however, was found in the results of these studies. Aggarwal *et al.* [36], Drosos., *et al*. [44] and Tzatzairis., *et al.* [49] showed higher volumes of blood loss in the IV group than the IA one while the opposite was noticed in Aguilera., *et al.* [37] and Keyhani., *et al.* [45] results. However, Keyhani., *et al*. [45] results were generally compared with a control group with no specifications between the IA and IV TXA groups. A previously published meta-analysis showed that IA administration was statistically significant that repeated doses of IV injection in terms of reducing the blood loss volume and postoperative hemoglobin. However, single doses of IV and IA TXA administration were equal [56]. All of the included studies reported different rates of blood transfusions except for Subramanyam., *et al.* [40] and Gomez-Barrena., *et al.* [42] who reported zero blood transfusions among their patients despite what was mentioned earlier that Gomez-Barrena., *et al.* [42] reported the highest average of lost blood volume among all of the included studies. Besides, Seo., *et al.* [47] recorded the highest transfusion rates in the IA (= *10*) and the IV (= *17*) groups with a significant difference ($P < .001$). Irrespective of the various rates, only Aggarwal., *et al.* [36] and Drosos., *et al.* [44] together with Seo., *et al.* [47] reported a statistical significance between IA and IV TXA injection groups in terms of blood transfusion rates.

Another factor to be accounted for when comparing the efficacy is the amount of drained blood. It might be misleading as the amount of drained blood might be misleading when it comes to total blood loss estimation. Aguilera., *et al.* [37] reported a statistical significance ($p < 0.001$) between IA and IV groups in terms of blood volume of drainage. Although Gomez-Barrena., *et al.* [42] reported the highest

Study	Postoperative hemoglobin						
	IA			IV			P-value
	Mean	SD	Total	Mean	SD	Total	
Aggarwal 2016	1.6	0.68	35	2.69	1.16	35	< 0.001
Digas 2015	10.7	0.17	30	10.8	0.12	30	0.71
Gomez-Barrena 2014	3.1	1	39	3.4	0.9	39	0.167
May 2016	10.7	1.5	62	10.2	1.4	69	0.37
Patel 2014	3.42	1.07	46	3.06	1.02	42	0.108
Pinsornsak 2016	1.85	0.95	30	1.87	1.37	30	0.84
Sarzaeem 2014	3.9	1.1	50	2.6	0.9	50	< 0.001
Seo 2013	1.8	0.8	50	1.6	0.8	50	< 0.001
Soni 2014	2.21	0.64	30	2.42	0.86	30	0.48
Subramanyam 2018	1.66	0.98	91	1.65	0.9	91	0.97
Tzatzairis 2016	2.95	1.33	40	3.2	1.29	40	< 0.001

Table 2: *Comparing the reported postoperative hemoglobin values between intra-articular and intravenous groups.*

Study	Total blood loss						
	IA			IV			P-value
	Mean	SD	Total	Mean	SD	Total	
Aggarwal 2016	543	264	35	1039	483	35	< 0.001
Aguilera 2015	1021.57	481.09	47	817.54	324.82	48	< 0.001
Chen 2016	799	890.82	50	730	710.54	50	0.232
Digas 2015	943	87	30	1086	102	30	0.82
Drosos 2016	1048.15	214.49	30	1123.42	216.58	30	< 0.05
Gomez-Barrena 2014	1574.5	542.9	39	1626	519.2	39	0.656
Keyhani 2015	422	51	40	406	36	40	< 0.001
Maniar 2012	809	341.1	40	824	226.8	40	0.88
May 2016	977.7	342.6	62	1075.5	419	69	0.71
Subramanyam 2018*	565	(348 to 797)	91	571	(352 to 690)	91	0.45
Tzatzairis 2016	1205.63	300.69	40	1236.07	307.9	40	< 0.001

Table 3: *Comparing the total amounts of blood loss in both intra-articular and intravenous groups.*

**Data presented in median (IQR).*

Study	The blood volume of drainage						
	IA			IV			P-value
	Mean	SD	Total	Mean	SD	Total	
Aguilera 2015	200.1	163.5	47	144.9	108.49	48	< 0.001
Chen 2016	100	247.45	50	100	173.22	50	0.331
Digas 2015	121	17	30	192	21	30	0.006
Gomez-Barrena 2014	315.6	207.1	39	308.1	186.5	39	0.948
Maniar 2012	385	186.2	40	436	164.8	40	0.88
Patel 2014	630.2	331.6	46	558.7	370.3	42	0.339
Pinsornsak 2016	445	158	30	520	175	30	0.081
Sarzaeem 2014	173.9	610.5	50	476.8	114.8	50	N/S
Seo 2013	426	197	50	528	227	50	N/S
Soni 2014	386.5	89.08	30	409.5	185.82	30	0.48
Subramanyam 2018*	160	(50 to 180)	91	150	(150 to 180)	91	0.92

Table 4: *Comparing the drained blood volume between the intra-articular and intravenous injection groups. N/S: non-significant or non stated. *Data presented in median (IQR).*

Study	Thromboembolic complications				Wound infection				Blood transfusion rate				
	IA		IV		IA		IV		IA		IV		P-value
	Events	Total	Events	Total	Events	Total	Events	Total	Events	Total	Events	Total	
Aggarwal 2016	0	35	0	35	0	35	0	35	7	35	0	35	< 0.001
Aguilera 2015	0	47	0	48	0	47	0	48	4	50	0	50	0.005
Chen 2016	0	50	0	50	0	50	0	50	1	50	2	50	0.5
Digas 2015	0	30	1	30	1	30	0	30	5	30	7	30	N/S
Drosos 2016	0	30	0	30	0	30	1	30	3	30	4	30	< 0.001
Gomez-Barrena 2014	0	39	0	39	0	39	0	39	0	39	0	39	N/S
Keyhani 2015	0	40	0	40	0	40	0	40	3	40	2	40	0.013
Maniar 2012	0	40	0	40	0	40	0	40	3	40	5	40	N/S
May 2016	2	62	4	69	2	62	4	69	0	62	1	69	N/S
Patel 2014	0	46	0	42	0	46	0	42	1	46	0	42	0.342
Pinsornsak 2016	0	30	0	30	0	30	0	30	9	30	7	30	0.928
Sarzaeem 2014	0	50	0	50	0	50	0	50	4	50	0	50	N/S
Seo 2013	0	50	3	50	0	50	0	50	10	50	17	50	< 0.001
Soni 2014	0	30	0	30	0	30	0	30	4	30	3	30	0.69
Subramanyam 2018	4	91	7	91	0	91	0	91	0	91	0	91	N/S
Tzatzairis 2016	0	50	0	50	3	50	3	50	7	40	5	40	0.018

Table 5: *Thromboembolic complications and wound infection events associated with intra-articular (IA) and intravenous (IV) tranexamic acid (TXA) in total knee arthroplasty (TKA) together with the blood transfusion rates reported by the included studies.*

amount of lost blood, their results showed a major reduction in terms of drained blood volume while Subramanyam., *et al.* [40] results showed a slight increase in this volume when compared to other studies. Therefore, clinicians should be aroused that the total amount of blood loss is not only dependant on blood volume of drainage only, but also the hidden lost volume.

As mentioned before, IA might be favored over IV injection as this later can cause thromboembolic complications especially DVT. In this study, thromboembolic complications were reported by some authors (Table 5). Thromboembolic complications occurred in 15 patients in the IV group and six only in the IA one in four studies [38,40,43,47]. Furthermore, it has been noticed that IV complications always occurred in more patients than the IA ones which support that IA is superior to than IV injection at this point, however, no significance was reported. The number of studies that mentioned their followed procedures for DVT screening is nine [33,36,39,40,42,43,45,49] while these that did not state any method were seven [37,38,41,44,47,48,50]. Reported methods were mostly dependant on the clinical examination. Moreover, Doppler examination was reported by [33,40,42,45,49]. Patel., *et al*. [39] used extra methods as chest CT and ventilation-perfusion (VQ) scan. Tzatzasiri., *et al*. [49] reported using the d-dimer test and spiral computed tomography also. Thromboprophylaxis measures included low-molecular-weight heparin (LMWH) [27,37-39,41,42,45,48,49], DVT stockings, ankle pumps, early mobilization [36,46], tinzaparin sodium [43], and aspirin and calf pumps [40]. Furtherly, wound infection was reported by four studies [38,43,44,49] in 14 patients with eight of them in the IV group (Table 5). Therefore, prophylaxis antibiotics should be considered before injection as reported by Subramanyam., *et al* [40].

Study	Study year	Sample size	Dose and time of injection		Transfusion criteria	Tourniquet	Thromboprophylaxis	DVT screening method	Conclusion
			IA	IV					
Aggarwal., *et al*. [36]	2016	35:35	15 mg/kg TXA/100 mL NS after meticulous suturing	(1) 15 mg/kg TXA 30 min before tourniquet deflation (2) 15 mg/kg TXA after 2h	Hb < 8.0 g/dL postoperative blood loss >20%	Yes	DVT stockings; Ankle pumps; early mobilization	Clinical symptoms	IA better than IV
Aguilera., *et al*. [37]	2015	50:50	1g TXA/10 mL NS	(1) 1g TXA 15-30 min before tourniquet inflation (2) 1g TXA when tourniquet deflation	Hb < 8.0 g/dL Hb < 8.5 g/dL+heart disease or >70 years 8.5 g/ dL < Hb < 9.0 g/dL+low orthostatic tolerance	Yes	LMWH	N/S	No difference
Chen., *et al*. [41]	2016	50:50	1.5g TXA//100 mL NS after cementing the prostheses	1.5g TXA/100 mL NS 20 min after cementing the prostheses	Hb < 8.0 g/dL Hb < 10.0 g dL+symptoms Hb < 8.5 g/dL Hb < 9.5 g/dL+heart disease	Yes	LMWH	N/S	No difference
Digas., *et al*. [43]	2015	30:30	2g TXA after skin closure	15 mg/kg TXA before tourniquet deflation	Physiological signs of inadequate oxygenation symptoms of myocardial ischemia occur	Yes	Tinzaparin sodium	Clinical symptoms	IA better than IV

Drosos., *et al*. [44]	2016	30:30	1g TXA/30 mL NS at the start of the wound suturing	1g TXA at the start of the wound suturing	Hb < 10.0 g/dL symptoms or any anemia-related organ dysfunctions	Yes	N/S	N/S	No difference
Gomez-Barrena., *et al*. [42]	2014	39:39	3.0g TXA/100 mL NS (1) Half of the volume: irrigation before joint closure (2) Another half: intra-articularly after skin closure	(1) 15 mg/kg TXA, 15-20 min before tourniquet deflation (2) 15 mg/kg TXA 3h after surgery	Hb < 8.0 g/dL Hb < 10.0 g dL+symptoms	Yes	LMWH	Clinical exam +Doppler ultrasound	No difference
Keyhani., *et al*. [45]	2015	40:40	1) 1.5g TXA/50 mL NS before joint closure (2) 1.5g TXA/50 mL NS after wound closure by a portovac drain	500 mg TXA/100 mL NS at the end of the surgery	Hb < 8.0 g/dL	Yes	LMWH	Clinical exam +Doppler ultrasound	No difference
Maniar., *et al*. [33]	2012	40:40	3.0g TXA/100 mL NS 5 min before tourniquet deflation	10 mg/kg TXA 15 min before tourniquet deflation	Hb < 8.5 g/dL Hb < 10.0 g/dL+heart disease 8.5 g/dl < Hb < 10.0 g/dL+symptoms	Yes	LMWH	Clinical exam +Doppler ultrasound	IV better than IA
May., *et al*. [38]	2016	62:69	2g TXA/50 min after capsular closure	1) 1g TXA before tourniquet inflation, (2) 1g TXA after capsular closure	HB < 7.0 g/dL Hb < 10.0 g dL+symptoms	Yes	LMWH	N/S	No difference
Patel., *et al*. [39]	2014	47:42	2g TXA/100 mL NS, 2 min before tourniquet deflation	10 mg/kg, 10 min before tourniquet deflation	Hb < 8.0 g/dL+symptoms	Yes	LMWH	Doppler ultrasound +Chest CT +V/Q scans	No difference
Pinsorn-sak., *et al*. [46]	2016	30:30	750 mg TXA before tourniquet deflation	750 mg TXA before tourniquet deflation	Hb < 10.0 g/dL or symptoms of anemia	Yes	Foot pump exercise and early ambulation	Clinical exam	No difference

Sarzaeem., *et al*. [29]	2014	50:50	1.5g TXA/100 mL NS, after closing the wound immediately	1.5g TXA/100 mL NS after closing the wound immediately injected through the portovac drain	Hb < 8.0 g/ dL Hb < 10 g/ dL+symptoms	Yes	N/S	N/S	IV better than IA
Seo., *et al*. [47]	2013	50:50	1.5g TXA/100 mL NS before tourniquet deflation	1.5g TXA/100 mL NS before tourniquet deflation	Hb < 8.0 g/ dL Hb < 10 g/ dL+symptoms	Yes	N/S	N/S	IA better than IV
Soni., *et al*. [48]	2014	30:30	3g TXA/100 mL NS after cementing the implant and before tourniquet deflation	(1) 10 mg/kg TXA 20 min before T ourniquet application (2) 10 mg/kg TXA 15 min before deflation of the tourniquet (3) 10 mg/kg TXA 3 hours after intraoperative dose	Hb < 8.0 g/dL	Yes	LMWH	N/S	No difference
Tzatzairis., *et al*. [49]	2016	40:40	1g TXA/100 mL NS intraarticular after joint capsule closure	1g TXA/100 mL NS 10 min before incision	Hb level < 10 g/dL symptoms or anemia-related organ dysfunction	No	LMWH	Doppler ultrasound, D-dimers test, spiral computed tomography	No difference
Subramanyam., *et al*. [40]	2018	91:91	1.5g TXA/10 mL NS intraarticular after the closure of the wound before the release of the tourniquet	(1) 10 mg/kg TXA 10 min before the tourniquet was inflated (2) 10 mg/ kg TXA 10 min before the tourniquet was released	Hb level < 8 g/ dl or for symptomatic patients with a level between 8 g/dl and 10 g/dl	Yes	Calf pumps, oral aspirin	Clinical exam +Doppler ultrasound	No difference

Supp. table 1. *Summary of the included randomized controlled trials (RCTs) comparing intra-articular (IA) and intravenous (IV) tranexamic acid (TXA) in total knee arthroplasty (TKA).*

DVT: Deep Venous Thrombosis; Hb: Hemoglobin.

Limitation of the Study

Limitations to this study include the small sample size of the included studies. Besides, heterogeneity was noticed in terms of the timing and dosage of TXA application and assessment of blood loss and postoperative hemoglobin.

Conclusion

We found that IA and IV routes were reported to have similar clinical outcomes and even the number of studies that favored IA over IV application was equal to that reported vice versa. In general, both routes were useful in terms of reducing blood loss, transfusion rates and

postoperative hemoglobin. We recommend that further investigations should be conducted with larger sample sizes and fewer limitations to assess the efficacy of IA and IV TXA administration in TKA procedures.

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