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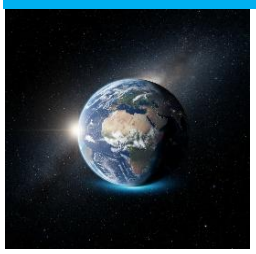

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Tranexamic Acid in Total Knee and Hip Arthroplasty: Dosing Strategies and Routes of Administration – A Narrative Review

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ABSTRACT:

Introduction and purpose: Perioperative blood loss remains a significant concern in total knee and hip arthroplasty (TKA, THA), leading to decreased hemoglobin levels and an increased requirement for blood transfusions. Tranexamic acid (TXA), a potent antifibrinolytic agent, is widely utilized to mitigate perioperative bleeding. The objective of this review is to evaluate TXA dosing strategies and administration routes, with a particular focus on timing, multidose protocols, and their subsequent impact on blood loss and clinical outcomes.

Description of the state of knowledge: TXA effectively reduces total blood loss, hidden blood loss, and hemoglobin decline in TKA and THA. A single preoperative dose limits early bleeding but fails to suppress postoperative hyperfibrinolysis. Extended and multidose regimens within the first 24 hours provide superior control of fibrinolytic activity. Intravenous, oral, and topical routes show comparable efficacy, while combined strategies may enhance hemostasis. Additionally, TXA exerts anti-inflammatory effects (lowering IL-6 and CRP), reducing pain and edema while improving early clinical outcomes.

Conclusions: TXA effectively reduces total and hidden blood loss in TKA and THA without increasing thromboembolic risk. Maximum clinical benefits are achieved through

individualized, extended multidose regimens that ensure sustained suppression of postoperative hyperfibrinolysis and inflammation (IL-6, CRP). Optimized TXA protocols significantly enhance early recovery by reducing postoperative pain and edema.

Keywords: Tranexamic acid; total knee arthroplasty; total hip arthroplasty; blood loss; hidden blood loss; antifibrinolytic therapy; dosing strategies; route of administration; perioperative management; inflammation; IL-6; CRP

INTRODUCTION

Blood loss remains a significant clinical problem in total knee arthroplasty (TKA) and total hip arthroplasty (THA), and can lead to a significant drop in haemoglobin levels and the need for blood transfusions (1,2,3,4,5). Bleeding following arthroplasty results not only from direct tissue damage during surgery, but also from the activation of the fibrinolytic system. It has been demonstrated that fibrinolysis activity following TKA and THA is biphasic and may persist for up to 24 hours post-operatively, accompanied by a sustained elevation in fibrinolysis markers such as D-dimers and fibrin degradation products (FDP) (6,7,8,9,10,11). A significant proportion of total blood loss following arthroplasty is also accounted for by so-called hidden blood loss (HBL), which includes bleeding into soft tissues and joint spaces in the postoperative period (1,2,12). Numerous studies have shown that HBL may account for a significant proportion of total blood loss following TKA and THA and correlates with levels of fibrinolysis markers (1,2,4,8,9,10,12).

To reduce perioperative blood loss in joint replacement surgery, tranexamic acid (TXA) is widely used; this synthetic lysine analogue inhibits plasminogen activation and blocks the binding of plasmin to fibrin, thereby stabilising the developing clot and limiting fibrin degradation within the surgical field (6,7,10,13). This mechanism is of particular importance in joint replacement surgery, where surgical trauma leads to increased fibrinolysis in the first few hours following the procedure. Clinical studies have shown that the use of TXA leads to a significant reduction in total blood loss, hidden blood loss and the need for blood transfusion following TKA and THA (1,2,3,4,5,11). Clinical trials have analysed various strategies for the use of tranexamic acid in joint replacement surgery, encompassing both different dosing regimens and various routes of administration, including systemic, local and combined strategies (1,2,7,10,13,14,15,16,17).

AIM

This literature review aims to explore the role of various tranexamic acid dosing strategies in total hip and knee arthroplasty, focusing on their applications in different administration routes, multiple-dose regimens, and perioperative timing. It evaluates the effectiveness of these protocols in reducing blood loss and stabilizing fibrinolytic biomarkers to improve clinical outcomes. The review synthesizes recent advances to highlight optimal pharmacological approaches for integrating effective blood management into orthopedic care.

MATERIAL AND METHODS

For the literature review a database such as Pubmed was used with the keywords: ("tranexamic acid") AND ("total knee arthroplasty" OR "total hip arthroplasty"). Articles with publication dates between 2020 and 2026 were considered to ensure relevance to contemporary understanding and practice.

3. STRATEGIES FOR ADMINISTERING TXA

Single preoperative dose:

The administration of a single dose of TXA prior to surgery is one of the most commonly used strategies for reducing blood loss in joint replacement surgery. This regimen leads to a significant reduction in total blood loss and a decrease in haemoglobin levels compared with control groups (14,18). Liu et al., comparing oral and intravenous administration of a single dose of TXA in patients undergoing TKA, obtained calculated blood loss values of 880 ± 267 mL in the intravenous group and 840 ± 278 mL in the oral group, with a decrease in haemoglobin concentration of approximately 2.4-2.5 g/dL, without an increase in the incidence of thromboembolic complications (1). Zhang et al. also demonstrated that the use of TXA prior to surgery led to a significantly smaller decrease in haemoglobin concentration compared with the group not receiving TXA (18).

Despite the efficacy of a single dose of TXA in limiting early blood loss, studies assessing the dynamics of fibrinolysis markers found that elevated levels of D-dimers and FDP persisted for at least 24 hours post-surgery (8,9,10,11,19). For this reason, a single dose may be insufficient to inhibit late hyperfibrinolysis.

Postoperative and multiple-dose intravenous TXA regimens:

In response to persistent fibrinolytic activity, regimens involving additional doses of TXA administered in the postoperative period were introduced. Extending the regimen to include doses administered within the first 24 hours post-operatively leads to a further reduction in hidden blood loss and a smaller decrease in haemoglobin concentration compared with a regimen comprising only a pre-operative dose (2,7,8,9,10,19). In the study by Xie et al., the use of postoperative doses of TXA led to a significant reduction in total blood loss and hidden blood loss without increasing the incidence of thromboembolic complications (7). Similarly, Zhang et al. demonstrated the superiority of a regimen involving TXA administration within the first 24 hours post-surgery over a single preoperative dose regimen in terms of reducing hidden blood loss and the drop in haemoglobin (9). These observations suggest that maintaining the antifibrinolytic effect of TXA during the first postoperative day may significantly reduce late-phase postoperative blood loss.

One development of this strategy involves multi-dose protocols comprising several administrations of TXA during the first postoperative day. The use of such regimens leads to a further reduction in hidden blood loss and a greater reduction in fibrinolysis markers compared with regimens involving a single dose of the drug (8,9,10). In a study by Zhang et al. comparing a single dose of TXA (20 mg/kg) with a protocol of six doses administered over 24 hours following TKA, a significant reduction in hidden blood loss and haemoglobin decline was demonstrated in the multi-dose regimen. Hidden blood loss was 756 ± 227 mL in the single-dose group and 515 ± 246 mL in the multi-dose group, whilst the maximum haemoglobin drop was 2.77 ± 0.78 g/dL and 2.06 ± 0.73 g/dL, respectively. At the same time, lower levels of inflammatory markers were observed, including C-reactive protein (CRP) (134.7 ± 28.8 vs 93.7 ± 22.2 mg/L) and interleukin-6 (IL-6) (161.6 ± 64.4 vs 108.8 ± 41.7 pg/mL) in the multiple-dose group (8). Similarly Lei et al. demonstrated that a more intensive TXA dosing regimen led to a significant reduction in total blood loss and hidden blood loss. In this study total blood loss was 536 ± 215 mL in the high-dose group compared with 850 ± 259 mL in the standard group, and hidden blood loss was 456 ± 214 mL and 761 ± 259 mL, respectively (10).

High loading dose:

Regimens involving an initial TXA dose of 30–60 mg/kg led to a significant reduction in total blood loss and hidden blood loss compared with standard dosing protocols (11,20).

In the study by Lei et al., the use of such a dosing regimen was associated with lower levels of fibrinolysis markers, including D-dimers and FDP, compared to standard doses (11). Additionally, the use of a higher initial dose was associated with lower levels of inflammatory markers on the third postoperative day (IL-6 levels were 16.67 ± 4.75 pg/mL in the high-dose group compared to 29.84 ± 6.91 pg/mL in the standard-dose group, while CRP levels were 47.83 ± 25.07 mg/L and 76.52 ± 29.44 mg/L, respectively) (21).

Table 1. TXA dosing strategies and their effects on blood loss and fibrinolysis markers in TKA and THA

Strategy	Typical dosing regimen	Effects	References
Single preoperative dose	10-20 mg/kg IV	reduced total blood loss and hemoglobin drop; persistent elevation of fibrinolysis markers postoperatively	[8,9,10,11,14,18,19]
Postoperative dosing	doses within 24 h	reduced hidden blood loss and hemoglobin drop	[2,7,8,9,10,19]
Multiple-dose regimen	repeated doses within 24 h	reduced hidden blood loss; lower CRP and IL-6 levels	[8,9,10]
High loading dose	30-60 mg/kg	lower D-dimer, FDP, CRP and IL-6 levels	[11,20,21]

4. ROUTE OF ADMINISTRATION OF TXA

Systemic administration of TXA:

Systemic administration of TXA produces an antifibrinolytic effect throughout the body and remains one of the most commonly used methods of drug administration in joint replacement

surgery. Studies comparing oral and intravenous administration of TXA have demonstrated similar efficacy of both routes in reducing blood loss (14,22). Liu et al., comparing oral and intravenous administration of a single dose of TXA in patients undergoing TKA, obtained comparable calculated blood loss values of 880 ± 267 mL in the intravenous group and 840 ± 278 mL in the oral group, with a similar decrease in hemoglobin concentration of approximately 2.4-2.5 g/dL (14). In another study, oral TXA regimens were associated with a total blood loss of approximately 700 mL, with hidden blood loss at approximately 560 mL, confirming the efficacy of the drug's systemic action (22).

Local administration of TXA: □

An alternative to systemic administration is the local application of TXA directly within the surgical field, including both intra-articular (IA) administration and local application of the drug to the surgical tissues. Intra-arterial administration of TXA led to a significant reduction in total blood loss compared to control groups not receiving antifibrinolytic therapy (1,13,15,16,23,24,25). A reduction in total blood loss to approximately 830 mL, accompanied by a decrease in hemoglobin drop of about 1 g/dL, has been reported following intra-articular administration of TXA (1). The mechanism of this effect is explained by the drug's pharmacokinetic properties. It has been demonstrated that local administration leads to significantly higher TXA concentrations in synovial fluid than in plasma, enabling effective local suppression of fibrinolytic activity within the surgical field (12,16). At the same time, when comparing different doses of intra-articularly administered TXA, a gradual reduction in total blood loss was also observed as the drug dose increased, without an increase in the incidence of thromboembolic complications (13,26,27).

Combined strategies:

To maximize the hemostatic effect, combined strategies have been developed that involve the simultaneous systemic and local administration of TXA. These strategies allow for simultaneous systemic action of the drug and the achievement of high local TXA concentrations within the surgical field, which may lead to more effective suppression of fibrinolytic activity at the surgical site (1,6,12,15,16,17). Abdallah et al., comparing intravenous, intra-articular, and combined IV + IA administration, demonstrated a gradual reduction in total blood loss

among the analyzed strategies. Total blood loss was approximately 1,000 mL in the IV group, approximately 830 mL in the IA group, and approximately 700 mL in the IV + IA group, corresponding to an additional reduction in blood loss of approximately 130-300 mL in the combined regimen. At the same time, the maximum decrease in hemoglobin concentration was approximately 2.3 g/dL in group IV, approximately 2.0 g/dL in group IA, and approximately 1.7 g/dL in group IV + IA, indicating a further reduction in perioperative blood loss with the combined strategy (1). Similar results were reported in the study by Qin et al., in which the use of a regimen involving the simultaneous intravenous and intra-articular administration of TXA was associated with a total blood loss of 431.7 ± 288.4 mL, compared with 644. 6 ± 237.5 mL in the group receiving hemocoagulase atrox, with a smaller decrease in hemoglobin concentration (1.21 ± 0.85 vs. 2.08 ± 0.77 g/dL) (28). At the same time, some analyses did not confirm a clear advantage of combined strategies. In a study by Yin et al. comparing the simultaneous intravenous and topical administration of TXA with a single route of administration, no significant differences were found in either total blood loss or the decrease in hemoglobin levels between the treatment regimens analyzed (29).

Table 2. Routes of TXA administration and blood loss in TKA and THA

Route	Description	Effect	References
Intravenous (IV)	Systemic administration	reduced blood loss	[14,22]
Oral	Systemic administration	similar blood loss compared to IV	[14,22]
Intra-articular (IA)	Local administration into the joint	reduced blood loss	[1,12,13,15,16,23,24,25]
Combined (IV + IA)	Systemic and local administration	lower blood loss compared to single-route administration	[1,6,12,15,16,17]

5. TXA AND INFLAMMATORY RESPONSE

In addition to its antifibrinolytic effects, TXA may also influence the postoperative inflammatory response following total knee and hip arthroplasty. Surgical trauma leads to the activation of numerous inflammatory mediators, including IL-6 and CRP, which play a

significant role in the development of pain, swelling, and the inflammatory response in the operated tissues (8,11,21,30).

It has been demonstrated that the use of TXA can lead to a reduction in inflammatory marker levels in the postoperative period. Huang et al., using higher initial doses of TXA, obtained significantly lower levels of inflammatory mediators on the third postoperative day. The IL-6 level was 16.67 ± 4.75 pg/ mL in the high-dose TXA group, compared to 29.84 ± 6.91 pg/mL in the standard-dose group, while CRP levels were 47.83 ± 25.07 mg/L and 76.52 ± 29.44 mg/L, respectively (21).

Similar findings have been reported in studies examining the effects of multiple-dose TXA regimens. By maintaining the drug's effect during the first postoperative day using multiple-dose regimens, lower levels of inflammatory markers and a reduction in the inflammatory response within the operated joint were achieved (8,11).

A reduction in the inflammatory response may also translate into improved clinical parameters in the postoperative period. Studies evaluating the postoperative clinical picture of patients undergoing TKA have shown that the use of TXA was associated with less joint swelling and lower levels of postoperative pain, which may facilitate earlier patient mobilization (5,11,13,31).

Attention has also been drawn to the potential for enhancing the anti-inflammatory effect of TXA when used concomitantly with dexamethasone. It has been demonstrated that the combination of both drugs led to lower levels of inflammatory markers, including IL-6 and CRP, and reduced postoperative pain intensity compared to TXA monotherapy (21,32).

Table 3. Effects of TXA on IL-6, CRP, pain and swelling after TKA and THA

Parameter	Observation	Comparison	References
IL-6	lower levels	16.67 ± 4.75 vs 29.84 ± 6.91 pg/mL (high-dose vs standard-dose)	[21]
	lower levels	108.8 ± 41.7 vs 161.6 ± 64.4 pg/mL (multiple-dose vs single-dose)	[8]
CRP	lower levels	47.83 ± 25.07 vs 76.52 ± 29.44 mg/L (high-dose vs standard-dose)	[21]
	lower levels	93.7 ± 22.2 vs 134.7 ± 28.8 mg/L (multiple-dose vs single-dose)	[8]
Swelling	reduced	-	[5,11,13,31]
Pain	reduced	-	[5,11,13,31]

6. PATIENT PHENOTYPE- PERSONALIZATION OF TXA TREATMENT STRATEGIES

Patients with rheumatoid arthritis (RA) are characterized by greater blood loss and more frequent preoperative anemia, which may limit the effectiveness of standard TXA regimens. In this group, a multiple-dose TXA protocol, compared with a single preoperative dose, is associated with lower total blood loss (506.1 ± 227.0 vs. 608.8 ± 244.8 mL), hidden blood loss (471.6 ± 224.0 vs. 574.0 ± 242.3 mL), and a decrease in hemoglobin (17.5 ± 7.7 vs. 23.4 ± 9.2 g/L), reflecting more effective inhibition of enhanced fibrinolysis (2).

Analysis of the safety profile of TXA in patients at high risk of thromboembolic events did not reveal a statistically significant increase in the incidence of deep vein thrombosis or pulmonary embolism compared to control groups, regardless of the dosing regimen used. These findings remain consistent for both multiple-dose protocols and those using high loading doses (60 mg/kg), demonstrating that the use of TXA in orthopedic surgery remains safe even in patients with significant vascular risk factors (10,20,33).

7. TXA COMPARED WITH OTHER HAEMOSTATIC AGENTS

A study comparing TXA with hemocoagulase atrox, a procoagulant enzyme derived from the venom of the Agkistrodon snake, demonstrated that TXA was more effective in reducing blood loss following TKA. Total blood loss was approximately 432 mL in the TXA group and 645 mL in the hemocoagulase group, with a decrease in hemoglobin concentration of 1.21 ± 0.85 g/dL and 2.08 ± 0.77 g/dL, respectively (34).

A comparison of TXA with ε-aminocaproic acid (EACA), which belongs to the same group of fibrinolysis inhibitors, indicates similar efficacy of both drugs. Total blood loss is approximately 800-900 mL after TXA administration and 820-950 mL after EACA administration, with no significant differences in the decrease in hemoglobin concentration or the incidence of thromboembolic complications (22,35).

The hypothesis that an additional hemostatic effect could be achieved through the use of local biological preparations, such as platelet-rich fibrin (PRF) or other fibrin matrices, was not supported. Studies have shown that the simultaneous use of these methods with TXA does not lead to a significant additional reduction in total blood loss compared to TXA monotherapy (33,36).

The study by Li et al. included the use of additional hemostatic agents, such as carbazochrome, which acts to stabilize the capillary walls. The combination of carbazochrome with TXA allowed for a further reduction in perioperative bleeding, reducing total blood loss by an additional 150-200 mL compared to tranexamic acid monotherapy (30).

Table 4. Comparison of TXA with other hemostatic agents

Agent	Total blood loss (mL)	Hemoglobin drop (g/dL)	References
TXA	~432	1.21 ± 0.85	[34]
Hemocoagulase atrox	~645	2.08 ± 0.77	[34]
EACA	800-900	no significant differences between EACA and TXA	[22,35]
TXA + carbazochrome	reduction of 150–200 mL	not specified	[30]

8. CONCLUSIONS

Tranexamic acid is effective in reducing perioperative blood loss during total knee and hip arthroplasty, leading to a reduction in total blood loss, hidden blood loss, and a decrease in hemoglobin levels, without increasing the risk of thromboembolic complications.

Although a single preoperative dose effectively reduces early bleeding, it does not provide complete control of postoperative hyperfibrinolysis. For this reason, extended regimens, involving TXA administration within the first 24 hours postoperatively- particularly in the form of multi-dose protocols or with a higher initial dose- allow for more effective reduction of hidden blood loss and stabilization of fibrinolytic activity.

Regardless of the route of administration- including intravenous, oral, and topical- the efficacy of TXA remains comparable. Topical administration, however, allows for high drug concentrations within the surgical field. Combination strategies may further enhance the hemostatic effect, though their superiority has not been unequivocally confirmed.

TXA also modulates inflammatory processes, as evidenced by reductions in IL-6 and C-reactive protein levels. Limiting the inflammatory cascade results in reduced pain and swelling, which contributes to improved outcomes in the early postoperative period.

The clinical benefits of TXA are particularly evident in a personalized approach, where extended dosing regimens prove most effective in patients with severe inflammation or increased fibrinolytic activity. This is particularly relevant in patient phenotypes such as rheumatoid arthritis, characterized by increased blood loss and enhanced fibrinolysis.

Importantly, TXA remains safe even in high thromboembolic risk patients, without increasing the incidence of deep vein thrombosis or pulmonary embolism. Compared to other hemostatic methods, TXA maintains at least comparable, and often higher, efficacy, remaining one of the key elements of modern bleeding management in joint replacement surgery.

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All authors contributed to the article. Conceptualization: SK, KK; methodology: SK, KK, MW; software: AW, PB, MW; check: KK, PB, AW; formal analysis: SK, AW, KK; investigation: MW,PB; resources: SK, KK, MW; data curation: AW, PB; writing -rough preparation: SK; writing -review and editing: SK, KK, MW, AW, PB; visualization: AW.; supervision: SK; project administration: KK.

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