Topical Tranexamic Acid in Hip and Knee Surgery: A Meta-Analysis of Randomized Controlled Trials

Saran Tantavisut
Chulalongkorn University
Sanzhar Artykbay
Chulalongkorn University
Pasawiss Tangwiwat
Relief and Community Health Bureau, Thai Red Cross Society
Paweena Susantitaphong
susantitaphongp@gmail.com
Chulalongkorn University

Article

Keywords: Tranexamic Acid, Hip fracture, Hip arthroplasty, Knee arthroplasty, Total blood loss, Blood transfusion

Posted Date: March 19th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4007605/v1

Additional Declarations: No competing interests reported.

Abstract

Tranexamic Acid (TXA) has been widely used in orthopedic operations, including hip and knee surgery, to decrease blood loss. However, the optimal tranexamic acid regimen is still debated between topical or systematic such as oral or intravenous. We conducted a meta-analysis of randomized controlled trials that compare the efficacy and safety of the topical application of transamine in hip and knee surgery with other routes. Outcomes of interest were the comparative aspects of bleeding, hospitality, and morbidity associated with topical TXA, in contrast to alternative administration routes. Eighty RCTs, involving 13,969 patients, assessed the outcomes of topical tranexamic acid in hip fracture surgery, hip arthroplasty, and knee arthroplasty, comparing it with intravenous, oral, and placebo administration. Overall, topical TXA decreased total blood loss [-353 mL (95%CI -395, -311), P<0.001], drainage volume [-239.802 mL (95% CI -298.744, -180.859), P<0,001], intraoperative blood loss [-14.994 mL (95% CI -34.370, 4.382), P<0.001], hidden blood loss [-123.711 mL (95% CI -153.703, -93.719), P<0.001], total hemoglobin loss [-0.970 gr/dL (95% CI -1.289, -0.651), P<0.001], total hematocrit loss [-0.937 (95% CI -1.289, -0.584), P<0.001], and blood transfusion rate [RR diff. 0.480 (95% CI 0.386, 0.597), P<0.001] compared to placebo. Topical TXA administration consistently demonstrated significant reductions in total blood loss, drain volume, intraoperative blood loss, total hemoglobin loss, and the need for blood transfusions compared to the placebo group. Subgroup analysis results also indicated that topical TXA performed better than placebo and was comparable to intravenous and oral routes.

1 Introduction

Surgical procedures for hip and knee surgeries often result in significant blood loss, which can harm patients, particularly the elderly, causing hemodynamic stress, increased cardiac demand, and potential tissue hypoxia [1, 2, 3]. Anemia can, therefore, contribute to the higher morbidity and mortality rates observed after hip fracture surgery. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are well-known for substantial blood loss, with TKA ranging from 500 to 1,500 ml and THA from 1,188 to 1651 ml [4, 5]. It's worth noting that over 10% of TKA and THA patients require blood transfusions, which have been linked to increase in-hospital mortality risk [6]. Reducing blood loss is crucial for mitigating these risks and improving surgical outcomes.

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine-binding site of plasminogen [7, 8]. Previous Meta-analyses showed Tranexamic acid reduced blood loss and decreased transfusion rates in hip fracture, TKA [9, 10] and THA [11]. Three main routes of TXA administration have been reported in the literature, that are topical [12] or systemic including intravenous [13], and oral [14]. There is still a controversy regarding the optimal route for administering tranexamic acid (TXA) to patients undergoing hip and knee surgery.

Intravenous TXA administration can rapidly reach peak plasma levels at 5 to 15 minutes after injection [12]. However, patients with specific medical conditions, such as renal insufficiency, prior deep vein thrombosis (DVT), cerebrovascular or cardiac issues, may experience adverse effects, including seizures [15, 16], myocardial infarction [17], and other thrombotic complications [18, 19, 20]. Intravenous TXA has also been associated with anaphylactic shock and drug allergies [21]. Given safety concerns with intravenous administration in certain conditions, the oral route may serve as an alternative approach. However, limited data exist regarding its efficacy in reducing blood loss during surgery [14]. Moreover, challenges persist in determining the optimal timing of oral administration.

Conversely, topical TXA at the operative site is gaining favor for its ability to reduce systemic side effects [22]. It is usually administered via wash or retrograde injection into the knee joint post-wound closure, utilizing the intra-articular injection and drain routes [23]. This approach is advantageous, offering easy administration, high local drug concentrations, and minimal systemic absorption [13, 24].

There is currently no agreement among experts regarding the use of topical tranexamic acid in hip and knee surgery patients. To address this uncertainty, we conducted a meta-analysis to examine potential differences between topical tranexamic acid and other administration routes, including intravenous, oral, and placebo.

2 Methods

2.1 Data Sources and Searches

The eligible papers were searched in PubMed and Scopus until 10 December 2022 to retrieve relevant studies published. The search term in PubMed was "((hip surgery) OR (knee surgery)) AND (tranexamic)" and in Scopus was “(TITLE-ABS-KEY (tranexamic) AND TITLE-ABS-KEY (hip AND surgery) OR TITLE-ABS-KEY (knee AND surgery))" We used broad search terms to maximize search specificity. Additionally, we used Endnote to collect the data.

2.2 Eligibility Criteria

Only randomized controlled trials evaluating hip and knee surgery patients using topical tranexamic acid compared to other routes were included. Outcomes assessed included total blood loss, total drain output, intraoperative blood loss, hidden blood loss, total blood transfusion, number of patients receiving transfusions, total hemoglobin and hematocrit reduction, length of hospital stay, and morbidity. Abstracts, interim reports, and duplicate articles were excluded. Patients receiving two different tranexamic acid routes within the same study were also excluded.

2.3 Study Selection

Three authors (S.T., S.A., and P.T.) independently screened the titles and abstracts of all electronic citations. Full-text articles were retrieved for a comprehensive review and independently rescreened. Three authors independently assessed each study, and any disagreements were resolved through adjudication by a fourth author (P. S.). The reasons for exclusion are outlined in the PRISMA flowchart below.

2.4 Data Extraction

The following data were independently extracted from the included studies: first author’s name, year of publication, patient population, surgical operation, topical type, and comparator type. The clinical outcomes were also extracted to evaluate the mean difference. We further subgroup analysis results exploring the same outcomes stratified by hip and knee, route of administration.

2.5 Quality Assessment

Pairs of authors independently assessed study quality with disagreements resolved by discussion and consensus. Study quality was assessed using a modified JADAD scale, which is based on the adequacy of randomization, blinding, and attrition. A score of 2–3, and 4–5 corresponds to a study of fair and good quality, respectively.

2.6 Data Analysis

We tabulated and systemized the results of the systemic review qualitatively. We performed a random effect model meta-analysis to compute the absolute net change in continuous variables, such as blood loss and risk ratio for binary outcomes. All pooled estimates were displayed with a 95% CI. We assessed the heterogeneity among the effect size of individual studies by the I^2 index, in which a value of 75% or higher indicates medium to high heterogeneity. We assessed a publican's bias by the Egger test. The analyses were performed by Comprehensive Meta-Analysis version 2.0.

3 Results

3.1 Characteristics and Quality of the Study.

A total of 2,055 potentially relevant citations were identified and screened, and 141 articles were retrieved for detailed evaluation **(Fig. 1.)**. Eighty studies with 87 study arms fulfilled the eligibility criteria for inclusion in the meta-analysis and reported on the outcomes of using topical tranexamic acid in hip and knee surgery, involving a total of 13,969 participants. Among these, there were 57 knee studies with 10,505 participants and 23 hip studies with 3,464 participants. All trials included in the analysis were published between 2010 and 2022, and the participant numbers ranged from 22 to 640. The topical dose of tranexamic acid ranged from 1g to 3g, oral dose ranged from 2g to 4g, and intravenous dose ranged from 10mg/kg to 30mg/kg. Most studies had fair to good study quality. Characteristics of the individual trial were demonstrated in Table 1.

Table 1
The characteristics of included studies

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Wong, J. 2010 [15]	100 (31/34/35)	OA knee	TKA cemented	**Local**: 1.5g/100 ml **Local**: 3.0g/100 ml	**Placebo**	Good
Ishida, K. 2011 [16]	100 (50/50)	OA knee	TKA cemented	**IA**: 2.0g/20 ml	**Placebo**	Fair
Sa-Ngasoongsong, P. 2011 [17]	135 (45/45/45)	OA knee	TKA	**IA**: 250mg/5 ml **IA**: 500mg/10 ml	**Placebo**	Good
Maniar, R. N. 2012 [18]	216 (40/40/40/40/40)	OA knee	TKA	**Local**: 3.0g/100 ml	**IV**: 10 mg/kg 15 min before deflation of the tourniquet (IO group) **IV**: IO + 10 mg/kg 3h after the first dose (IOPO group) **IV**: 10 mg/kg at least 20 min before tourniquet inflation + 10 mg/kg 15 min before deflation of the tourniquet (POIO group) **IV**: 10 mg/kg 20 min before tourniquet application + 10 mg/kg 15 min before deflation + 10 mg/kg 3h after the second dose (POIOPO group)	Good
Roy, S. P. 2012 [19]	50 (25/25)	OA knee	TKA	**IA**: 500 mg/5 ml	**Placebo**	Good
Alshryda, S. 2013 [20]	161 (80/81)	OA hip	THA	**IA**: -	**Placebo**	Good
Georgiadis, A. G. 2013 [21]	101 (50/51)	OA knee	TKA	**Local**: 2.0 g/75 ml	**Placebo**	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Seo, J. G. 2013 [22]	150 (50/50/50)	OA knee	TKA	**IA**: 1.5g/100 ml	**IV**: 1.5g/100 ml **Placebo**	Fair
Emara, W. M. 2014 [23]	60 (20/20/20)	Fracture hip	Hemiarthroplasty	**Local**: 1.5g/100 ml	**IV**: 10 mg/kg in 20 ml prior to skin incision + 500 mg TXA in 250 ml **Placebo**	Fair
Gomez-Barrena, E. 2014 [24]	78 (39/39)	OA knee	TKA cemented	**IA**: 3.0g/100 ml +	**IV**: 2 doses of 15 mg/kg in 100 ml (during surgery + 3h after surgery) + IA	Fair
Martin, J. G. TKA 2014 [25]	100 50 TKA (25/25) and 50 THA (25/25)	OA hip or knee, Congenital hip deformity, AVN	THA TKA	**IA**: 2.0g/100 ml	**Placebo**	Good
Patel, J. N. 2014 [26]	89 (47/42)	OA knee	TKA	**Local**: 2.0g/100 ml	**IV**: 10 mg/kg 10 min prior to tourniquet deflation	Fair
Soni, A. 2014 [27]	80 (40/40)	OA knee	TKA	**IA**: 3.0g/100 ml	**IV**: 10 mg/kg pre-operative 20 min before tourniquet application + 10 mg/kg 15 min before deflation of the tourniquet + 10 mg/kg 3h after surgery	Fair
Wei, W. 2014 [28]	303 (102/101/100)	NR hip	THA cementless	**Local**: 3.0g/100 ml	**IV**: 3.0 g 10 min prior to incision **Placebo**	Fair
Yue, C 2014 [29]	103 (52/49)	OA hip, ONFH	THA	**Local + IA**: 3.0g/150 ml	**Placebo**	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Aguilera, X. 2015 [30]	150 (50/50/50)	OA knee	TKA	**Local**: 1.0g/10 ml	**IV**: 1.0g 15–30 min before tourniquet application + 1g 60–90 min after tourniquet was removed **Placebo**	Fair
Digas, G. 2015 [31]	90 (30/30/30)	OA knee	TKA cemented	**IA**: 2.0 g	**IV**: 15 mg/kg before deflation of the tourniquet **Placebo**	Fair
Öztaş S. 2015 [32]	90 (30/30/30)	OA knee	TKA	**IA**: 2.0g	**IV**: 15 mg/kg 1h before the inflation of the tourniquet + 10 mg/kg 1 h after the deflation of the tourniquet **Placebo**	Fair
Wang, C. G. 2015 [33]	60 (30/30)	NR knee	TKA	**IA**: 0.5g/10 ml	**Placebo**	Good
Wang, G. 2015 [34]	100 (50/50)	NR knee	TKA	**IA**: 1.0g/50 ml	**Placebo**	Fair
Yang, Y. 2015 [35]	80 (40/40)	OA knee RA, TA	TKA	**IA**: 0.5g/20 ml	**Placebo**	Good
Aggarwal, A. K. 2016 [36]	70 (35/35)	OA knee	TKA	**Local**: 15 mg/kg in 100ml	**IV**: 15 mg/kg 30 min before tourniquet deflation + 15 mg/kg after 2 hours	Fair
Chen, J. Y. 2016 [37]	100 (50/50)	OA knee	TKA	**IA**: 1.5g/100 ml	**IV**: 1.5g/100 ml 20 min after cementing the prostheses	Good
Drakos A. 2016 [38]	200 (100/100)	Intertrochanteric fracture	CRIF	**Local**: 3.0g/30 ml	**Placebo**	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Drosos, G. I. 2016 [39]	120 (40/40/40)	OA knee	TKA	**IA**: 1.0g/100 ml	**IV**: 1.0g/100 ml 10 min before incision **Placebo**	Fair
Guzel, Y. 2016 [40]	150 (50/50/50)	NR Knee	TKA cemented	**IA**: 1.5g/100 ml	**PAT**: CellTrans 150 ml of blood was re-infused **Placebo**: a low-suction drain	Fair
May, J. H. 2016 [41]	131 (69/62)	OA knee	TKA	**IA**: 2.0g/50 ml after capsular closure + 100 ml (placebo) postcapsular closure	**IV**: 1.0g/100 ml before tourniquet inflation + 50 ml (placebo) after capsular closure	Fair
North, W. T. 2016 [42]	139 (69/70)	NR hip	THA	**Local**: 2.0g/100 ml	**IV**: 2.0/50ml 10 min before incision + 2.0/50 ml during the fascial closure	Fair
Pinsornsak, P. 2016 [43]	60 (30/30)	OA knee	TKA	**PA**: 750 mg/15 ml	**IV**: 750 mg/15 ml	Fair
Triyudanto, A. N. 2016 [44]	22 (7/6/9)	OA knee	TKA	**IA**: 0.5g	**IV**: 0.5g 10 min before tourniquet was extended **Placebo**	Fair
Tzatzairis, T. K. 2016 [45]	120 (40/40/40)	OA knee	TKA	**IA**: 1.0g/100 ml	**IV**: 1.0g/100 ml 10 min before incision **Placebo**	Fair
Xie, J. 2016 [46]	210 (70/70/70)	NR HIP	THA	**Local + IA**: 3.0g/150 ml	**IV**: 1.5g 15 min before skin incision **Combined**: 1.0g IV + 2.0/150 ml locally	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Zekcer, A. 2016 [47]	90 (30/30/30)	NR knee	TKA	**Local**: 1.5g/50 ml	**IV**: 20 mg/kg 100 ml at the same time as anesthesia was administered **Placebo**	Good
Guerreiro, J. P. F. 2017 [48]	43 (22/21)	OA knee	TKA	**Local**: 1.0g	**Placebo**	Fair
Lacko, M. 2017 [49]	90 (30/30/30)	OA knee	TKA	**Local**: 3.0g/50 ml	**IV**: 10 mg/kg 20 min preoperatively + 10 mg/kg 3h after first dose **Placebo**	Fair
Lee, S. Y. 2017 [50]	376 (93/93/95/95)	OA knee	TKA	**Local**: 2.0g/30 ml	**IV**: 10 mg/kg 30 min before tourniquet deflation + 10 mg/kg 3h after surgery **Low dose combined**: 1.0g/30 ml IA + 10 mg/kg IV. **High dose combined**: 2.0/30 ml IA + 10 mg/kg IV.	Fair
Maniar, R. N. 2017 [51]	75 (25/25/25)	OA knee	TKA bilateral	**Local**: 3.0g/100 ml after cementing the implant on the first side + 3.0g/100 ml after cementing the implant on the second side (LALA)	**IV**: 10 mg/kg 15 min before deflation of tourniquet on the first side + 10 mg/kg 15 min before deflation of tourniquet on the second side (IOIO) **IV**: 10 mg/kg, 20 min before tourniquet inflation + 10 mg/kg before tourniquet deflation on the first side + 10 mg/kg before tourniquet deflation on the second side	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Prakash, J. 2017 [52]	200 (50/50/50/50)	OA knee	TKA	**Local**: 3.0g/50 ml 5 min prior to closure **Drain**: 3.0g/50 ml retrograde through the drain	**IV**: 10 mg/kg 20 min before tourniquet application + 10 mg/kg 15 min before deflation of the tourniquet + 10 mg/kg 3 h after the second dose **Placebo**	Fair
Song, E. K. 2017 [53]	200 (50/50/50/50)	OA knee	TKA	**Drain**: 1.5g/50 ml retrograde through the drain	**IV**: 10 mg/kg 20 min before tourniquet application + 10 mg/kg 15 min before deflation of the tourniquet + 10 mg/kg 3 h after the second dose **Combined**: 10 mg/kg 20 min before tourniquet application IV + 1.5g/50 ml retrograde through the Drain Placebo	Good
Wang, J. 2017 [54]	150 (50/50/50)	OA knee	TKA	**IA**: 1.0g/50 ml	**IV**: 1.0g + 50 ml IA saline **Placebo**	Fair
Yen, S. H. 2017 [55]	93 (32/31/30)	OA knee	TKA	**Drain**: 3.0g/100 ml	**IV**: 1.0g/20 ml 10 min before skin closure + 160 ml IA saline **Placebo**	Fair
Yuan, X. 2017 [56]	560 (140/140/140/140)	OA knee, RA	TKA	**IA**: 3.0g/60 ml	**IV**: 20 mg/kg 30 min before skin incision + 20 mg/kg 12h after TKA **Oral**: 20mg/kg 2h before the operation + 20 mg/kg 12h after TKA **Placebo**	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Zekcer, A. 2017 [57]	90	NR knee	TKA	**Local**: 1.5g/50 ml	**IV**: 20 mg/kg with anesthesia in 10 min **Placebo**	Good
Abdel, M. P. 2018 [58]	640 (320/320)	OA knee	TKA	**Local**: 3.0g/45ml	**IV**: 1.0g prior to tourniquet inflation + 1.0g at closure	Fair
Ahmed, S. 2018 [59]	140 (70/70)	NR Knee	TKA bilateral	**IA**: 1.5g/100 ml	**IV**: 1.5g/100 ml	Fair
Luo, Z. Y. 2018 [60]	117 (58/59)	OA hip, AVN	THA	**Local + IA**: 3.0g/150 ml	**Oral**: 2.0g 2 h before surgery + 1g postoperatively with a 6-h interval	Good
Luo, Z. Y. 2018 [61]	180 (60/60/60)	OA hip, AVN	THA	**Local**: 2.0g/150 ml	**Oral**: 2.0g 2 h before surgery **IV**: 20 mg/kg 5 minutes before the skin incision	Good
Pérez-Jimeno, N. 2018 [62]	254 (125/129)	OA hip, AVN, Dysplasia	THA	**Drain**: 2.0g	**Placebo**	Fair
Prakash, J. 2018 [63]	150 (50/50/50)	OA knee	TKA	**Drain**: 1.5g/50 ml retrograde through the drain	**IV**: 10 mg/kg 20 min before tourniquet application + 10 mg/kg 15 min before deflation of the tourniquet + 10 mg/kg 3 h after the second dose **Combined**: IV + Drain	Good
Tavares, S-M. 2018 [64]	124 (62/62)	OA hip	THA cementless	**Local**: 1.5g/45 ml	**Placebo**	Good
Wang, D. 2018 [65]	180 (60/60/60)	OA knee	TKA	**IA**: 2.0g/100 ml	**Oral**: 2.0g 2h before surgery **IV**: 20 mg/kg 5 min prior to incision	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Wang, D. 2018 [66]	147 (73/74)	OA knee	TKA	**IA**: 3.0g/100 ml	**Oral**: 2g 2h before surgery + 1.0g 6h after surgery + 1.0g 12h after surgery	Good
Zhou, K. D. 2018 [67]	170 (57/57/56)	OA hip, AVN, Dysplasia, Fracture Hip	THA	**Local**: 3.0g/60 ml	**IV**: 10 mg/kg 100 ml 15 min before skin incision + 10 mg/kg 100 ml 3h after the first dose **Placebo**	Good
Jia, J. 2019 [68]	180 (60/60/60)	OA hip, AVN,	THA	**IA**: 3.0g/30 ml	**IV**: 15 mg/kg 30 min before skin incision **Combined**: IV + IA	Fair
Jules-Elysee, K. M. 2019 [69]	63 (32/31)	OA knee	TKA	**Local**: 3.0g/75 ml	**IV**: 1.5g before tourniquet inflation	Good
Kyriakopoulos, G. THA 2019 [70]	125 THA (41/41/43) 124 TKA (42/41/41)	OA hip OA knee	THA TKA	**Local**: 2.0g/75 ml for THA group **Local**: 2.0g/75 ml for TKA group	**IV**: 1.0g immediately before skin incision for THA group **IV**: 0.5g before tourniquet inflation + 0.5g before tourniquet release for TKA **Placebo**	Good
Mehta, N. 2019 [71]	300 (100/100/100)	OA knee	TKA bilateral	**IA**: 2.5g/25 ml	**IV**: 1.0g before inflation of tourniquet **Placebo**	Fair
Qiu, J. 2019 [72]	102 (55/47)	NR hip	THA	**Local + IA**: 3.0g/150 ml	**Placebo**	Fair
Wu, J. 2019 [73]	101 (54/47)	OA knee	TKA	**IA**: 1.5g/50 ml	**Placebo**	Fair
Zhang, Y. M. 2019 [74]	150 (50/50/50)	OA knee	TKA	**IA**: 3.0g	**IV**: 20 mg/kg before skin incision **Combined**: IV + IA	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Gómez-Aparicio MDS 2020 [75]	195 (85/110)	OA hip AVN	THA	**Drain**: 2.0g/100 ml	**IV**: 15 mg/kg 15–20 min before surgery + 15 mg/kg 15–20 min after surgery	Fair
Lostak, J. 2020 [76]	400 (100/100/100/100)	OA knee	TKA	**Local**: 2.0g/50 ml	**IV**: 15 mg/kg prior to skin incision **IV**: 15 mg/kg prior to skin incision + 15 mg/kg 6 h after the first dose **Combined**: IV 15 mg/kg prior to skin incision + 2.0g/50 ml Local	Fair
Morales Santias, M. 2020 [77]	230 (115/115)	NR knee	TKA	**IA**: 2.0g/50 ml	**Placebo**	Good
Song, S. J. CR TKA 2020 [78]	110 (55/55)	OA knee	TKA	**IA**: 1.0g/50 ml	**Placebo**	Fair
Torkaman, A. 2020 [79]	85 (46/39)	OA knee	TKA	**IA**: 1.0g/10 ml	**IV**: 15 mg/kg 10 min before tourniquet inflation	Fair
Zhang, X. 2020 [80]	72 (36/36)	AVN, OA, RA, Fracture hip	THA	**Drain**: 2.0g/10 ml	**IV**: 2.0g/100 ml 30 min before skin incision	Fair
Abdallah, A. A. 2021 [81]	94 (31/31/32)	OA knee	TKA	**IA + Drain**: 1.5g/100 ml	**IV**: 2.0g 10 min before tourniquet inflation **Combined**: IV + IA	Good
Costain, D. 2021 [82]	65 (31/34)	Fracture hip	DHS, Hemiarthroplasty, IMN, ORIF, TFN, THA	**Local**: 3.0g/50 ml	**Placebo**	Fair

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Juraj, M. 2021 [83]	123 (41/41/41)	OA hip	THA	**Local**: 2.0g/50 ml	**IV**: 1.0g/100 ml 30 min before skin incision + 1.0g/100 ml 3h later **Placebo**	Fair
Kim, J. K. 2021 [84]	325 (65/65/65/65/65)	OA knee	TKA	**IA**: 0.5g/50 ml **IA**: 1.0g/50 ml **IA**: 2.0g/50 ml **IA**: 3.0g/50 ml	**Placebo**	Good
Monteiro, O. M. 2021 [85]	42 (14/14/14)	OA knee	TKA	**Local**: 15 mg/kg 100 ml	**IV**: 15 mg/kg 30 minutes before tourniquet deflation **Placebo**	Fair
Örs, Ç. 2021 [86]	90 (30/30/30)	OA hip, AVN	THA c osteotomy	**Local**: 2.0g	**IV**: 15 mg/kg 100 ml 5 min prior to surgery **Combined**: IV + IA	Good
Palija, S. 2021 [87]	200 (40/40/40/40/40)	OA hip, others	THA	**Local + IA**: 2.0g/100 ml	**IV**: 1.0g/250 ml 10 min before skin incision + 1.0g/250 ml 3h after **Combined**: 1.0g/250 ml 10 min before skin incision IV + 1.0g/100 ml IA **Combined**: 1.0g/250 ml 10 min before skin incision IV + 2.0g/100 ml IA + 1.0g/250 ml IV 3h after	Fair
Peng, H. M. 2021 [88]	93 (46/47)	OA knee RA	TKA	**PA**: 1.0g/10 ml	**IV**: 1.0g/110 ml 10 min before skin incision	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

Author first, year	Sample Size (E/C)	Dx	Surgical methods	TXA Intervention	Comparator type	JADAD Quality
Pinsornsak, P. 2021 [89]	108 (36/36/36)	OA knee RA	TKA	**IA**: 2.0g	**PA**: 15 mg/kg **Placebo**	Good
Vles, G. F. 2021 [90]	120 (60/60)	OA hip, AVN	THA	**Drain**: 3.0g/100 ml	**IV**: 1.5g/100 ml before wound closure	Good
Yen, S. H. 2021 [91]	103 (34/34/35)	NR knee	TKA	**IA**: 3.0g/100 ml	**IA**: 10 ml of Floseal® **Placebo**	Good
Lostak, J. 2022 [92]	400 (100/100/100/100)	NR knee	TKA	**Local**: 2.0g/50 ml	**IV**: 15 mg/kg prior to skin incision **IV**: 15 mg/kg prior to skin incision + 15 mg/kg 6h after the first dose **Combined**: 15 mg/kg prior to skin incision IV + 2.0g/50 ml Local	Fair
Oliva-Moya, F. 2022 [93]	150 (75/75)	OA knee	TKA	**Local**: 3.0g/30 ml	**Placebo**	Good
Yee, D. K. 2022 [94]	121 (61/62)	Intertrochanteric fracture	PFNA	**Local**: 1.0g/10 ml	**Placebo**	Good

Intra-articular (IA), Peri-articular (PA), Avascular Necrosis (AVN), Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), Postoperative Autologous Transfusion (PAT), Rheumatoid Arthritis (RA), Cruciate Retaining (CR), Posterior Stabilized (PS), Proximal Femoral Nailing Antirotation (PFNA), Open Reduction Internal Fixation (ORIF), Dynamic Hip Screw (DHS)

3.2 Topical Tranexamic acid VS various methods

Total blood loss (9,416 participants, 87 study arms, Table 2**)**

Table 2
Results of topical tranexamic acid compared with the other interventions in both hip and knee surgery.

	No. of study arms	No. of patients	Mean diff (95% CI)	p-value	I^2	p-value	Egger's test
Total blood loss (mL)	87	9416	-147.559 (-191.264, -103.854)	< 0.001	98.1	< 0.001	0.003
vs iv	46	5154	4.178 (-22.673, 31.029)	0.76	88.1	< 0.001	
vs oral	3	384	64.769 (-14.963, 144.502)	0.111	0	0.902	
vs placebo	38	3878	-353.413 (-395.476, -311.351)	< 0.001	90.9	< 0,001	
Total drain (mL)	74	7905	-96.705 (-128.005, -65.406)	< 0.001	98,7	< 0,001	0.247
vs iv	40	4215	17.660 (-10.578, 45.897)	0.22	96.2	< 0.001	
vs oral	1	280	-0.140 (-10.063, 9.783)	0.978	0	1	
vs placebo	33	3410	-239.802 (-298.744, -180.859)	< 0,001	98.9	< 0.001	
Intr.op. blood loss (mL)	20	2059	-0.731 (-20.825, 19.363)	0.943	95	< 0.001	0.742
vs iv	9	877	14.001 (-41.371, 69.374)	0.62	97.5	< 0.001	
vs oral	3	384	1.563 (-4.632, 7.758)	0.621	0	0.48	
vs placebo	8	798	-14.994 (-34.370, 4.382)	0.129	80.3	< 0.001	
Hidden blood loss (mL)	18	1903	-24.896 (-67.160, 17.369)	0.248	88,5	< 0.001	0.619
vs iv	14	1522	1.750 (-45.297, 48.797)	0.942	85.3	< 0,001	
vs placebo	4	381	-123.711 (-153.703, -93.719)	< 0.001	3,67	0.374	
Hb fall (g/dL)	42	4754	-0.497 (-0.639, -0.356)	< 0.001	97.1	< 0.001	0.005
vs iv	17	1731	-0.003 (-0.136, 0.130)	0.968	92	< 0.001	
vs oral	3	520	0.036 (-0.058, 0.129)	0.454	0	0.623	
vs placebo	22	2503	-0.970 (-1.289, -0.651)	< 0.001	96.7	< 0.001	
Hct fall (%)	14	1380	-0.776 (-1.084, -0.469)	< 0.001	90	< 0.001	0.047
vs iv	5	484	-0.511 (-1.742, 0.720)	0.416	80.6	< 0.001	
vs placebo	9	896	-0.937 (-1.289, -0.584)	< 0.001	84.9	< 0.001	
	No. of study arms	No. of patients	RR diff (95% CI)	p-value	I^2	p-value	Egger's test

(iv) intravascular, (Hb) hemoglobin, (Hct) hematocrit

	No. of study arms	No. of patients	Mean diff (95% CI)	p-value	I^2	p-value	Egger's test
Blood transfusion	62	7401	0.610 (0.508, 0.732)	< 0.001	43	< 0.001	0.305
vs iv	26	3216	0.808 (0.586, 1.114)	0.194	43	0.011	
vs oral	4	667	1.247 (0.747, 2.082)	0.399	0	0.927	
vs placebo	32	3518	0.480 (0.386, 0.597)	< 0.001	35,7	0.025	
	No. of study arms	No. of patients	Mean diff (95% CI)	p-value	I^2	p-value	Egger's test
Hospital Stay (day)	42	5299	-0.046 (-0.136,0.044)	0.317	91.1	< 0.001	0.605
vs iv	20	2455	-0.119 (-0.328, 0.089)	0.261	93.5	< 0.001	
vs oral	5	790	-0.163 (-0.591, 0.264)	0.455	90.3	< 0.001	
vs placebo	17	2054	0.067 (-0.037, 0.171)	0.205	82.9	< 0.001	
	No. of study arms	No. of patients	RR diff (95% CI)	p-value	I^2	p-value	Egger's test
Morbidity	47	5915	0.733 (0.533, 1.007)	0.056	0	1	0.238
vs iv	19	2705	0.616 (0.343, 1.108)	0.106	0	0.959	
vs oral	2	427	0.336 (0.035, 3.198)	0.342	0	0.995	
vs placebo	26	2783	0.807 (0.549, 1.187)	0.276	0	0.995	

(iv) intravascular, (Hb) hemoglobin, (Hct) hematocrit

The analysis comparing topical and intravenous TXA revealed no statistically significant difference in total blood loss (5,145 participants, 46 study arms, *P*-value = 0.76). Likewise, no significant difference in total blood loss was observed between topical and oral TXA (384 participants, 3 study arms, *P*-value = 0.111). However, the topical TXA demonstrated a statistically significant reduction in total blood loss compared with placebo (3,878 participants, 38 study arms, mean difference = -353.413 mL, 95% CI: -395.413 to -311.351 mL, $P < 0.001$).

Drainage volume (7,905 participants, 74 study arms, Table 2**)**

The comparison between topical and intravenous TXA showed no significant difference in total drain volume (4,215 participants, 40 study arms, *P*-value = 0.22). Likewise, a similar result was found when comparing topical and oral TXA (280 participants, 1 study arm, *P*-value = 0.978). However, the topical tranexamic acid (TXA) demonstrated a statistically significant reduction in total drain volume compared to the placebo (3,410 participants, 33 study arms, mean difference = -239.802 mL, 95% CI: -298.744 to -180.859 mL, $P < 0.001$).

Intraoperative blood loss (2,059 participants, 20 study arms, Table 2**)**

No significant differences in intraoperative blood loss were observed between topical and intravenous TXA (877 participants, 9 study arms, *P*-value = 0.62), or between topical and oral TXA (384 participants, 3 study arms, *P*-value = 0.621). Additionally, there was no significant difference in intraoperative blood loss between topical TXA and the placebo group (798 participants, 8 study arms, *P*-value = 0.129).

Hidden blood loss (1,903 participants, 18 study arms, Table 2**)**

There was no significant difference in hidden blood loss observed between topical and intravenous administration of TXA (1,522 participants, 14 study arms, *P*-value = 0.942). However, the use of topical TXA demonstrated a significant decrease in hidden blood loss compared to the placebo group (381 participants, 4 study arms, mean difference = -123.711 mL, 95% CI: -153.703 to -93.719 mL, $P < 0.001$).

Total hemoglobin loss (4,757 participants, 42 study arms, Table 2**)**

The comparison of topical versus intravenous TXA and the comparison of topical versus oral TXA did not reveal a significant difference in the total hemoglobin loss (1,731 participants, 17 study arm, *P*-value = 0.968 and 520 participants, 3 study arms, *P*-value = 0.454 respectively). The topical TXA significantly reduced total hemoglobin loss compared to the placebo group (2,503 patients, 22 study arms, mean difference = -0.970 g/dL, 95% CI: -1.289 to -0.651 g/dL, $P < 0.001$).

Total hematocrit loss (1,380 participants, 14 study arms, Table 2**)**

The level of total hematocrit loss was not found to be significant when comparing topical versus intravenous TXA (484 participants, 5 study arms, *P*-value = 0.416). However, the topical TXA showed significant reduction in total hematocrit loss compared to the placebo group (896 participants, 9 study arms, mean difference = -0.937%, 95% CI: -1.289 to -0.584%, $P < 0.001$).

Blood transfusion (7,401 participants, 62 study arms, Table 2**)**

No significant difference in blood transfusion rates were found between topical and intravenous TXA (3,216 participants, 26 study arms, *P*-value = 0.194). Similar findings were observed in the comparison of topical and oral TXA (667 participants, 4 study arms, *P*-value = 0.399). However, the analysis demonstrated significantly lower transfusion rate in the topical TXA compared to the placebo group (3,518 participants, 32 study arms, RR = 0.480, 95% CI: 0.386 to 0.597, $P < 0.001$).

Hospital stays (5,299 participants, 42 study arms, Table 2**)**

The analysis showed no significant distinctions observed between topical and intravenous TXA (2,455 participants, 20 study arms, *P*-value = 0.261), nor between topical and oral TXA (790 participants, 5 study arms, *P*-value = 0.455). Furthermore, there was no significant difference in hospital stay between the use of topical TXA (2,054 participants, 17 study arms, *P*-value = 0.205).

Morbidity rate (5,915 participants, 47 study arms, Table 2**)**

No significant differences were found between topical and intravenous TXA (2,705 participants, 19 study arm, *P*-value = 0.106), or between topical and oral TXA (427 participants, 2 study arms, *P*-value = 0.342). Similarly, there was no significant difference in morbidity rate between the use of topical TXA and the placebo group (2,783 participants, 26 study arms, *P*-value = 0.276).

3.3 Investigations of heterogeneity

This part presents the results of knee and hip subgroup analyses that explore the total blood loss, total drain, total hemoglobin loss, blood transfusion and morbidity outcomes (Table 3). The comparisons were made between the use of topical tranexamic acid and other systemic administrations, as well as with a placebo group.

Table 3
Subgroup by organ to compare topical and hip surgery.

Knee	No. of study arms	No. of patients	Mean diff (95% CI)	p-value	Hip	No. of study arms	No. of patients	Mean diff (95% CI)	p-value
Total blood loss (mL)	69	7478	-164.509 (-216.279, -112.740)	< 0.001	Total blood loss (mL)	18	1938	-83.232 (-183.923, 17.460)	0.105
vs iv	37	4133	-0.643 (-46.301, 45.014)	0.978	vs iv	9	1021	6.285 (-25.244, 37.813)	0.696
vs oral	1	147	83.600 (-36.545, 203.745)	0.173	vs oral	2	237	49.949 (-56.637, 156.535)	0.358
vs placebo	31	3198	-368.730 (-412.145, -325.315)	< 0.001	vs placebo	7	680	-285.447 (-444.295, -126.599)	< 0.001
Total drain (mL)	55	6808	-99.491 (-134.717, -64.265)	< 0.001	Total drain (mL)	9	1097	-72.525 (-129.960, -15.091)	0.013
vs iv	36	3747	19.162 (-11.074, 49.398)	0.214	vs iv	4	468	8.737 (-31.080, 48.553)	0.667
vs oral	1	280	-0.140 (-10.063, 9.783)	0.978					
vs placebo	28	2781	-257.438 (-324.195, -190.682)	< 0.001	vs placebo	5	629	-138.452 (-237.450, -39.454)	0.006
Hb fall (g/dL)	32	3603	-0.369 (-0.524, -0.213)	< 0.001	Hb fall (g/dL)	10	1151	-0.961 (-1.741, -0.181)	0.016
vs iv	12	1187	0.019 (-0.157, 0.195)	0.831	vs iv	5	544	-0.148 (-0.539, 0.2)	0.457
vs oral	3	520	0.036 (-0.058, 0.129)	0.454					
vs placebo	17	1896	-0.667 (-0.790, -0.545)	< 0.001	vs placebo	5	607	-1.725 (-3.739,0.289)	0.093
Knee	No. of study arms	No. of patients	RR (95% CI)	p-value	Hip	No. of study arms	No. of patients	RR (95% CI)	p-value
Blood transfusion	40	4963	0.577 (0.464, 0.719)	< 0.001	Blood transfusion	22	1232	0.658 (0.485, 0.894)	0.007
vs iv	15	2042	1.112 (0.788, 1.569)	0.545	vs iv	11	600	0.595 (0.343, 1.033)	0.065
vs oral	3	547	1.151 (0.651, 2.036)	0.628	vs oral	1	60	1.750 (0.540, 5.668)	0.351
vs placebo	22	2374	0.398 (0.318, 0.500)	0.886	vs placebo	10	572	0.670 (0.461, 0.974)	0.036

(iv) intravascular, (Hb) hemoglobin, (Hct) hematocrit

Knee	No. of study arms	No. of patients	Mean diff (95% CI)	p-value	Hip	No. of study arms	No. of patients	Mean diff (95% CI)	p-value
Morbidity	35	4763	0.806 (0.565, 1.151)	0.236	Morbidity	12	1152	0.496 (0.242, 1.016)	0.055
vs iv	15	2314	0.727 (0.381, 1.385)	0.332	vs iv	4	391	0.280 (0.068, 1.148)	0.077
vs oral	2	427	0.336 (0.035, 3.198)	0.342					
vs placebo	18	2022	0.873 (0.566, 1.348)	0.541	vs placebo	8	761	0.606 (0.264, 1.391)	0.237
(iv) intravascular, (Hb) hemoglobin, (Hct) hematocrit									

3.3.1 Knee subgroup analysis

The knee subgroup analysis comprised 57 studies with 10,505 participants (Table 3), all of whom underwent TKA for knee osteoarthritis. There were no significant differences between topical, intravenous, or oral TXA in terms of total blood loss, drain output, and hemoglobin loss. Topical TXA, in particular, demonstrated significant reductions in total blood loss (MD: -368.730 mL; 95% CI: -412.145 to -325.315 mL; $P < 0.001$), total drain output (MD: -257.428 mL; 95% CI: -324.195 to -190.682 mL; $P < 0.001$), and hemoglobin loss (MD: -0.667g/dL; 95% CI: -0.790 to -0.545 g/dL; $P < 0.001$) compared to the placebo group. Notably, there were no significant differences in blood transfusion rates or morbidity rate among all modalities within the knee subgroup analysis.

3.3.2 Hip subgroup analysis

The hip subgroup analysis comprised 23 studies involving 3,464 patients (Table 3). Among these, the majority (17 studies, 74%) focused on hip diseases like osteoarthritis and avascular necrosis, which underwent hip arthroplasty, while the rest (6 studies, 26%) addressed hip fractures, involving fixation and hip arthroplasty.

There were no significant differences between topical, intravenous, or oral TXA in terms of total blood loss, and the blood transfusion rate. The total drain output is also comparable between topical TXA and intravenous TXA group. The topical TXA demonstrated significant reductions in total blood loss (MD: -285.447 mL; 95% CI: -444.295 to -125.599 mL; $P < 0.001$), total drain output (MD: -138.452 mL; 95% CI: -237.450 to -39.454 mL; *P*-value 0.006). and the blood transfusion rate (RR: 0.670; 95% CI: 0.461 to 0.974; *P*-value: 0.036) compared to the placebo group. Notably, there were no significant differences in the hemoglobin loss or morbidity rate among all modalities within the hip subgroup analysis.

3.4 Assessment of publication bias

All outcomes for heterogeneity were tested for by Egger's test. In cases where the *P*-value < 0.05, it was considered statistically significant, indicating the presence of publication bias. All publication bias outcomes were reported in Table 2.

4 Discussion

Our meta-analysis of 13,969 patients undergoing hip and knee surgeries showed that topical TXA offered significant benefits over placebo, reducing blood loss, drainage, and hemoglobin loss. Compared with systemic TXA, the topical TXA demonstrated equivalence in efficacy and safety to intravenous and oral TXA. In knee and hip subgroup analysis, similar trends were observed. A random effect model was chosen to account for potential heterogeneity. No significant differences were found between topical, intravenous, and oral routes in either hip or knee surgeries.

There were few previous meta-analyses comparing topical TXA with systemic application in hip and knee surgery. Chen et al found that topical and intravenous TXA resulted in no significant differences in total blood loss and transfusion rates for both TKA and THA, suggesting both methods are equally effective [105]. On the other hand, Alshryda S. et al highlighted a significant advantage of topical TXA in reducing transfusion rates for both TKA and THA [106]. Furthermore, Sun Q. et al investigation

emphasized that intravenous and topical routes had comparable outcomes and risk of venous thromboembolism (VTE) [107]. All three articles support the efficacy of TXA in minimizing blood loss during joint arthroplasty, the significant difference lies in the advantage of topical TXA over intravenous TXA in reducing transfusion rates (as noted by Alshryda S.). The outcomes of our study align with those of three prior meta-analyses, reaffirming that topical TXA demonstrates comparable effectiveness and safety to intravenous TXA in reducing blood loss and transfusion frequencies after TKA or THA.

Our knee subgroup analysis results, compared to previous meta-analyses in knee arthroplasty, are presented in Table 4. Panteli et al [108] (2013) assessed topical tranexamic acid (TXA) vs. placebo in seven RCTs (497 participants), reporting reduced postoperative drainage, total blood loss, hemoglobin drop, and transfusion need (RR = 0.47), consistent with our meta-analysis affirming topical TXA's efficacy. Wang et al [109] (2014) studied local and intravenous TXA in six RCTs (679 participants), finding decreased transfusion needs with topical TXA, aligning with our findings. Fillingham et al [110] compared topical and oral TXA, showing topical's superiority in blood loss and transfusion rate. Lu Feifan et al [111] found similar results. Our meta-analysis reinforces topical TXA's efficacy in reducing blood loss and transfusion needs during knee surgery. Overall, the pooling of various meta-analyses, including our own, highlights the apparent effectiveness of topical TXA in reducing blood loss, reducing the need for blood transfusion, and preserving hemoglobin levels in knee surgery. Notably, topical TXA demonstrates superiority over placebo and is as effective as intravenous TXA for knee surgery.

Table 4
Comparison between previous knee meta-analyses

	Panteli M. (2013) [105]	Wang H. (2014) [106]	Fillingham YA (2018) [107]	Lu F (2020) [108]	Present Metanalysis
Population	Patients undergoing TKA	Patients undergoing TKA	Patients undergoing TKA	Patients undergoing TKA	Patients undergoing TKA
Methods					
Data sources	PubMed Medline, Ovid Medline; Embase; and the Cochrane Library,	PubMed, CENTRAL Web of Science, and Embase	Ovid MEDLINE, Embase, Cochrane Reviews, Scopus, and Web of Science databases	PubMed, Medline, Web of Science, and Embase	PubMed, Scopus
Years	2010–2012	2012–2014	2017	2016–2020	2010–2022
Intervention	Topical	Topical	Topical	Topical	Topical
Comparator	Placebo	IV	Oral and placebo	IV	IV, Oral and Placebo
Number of RCTs	6 RCTs + 1 PCCs	6 RCTs	67 RCTs	28 RCTs	57 RCTs
Analytic approach	Fixed and random effect model, Inverse variance statistical method	Fixed and random effect model	N/R	Random effect model	Random effect model
Results					
Blood loss	MD = − 220.08 ml, 95% CI (− 279.54 to − 160.63), p < 0.00001, I^2 = 0%	MD = − 14.36 ml, 95% CI (− 92.02 to 63.30), p = 0.72, I^2 = 51%	Oral: MD = − 99.06 ml, 95% CI (− 296.33 to 93.6), Placebo: MD = − 329.4 ml, 95% CI (− 426.63 to − 240.21)	MD = 11.55 ml, 95% CI (− 10.23 to 33.34), p = 0.30, I^2 = 28.0%	IV: MD = -0.643 ml, 95% CI (-46.301 to 45.014), p = 0.978, I^2 = 89.7%. Oral: MD = 83.600 ml, 95% CI (-36.545 to 203.745), p = 0.173, I^2 = 0%. Placebo: MD = -368.730 ml, 95% CI (-412.145 to -325.315), p < 0.001, I^2 = 87.2%.

IV – intravenous; N/R – Not Reported; MD – Mean Difference; RR – Risk Ratio; TKA – Total Knee Arthroplasty

	Panteli M. (2013) [105]	Wang H. (2014) [106]	Fillingham YA (2018) [107]	Lu F (2020) [108]	Present Metanalysis
Total drain	MD = − 268.36 ml, 95% CI (− 491.55, − 45.18), p = 0.02 I^2 = 94%	MD = 21.91 ml, 95% CI (− 85.01 to 128.82), p = 0.69, I^2 = 94%	N/R	N/R	IV: MD = 19.162 ml, 95% CI (-11.074 to 49.398), p = 0.214, I^2 = 96.5%. Oral: MD = -0.140, 95% CI (-10.063, 9.783), p = 0.978, I^2 = 0%. Placebo: MD = -257.438 ml, 95% CI (-324.195, -190.682), p < 0.001, I^2 = 98.7%
Hemoglobin loss	MD = − 0.94 gr/dL, 95% CI (− 1.24, − 0.65), p < 0.00001, I^2 = 0%	MD = 0.43 gr/dL 95% CI (− 0.25 to 1.110, p = 0.22, I^2 = 95%	N/R	N/R	IV: MD = 0.019 gr/dL, 95% CI (-0.157, 0.195), p = 0.831, I^2 = 88%. Oral: MD = 0.036 gr/dL, 95% CI (-0.058, 0.129), p = 0.454, I^2 = 0%. Placebo: MD = -0.667 gr/dL, 95% CI (-0.790, -0.545), p < 0.001, I^2 = 68%
Mean blood transfusion	RR = 0.47, 95% CI (0.26 to 0.84), p = 0.01, I^2 = 0%	MD = − 0.40 95% CI (− 0.75 to − 0.05), p = 0.03, I^2 = 15%	Oral: RR = 1.06, 95% CI (0.48, 2.38) Placebo: RR = 0.26 95% (0.15, 0.4)	RR = 1.04 95% CI (0.64 to 1.69), p = 0.88, I^2 = 7%	IV: RR = 1.112, 95% CI (0.788, 1.569), p = 0.545, I^2 = 0%. Oral: RR = 1.151, 95% CI (0.651, 2.036), p = 0.628, I^2 = 0%. Placebo: RR = 0.398, 95% CI (0.318, 0.500), p = 0.886, I^2 = 0%.
Thromboembolic complications	N/R	RR = 7.00 95% CI (0.37 to 132.10), p = 0.19;	N/R	RR, 1.43 95% CI (0.81 to 2.54), p = 0.22, I^2 = 0%	N/R

IV – intravenous; N/R – Not Reported; MD – Mean Difference; RR – Risk Ratio; TKA – Total Knee Arthroplasty

Our hip subgroup analysis results, compared to previous meta-analyses in hip arthroplasty, are presented in Table 5. Chen et al [112] found a significant reduction in blood loss, drain output, and hemoglobin loss with topical tranexamic acid in 2,594 patients. Liu et al [113] reported that combining topical and intravenous tranexamic acid in 747 patients during THA may reduce blood loss without raising postoperative complications. Yoon et al's network meta-analysis [114] found comparable results across various tranexamic acid application methods. All prior meta-analyses on topical tranexamic acid usage in hip surgery align with the findings of our current meta-analysis.

Table 5
Comparison between previous hip meta-analyses

	Chen S. (2016) [109]	Liu X. (2017) [110]	Yoon BH (2018) [111]	Present metanalysis
Population	Patients undergoing primary THA	Patients undergoing primary THA	Patients undergoing primary THA	Patients with hip fracture, OA, AVN
Methods				
Data sources	PubMed, Embase, the Cochrane Library, Web of Science, and Chinese Biomedical Database	PubMed, Medline, Embase, Web of Science, the Cochrane Library, ChinaWanfang database, and Google database	PubMed-Medline, Embase, and the Cochrane Library	PubMed, Scopus
Years	2013–2014	2015–2016	2000–2017	2010–2022
Intervention	Topical (intra-articular)	Topical + IV	Topical	Topical
Comparator	Placebo	IV	IV, Combined, Placebo	IV, Oral, Placebo
Number of RCTs	7 RCTs + 7 cohort	6 RCTs	25 RCTs	23 RCTs
Analytic approach	Fixed-effects and random-effect models	Fixed-effects and random-effect models	Fixed-effects model	Random-effect models
Results				
Blood loss	MD = − 297.65 ml, 95% CI (− 371.68 to 116.08), $p < 0.01$, $I^2 = 71\%$.	MD = − 250.37 ml, 95% CI (− 376.43 to − 124.31), $p = 0.000$, $I^2 = 94.3\%$.	IV: OR = 0.99, 95% CI (0.65 to 1.52). Combined: OR = 0.63, 95% CI (0.19 to 2.06). Placebo: OR = 2.00, 95% CI (1.35 to 2.96).	IV: MD = 6.285 ml, 95% CI (− 25.244 to 37.813), p = 0.696, $I^2 = 72.2\%$. Oral: MD = 49.949 ml, 95% CI (− 56.637 to 156.535), $p = 0.358$, $I^2 = 0\%$. Placebo: MD = − 285.447 ml, 95% CI (− 444.295 to − 126.599), $p < 0.001$, $I^2 = 95.4\%$.
Total drain	MD = − 164.68 ml, 95% CI (− 236.63 to − 92.73), $p < 0.01$, $I^2 = 96\%$.	N/R	IV: OR = 0.92, 95% CI (0.26 to 3.19). Combined: OR = 0.93, 95% CI (0.17 to 5.02). Placebo: OR = 2.09, 95% CI (0.74 to 5.92);	IV: MD = 8.737 ml, 95% CI (− 31.080 to 48.553), p = 0.667, $I^2 = 39.3\%$. Placebo: MD = − 138.452 ml, 95% CI (− 237.450 to − 39.454), $p = 0.006$, $I^2 = 96.8\%$.

IV – intravenous; N/R – Not Reported; MD – Mean Difference; OR – Odds Ratio; RR – Risk Ratio; THA – Total Hip Arthroplasty;

	Chen S. (2016) [109]	Liu X. (2017) [110]	Yoon BH (2018) [111]	Present metanalysis
Hemoglobin loss	SMD = − 0.66, 95% CI (− 0.91 to − 0.41), p < 0.01, I^2 = 81%.	MD = − 0.11, 95% CI (− 0.11 to 0.17), p = 0.443, I^2 = 78.1%.	N/R	IV: MD = − 0.148, 95% CI (− 0.539 to 0.2), p = 0.457; I^2 = 92.3%. Placebo: MD = − 1.725, 95% CI (− 3.739 to 0.289), p = 0.093, I^2 = 99.0%.
Mean blood transfusion	OR = 0.26, 95% CI (0.17 to 0.40), p < 0.01, I^2 = 41%.	RR = 0.32, 95% CI (0.17 to 0.63), p = 0.001, I^2 = 0%.	IV: OR = 0.88, 95% CI (0.52 to 1.49). Combined: OR = 0.12, 95% CI (0.02 to 0.64), p-value 0.014. Placebo: OR = 3.31, 95% CI (2.03 to 5.18).	IV: RR = 0.595, 95% CI (0.343 to 1.033), p = 0.065, I^2 = 67.7%. Oral: RR = 1.750, 95% CI (0.540 to 5.668), p = 0.351, I^2 = 0%. Placebo: RR = 0.670 95% CI (0.461 to 0.974), p = 0.036, I^2 = 57.5%.
Thromboembolic complications	DVT (OR = 1.19, 95% CI (0.40 to 3.57) p = 0.006), PE (OR = 1.11, 95% CI (0.11 to 10.81); p = 0.006), I^2 = 0%.	RR = 1.23, 95% CI (0.38 to 4.00), p = 0.729.	IV: OR = 0.38, 95% CI (0.10 to 1.50). Combined: OR = 3.51, 95% CI (0.69 to 17.81); Placebo: OR = 0.59, 95% CI (0.20 to 1.78), p-value 0.31;	N/R
IV – intravenous; N/R – Not Reported; MD – Mean Difference; OR – Odds Ratio; RR – Risk Ratio; THA – Total Hip Arthroplasty;				

Our meta-analysis stands out for several reasons. Firstly, it's the most extensive analysis of its kind, involving 13,969 patients in randomized controlled trials, making it the largest study to date on topical tranexamic acid in orthopedic surgery. Secondly, we gathered data over a considerable timeframe, spanning from 2010 to 2022, providing a comprehensive and up-to-date analysis. Thirdly, we included both hip and knee surgery, considering various methods of administering tranexamic acid compared to placebo. However, there are notable limitations. Concerns about study heterogeneity and publication bias persist. The diverse forms of the topical route, such as intra-articular, peri-articular, and local, pose challenges in comparison. In future studies, we plan to address this by systematically comparing each route. Additionally, we acknowledge the differences in surgical approaches between knee and hip surgeries. Although there's a greater volume of knee surgery trials, we categorized and reported them as subgroup analyses to maintain meaningful insights.

5 Conclusion

In this meta-analysis of 80 RCTs with 13,969 patients undergoing hip and knee surgeries, topical tranexamic acid emerged as a significant asset, notably reducing blood loss, drainage, and hemoglobin loss when compared to a placebo. Knee surgeries showed clear benefits, while similar trends were observed in hip surgeries with fewer studies. Topical tranexamic acid exhibited equivalence to intravenous and oral administration, providing a practical, effective and safe option. Our study affirms and consolidates findings from previous meta-analyses, underscoring the consistent effectiveness of topical tranexamic acid in orthopedic surgery. However, concerns about study heterogeneity and publication bias warrant consideration, guiding our plans for future comprehensive investigations.

Declarations

Author contributions

S.T. conceived and designed the analysis. P.T. performed the meta-analysis search. Any disagreement or inconsistency were resolved by P.S. and P.T. extracted the data. P.S. performed the statistical analysis. S.T. and S.A. wrote the article. P.S. and P.T. critically reviewed the data and the manuscript. All authors reviewed the final manuscript and approved it. P.S. is the guarantor.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics declarations

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

Funding

There is no funding source.

References

1. Hu, Y., Li, Q., Wei, B. G., Zhang, X. S., Torsha, T. T., Xiao, J., & Shi, Z. J. Blood loss of total knee arthroplasty in osteoarthritis: an analysis of influential factors. J Orthop Surg Res. 13(1), 325. https://doi.org/10.1186/s13018-018-1038-0 (2018).
2. Partridge, J., Harari, D., Gossage, J., & Dhesi, J. Anaemia in the older surgical patient: a review of prevalence, causes, implications and management. J R Soc Med., 106(7), 269–277. https://doi.org/10.1177/0141076813479580 (2013).
3. Smeets, SJM, Verbruggen, JPAM, Poeze, M. Effect of blood transfusion on survival after hip fracture surgery. Eur J Orthop Surg Traumatol. 28(7), 1297–1303. https://doi.org/10.1007/s00590-018-2205-z (2018).
4. Levine, B.R., Haughom, B., Strong, B., Hellman, M., Frank, R.M. Blood management strategies for total knee arthroplasty. J Am Acad Orthop Surg. 22(6), 361–371. https://doi.org/10.5435/JAAOS-22-06-361 (2014).
5. Gibon, E., Courpied, J.P., Hamadouche, M. Total joint replacement and blood loss: what is the best equation? Int Orthop. 37(4), 735–739. https://doi.org/10.1007/s00264-013-1801-0 (2013).
6. Rasouli, M.R., Maltenfort, M.G., Erkocak, O.F., Austin, M.S., Waters, J.H., Parvizi, J. Blood management after total joint arthroplasty in the United States: 19-year trend analysis. Transfusion. 56(5), 1112–1120. https://doi.org/10.1111/trf.13518 (2016).

7. Dunn, C. J., & Goa, K. L. Tranexamic acid: a review of its use in surgery and other indications. Drugs, 57(6), 1005–1032. https://doi.org/10.2165/00003495-199957060-00017 (1999).
8. Eubanks, J.D. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg. 18(3), 132–138. (2010).
9. Yang, Z.G., Chen, W.P., Wu, L.D. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am. 94(13), 1153–1159. https://doi.org/10.2106/JBJS.K.00873 (2012).
10. Alshryda, S., Sukeik, M., Sarda, P., Blenkinsopp, J., Haddad, F.S., Mason, J.M. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J. 96-B(8), 1005–1015. https://doi.org/10.1302/0301-620X.96B8.33745 (2014).
11. Sukeik, M., Alshryda, S., Haddad, F.S., Mason, J.M. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br. 93(1), 39–46. https://doi.org/10.1302/0301-620X.93B1.24984 (2011).
12. Wong, J., Abrishami, A., El Beheiry, H., et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 92(15), 2503–2513. https://doi.org/10.2106/JBJS.I.01518 (2010).
13. Rajesparan, K., Biant, L. C., Ahmad, M., & Field, R. E. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br. 91(6), 776–783. https://doi.org/10.1302/0301-620X.91B6.22393 (2009).
14. Zohar, E., Ellis, M., Ifrach, N., Stern, A., Sapir, O., & Fredman, B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg. 99(6), 1679–1683. https://doi.org/10.1213/01.ANE.0000136770.75805.19 (2004).
15. Lin, Z., & Xiaoyi, Z. Tranexamic acid-associated seizures: A meta-analysis. Seizure, 36, 70–73. https://doi.org/10.1016/j.seizure.2016.02.011 (2016).
16. Lier, H., Maegele, M., & Shander, A. Tranexamic Acid for Acute Hemorrhage: A Narrative Review of Landmark Studies and a Critical Reappraisal of Its Use Over the Last Decade. *Anesth Analg.*, 129(6), 1574–1584. https://doi.org/10.1213/ANE.0000000000004389 (2019).
17. Sprigg, N., Flaherty, K., Appleton, J.P., et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 391(10135), 2107–2115. https://doi.org/10.1016/S0140-6736(18)31033-X (2018).
18. Morrison, J. J., Dubose, J. J., Rasmussen, T. E., & Midwinter, M. J. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 147(2), 113–119. https://doi.org/10.1001/archsurg.2011.287 (2012).
19. Gruen, R. L., Jacobs, I. G., Reade, M. C., & PATCH-Trauma study. Trauma and tranexamic acid. Med J Aust., 199(5), 310–311. https://doi.org/10.5694/mja13.10747 (2013).
20. Cole, E., Davenport, R., Willett, K., & Brohi, K. (2015). Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg.* 261(2), 390–394. https://doi.org/10.1097/SLA.0000000000000717 (2015).
21. Lucas-Polomeni, M. M., Delaval, Y., Menestret, P., Delaval, P., & Ecoffey, C. Un cas de choc anaphylactique à l'acide tranexamique (Exacyl) [A case of anaphylactic shock with tranexamique acid (Exacyl)]. Ann Fr Anesth Reanim. 23(6), 607–609. https://doi.org/10.1016/j.annfar.2004.04.012 (2004).
22. Patel, J. N., Spanyer, J. M., Smith, L. S., Huang, J., Yakkanti, M. R., & Malkani, A. L. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. J Arthroplasty., 29(8), 1528–1531. https://doi.org/10.1016/j.arth.2014.03.011 (2014).
23. Kim, K. I., Bae, J. K., Kim, J. H., Gwak, H. G., & Lee, S. H. Tranexamic acid in a periarticular multimodal cocktail injection for blood management in total knee arthroplasty: a prospective randomized study. BMC musculoskeletal disorders, 22(1), 675. https://doi.org/10.1186/s12891-021-04551-8 (2021).
24. Benoni, G., Lethagen, S., & Fredin, H. The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. Thromb Res., 85(3), 195–206. https://doi.org/10.1016/s0049-3848(97)00004-2 (1997).

25. Wong, J., Abrishami, A., El Beheiry, H., et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 92(15), 2503–2513. https://doi.org/10.2106/JBJS.I.01518 (2010).
26. Ishida, K., Tsumura, N., Kitagawa, A., et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop. 35(11), 1639–1645. https://doi.org/10.1007/s00264-010-1205-3 (2011).
27. Sa-Ngasoongsong, P., Wongsak, S., Chanplakorn, P., et al. Efficacy of low-dose intra-articular tranexamic acid in total knee replacement; a prospective triple-blinded randomized controlled trial. BMC Musculoskelet Disord. 14, 340. https://doi.org/10.1186/1471-2474-14-340 (2013).
28. Maniar, R. N., Kumar, G., Singhi, T., Nayak, R. M., & Maniar, P. R. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res., 470(9), 2605–2612. https://doi.org/10.1007/s11999-012-2310-y (2012).
29. Roy, S. P., Tanki, U. F., Dutta, A., Jain, S. K., & Nagi, O. N. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc, 20(12), 2494–2501. https://doi.org/10.1007/s00167-012-1942-5 (2012).
30. Alshryda, S., Mason, J., Sarda, P., et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX-H). J Bone Joint Surg Am. 95(21), 1969–1974. https://doi.org/10.2106/JBJS.L.00908 (2013).
31. Georgiadis, A. G., Muh, S. J., Silverton, C. D., Weir, R. M., & Laker, M. W. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. J Arthroplasty., 28(8 Suppl), 78–82. https://doi.org/10.1016/j.arth.2013.03.038 (2013).
32. Seo, J. G., Moon, Y. W., Park, S. H., Kim, S. M., & Ko, K. R. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc., 21(8), 1869–1874. https://doi.org/10.1007/s00167-012-2079-2 (2013).
33. Emara, W. M., Moez, K. K., & Elkhouly, A. H. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesth Essays Res., 8(1), 48–53. https://doi.org/10.4103/0259-1162.128908 (2014).
34. Gomez-Barrena, E., Ortega-Andreu, M., Padilla-Eguiluz, N. G., Pérez-Chrzanowska, H., & Figueredo-Zalve, R. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. J Bone Joint Surg Am., 96(23), 1937–1944. https://doi.org/10.2106/JBJS.N.00060 (2014).
35. Martin, J. G., Cassatt, K. B., Kincaid-Cinnamon, K. A., Westendorf, D. S., Garton, A. S., & Lemke, J. H. Topical administration of tranexamic acid in primary total hip and total knee arthroplasty. J Arthroplasty., 29(5), 889–894. https://doi.org/10.1016/j.arth.2013.10.005 (2014).
36. Patel, J. N., Spanyer, J. M., Smith, L. S., Huang, J., Yakkanti, M. R., & Malkani, A. L. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. J Arthroplasty., 29(8), 1528–1531. https://doi.org/10.1016/j.arth.2014.03.011 (2014).
37. Soni, A., Saini, R., Gulati, A., Paul, R., Bhatty, S., & Rajoli, S. R. Comparison between intravenous and intra-articular regimens of tranexamic acid in reducing blood loss during total knee arthroplasty. J Arthroplasty., 29(8), 1525–1527. https://doi.org/10.1016/j.arth.2014.03.039 (2014).
38. Wei, W., & Wei, B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty., 29(11), 2113–2116. https://doi.org/10.1016/j.arth.2014.07.019 (2014).
39. Yue, C., Kang, P., Yang, P., Xie, J., & Pei, F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty., 29(12), 2452–2456. https://doi.org/10.1016/j.arth.2014.03.032 (2014).
40. Aguilera, X., Martínez-Zapata, M.J., Hinarejos, P., et al. Topical and intravenous tranexamic acid reduce blood loss compared to routine hemostasis in total knee arthroplasty: a multicenter, randomized, controlled trial. Arch Orthop Trauma Surg. 135(7),

1017–1025. https://doi.org/10.1007/s00402-015-2232-8 (2015).

41. Digas, G., Koutsogiannis, I., Meletiadis, G., Antonopoulou, E., Karamoulas, V., & Bikos, C.h Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty. Eur J Orthop Surg Traumatol., 25(7), 1181–1188. https://doi.org/10.1007/s00590-015-1664-8 (2015).
42. Öztaş, S., Öztürk, A., Akalin, Y., et al. The effect of local and systemic application of tranexamic acid on the amount of blood loss and allogeneic blood transfusion after total knee replacement. Acta Orthop Belg. 81(4), 698–707. (2015)
43. Wang, C. G., Sun, Z. H., Liu, J., Cao, J. G., & Li, Z. J. Safety and efficacy of intra-articular tranexamic acid injection without drainage on blood loss in total knee arthroplasty: A randomized clinical trial. Int J Surg., 20, 1–7. https://doi.org/10.1016/j.ijsu.2015.05.045 (2015).
44. Wang, G., Wang, D., Wang, B., Lin, Y., Sun, S. Efficacy and safety evaluation of intra-articular injection of tranexamic acid in total knee arthroplasty operation with temporarily drainage close. Int J Clin Exp Med., 8(8), 14328–14334. (2015).
45. Yang, Y., Lv, Y. M., Ding, P. J., Li, J., Ying-Ze, Z. The reduction in blood loss with intra-articular injection of tranexamic acid in unilateral total knee arthroplasty without operative drains: a randomized controlled trial. Eur J Orthop Surg Traumatol., 25(1), 135–139. https://doi.org/10.1007/s00590-014-1461-9 (2015).
46. Aggarwal, A. K., Singh, N., Sudesh, P. Topical vs Intravenous Tranexamic Acid in Reducing Blood Loss After Bilateral Total Knee Arthroplasty: A Prospective Study. J Arthroplasty., 31(7), 1442–1448. https://doi.org/10.1016/j.arth.2015.12.033 (2016).
47. Chen, J.Y., Chin, P.L., Moo, I.H., et al. Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial. Knee. 23(1), 152–156. https://doi.org/10.1016/j.knee.2015.09.004 (2016).
48. Drakos, A., Raoulis, V., Karatzios, K., et al. Efficacy of Local Administration of Tranexamic Acid for Blood Salvage in Patients Undergoing Intertrochanteric Fracture Surgery. J Orthop Trauma. 30(8), 409–414. https://doi.org/10.1097/BOT.0000000000000577 (2016).
49. Tzatzairis, T. K., Drosos, G. I., Kotsios, S. E., Ververidis, A. N., Vogiatzaki, T. D., & Kazakos, K. I. Intravenous vs Topical Tranexamic Acid in Total Knee Arthroplasty Without Tourniquet Application: A Randomized Controlled Study. J Arthroplasty., 31(11), 2465–2470. https://doi.org/10.1016/j.arth.2016.04.036 (2016).
50. Guzel, Y., Gurcan, O. T., Golge, U. H., Dulgeroglu, T. C., & Metineren, H. Topical tranexamic acid versus autotransfusion after total knee arthroplasty. J Orthop Surg (Hong Kong)., 24(2), 179–182. https://doi.org/10.1177/1602400212 (2016).
51. May, J. H., Rieser, G. R., Williams, C. G., Markert, R. J., Bauman, R. D., & Lawless, M. W. The Assessment of Blood Loss During Total Knee Arthroplasty When Comparing Intravenous vs Intracapsular Administration of Tranexamic Acid. J Arthroplasty., 31(11), 2452–2457. https://doi.org/10.1016/j.arth.2016.04.018 (2016).
52. North, W. T., Mehran, N., Davis, J. J., Silverton, C. D., Weir, R. M., & Laker, M. W. Topical vs Intravenous Tranexamic Acid in Primary Total Hip Arthroplasty: A Double-Blind, Randomized Controlled Trial. J Arthroplasty., 31(5), 1022–1026. https://doi.org/10.1016/j.arth.2015.11.003 (2016).
53. Pinsornsak, P., Rojanavijitkul, S., & Chumchuen, S. Peri-articular tranexamic acid injection in total knee arthroplasty: a randomized controlled trial. BMC Musculoskelet Disord., 17, 313. https://doi.org/10.1186/s12891-016-1176-7 (2016).
54. Triyudanto, A.N. and Lubis, A.M. The effects of intra-articular tranexamic acid given intraoperatively, and intravenous tranexamic acid given preoperatively on post-surgical bleeding and transfusion rate post total knee arthroplasty. Med J Indones. 25(4), 234–9. https://doi.org/10.13181/mji.v25i4.1502 (2017)
55. Tzatzairis, T. K., Drosos, G. I., Kotsios, S. E., Ververidis, A. N., Vogiatzaki, T. D., & Kazakos, K. I. Intravenous vs Topical Tranexamic Acid in Total Knee Arthroplasty Without Tourniquet Application: A Randomized Controlled Study. J Arthroplasty., 31(11), 2465–2470. https://doi.org/10.1016/j.arth.2016.04.036 (2016).
56. Xie, J., Ma, J., Yue, C., Kang, P., & Pei, F. Combined use of intravenous and topical tranexamic acid following cementless total hip arthroplasty: a randomised clinical trial. Hip Int., 26(1), 36–42. https://doi.org/10.5301/hipint.5000291 (2016).
57. Zekcer, A., Del Priori, R., Tieppo, C., da Silva, R. S., & Severino, N. R. Topical vs. intravenous administration of tranexamic acid in knee arthroplasty and prevalence of deep venous thrombosis: a randomized clinical trial. J Vasc Bras., 15(2), 120–125. https://doi.org/10.1590/1677-5449.007515 (2016).

58. Guerreiro, J. P. F., Badaro, B. S., Balbino, J. R. M., Danieli, M. V., Queiroz, A. O., & Cataneo, D. C. Application of Tranexamic Acid in Total Knee Arthroplasty - Prospective Randomized Trial. Open Orthop J., 11, 1049–1057. https://doi.org/10.2174/1874325001711011049 (2017).
59. Lacko, M., Cellar, R., Schreierova, D., & Vasko, G. Comparison of intravenous and intra-articular tranexamic acid in reducing blood loss in primary total knee replacement. Eklem Hastalik Cerrahisi., 28(2), 64–71. https://doi.org/10.5606/ehc.2017.54914 (2017).
60. Lee, S. Y., Chong, S., Balasubramanian, D., Na, Y. G., & Kim, T. K. What is the Ideal Route of Administration of Tranexamic Acid in TKA? A Randomized Controlled Trial. Clin Orthop Relat Res., 475(8), 1987–1996. https://doi.org/10.1007/s11999-017-5311-z (2017).
61. Maniar, R. N., Singhi, T., Patil, A., Kumar, G., Maniar, P., & Singh, J. Optimizing effectivity of tranexamic acid in bilateral knee arthroplasty - A prospective randomized controlled study. Knee., 24(1), 100–106. https://doi.org/10.1016/j.knee.2016.10.014 (2017).
62. Prakash, J., Seon, J. K., Park, Y. J., Jin, C., & Song, E. K. A randomized control trial to evaluate the effectiveness of intravenous, intra-articular and topical wash regimes of tranexamic acid in primary total knee arthroplasty. J Orthop Surg (Hong Kong)., 25(1), 2309499017693529. https://doi.org/10.1177/2309499017693529 (2017).
63. Song, E. K., Seon, J. K., Prakash, J., Seol, Y. J., Park, Y. J., & Jin, C. Combined Administration of IV and Topical Tranexamic Acid is Not Superior to Either Individually in Primary Navigated TKA. J Arthroplasty., 32(1), 37–42. https://doi.org/10.1016/j.arth.2016.06.052 (2017).
64. Wang, J., Wang, Q., Zhang, X., & Wang, Q. Intra-articular Application is More Effective Than Intravenous Application of Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Controlled Trial. J Arthroplasty. 32(11), 3385–3389. https://doi.org/10.1016/j.arth.2017.06.024 (2017).
65. Yen, S. H., Lin, P. C., Chen, B., Huang, C. C., & Wang, J. W. Topical Tranexamic Acid Reduces Blood Loss in Minimally Invasive Total Knee Arthroplasty Receiving Rivaroxaban. *Biomed Res Int*., 2017, 9105645. https://doi.org/10.1155/2017/9105645 (2017).
66. Yuan, X., Li, B., Wang, Q., & Zhang, X. (2017). Comparison of 3 Routes of Administration of Tranexamic Acid on Primary Unilateral Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. J Arthroplasty. 32(9), 2738–2743. https://doi.org/10.1016/j.arth.2017.03.059
67. Zekcer, A., Priori, R. D., Tieppo, C., Silva, R. S. D., & Severino, N. R. (2017). Comparative study of topical vs. intravenous tranexamic acid regarding blood loss in total knee arthroplasty. Rev Bras Ortop., 52(5), 589–595. https://doi.org/10.1016/j.rboe.2017.08.005
68. Abdel, M.P., Chalmers, B.P., Taunton, M.J., et al. Intravenous Versus Topical Tranexamic Acid in Total Knee Arthroplasty: Both Effective in a Randomized Clinical Trial of 640 Patients. J Bone Joint Surg Am. 100(12), 1023–1029. https://doi.org/10.2106/JBJS.17.00908 (2018).
69. Ahmed, S., Ahmed, A., Ahmad, S., Atiq-uz-Zaman, Javed, S., & Aziz, A. Blood loss after intraarticular and intravenous tranexamic acid in total knee arthroplasty. J Pak Med Assoc., 68(10), 1434–1437. (2018).
70. Luo, Z. Y., Wang, D., Meng, W. K., et al. Oral tranexamic acid is equivalent to topical tranexamic acid without drainage in primary total hip arthroplasty: A double-blind randomized clinical trial. Thromb Res., 167, 1–5. https://doi.org/10.1016/j.thromres.2018.04.026 (2018).
71. Luo, Z. Y., Wang, H. Y., Wang, D., Zhou, K., Pei, F. X., & Zhou, Z. K. Oral vs Intravenous vs Topical Tranexamic Acid in Primary Hip Arthroplasty: A Prospective, Randomized, Double-Blind, Controlled Study. J Arthroplasty., 33(3), 786–793. https://doi.org/10.1016/j.arth.2017.09.062 (2018).
72. Pérez-Jimeno, N., Muñoz, M., Mateo, J., Mayoral, A. P., & Herrera, A. Efficacy of topical tranexamic acid within a blood-saving programme for primary total hip arthroplasty: a pragmatic, open-label randomised study. Blood Transfus., 16(6), 490–497. https://doi.org/10.2450/2018.0133-18 (2018).
73. Prakash, J., Seon, J. K., Song, E. K., Lee, D. H., Yang, H. Y., & Jin, C. Is Combined Administration of Tranexamic Acid Better than Both Intravenous and Topical Regimes for Total Loss, Hidden Loss and Post-operative Swelling? A Randomized Control Trial. Indian J Orthop., 52(2), 117–123. https://doi.org/10.4103/ortho.IJOrtho_179_16 (2018).

74. Tavares Sánchez-Monge, F. J., Aguado Maestro, I., Bañuelos Díaz, A., Martín Ferrero, M. Á., & García Alonso, M. F. Efficacy and safety of the topical application of tranexamic acid in primary cementless hip arthroplasty: prospective, randomised, double-blind and controlled study. Eficacia y seguridad de la aplicación del ácido tranexámico tópico en la artroplastia primaria no cementada de cadera: estudio prospectivo, aleatorizado, doble ciego y controlado. Rev Esp Cir Ortop Traumatol (Engl Ed)., *62*(1), 47–54. https://doi.org/10.1016/j.recot.2017.09.003 (2018).
75. Wang, D., Wang, H. Y., Cao, C., et al. Tranexamic acid in primary total knee arthroplasty without tourniquet: a randomized, controlled trial of oral versus intravenous versus topical administration. Sci Rep., 8(1), 13579. https://doi.org/10.1038/s41598-018-31791-x (2018).
76. Wang, D., Zhu, H., Meng, W. K., et al. Comparison of oral versus intra-articular tranexamic acid in enhanced-recovery primary total knee arthroplasty without tourniquet application: a randomized controlled trial. BMC Musculoskelet Disord., 19(1), 85. https://doi.org/10.1186/s12891-018-1996-8 (2018).
77. Zhou, K. D., Wang, H. Y., Wang, Y., Liu, Z. H., He, C., & Feng, J. M. Is topical or intravenous tranexamic acid preferred in total hip arthroplasty? A randomized, controlled, noninferiority clinical trial. PloS one, 13(10), e0204551. https://doi.org/10.1371/journal.pone.0204551 (2018).
78. Jia J. Combined use of intravenous and topical tranexamic acid in patients aged over 70 years old undergoing total hip arthroplasty. J Orthop Surg Res. 14(1), 345. https://doi.org/10.1186/s13018-019-1384-6 (2019).
79. Jules-Elysee, K. M., Tseng, A., Sculco, T. P., et al. Comparison of Topical and Intravenous Tranexamic Acid for Total Knee Replacement: A Randomized Double-Blinded Controlled Study of Effects on Tranexamic Acid Levels and Thrombogenic and Inflammatory Marker Levels. J Bone Joint Surg Am., 101(23), 2120–2128. https://doi.org/10.2106/JBJS.19.00258 (2019).
80. Kyriakopoulos, G., Oikonomou, L., Panagopoulos, A., et al. Transfusion rate, hospital stay and cost-effectiveness of intravenous or local administration of tranexamic acid in total hip and knee arthroplasty: A single-center randomized controlled clinical study. Orthopedic reviews, 11(2), 7866. https://doi.org/10.4081/or.2019.7866 (2019).
81. Mehta, N., Goel, N., Goyal, A., et al A prospective comparative study between intravenous and intraarticular tranexamic acid administration in decreasing the perioperative blood loss in total knee arthroplasty. Journal of Arthroscopy and Joint Surgery. 6(1): 70–73, https://doi.org/10.1016/j.jajs.2018.11.002 (2019)
82. Qiu, J., Sun, X., Zhang, W., Ke, X., Yang, G., & Zhang, L. Effect of topical tranexamic acid in total hip arthroplasty patients who receive continuous aspirin for prevention of cardiovascular or cerebrovascular events: A prospective randomized study. Orthop Traumatol Surg Res., 105(7), 1327–1332. https://doi.org/10.1016/j.otsr.2019.06.018 (2019).
83. Wu, J., Feng, S., Chen, X., et al. Intra-Articular Injection of Tranexamic Acid on Perioperative Blood Loss During Unicompartmental Knee Arthroplasty. Med Sci Monit., 25, 5068–5074. https://doi.org/10.12659/MSM.914817 (2019).
84. Zhang, Y. M., Yang, B., Sun, X. D., & Zhang, Z. Combined intravenous and intra-articular tranexamic acid administration in total knee arthroplasty for preventing blood loss and hyperfibrinolysis: A randomized controlled trial. Medicine (Baltimore)., 98(7), e14458. https://doi.org/10.1097/MD.0000000000014458 (2019).
85. Gómez-Aparicio, M. D. S., Gómez-Barbero, P., Blas-Dobón, J. A., Villar-Blanco, A., Morales-Suárez-Varela, M., & Rodrigo-Pérez, J. L. Results after the application of tranexamic acid intravenous or intra-articular in the control of postsurgical bleeding after total hip arthroplasty: a randomized controlled trial. Eur J Orthop Surg Traumatol. 30(7), 1221–1230. https://doi.org/10.1007/s00590-020-02688-1 (2020).
86. LoŠŤÁk, J., Gallo, J., BalÁŽ, Ľ., & ZapletalovÁ, J. Optimal Route for Tranexamic Acid in Diabetics and Obese Patients Undergoing Primary Total Knee Arthroplasty - a Data from Randomized Study. Optimální způsob podání tranexamové kyseliny u diabetiků a obézních pacientů – data z randomizované klinické studie. *Acta Chir Orthop Traumatol Cech.*, 87(6), 429–437. http://dx.doi.org/10.55095/achot2020/067 (2020).
87. Morales Santias, M., Mas Martinez, J., Sanz-Reig, J., Martínez Gimenez, E., Verdu Román, C., & Bustamante Suarez de Puga, D. Topical tranexamic acid in cemented primary total knee arthroplasty without tourniquet: a prospective randomized study. Eur J Orthop Surg Traumatol., 30(6), 1003–1008. https://doi.org/10.1007/s00590-020-02656-9 (2020).
88. Song, S. J., Lee, H. W., Bae, D. K., & Park, C. H. Daily blood loss transition after total knee arthroplasty with topical administration of tranexamic acid: Paradoxical blood loss after action of tranexamic acid. J Orthop Surg (Hong Kong). 28(1), 2309499019895816. https://doi.org/10.1177/2309499019895816 (2020).

89. Torkaman, A., Rostami, A., Sarshar, M. R., Akbari Aghdam, H., Motaghi, P., & Yazdi, H. The Efficacy of Intravenous Versus Topical Use of Tranexamic Acid in Reducing Blood Loss after Primary Total Knee Arthroplasty: A Randomized Clinical Trial. Arch Bone Jt Surg., 8(3), 363–367. https://doi.org/10.22038/abjs.2020.40528.2099 (2020).
90. Zhang, X., Ma, D., Wen, L., & Pan, J. Better Treatment Values in Local Application of Tranexamic Acid (TXA) than Intravenous Application with the Same Dose in Total Hip Arthroplasty. Adv Ther., 37(10), 4346–4355. https://doi.org/10.1007/s12325-020-01454-3 (2020).
91. Abdallah, A. A., Sallam, A. A., Arafa, M. S., & Henawy, A. T. Topical Tranexamic Acid in Total Knee Arthroplasty: Does It Augment the Effect of the Intravenous Administration in Patients with Moderate-to-High Risk of Bleeding? A Randomized Clinical Trial. J Knee Surg., 34(14), 1570–1578. https://doi.org/10.1055/s-0040-1710549 (2021).
92. Costain, D., Elder, G., Fraser, B., Slagel, B., Kelly, A., Cheong, Y., & Fera, L. Topical tranexamic acid in hip fractures: a randomized, placebo-controlled double-blinded study. Can J Surg., 64(4), E449–E456. https://doi.org/10.1503/cjs.014220 (2021).
93. Juraj, M., Jaroslav, V., Gažová, A., Žufková, V., Kyselovič, J., & Šteňo, B. Evaluation of efficacy and safety of systemic and topical intra-articular administration of tranexamic acid in primary unilateral total hip arthroplasty. Medicine, 100(26), e26565. https://doi.org/10.1097/MD.0000000000026565 (2021).
94. Kim, J. K., Park, J. Y., Lee, D. Y., Ro, D. H., Han, H. S., & Lee, M. C. Optimal dose of topical tranexamic acid considering efficacy and safety in total knee arthroplasty: a randomized controlled study. Knee Surg Sports Traumatol Arthrosc., 29(10), 3409–3417. https://doi.org/10.1007/s00167-020-06241-9 (2021).
95. Monteiro, O. M., Perrone, R. T., Almeida, F. N., Moura, C. P., Oliveira, S. G., & Almeida, G. D. B. COMPARISON OF HEMOSTASIS WITH TRANEXAMIC ACID IN TOTAL KNEE ARTHROPLASTY. Acta Ortop Bras., 29(4), 184–188. https://doi.org/10.1590/1413-785220212904235714 (2021).
96. Örs, Ç., & Çaylak, R. The efficacy, safety, and cost-effectives of combined administration of Intravenous and Local Tranexamic Acid in the management of Patients Undergoing Primary Total Hip Arthroplasty: A prospective, blinded and randomized clinical study. Acta Orthop Traumatol Turc., 55(5), 422–427. https://doi.org/10.5152/j.aott.2021.20397 (2021).
97. Palija, S., Bijeljac, S., Manojlovic, S., Jovicic, Z., Jovanovic, M., Cvijic, P., & Dragicevic-Cvjetkovic, D. Effectiveness of different doses and routes of administration of tranexamic acid for total hip replacement. Int Orthop., 45(4), 865–870. https://doi.org/10.1007/s00264-020-04585-y (2021).
98. Peng, H. M., Wang, W., Lin, J., Weng, X. S., Qian, W. W., & Wang, W. D. Multimodal Peri-articular Injection with Tranexamic Acid can reduce postoperative blood loss versus Intravenous Tranexamic Acid in Total Knee Arthroplasty: A Randomized Controlled Trial. J Orthop Surg Res., 16(1), 546. https://doi.org/10.1186/s13018-021-02685-y (2021).
99. Pinsornsak, P., Phunphakchit, J., & Boontanapibul, K. Efficacy and Systemic Absorption of Peri-articular Versus Intra-articular Administration of Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Controlled Trial. Arthroplast Today., 11, 1–5. https://doi.org/10.1016/j.artd.2021.06.005 (2021).
100. Vles, G. F., Corten, K., Driesen, R., van Elst, C., & Ghijselings, S. G. Hidden blood loss in direct anterior total hip arthroplasty: a prospective, double blind, randomized controlled trial on topical versus intravenous tranexamic acid. Musculoskelet Surg., 105(3), 267–273. https://doi.org/10.1007/s12306-020-00652-0 (2021).
101. Yen, S. H., Lin, P. C., Wu, C. T., & Wang, J. W. Comparison of Effects of a Thrombin-Based Hemostatic Agent and Topical Tranexamic Acid on Blood Loss in Patients with Preexisting Thromboembolic Risk Undergoing a Minimally Invasive Total Knee Arthroplasty. A Prospective Randomized Controlled Trial. *Biomed Res Int.*, 2021, 2549521. https://doi.org/10.1155/2021/2549521 (2021).
102. Lostak, J., Gallo, J., Balaz, L., & Zapletalova, J. Combined and intravenous administration of TXA reduces blood loss more than topical administration in primary total knee arthroplasty: A randomized clinical trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub., 166(1), 68–76. https://doi.org/10.5507/bp.2020.045 (2022).
103. Oliva-Moya, F., Belloso-Moreno, I., Vilches-Fernández, J. M., Casas-Ruiz, M., & Andrés-García, J. A. [Translated article] Randomized, placebo-controlled, double-blind clinical trial to evaluate efficacy and safety of topical tranexamic acid in saving blood loss in patients undergoing prosthetic knee surgery. Rev Esp Cir Ortop Traumatol., 66(6), T67–T72. https://doi.org/10.1016/j.recot.2022.02.008 (2022).

104. Yee, D. K., Wong, J. S. H., Fang, E., Wong, T. M., Fang, C., & Leung, F. Topical administration of tranexamic acid in elderly patients undergoing short femoral nailing for intertrochanteric fracture: A randomised controlled trial. Injury, 53(2), 603–609. https://doi.org/10.1016/j.injury.2021.11.055 (2022).
105. Chen, Y., Chen, Z., Cui, S., Li, Z., & Yuan, Z. Topical versus systemic tranexamic acid after total knee and hip arthroplasty: A meta-analysis of randomized controlled trials. Medicine, 95(41), e4656. https://doi.org/10.1097/MD.0000000000004656 (2016).
106. Alshryda, S., Sukeik, M., Sarda, P., Blenkinsopp, J., Haddad, F. S., & Mason, J. M. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J., 96-B(8), 1005–1015. https://doi.org/10.1302/0301-620X.96B8.33745 (2014).
107. Sun, Q., Li, J., Chen, J., Zheng, C., Liu, C., & Jia, Y. Comparison of intravenous, topical or combined routes of tranexamic acid administration in patients undergoing total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. BMJ open, 9(1), e024350. https://doi.org/10.1136/bmjopen-2018-024350 (2019).
108. Panteli, M., Papakostidis, C., Dahabreh, Z., & Giannoudis, P. V. Topical tranexamic acid in total knee replacement: a systematic review and meta-analysis. Knee, 20(5), 300–309. https://doi.org/10.1016/j.knee.2013.05.014 (2013).
109. Wang, H., Shen, B., & Zeng, Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. Knee, 21(6), 987–993. https://doi.org/10.1016/j.knee.2014.09.010 (2014).
110. Fillingham, Y. A., Ramkumar, D. B., Jevsevar, D. S., et al. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. J Arthroplasty., 33(10), 3090–3098.e1. https://doi.org/10.1016/j.arth.2018.04.043 (2018).
111. Lu, F., Sun, X., Wang, W., Zhang, Q., & Guo, W. What is the ideal route of administration of tranexamic acid in total knee arthroplasty? A meta-analysis based on randomized controlled trials. Ann Palliat Med., 10(2), 1880–1894. https://doi.org/10.21037/apm-20-1857 (2021).
112. Chen, S., Wu, K., Kong, G., Feng, W., Deng, Z., & Wang, H. The efficacy of topical tranexamic acid in total hip arthroplasty: a meta-analysis. BMC musculoskeletal disorders, 17, 81. https://doi.org/10.1186/s12891-016-0923-0 (2016).
113. Liu, X., Liu, J., & Sun, G. A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: A meta-analysis. Int J Surg., 41, 34–43. https://doi.org/10.1016/j.ijsu.2017.03.031 (2017).
114. Yoon, B. H., Kim, T. Y., Ko, Y. S., Lee, Y. K., Ha, Y. C., & Koo, K. H. Optimal use of tranexamic acid for total hip arthroplasty: A network meta-analysis. PloS one, 13(10), e0206480. https://doi.org/10.1371/journal.pone.0206480 (2018).

Figures

Fig. 1. Flow diagram for selection of studies of topical tranexamic acid on hip and knee surgery.

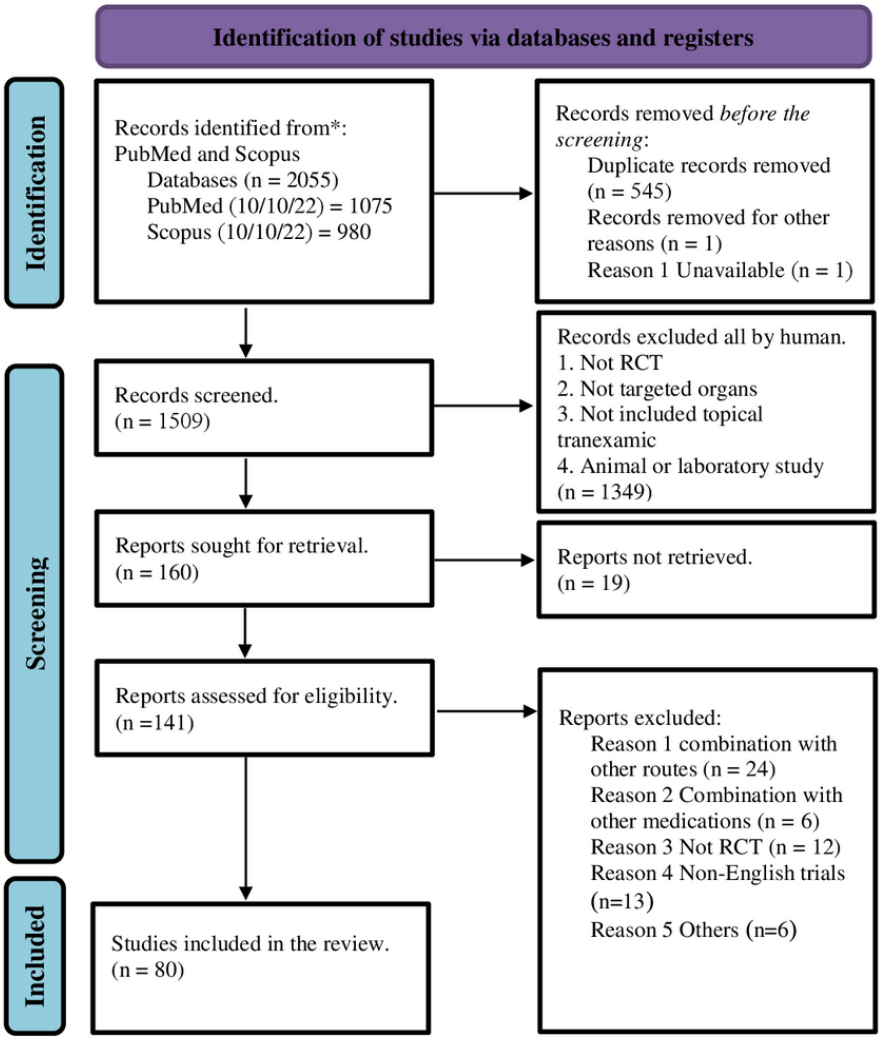

Figure 1

See image above for figure legend.