SVOA Orthopaedics

ISSN: 2752-9576

ScienceVolks Open Access

Systematic Review

A Systematic Review and Meta-Analysis of Tranexamic Acid in Total Knee Replacement

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***Received:** September 30, 2022 **Published:** November 16, 2022*

Abstract

Background: This study aims to examine the effects of tranexamic acid (TXA) on blood loss and transfusion needs in patients with total knee replacements (TKR). TXA is commonly used to prevent excessive bleeding. In a TKR, goal is to minimize blood loss and associated risks in a variety of surgical procedures, including TKR, such as infection and deep vein thrombosis.

Purpose: To investigate influence of TXA in TKR, dosing such as single dose, IV/topical TXA, side effects, contraindications, safety, and efficacy of using TXA in comorbidities like diabetics, obese, and smokers.

Methods: A comprehensive literature search of databases including PubMed-Medline, Ovid-EMBASE, and Cochrane Library was performed to collect related literature. We analyzed all RCTs. 48 articles were included in the study. The outcomes like post-operative blood loss and TXA use in comorbid conditions were extracted from the study along with effective dosages and methods of application.

Results: Multiple intravenous TXA doses can reduce postoperative blood loss and improve functional outcome in total knee arthroplasty without a tourniquet (1). There is no major difference in mechanism of action, coagulation, and fibrinolytic profile between topical TXA and a single dose of IV TXA, it may be simpler to use a single dose of IV TXA when safety is a concern (2).

Conclusion: TXA reduces postoperative blood loss and improves functional outcome in TKR. TXA is safe to use in comorbid health issues such as smoking, diabetes, and obesity.

***Keywords:** Osteoarthritis, tranexamic acid (TXA), Total Knee Replacement*

Introduction

Osteoarthritis is a painful disease that affects millions of patients. Current treatments for OA include acetaminophen, non-steroidal anti-inflammatories, cyclooxygenase 2 inhibitors. These are moderately effective, leaving patients with pain (1). Individuals with symptomatic osteoarthritis in at least two of three knee compartments who failed conservative treatment should consider TKA.

TKA is a common orthopedic procedure and reports suggest that it improves functional status, alleviates joint pain, stiffness but previous studies show that TKA has been associated with substantial blood loss and risk of transfusion. However, a surgical procedure might result in significant blood loss of up to 2000 mL. According to reports, 10–38% of patients who undergo TKA need a blood transfusion.

Allogenic blood transfusions results in adverse effects (2). Over recent years, Use of TXA has become common due to its effects in reducing post-operative blood loss.

TXA is a synthetic antifibrinolytic agent. A lysine derivative, TA prevents plasminogen activation by acting as a competitive inhibitor. By doing so, it preserves platelet function. It is less expensive and simpler to use than other blood preservation methods (3). It has been used successfully to halt bleeding after surgeries and in hemophiliac patients.

TXA is safer than aprotinin and more potent than EACA, with overall good penetration into major joints (4). Numerous studies have investigated their efficacy in reducing blood loss in TKA (5-8). Without causing an increase in complications, topical application of TXA directly into surgical wounds reduced postoperative bleeding and led to 16% to 17% higher postoperative hemoglobin levels compared to placebo (9). We therefore carried out a large sample meta-analysis to assess efficacy and safety of TXA usage.

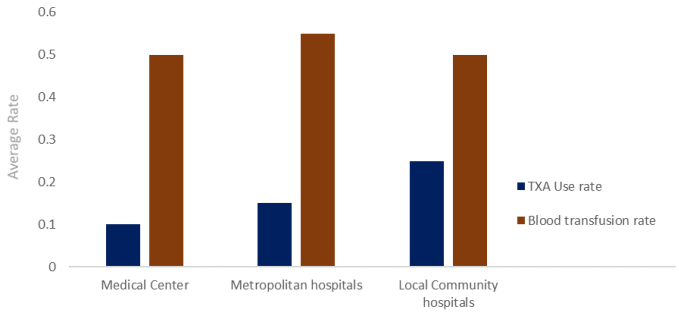

Figure 1: *Shows Volume of blood transfusion between TXA and non*

Materials and methods

i. Search Strategy

As per PRISMA recommendations, this meta-analysis was carried out. The following databases were searched for scientific articles: PubMed, Springer, ScienceDirect, Cochrane Library, and Ovid-EMBASE. We analyzed RCTS conducted from January 2014 to June 2022. After a critical appraisal of available 113 publications, 48 articles were included in study. Outcomes like post-operative blood loss and TXA use in comorbid conditions were extracted from study.

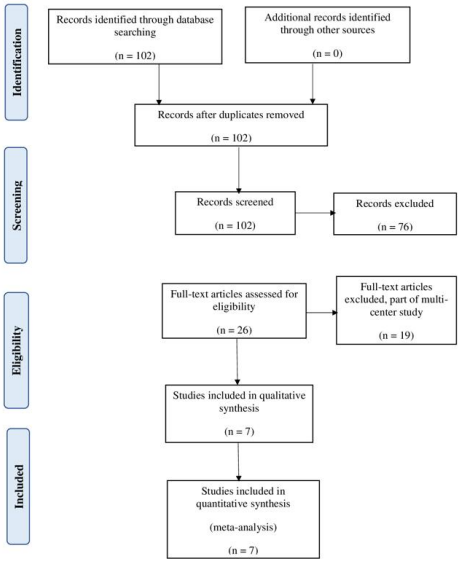

Figure 2: *PRISMA chart of literature search according to the Preferred Reporting Items.*

ii. Inclusion criteria

Studies were considered eligible for inclusion if

(1) Patients received initial TKA treatment; (2) the control group was given a placebo or no medication, and the experimental group received peri articular injection TXA; (4) The clinical results included hemoglobin drop, postoperative drainage volume, the need for blood transfusions, and surgical complications. All studies discovered was evaluated by two separate reviewers. Any differences were handled by a third reviewer.

iii. Exclusion criteria

Articles that were excluded (1) duplicate articles or identical patients (2) reports from conferences, case studies, theoretical analysis, opinions from professionals, and economic analysis; (3) irrelevant studies. (4) Studies where TXA was combined with another regimen.

Selection of studies

Selection criteria were applied separately by two authors. Full text was screened to see if it was eligible for this meta-analysis. Disagreements were settled through discussion, and the third author made the ultimate decision.

Data extraction

Data was uprooted by two authors who worked unaided. Third author was in charge of resolving disagreements. Author name, title, year of publication, region, sex, study design, TXA administration, transfusion criteria, PT, Active PTT, tourniquet time, hemoglobin change, and blood transfusion were extracted into a data collection sheet. We used McGrath et al. methods to estimate mean and SD (10). We used following formula to determine net change in measurements (MD): Measure after the follow-up period (post-operative)—measure at beginning (preoperative).

Risk of bias evaluation

Cochrane Collaboration risk-of-bias tool (Version 2.0) for RCTs was used by two authors to assess risk of bias. Newcastle –Ottawa Scale (NOS) (11) was used to assess non-randomized clinical research. (12).

Results

A. Efficacy of topical dose

More so than intravenously or without TXA delivery, topical treatment of 1g TXA decreased blood loss in patients getting TKA (13) or equal efficacy of TXA in blood conservation in minimally invasive TKA patients receiving rivaroxaban for thromboprophylaxis (14).

Results showed that 20 mg/kg single-dose IV bolus or 3 g topical TA application reduced transfusion requirement without raising the risk of thromboembolic events in unilateral TKA (15).

Other studies concluded that intra-articular administration through drain and IV administration are equally effective and superior to topical wash (16).

B. Efficacy of IV dose

TXA administered intravenously has the strongest antifibrinolytic effect. Compared to simply cleaning the wound surfaces with TXA, intravenously administered TXA can more effectively prevent the formation of a fibrin plug (17).

C. Combined Topical and IV

Following TKA, the combined administration of topical/local and IV TXA significantly reduced post-operative bleeding and hemoglobin levels (18-20).

In comparison to a control group, patients having unilateral primary cemented TKA without a tourniquet or drain benefit from a single dosage of 2-g TXA in 50 mL topical administration because less blood is lost during the procedure (21).

Patients undergoing TKA, rate of transfusions was low when TXA was administered intravenously and topically (22, 23). While IV TXA was associated with less calculated blood loss, lower drain output, and fewer transfusions (22).

D. Intra-articular versus Intravenous injection

Intraarticular (IA) administration of TXA was more effective than intravenous (IV) administration in terms of reducing blood loss (24) and drainage volume (25). During the initial TKA, Knee and hip flexion at 45 degrees and intra-articular TXA can effectively reduce CBL and hemoglobin loss without causing any negative side effects (7).

Whereas other studies claim that IA TXA is not inferior to IV TXA concerning efficacy and safety and may be preferred considering ease of administration and lack of systemic absorption (26). IV administration of TA during TKR is superior compared to IA administration of TA (27) and combined administration of IA+IV (28).

Less blood loss and fibrinolytic activity are produced when IV and IA TXA injections are combined (29, 30). Combination of 1 g IV with 2 g IA could be optional choice (30). Compared with intra-articular TXA alone, combined intravenous plus intra-articular TXA reduced hemoglobin loss and need for transfusion without increase in thromboembolic events in patients with revision TKA (31).

E. Peri-articular injection vs IV

Peri-articular injection (PAI) of TXA reduced total blood loss to a greater degree than IV injection in TKA without reduction of drainage volume (32).

Combined use of IAI and PAI of TXA can reduce TBL and need for blood transfusion without delaying wound healing or increasing risk of DVT and PE. In short term after surgery, this combined method reduces pain VAS scores and improves ROM; however, there are no long-term effects on VAS and ROM (33).

F. 3g/2g vs 1g

When used in conjunction with reverse hybrid TKA, the hemostatic efficacy of TXA with 2 g of intraarticular injection (IAI) was superior to that with 1 g. While not reducing the requirement for blood transfusions, this technique can lower the incidence of postoperative anemia (34).

When compared to a low dose of 500 mg in primary TKA, the use of high-dose, IA-TXA topical dosage of 3 g was 43% more efficient in lowering postoperative blood loss. Further research into the ideal doses between the above two doses would be helpful (35).

Preoperative dose plus an extra dose of TA were superior to a single preoperative dose of TA in minimizing blood loss in TKA with the same total dose of TA. Additionally, 1 additional dose reduced blood loss as effectively as 2 additional doses of TA (36).

G. Repeated dosing

The least demanding postoperative regimen for clinical success in primary unilateral TKA is a two-dose regimen. Three-dose regimen produced a maximum reduction of blood loss (37). Maximum decreases in blood loss and inflammatory response were obtained with a four-dose regimen, which also enhanced analgesia and encouraged early recuperation. For these results to be repeatable, additional research is needed (38).

Reduced HBL after TKA without a discernible rise in thromboembolic events was the consequence of six-dose IV-TXA delivery within the first 24 hours (39).

H. Cost-effectiveness

In comparison to IA TXA, oral TXA showed non-inferiority for primary TKA with no safety issues and a significantly lower cost. This RCT backs oral TXA treatment in TKA (40).

I. Local or systematic

Blood loss was reduced when TXA was used, either locally or systemically. In contrast, local TXA appeared to have similar effects to systemic + short infusion, however systemic + long infusion and systemic + oral TXA consumption appeared to have more negative effects. The use of systemic + short, systemic + long, and systemic + oral combination TXA did not differ in terms of blood loss, transfusion rates, or drain follow-up (41).

J. Optimal route and safety in comorbid conditions

Two intravenous TXA dosages and a combination topical/intravenous TXA treatment were the most successful TXA therapies for diabetic and obese patients (BMI > 30 kg/m2). But among smokers, there was no evidence that any method of administering TXA was preferable (42). TXA appears safe in patients with a history of thromboembolic, cardiovascular, and cerebrovascular disease (43).

K. Wound closure and tourniquet

One study investigated two different methods of applying TXA are effective: in first, wound is closed before tourniquet is loosened; In second, after tourniquet has been relaxed, wound is closed. According to a study, there is less blood in drains after applying TXA to suprapatellar space using the control approach and prior to tourniquet being released (44).

L. Absence of tourniquet in End-stage OA

In TKA patients with end-stage knee osteoarthritis, without tourniquet did not seem to have any impact on blood loss and cement penetration, better knee function and less inflammatory reaction can be attained. When administering TXA during primary TKA, we advise against using a tourniquet on patients who have end-stage osteoarthritis. (45).

M. Effect of knee position

Keeping knee in flexion position combined with topical and intravenous TXA application in patients undergoing primary unilateral TKA reduced post-operative bleeding and transfusion rate compared with what was found after treatment with extension knee position or single intravenous TXA application (46)

Efficacy of IV 3 doses post-op

Three doses of postoperative IV-TXA decreased blood loss and diminished postoperative inflammatory and fibrinolytic response more than a single dose or two doses in elderly patients following TKA without increasing incidence of adverse events (47)

Additional studies revealed that use of TXA for 3 days after a TKR can be more beneficial for minimizing blood loss (5, 48).

In patients with RA, three doses of postoperative IV-TXA further facilitated HBL, and Hb level decreased without increasing incidence of adverse events in a short period after TKA (49).

Post-op TXA Doses

Repeated TXA dosages up to 24 hours can lessen HBL, give more fibrinolysis and inflammatory control, and lessen postoperative discomfort after TKA (50). But administration of TXA after first 24 h had no significant effect (51).

1g IV TXA regime perioperatively and four oral 1g doses over 24 hours postoperatively reduces blood loss as compared with a single IV 1g perioperative dose alone (43).

Prior to surgery, a large initial dose of IV-TXA (60 mg/kg) can be followed by five doses to further reduce blood loss without raising the risk of treatment-related problems (52).

Intravenous and long-term oral TXA produced less blood loss, less swelling, and ecchymosis compared with short-term TXA without increasing risk of complications (53) but another evidence proves that short-term application of postoperative intravenous TXA resulted in reduced HBL without an increase in VTE or thrombosis (51).

Ineffective Post-op dose

In patients receiving intraoperative combination IV and IA TXA, postoperative IV TXA had no additional benefit on lowering perioperative blood loss (54).

TXA in revision TKR

Even though revision TKA carries a higher risk of blood loss, all TXA regimens studied showed comparable blood-sparing abilities (55).

TXM and immune effect

According to a study entitled "Effect of IV-TXA on inflammation and immunological response following primary TKA," six doses of IV-TXA were able to reduce post-TKA DXM-induced immunosuppression in patients and attenuate the inflammatory effect (8).

Other regimens vs TXA

Hemocoagulase Atrox was not superior to TXA in reducing perioperative blood loss (56) another prospective RCT showed that intra-articular application of TXA was superior to hemostatic matrix (Floseal®) in blood conservation. (57).

Discussion

A TKA is performed to alleviate severe pain caused by osteoarthritis of knee. Patients who require knee replacement surgery have difficulty performing activities. TKA, however, carries a risk of blood loss. After surgery, there may be significant bleeding; patients may lose all their blood, necessitating blood transfusions. TXA is used to control postoperative blood loss in TKA (13).

TXA reduces bleeding and risk of blood transfusion in patients undergoing lower limb arthroplasty (58). TXA has typically been administered intravenously (IV). In the meantime, it has been demonstrated that intra-articular (IA) TXA administration is equally as effective as IV TXA administration in terms of blood preservation following TKA. Recent RCTs found that compared to IV TXA treatment alone, IA TXA administration could decrease blood loss following unilateral TKA without increasing thrombotic events (59). Without raising the risk of problems, a 5-dose TXA regimen can further reduce blood loss and the maximum hemoglobin (Hb) decline. When fibrinolysis persists after a 5-dose regimen has been administered, a further dose may be necessary (60).

While undergoing TKA, the TXA administered as peri-articular lowered overall blood loss, hemoglobin decline, and blood transfusion rate without raising infection or DVT risk. Additionally, no TXA-related side effects have been recorded. Regarding the best method of administration, there are still concerns.

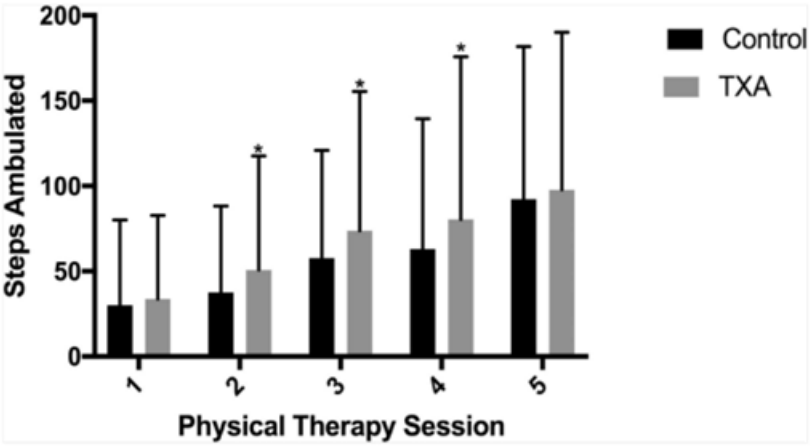

Figure 3: *Illustrates the difference in the number of steps ambulated between patients who received TXA and those who did not receive TXA throughout the first five physical therapy sessions. *P < .05.*

One 1.5-g dosage of topical TXA administered intraoperatively, either systemically or topically, successfully lowers blood loss in the context of elective TKA without increasing complications (23). IA TXA is not less safe or effective than IV TXA, and while IV TXA may be more popular due to its ease of administration and lack of systemic absorption, it offers no advantages over oral TXA. Although less than that reported for conventional arthroplasty in the literature, TXA usage reduces blood loss in navigation-assisted arthroplasty. Additionally, the combination group (IV and topical) does not have a distinct advantage over other drug delivery techniques. Adding more TXA to a combination regimen may not be clinically beneficial.

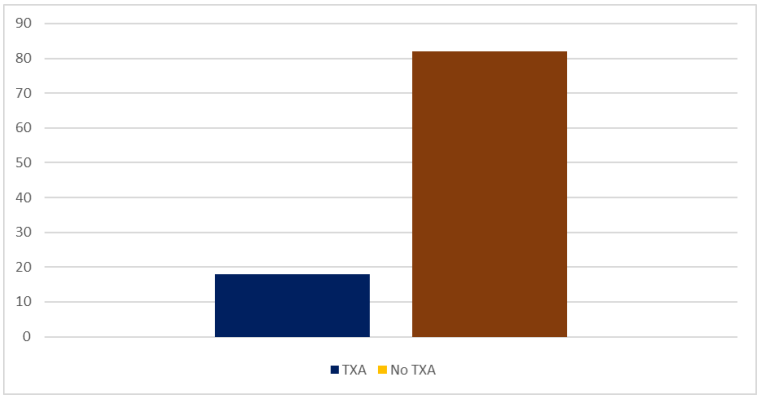

Figure 4: *Bar chart of average rates of TXA use and blood transfusion by three hospital levels.*

The functional recovery of TXA group over control group was not superior (61). Perioperative blood loss (PBL) and blood transfusions could both be decreased by IA-TXA and IV-TXA. After TKA, IA-TXA may reduce VAS for pain and morphine consumption. As a result, IA-TXA may reduce blood loss and be used as an adjuvant to TKA pain management (62). There was less unnoticed blood loss, a lower ratio of postoperative knee edema, less postoperative knee pain, lower levels of inflammatory biomarkers, greater early knee function, and even higher early satisfaction in patients treated with multiple doses of IV and topical TXA without a tourniquet (63).

In comparison to not using TXA, any prosthetic might be used with either IA- or IV-TXA to lessen computed blood loss (CBL) (No-TXA) (64). Combining topical and IV TXA dramatically decreased postoperative blood loss and post-TKA hemoglobin levels but had little effect on the frequency of allogeneic blood transfusions. This research is a Level I therapeutic investigation (18). TXA therapies include intraoperative spraying, drug-soaked gauze over the incision, and local injection into the articular cavity. These procedures have a high safety profile and can reduce discomfort while lowering bleeding and the need for blood transfusions (65). The application of a tourniquet or drain clamp, which can injure TKA, is less effective at decreasing bleeding than TXA injection. Without influencing the frequency of postoperative problems during TKA, TXA can be beneficial in lowering perioperative blood loss and blood transfusion rates.

When TXA was present, anti-inflammatory cytokine levels increased while pro-inflammatory cytokine levels were markedly reduced. These results imply that TXA might help with inflammatory and immunological responses in primary TKA.

Fillingham et al. (2019) investigated efficacy of TXA in revision TKR, results of study showed that e bolus-only group had less blood loss at 24 hours post-surgery than bolus + infusion group (mean difference = -107.9 mL, 95% CI -162.0 to -53.8 mL, p < 0.001). Other outcomes, such as blood transfusion rates, length of hospital stay, or post-operative problems, did not significantly differ between the two groups.

Table 1: Study Characteristics for IV Versus IA TXA*

Study	Design	MQOE	Country	No of Patients		Mean Age and Std. Dev (yr)		Sex, M/F		Follow-up (mo)	Primary or Revision	Conclusion
				IV	IA	IV	IA	IV	IA			
Aggarwal et al. 2016	PCS	5	India	35	35	58.8 6 10.1	55.7 6 8.7	13/22	Dec-23	6	Primary	IA.IV
Aguilera et al. 2015	RCT	3	Spain	50	50	72.5 6 7.7	72.53 6 6.6	18/32	Dec-38	NR	Primary	Neutral
Çavus¸oglu˘ et al. 2015	RCT	3	Turkey	20	20	67.8	67.8	NR	NR	NR	Primary	Neutral
Chen et al. 2016	RCT	3	Singapore	50	50	65 6 8	65.0 6 8	15/35	Oct-40	NR	Primary	Neutral
Digas et al. 2015	PCS	8	Greece	30	30	70.0 6 6.5	71.0 6 7.0	Feb-28	Jul-23	12	Primary	IA.IV
Drosos et al. 2016	RCT	3	Greece	45	45	69.3 6 7.2	71.1 6 6.3	Jun-24	Jun-24	NR	Primary	Neutral
Gomez-Barrena et al. 2014	RCT	5	Spain	39	39	70.1 6 9.1	71.8 6 10.3	13/26	14/25	1	Primary	Neutral
Goyal et al. 2017	RCT	5	Australia	85	83	68.8 6 7.4	66.7 6 8.9	40/47	38/43	NR	Primary	Neutral
Hamlin et al. 2015	RCS	5	U.S.A.	373	198	68.7 6 6.7	62.0 6 9.0	134/239	67/131	NR	Primary	IA.IV
Hegde et al. 2013	PCS	5	India	30	30	65.5 6 6.5	66.6 6 8.5	NR	NR	NR	Primary	Neutral
Keyhani et al. 2016	RCT	1	Iran	40	40	68.4 6 10.4	67.06 11.9	26/14	23/17	NR	Primary	Neutral
Maniar et al. 2012	RCT	5	India	160	40	67.5 6 8.1	67.4 6 7.9	36/124	Jun-34	3	Primary	IV.IA
May et al. 2016	RCT	3	U.S.A.	69	62	65.0 6 9.6	63.0 6 10.6	Nov-58	18/44	NR	Primary	Neutral
Patel et al. 2014	RCT	5	U.S.A.	42	47	64.9 6 7.8	64.8 6 9.7	Oct-32	13/34	4.6	Primary	Neutral
Pinsornsak et al. 2016	RCT	3	Thailand	30	30	70.0 6 7.6	67.6 6 8.0	Jul-23	May-25	0.5	Primary	Neutral
Pispati et al. 2013	RCT	3	India	40	46	65.1 6 14.1	65.6 6 13.5	Nov-29	14/32	6	Primary	Neutral
Pitta et al. 201651	RCS	5	U.S.A.	202	201	65.3 6 10.6	65.8 6 10.9	61/141	68/133	NR	Primary	IV.IA
Sarzaeem et al. 201431	RCT	3	Iran	50	100	66.9 6 7.2	67.8 6 7.2	Jul-43	13/67	NR	Primary	IV.IA
Seo et al. 2013	RCT	5	South Korea	50	50	66.8 6 6.3	67.5 6 6.6	Jun-44	May-45	2	Primary	IA.IV
Song et al. 2017	RCT	5	South Korea	50	50	69.2 6 6.4	69.8 6 6.8	Jun-44	Aug-42	0.5	Primary	Neutral

Soni et al. 2014	RCT	1	India	40	40	69.5 6 4.7	69.1 6 4.1	17/23	19/21	1.5	Primary	Neutral
Tzatzairis et al. 2016	RCT	3	Greece	40	40	69.6 6 6.6	69.1 6 8.7	Sep-31	Jul-33	NR	Primary	Neutral
Ugurlu˘ et al. 2017	RCT	3	Turkey	40	42	69.4 6 7.5	70.6 6 8.6	Nov-29	Sep-33	NR	Primary	Neutral
THA												
Emara et al. 2014	RCT	1	Egypt	20	20	56.5 6 2.8	55.0 6 2.6	12-Aug	10-Oct	NR	Primary	IA.IV
North et al. 2016	RCT	5	U.S.A.	70	69	64.1 6 12.0	65.7 6 10.6	38/42	39/30	NR	Primary	IV.IA
Ueno et al. 2016	RCS	4	Japan	265	319	64.9 6 10.5	65.8 6 9.4	33/232	46/273	NR	Primary	IV.IA
Wei and Wei 2014	RCT	5	China	101	102	63.6 6 7.0	60.2 6 6.5	67/35	62/39	NR	Primary	Neutral
Wind et al. 2014	RCS	5	U.S.A.	478	70	NR	NR	NR	NR	NR	Primary	IV.IA
Xie et al. 2016	RCT	5	China	70	70	59.5 6 11.5	62.2 6 11.0	20/50	25/45	3	Primary	Neutral
Zhang et al. 2016	RCT	3	China	25	25	44.5 6 2.4	44.3 6 3.7	14-Nov	13-Dec	NR	Primary	IA.IV

Table 2: Study Characteristics for IV Versus IV1IA TXA*

Study	Design	MQOE	Country	No of Patients		Mean Age and Std. Dev (yr)		Sex, M/F		Follow-up (mo)	Primary or Revision	Conclu-sion
				IV	IA	IV	IA	IV	IA			
TKA												
Huang et al. 2014	RCT	5	China	92	92	64.7 6 9.5	65.4 6 8.7	30/62	37/55	NR	Primary	IV/IA . IV
Jain et al. 2016	RCT	3	India	60	59	70.0 6 6.6	68.3 6 8.7	24/36	20/39	NR	Primary	IV/IA . IV
Nielsen et al. 2016	RCT	5	Denmark	30	30	63.2 6 8.6	65.5 6 7.8	13/17	15/15	3	Primary	IV/IA . IV
Song et al. 2017	RCT	5	South Korea	50	50	69.2 6 6.4	70.8 6 6.8	Jun-44	Jul-43	0.5	Primary	Neutral
THA												
Machin et al. 2014	RCS	5	U.K.	50	100	67.5	61	36/64	18/32	NR	Primary	IV/IA . IV
Wu et al. 2016	RCT	3	China	42	42	60.1 6 10.4	59.5 6 11.3	23/19	21/21	3	Primary	Neutral
Xie et al. 2016	RCT	5	China	70	70	59.5 6 11.50	60.5 6 11.0	20/50	22/48	3	Revision	IV/IA . IV
Yi et al. 2016	RCT	3	China	50	50	53.6 6 14.8	54.0 6 12.6	29/21	24/26	6	Primary	IV/IA . IV

Conclusion

TXA reduces postoperative blood loss and improves functional outcome in TKR. TXA is safe to use in comorbid health issues such as smoking, diabetes, and obesity.

Conflict of Interest

The authors declare no conflict of interest.

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Citation: Alshareef HM, Imran WM, Imran SM. "A Systematic Review and Meta-Analysis of Tranexamic Acid in Total Knee Replacement" *SVOA Orthopaedics 2022,* 2:6, 118-129.