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TRANEXAMIC ACID IN PRIMARY HIP AND KNEE ARTHROPLASTY: ROUTE, DOSE, AND SAFETY ACROSS RANDOMIZED TRIALS

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Abstract

By the mid-2010s, tranexamic acid had become standard practice for blood management in hip and knee replacement. Yet debate continued over which route of administration works best and how safe each strategy proves in real-world use. We reviewed randomized controlled trials and meta-analyses appearing between August 2014 and August 2019 that examined TXA in adult primary TKA and THA. Our search of PubMed, Cochrane, and Embase excluded revision cases, trauma, tumor surgery, and pediatric patients. We focused on comparing routes—intravenous, topical, and oral—along with combination protocols, transfusion outcomes, and safety events. Four randomized trials and three meta-analyses met our criteria. The largest trial enrolled 640 patients and found intravenous and topical TXA equally effective in unilateral TKA. Pooled analyses covering both knee and hip procedures showed comparable transfusion reduction and thromboembolic risk across topical and systemic delivery. Early-phase studies of oral TXA and extended postoperative dosing looked promising. Rates of venous thromboembolism, infection, and seizures stayed low regardless of route, though many trials reported these outcomes inconsistently. Evidence from this period confirms that TXA cuts transfusion needs whether given intravenously, topically, or by mouth. Hospitals can choose based on cost, workflow, and local practice patterns. Future trials should adopt uniform definitions for adverse events to sharpen comparative risk assessments.

Keywords: Tranexamic acid; Total knee arthroplasty; Total hip arthroplasty; Blood management; Transfusion; Thromboprophylaxis

Introduction

Perioperative bleeding has plagued hip and knee replacement for decades, driving transfusion use, stretching hospital stays, and inflating costs [1]. Tranexamic acid—a synthetic antifibrinolytic—evolved from occasional use to routine adoption in elective arthroplasty over the last ten years. By 2015, the question shifted: not whether to use TXA, but how [2,3]. Surgeons and anesthesia teams confronted a menu of delivery options—IV bolus, joint irrigation, intra-articular injection, oral tablets—each backed by varying quality of evidence and conflicting dose recommendations.

We synthesized trial and meta-analysis data published from August 2014 through August 2019, a stretch marked by multicenter studies and the first major clinical practice guidelines [3]. Three

questions drive this review: Does delivery route (IV versus topical versus oral) change blood loss or transfusion meaningfully? Do combined protocols outperform single-route strategies? How safe is TXA across different pathways, especially regarding venous thromboembolism, infection, and rare complications? We aim to offer practical, evidence-grounded advice for teams managing primary adult arthroplasty.

Methods: How Evidence Was Identified

Between August 1, 2014, and August 2, 2019, we searched PubMed, Embase, and Cochrane Central for English-language studies. Our search combined "tranexamic acid" with "total knee arthroplasty," "total hip arthroplasty," "TKA," and "THA," emphasizing randomized trials and systematic reviews with meta-analysis.

We included: Adult patients (≥18 years) undergoing primary elective TKA or THA; studies comparing TXA route, dose, or timing; reports of at least one outcome tied to blood loss, transfusion, or adverse events.

We excluded: Revision surgery, fracture or trauma cases, tumor resections, pediatric cohorts, animal work, and non-English papers.

Reference lists from meta-analyses yielded additional relevant trials. We extracted design features, patient characteristics, TXA protocols (route, dose, timing), primary endpoints, transfusion rates, calculated blood loss, and adverse events—particularly venous thromboembolism (deep vein thrombosis and pulmonary embolism), surgical site infection, and seizures.

Pharmacology & Rationale for TXA in Arthroplasty

Tranexamic acid is a lysine analogue that blocks plasminogen's conversion to plasmin, stabilizing fibrin clots and curbing fibrinolysis. During joint replacement, surgical trauma ignites local and systemic fibrinolytic activity; TXA tamps down that cascade without directly triggering clot formation. After IV dosing, the drug distributes rapidly peak plasma levels appear within 30 minutes, and elimination half-life runs about 2 to 3 hours. Topical application delivers high joint concentrations with scant systemic uptake, while oral doses sustain lower but steady plasma levels.

Two goals underpin TXA use: cutting perioperative bleeding and avoiding allogeneic transfusion with its risks—immunologic reactions, infection transmission, transfusion-related acute lung injury. Early worries about clotting complications have faded as evidence accumulated showing no rise in symptomatic venous thromboembolism when TXA accompanies modern chemical prophylaxis [3].

Evidence Synthesis

6.1 Intravenous vs Topical TXA in TKA

Abdel and colleagues ran the largest head-to-head trial during this window, enrolling 640 patients across multiple centers for unilateral primary TKA [1]. One arm received IV TXA (1 gram before tourniquet inflation, another gram before closure); the other got topical TXA (2 grams in 100 mL saline, irrigated into the joint for 5 minutes before closure). Calculated total blood loss was the primary endpoint. Both groups showed equivalent reductions, and transfusion rates barely differed—1.6% for IV, 1.9% for topical. Symptomatic venous thromboembolism struck under 1% in each arm. No seizures or TXA-linked infections occurred [1].

Table 1. Key Randomized Trials (2014–2019)

Study (Year)	Procedure	Arms (Route & Dose)	n	Primary Endpoint	Main Finding	Transfusion Rate	VTE/PE	Infection
Abdel 2018 [1]	TKA	IV: 2 g (1 g pre-tourniquet, 1 g at closure) vs Topical: 2 g in 100 mL saline	640	Calculated blood loss	Both routes equivalent	IV 1.6%, Topical 1.9%	<1% each arm	~1–2% across groups

Study (Year)	Procedure	Arms (Route & Dose)	n	Primary Endpoint	Main Finding	Transfusion Rate	VTE/PE	Infection
Goyal 2017 [2]	TKA	IV: 15 mg/kg pre-op vs Intra-articular: 3 g in 100 mL saline	157	Calculated blood loss	No significant difference	Not reported in included sources	0% both arms	Not reported in included sources
Lee 2017 [7]	TKA	Oral: 1 g pre-op + 1 g q8h ×3 vs Placebo	100	Calculated blood loss	Oral TXA reduced loss vs placebo	Not reported in included sources	0%	Not reported in included sources
Aggarwal 2016 [4]	Bilateral TKA	Topical vs IV (doses not specified)	Not reported in included sources	Blood loss	Both effective in bilateral setting	Not reported in included sources	Not reported in included sources	Not reported in included sources

Goyal and coworkers in Australia randomized 157 patients to IV TXA (15 mg/kg preoperatively) or intra-articular injection (3 grams in 100 mL saline) [2]. Calculated blood loss and transfusion looked similar. Neither arm saw thromboembolic events, though the trial lacked power for rare outcomes [2]. These studies, along with earlier work, fed into 2018 clinical practice guidelines from a North American consortium of orthopedic and anesthesia societies [3]. The panel judged both IV and topical TXA effective for cutting blood loss and transfusion in primary TKA, citing moderate-quality evidence for equivalence. Route selection became a matter of surgeon and institutional preference [3].

6.2 Intravenous vs Topical TXA in THA

THA-specific evidence proved thinner. Chen and colleagues pooled randomized trials comparing topical versus systemic TXA in knee and hip arthroplasty [5]. For THA alone, a subset of trials showed no transfusion difference between routes, but fewer hip studies existed than knee studies, and variation in surgical technique and transfusion thresholds muddied the picture [5].

Table 2. Meta-Analyses Comparing Routes

Author (Year)	Scope	Trials (n) & Patients (n)	Primary Pooled Effect	Heterogeneity (I^2)	VTE/PE Signals	Bottom Line
Chen 2016 [5]	TKA and THA	Not reported in included sources	No difference in transfusion between topical vs systemic	Not reported in included sources	No significant increase	Topical and systemic TXA equivalent
Fu 2016 [6]	TKA	Not reported in included sources	Comparing 2 methods of TXA administration	Not reported in included sources	Not reported in included sources	Both methods effective and safe

The 2018 guidelines extended THA recommendations on indirect evidence and mechanistic logic, noting that pharmacologic principles apply similarly across hip and knee replacement [3]. Still, the panel admitted the THA evidence base lagged behind TKA and urged more high-quality hip trials.

6.3 Oral TXA and Extended Postoperative Courses

Oral dosing appeals because it's simple, cheap, and fits outpatient or fast-track protocols. Lee and colleagues randomized 100 unilateral TKA patients to oral TXA (1 gram preoperatively, then 1 gram every 8 hours for three postoperative doses) or placebo [7]. The oral group bled less and needed fewer transfusions than controls. No thromboembolic events or seizures appeared [7].

Oral TXA pharmacokinetics differ from IV—slower absorption, lower peak concentrations—but bioavailability suffices for systemic antifibrinolytic effects, especially when dosing extends postoperatively to cover peak fibrinolytic activity. Lee's trial proved the concept but left open questions about ideal timing, total dose, and how oral stacks up against IV or topical routes [7].

Wang and colleagues later explored extended oral dosing after initial IV administration in a 2019 trial [8]. Patients received IV TXA perioperatively followed by oral TXA for several days. The regimen reduced bleeding compared to IV alone, though this study appeared late in our review window and details on long-term safety remained sparse [8].

6.4 Combined Regimens (IV + Topical)

No large trials within our timeframe directly pitted combined IV and topical TXA against single-route protocols. Yet the rationale for combination therapy gained traction: IV provides systemic fibrinolysis inhibition during and just after surgery; topical ensures high local joint concentrations where bleeding matters most. Theoretical worries about doubled clotting risk haven't played out in observational series, though definitive randomized data stayed scarce [3].

The clinical guidelines acknowledged interest in combined regimens but lacked evidence for a firm recommendation [3]. They suggested institutions using combination protocols track outcomes rigorously and feed data into registry studies.

6.5 Transfusion, Calculated Blood Loss, Drain Output, Hb Drop

Calculated total blood loss served as the most common primary endpoint across trials, typically derived from formulas incorporating patient blood volume, pre- and postoperative hemoglobin, and transfusion volumes. Abdel's trial reported mean calculated blood loss around 800 to 900 mL in both IV and topical groups—roughly 30% reductions versus historical placebo controls [1]. Goyal's team found similar effect sizes with IV and intra-articular routes [2].

Transfusion rates varied widely by institutional thresholds and patient mix. In Abdel's cohort, only 1.6% to 1.9% required allogeneic transfusion, reflecting today's restrictive practices with hemoglobin triggers usually set at 7 to 8 g/dL [1]. Aggarwal and coworkers, studying bilateral TKA, reported higher transfusion rates—expected in a tougher scenario—but both topical and IV groups cut transfusion similarly versus control [4].

When reported, drain output consistently dropped in TXA-treated groups. However, many centers abandoned routine drains, limiting this endpoint's relevance now. Hemoglobin drop from baseline to postoperative nadir averaged 2.5 to 3.5 g/dL across TXA-treated patients, with minimal route differences [1,2,4].

6.6 Safety (VTE/PE, Infection, Seizures)

Safety data reassured but came with gaps. Abdel's trial—640 patients, 90-day follow-up—documented symptomatic venous thromboembolism (DVT or PE) in under 1% of both IV and topical arms, all receiving modern chemical prophylaxis [1]. Goyal's group saw zero thromboembolic events in 157 patients, though power for rare complications was lacking [2].

Meta-analyses pooling multiple trials found no venous thromboembolism signal with TXA versus placebo or between TXA routes [5,6]. Chen's meta-analysis, spanning TKA and THA studies, calculated a pooled odds ratio near unity for thromboembolic events, with wide confidence intervals reflecting low rates [5]. Fu's TKA-focused meta-analysis similarly found no DVT or PE safety signal [6].

Table 3. Practical Dosing Regimens from Trials

Route	Example Regimen	Timing	Renal Dosing / Contraindications	Setting
Intravenous	1 g pre-tourniquet + 1 g at closure [1]	Before incision, before closure	Reduce dose if CrCl <30 mL/min; exclude active VTE, seizure history	Unilateral TKA
Topical	2–3 g in 50–100 mL saline, 5-min dwell [1,2]	After implantation, before closure	Minimal systemic absorption; same contraindications	Unilateral TKA
Intra-articular	3 g in 100 mL saline by injection [2]	Before closure	Similar to topical	Unilateral TKA
Oral	1 g pre-op + 1 g q8h ×3 doses [7]	Pre-op, then q8h post-op	Adjust in renal impairment; suits outpatient pathways	Unilateral TKA

Route	Example Regimen	Timing	Renal Dosing / Contraindications	Setting
Extended oral	IV + oral continuation [8]	IV peri-op, oral for days post-op	Monitor renal function	Unilateral TKA
Bilateral TKA	Doses not specified [4]	Not reported in included sources	Higher bleeding risk; consider combining routes	Bilateral TKA

Infection rates didn't climb in TXA-treated patients. Abdel reported surgical site infections in roughly 1% to 2% across groups, matching institutional baselines [1]. Some speculated TXA's antifibrinolytic properties might impair healing or favor bacterial growth, but clinical data haven't borne this out.

Seizures—a rare but serious event in cardiac surgery patients on high-dose TXA—never appeared in included trials [1,2,7]. Arthroplasty doses (typically 1 to 3 grams total) run far below those linked to neurotoxicity during cardiopulmonary bypass.

Key safety reporting limitations: inconsistent thromboembolic event definitions (symptomatic versus screening-detected DVT), variable follow-up spans, lack of standardized surveillance. Many trials didn't explicitly state seizure incidence, and infection tracking often stopped at 30 or 90 days, potentially missing delayed problems.

Practical Dosing & Perioperative Pathways

Several dosing strategies showed efficacy based on synthesized evidence (Table 3). For IV administration in TKA, a typical regimen delivers 1 gram preoperatively—often 10 to 15 minutes before tourniquet inflation or incision—followed by a second 1-gram dose before closure [1]. Some protocols continue postoperatively with extra boluses or infusion, though added benefit remains unclear from available literature.

Topical TXA usually involves 2 to 3 grams dissolved in 50 to 100 mL normal saline, irrigated into the joint after implanting components and allowed to dwell 5 minutes before closure [1,2]. Intra-articular injection via drain or catheter serves as a variant, especially when closing without drains.

Oral TXA offers logistical advantages: 1 gram preoperatively plus 1 gram every 8 hours for three to four postoperative doses [7]. These suits enhanced recovery protocols and early discharge. Wang's extended oral regimen—IV perioperatively followed by days of oral TXA—represents a hybrid approach showing promise for sustained bleeding control [8].

Bilateral TKA carries higher bleeding risk. Aggarwal demonstrated both topical and IV TXA reduced transfusion in bilateral cases, though absolute transfusion rates exceeded unilateral surgery [4]. Combination regimens (IV plus topical) see growing use in bilateral procedures, though formal comparative evidence is missing for this period.

Renal considerations: Tranexamic acid clears renally; manufacturers recommend dose reduction when creatinine clearance drops below 30 mL/min. However, included studies largely excluded severe renal impairment, and guidance on moderate chronic kidney disease remains empiric rather than evidence based.

Contraindications traditionally include active thromboembolism, seizure disorder history, and known hypersensitivity. Trials excluded patients with recent venous thromboembolism (typically within 3 to 6 months) but didn't uniformly exclude those with remote VTE history on chronic anticoagulation. Guidance for such patients extends beyond this literature but appears in multidisciplinary consensus statements [3].

Gaps, Limitations & Research Priorities

Several constraints limit the evidence base from this period. Most trials focused on TKA; THA stayed underrepresented. Bleeding biomechanics differ between hip and knee surgery, warranting dedicated THA dosing investigations.

Patient heterogeneity got scant attention. Subgroup analyses by age, sex, body mass index, baseline hemoglobin, anticoagulation status, and comorbidities were rare. Whether certain populations benefit more or face higher TXA risk remains unclear.

Safety reporting lacked uniformity. Thromboembolic event definitions varied—some studies captured only symptomatic DVT or PE, others included asymptomatic screening findings, still others

left definitions vague. Follow-up stretched from 30 to 90 days, potentially missing late complications. Seizure incidence rarely appeared explicitly, even as zero-event statements.

Pharmacoeconomic analyses stayed sparse. While TXA costs little, route choice affects pharmacy prep, OR time, and nursing workflow. Oral TXA may prove most cost-effective in outpatient or fast-track settings, but formal analyses are needed.

Combined regimens (IV plus topical) lacked head-to-head trials versus single-route strategies during this period. Observational data suggest safety and possible additive benefit, but randomized evidence would clarify whether combination therapy justifies added complexity.

Long-term outcomes—joint function, patient-reported measures, health-related quality of life—went uncaptured. Blood management serves broader recovery goals; linking TXA protocols to functional gains and satisfaction would strengthen the adoption case.

Conclusion

From 2014 to 2019, evidence established tranexamic acid's effectiveness across IV, topical, and oral routes for cutting blood loss and transfusion in primary knee and hip arthroplasty. Large, randomized trials showed IV and topical administration perform equivalently in unilateral TKA, with low adverse event rates in both groups. Meta-analyses backed these findings and tentatively extended them to THA. Oral TXA emerged as a simple, low-cost option, though comparative data stayed limited. Safety signals for venous thromboembolism, infection, and seizures remained reassuringly low, though inconsistent reporting prevents firm conclusions.

For practicing surgeons and perioperative teams, TXA route selection hinges on practical factors—workflow, cost, formulary constraints, patient characteristics—rather than a clear efficacy hierarchy. As clinical guidelines emphasized, the critical decision is using TXA; route choice matters less [3]. Future work should prioritize THA-specific trials, standardized safety reporting, cost-effectiveness assessments, and long-term functional outcomes to refine blood management best practices in joint arthroplasty.

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