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REVIEW

Tranexamic acid in hemostasis and resuscitation: A comprehensive clinical review

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ABSTRACT:

Tranexamic acid (TXA), a synthetic lysine analogue that stabilizes fibrin clots against premature degradation, has become a cornerstone in the management of acute hemorrhage. Its application has expanded from well-established indications like trauma and postpartum hemorrhage to a variety of other clinical scenarios. However, this widespread use is accompanied by a complex evidence base, with significant variations in dosing, timing, and administration routes, and a growing recognition of conditions where TXA's risk may outweigh its benefit. This narrative review aims to consolidate and critically appraise the evidence from landmark clinical trials and major international guidelines. We explore the established and emerging indications for TXA, delve into its nuanced safety profile, and highlight the critical importance of timely administration. Ultimately, this review provides clinicians with a practical, evidence-based synthesis to guide the safe and effective use of TXA in resuscitation and the management of bleeding.

Keywords: Antifibrinolytic agents; Fibrinolysis; Hemorrhage; Hemostasis; Resuscitation; Tranexamic acid

INTRODUCTION

The discovery of tranexamic acid (TXA) originated in Japan, motivated by the pressing issue of postpartum hemorrhage, the leading cause of maternal death at the time. Drs. Shosuke and Utako Okamoto began research to reduce this risk, starting with studies on epsilon-aminocaproic acid (EACA). Their work led to the synthesis of a new compound in 1962, 1-(aminomethyl)-cyclohexane-4-carboxylic acid, later known as TXA. This new compound was found to be 27 times more potent in its antifibrinolytic activity than EACA [1,2].

TXA is a synthetic derivative of lysine that acts as a competitive inhibitor of plasminogen activation. Its mechanism involves reversible binding to lysine-binding sites on plasminogen, preventing plasminogen's attachment to fibrin. Consequently, the conversion to the active enzyme plasmin is inhibited, resulting in the stabilization of the fibrin clot against premature degradation (Figure1) [3]. In addition, plasmin functions as a proinflammatory activator and can induce activation of inflammatory cells, stimulate the production of cytokines, free radical species, and other inflammatory mediators [4]. Therefore, TXA may attenuate the inflammatory response and associated hemodynamic instability [5]. Previous studies have shown that TXA can reduce inflammatory responses and the incidence of vasoplegic shock in cardiopulmonary bypass surgery. TXA has also been reported to decrease inflammatory markers such as D-dimer, plasminogen activator inhibitor-1, creatine kinase levels [6], tumor necrosis factor-α, interferon-γ, interleukin-6, and interleukin-10 [7].

This review synthesizes current studies and guidelines on the various forms and dosages of TXA used in a multitude of clinical scenarios, and potential adverse effects of TXA. The purpose is to provide a practical resource for the safe and effective application of TXA in clinical practice.

CLINICAL APPLICATION OF TXA

Uncontrolled bleeding remains a significant cause of death for many patient populations worldwide, including those with trauma, postpartum hemorrhage, and major surgeries. This has prompted extensive research into TXA, a compound known for its potent antifibrinolytic properties. The core question has been whether TXA can meaningfully reduce bleeding and improve survival in these vulnerable patient groups.

KEY MESSAGES:

- TXA is a synthetic lysine analogue that functions as an antifibrinolytic agent. It competitively binds to plasminogen, preventing fibrin clot degradation.
- TXA has broad clinical applications and can be administered through various routes.
- Evidence-based guidelines support its use in trauma, postpartum hemorrhage, and in coronary and major non-cardiac surgery.
- Thromboembolic events and seizures are the primary adverse reactions of concern, which can be mitigated with short-term use and appropriate dose adjustments, especially in patients with renal impairment.

1. Trauma-related bleeding

1.1 General trauma patients

The recognition that bleeding is a common cause of death in trauma patients led to the CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) trial [8], a randomized controlled trial (RCT) published in 2010. A total of 20,211 adult trauma patients with or at risk of significant bleeding were randomly assigned within 8 hours of injury to receive either TXA (a 1 g loading dose over 10 minutes followed by a 1 g infusion over 8 hours) or a placebo. All-cause mortality was significantly reduced with TXA (14.5% vs. 16.0%; RR 0.91; 95%CI, 0.85–0.97; P=0.0035). The risk of death due to bleeding was also significantly reduced (4.9% vs. 5.7%; RR 0.85; 95%CI, 0.76–

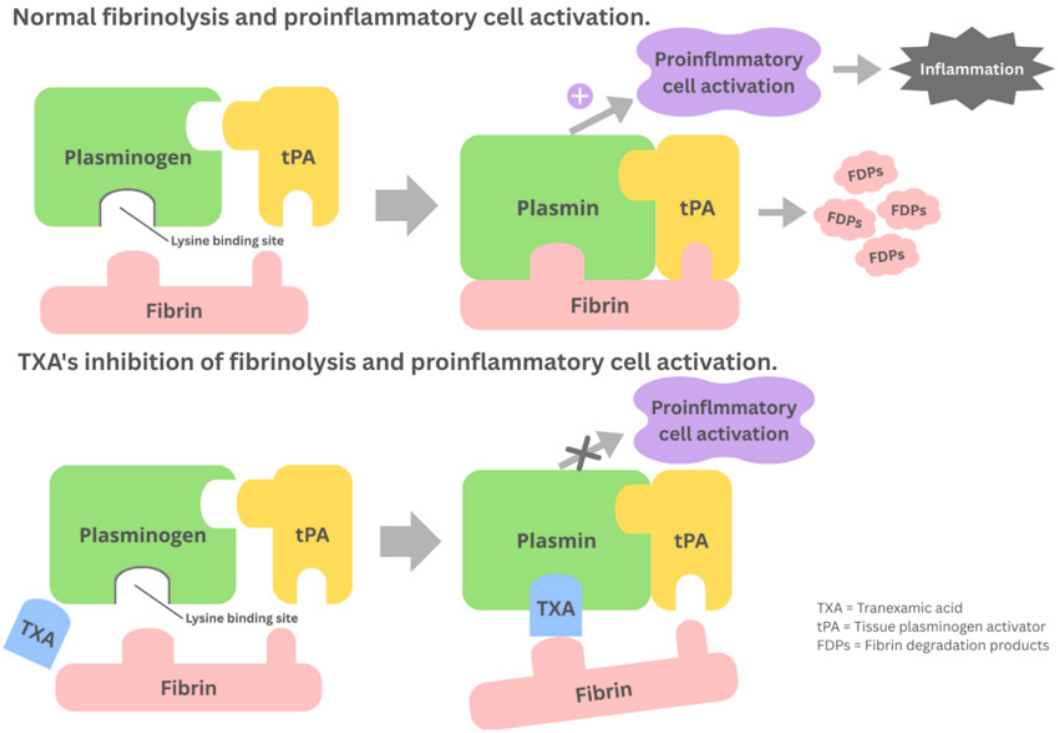

Figure 1. Normal fibrinolysis and proinflammatory activation: Inhibition by TXA.

0.96; P=0.0077). Notably, the therapeutic effect of TXA on death due to bleeding was highly dependent on the timing of administration. When initiated more than 3 hours after injury, TXA was associated with an increased risk of death from bleeding (4.4% vs. 3.1%; RR 1.44; 95%CI,1.12–1.84). This time-dependent effect is rooted in the biphasic nature of trauma-induced coagulopathy. Initially, hemorrhagic shock and tissue hypoxia trigger a hyperfibrinolytic state via the release of tissue-plasminogen activator. Consequently, in the early phase, the coagulopathy presents as a disseminated intravascular coagulation with a hyperfibrinolytic phenotype. However, this is followed several hours later by a surge in plasminogen activator inhibitor-1, which induces a fibrinolytic shutdown, a state where antifibrinolytics may be dangerous and result in failure of fibrinolysis and associated organ failure [9]. A 2018 meta-analysis in The Lancet [10] on acute severe bleeding quantified this urgency, finding that the survival benefit of TXA decreases by 10% for every 15 minutes of delay and disappears after 3 hours. While TXA remains beneficial in patients with hyperfibrinolysis, indiscriminate administration may increase the risk of fibrinolysis shutdown [11]. These findings support a more individualized approach to antifibrinolytic therapy in severe trauma, with the use of viscoelastic hemostatic assays to guide TXA administration and enhance clinical utility.

The benefits of TXA in the prehospital setting were investigated in the STAAMP (Study of Tranexamic Acid during Air Medical Prehospital Transport) trial [12] in 2020. This multicenter RCT enrolled 927 trauma patients at risk for hemorrhage, defined as a prehospital systolic blood pressure (SBP) of ≤90 mmHg or a heart rate of ≥110 bpm. Participants received a prehospital 1 g TXA infusion over 10 minutes and were allocated to varying in-hospital doses of TXA versus a placebo. The trial found that TXA did not reduce 30-day all-cause mortality. However, subgroup analyses showed a reduction in 30-day mortality when TXA was administered within one hour of injury (4.6% vs 7.6%; P<0.002). Patients with severe shock (SBP ≤70 mmHg) who received TXA also had lower 30-day mortality (18.5% vs 35.5%; P<0.003). A secondary analysis of the STAAMP trial [13] found that early TXA administration (within 1 hour of injury) was associated with 30-day survival benefits (HR 0.35; 95%CI, 0.19-0.65; P=0.001) and led to reduced rates of multiple organ failure and transfusion requirements.

Following this, the PATCH (Prehospital Administration of Tranexamic Acid in Collapse and Hemorrhage-Trauma) trial [14], an RCT, was published in 2023. This study included 1,310 severe trauma patients at risk for trauma-induced coagulopathy, defined by a Coagulopathy of Severe Trauma (COAST) score of ≥3. The intervention was a 1 g TXA bolus administered pre-hospital (within 3 hours of injury), followed by a 1 g infusion over 8 hours after hospital arrival. The study found that TXA did not improve favorable functional outcomes at 6 months, nor did it significantly reduce all-cause mortality at 28 days or 60 days.

Current PHTLS (PreHospital Trauma Life Support) 10th edition guidelines recommend a single 2 g slow IV/IO dose of TXA for prehospital patients with suspected severe hemorrhage or significant traumatic brain injury [15]. This aligns with ATLS (Advanced Trauma Life Support) 11th edition [16] recommendations for major hemorrhagic shock, which support a 1 g IV bolus followed by a 1 g infusion over 8 hours or a single 2 g dose. Both guidelines emphasize administration within 3 hours of injury and advise against later use unless hyperfibrinolysis is present.

1.2 Traumatic brain injury (TBI)

The CRASH-3 trial [17] an RCT conducted in 175 hospitals, enrolled 12,737 adults with TBI within 3 hours of injury who had a Glasgow coma scale (GCS) score < 12 or any intracranial bleeding on a CT scan and no major extracranial bleeding. Participants were assigned to receive TXA 1 g loading dose over 10 minutes followed by a 1 g infusion over 8 hours, or a placebo. TXA did not significantly reduce the overall risk of head injury-related death. However, subgroup analysis revealed that TXA reduced this risk in patients with mild-to-moderate TBI (RR 0.78; 95%CI, 0.64–0.95) and among those with bilateral reactive pupils (RR 0.87; 95%CI, 0.77–0.98), though this benefit was not observed in severe TBI. Furthermore, early treatment was also more effective in patients with mild to moderate TBI. Importantly, the trial provided strong evidence that TXA is safe in TBI patients.

The nuanced results from the CRASH-3 trial prompted updates in major trauma guidelines. The 2022 National Institutes of Health and Care Excellence (NICE) guideline [18] recommends considering a 2 g IV bolus for adults (GCS ≤ 12) and a weight-based dose (15-30 mg/kg) for children under 16, administered within 2 hours of injury. The 11th edition of ATLS [16] endorses TXA for moderate to severe TBI within 3 hours of injury, allowing either a single 2 g dose or the traditional 1 g bolus plus 1 g infusion over 8 hours.

2. Spontaneous intracranial bleeding

2.1 Non-traumatic intracerebral hemorrhage (ICH)

The efficacy of TXA in spontaneous ICH was investigated in 2018 in the TICH-2 (Tranexamic acid for hyperacute primary IntraCerebral Hemorrhage-2) trial [19], an RCT that enrolled 2,325 patients. The study excluded hemorrhage secondary to anticoagulation, thrombolysis, trauma, or known structural abnormality. The primary outcome, functional status at 90 days as assessed by the modified Rankin scale (MRS), did not improve with TXA (a 1 g bolus followed by a 1 g infusion over 8 hours, administered within 8 hours of symptom onset) compared to placebo. However, TXA did yield positive secondary results. TXA significantly reduces both hematoma expansion (25% vs. 29%; P=0.03) and early mortality by day 7 (9% vs. 11%; P=0.0406), without increasing venous thromboembolic events (VTE).

Subsequent trials have not consistently replicated the benefit of reducing hematoma growth. The 2020 STOP-AUST trial [20], a multicenter RCT focusing on patients with a spot sign on CT angiography, found that while not statistically significant, the TXA group trended towards greater ICH growth compared to placebo (52% vs. 44%; P=0.41). Similarly, the 2021 TRAIGE trial [21] and the 2023 TICH-NOAC trial [22], which studied patients with supratentorial ICH with expansion on imaging and NOAC-associated ICH, respectively, both concluded that

TXA did not significantly reduce hematoma expansion at 24 hours. The recent STOP-MSU trial [23], which administered TXA within 2 hours of symptom onset, also failed to demonstrate a reduction in hematoma growth. None of these four studies found that TXA increased thromboembolic events.

Reflecting this current evidence, the latest European Stroke Organization (ESO) 2025 guideline [24] highlights the "uncertainty about the balance of clinical benefits and adverse effects" of TXA. The guideline recommends recruiting patients into ongoing RCT for more definitive evidence. However, an expert consensus suggests that if trial enrollment is not feasible, "TXA may be considered for the purpose of reducing hematoma expansion."

2.2 Subarachnoid hemorrhage (SAH)

A 2020 multicenter RCT, the ULTRA trial [25], was conducted to assess the TXA in conjunction with standard management for adult patients with spontaneous CT-verified SAH. The study enrolled 955 participants who were administered TXA (a 1 g bolus immediately post-diagnosis, followed by a 1 g continuous infusion every 8 hours, ceasing before aneurysm treatment or at 24 hours). The results indicated that TXA failed to improve clinical status at six months, as determined by the MRS. Additionally, no statistically significant reduction in rebleeding events was observed. The serious adverse events, such as seizures, delayed cerebral ischemia (DCI), and thromboembolic complications during endovascular treatment, were not found to be different between the study arms.

A meta-analysis by Germans et al.[26] evaluated the efficacy and safety of antifibrinolytic agents for aneurysmal subarachnoid hemorrhage (aSAH). Drawing from 11 RCTs involving 2,717 participants, the study compared antifibrinolytics (primarily TXA) with placebo or standard care. The authors reported a significant 35% reduction in the risk of rebleeding with antifibrinolytic therapy (RR 0.65; 95%CI, 0.47-0.91; moderate-quality evidence). However, the therapy did not lead to a reduction in poor neurological outcomes or all-cause mortality. Furthermore, TXA was associated with a higher risk of DCI (RR 1.27; 95%CI,1.00-1.62; moderate-quality evidence), although this risk was mitigated in the subgroup of trials utilizing short-term (<72 hours) treatment protocols alongside modern DCI prevention strategies.

Synthesizing the currently evident, the 2023 guideline from the American Heart Association/American Stroke Association (AHA/ASA) does not recommend the routine use of antifibrinolytic therapy for individuals with aSAH [27]. Furthermore, the Neurocritical Care Society recommends against the administration of antifibrinolytic therapy to prevent rebleeding in patients with aSAH [28].

3. Obstetric and gynecologic bleeding

3.1 Postpartum hemorrhage (PPH)

Given that PPH is a major contributor to maternal deaths worldwide, the WOMAN (World Maternal Antifibrinolytic) trial [29] investigated the effect of early TXA administration on death and hysterectomy in women after vaginal birth or caesarean with PPH, a major contributor to maternal deaths worldwide. The protocol involved a 1 g TXA infusion over 10 minutes, with a repeat dose if bleeding persisted or recurred. TXA significantly reduced death due to bleeding, particularly when given within 3 hours of birth. However, TXA did not reduce the hysterectomy rate. The incidence of adverse events, including thromboembolic events, did not differ significantly between groups.

Building on the WOMAN trial's findings, researchers suggested TXA could be used for PPH prevention, not just treatment. This hypothesis led to the 2018 TRAAP (Tranexamic Acid for Preventing Postpartum Hemorrhage) trial [30], which investigated the prophylactic administration of TXA 1 g infusion during 2 min after delivery in conjunction with a standard uterotonic drug versus a uterotonic drug alone for the prevention of PPH in vaginal delivery. The addition of TXA did not significantly reduce the incidence of PPH of at least 500 mL. However, the subsequent 2021 TRAAP-2 trial [31] found that TXA did reduce the incidence of PPH of at least 1000 mL in patients undergoing caesarean section (aRR 0.84; 95%CI, 0.75-0.94), without increasing the thromboembolic events. More recently, the 2024 WOMAN-2 trial [32] in moderate to-severe anemic women undergoing vaginal delivery concluded that a 1 g TXA infusion within 15 minutes of cord clamping was not effective in preventing PPH.

The current 2017 World Health Organization (WHO) guideline for PPH [33] advocates for early TXA administration within 3 hours of birth. The recommended dose is an initial 1 g intravenous over 10 minutes, followed by a second 1 g if bleeding continues after 30 minutes or restarts within 24 hours.

3.2 Heavy menstrual bleeding (HMB)

Treatment for heavy menstrual bleeding (HMB) is highly individualized and includes several options. Foundational evidence for oral TXA comes from a double-blind RCT by Lukes et al.[34], which showed a 1.3 g regimen of TXA tid for five days led to a significantly greater reduction in menstrual blood loss (MBL) compared to placebo (40.4% vs. 18.2%; P<0.001) without associated thrombotic events.

A 2018 meta-analysis [35] confirmed TXA's superiority over NSAIDs and placebo. While comparable to progesterone, TXA was less effective than the levonorgestrel-releasing intrauterine system (LIUS). A 2023 meta-analysis [36] further refined this hierarchy, ranking LIUS as the best first line treatment for MBL reduction (MD -105.71 mL/cycle). TXA was the second-most effective option (MD -80.32 mL/cycle), demonstrating greater efficacy than both long-cycle oral progestogens and NSAIDs. Both comprehensive reviews were limited by the moderate to low certainty of the available evidence, highlighting a need for further high-quality comparative studies.

4. Acute medical bleeding (Non-traumatic)

4.1 Gastrointestinal bleeding (GIB)

The 2020 HALT-IT trial [37], an RCT, enrolled 12,009 patients to investigate TXA's efficacy in significant GIB. The study population included individuals at high risk

of death from hemorrhage (hypotension, tachycardia, or signs of shock). The TXA regimen (a 1 g intravenous bolus followed by a continuous infusion of 125 mg/hr for 24 hours) did not confer a survival benefit, as the rate of death within 5 days was comparable to placebo. The trial revealed a safety concern that TXA nearly doubled the risk of VTE (0.8% vs. 0.4%; RR 1.85; 95%CI,1.15-2.98). Moreover, it was associated with an increased risk of seizures (0.6% vs 0.4%; RR 1.73; 95%CI,1.03–2.93)

These outcomes have shifted current guidelines away from its use in GIB. The 2021 European Society of Gastrointestinal Endoscopy (ESGE) guideline does not recommend TXA for acute non-variceal upper gastrointestinal hemorrhage (NVUGIH) [38] or LGIB [39]. Similarly, the 2022 American College of Gastroenterology (ACG) guideline [40] recommends against the use of antifibrinolytic agents for LGIB.

4.2 Epistaxis

Two RCTs by Zahed et al. established that topical TXA (cotton pledget soaked in injectable form of TXA) is superior to anterior nasal packing (ANP) for epistaxis. A 2013 study [41] in idiopathic cases showed TXA achieved faster bleeding cessation within 10 minutes (71% vs.31.2%; P<0.001) and quicker ED discharge (95.3% vs. 6.4%; P<0.001). A 2018 [42] follow-up in patients on antiplatelet drugs confirmed these benefits for cessation (73% vs. 29%; P<0.001) and discharge (97% vs. 13%; P<0.001), while also finding less rebleeding at one week (5% vs. 21%; P=0.007) and higher patient satisfaction.

Further evidence from meta-analyses is mixed. A 2018 review by Joseph et al.[43] found that oral TXA reduced rebleeding versus placebo (RR 0.73; 95%CI, 0.55–0.96) and that topical TXA was effective for initial bleeding over other agents such as epinephrine/lidocaine or phenylephrine (RR 2.35; 95%CI,1.90–2.92). However, the 2021 NoPAC trial [44] presented conflicting evidence. In patients with spontaneous epistaxis persisting after first aid and a topical vasoconstrictor, topical TXA was no more effective than placebo at controlling bleeding and reducing the need for ANP.

Despite this, a subsequent 2022 meta-analysis [45] again supported topical TXA, reporting superior bleeding cessation rates over standard practices. Specifically, patients were 3.5 times more likely to achieve hemostasis at the first assessment (OR 3.5; 95%CI,1.3–9.7) and had a 63% lower chance of rebleeding within 24 to 72 hours.

4.3 Hemoptysis

A 2016 RCT found that intravenous TXA has limited efficacy for non-massive hemoptysis. Compared to placebo, a 1 g TXA loading dose followed by a 1 g infusion over 8 hours significantly reduced hemoptysis severity as measured by the visual analogue scale (VAS) score (P=0.001). However, it failed to demonstrate a significant reduction in the need for intervention, blood transfusion, or the hospital length of stay (LOS) [46].

In contrast, evidence for nebulized TXA appears more robust. A 2018 RCT by Wand et al.[47] compared nebulized TXA (500 mg tid) to placebo. Nebulized TXA significantly reduced expectorated blood volume, achieved a much higher rate of hemoptysis resolution within five days (96% vs. 50%; P<0.0005), shortened hospital LOS (2.5 vs. 4.6 days; P=0.046), and lowered the need for invasive procedures (0% vs. 18.2%; P<0.041), with no observed side effects.

A subsequent pilot RCT in 2023 [48] compared nebulized TXA to intravenous TXA in 55 patients with active non-massive hemoptysis. The nebulized route demonstrated a significantly higher rate of hemoptysis cessation at 30 minutes (P=0.0019). Hemoptysis volume was also significantly reduced in the nebulization arm at 6, 12, and 24 hours. Furthermore, the nebulized TXA group had higher discharge rates from the emergency department (ED) (67.9% vs 39.0%; P=0.005). While two patients in the nebulized arm experienced asymptomatic bronchoconstriction that resolved with a short-acting beta-agonist, this was not statistically significant.

Current evidence suggests nebulized TXA is an effective treatment for reducing hemoptysis volume, decreasing the need for interventional procedures, and achieving higher resolution rates without significant adverse effects.

5. Surgical and perioperative use

5.1 Cardiac surgery

The ATACAS (Aspirin and Tranexamic Acid for Coronary Artery Surgery) trial [49], a multicenter RCT, compared TXA versus placebo and aspirin versus placebo in patients undergoing coronary artery surgery at risk for perioperative complications. The TXA intervention was a 100 mg/kg infusion over 30 minutes after the induction of anesthesia (later reduced to 50 mg/kg due to seizure reports). The results showed that TXA significantly reduced the risk of bleeding. The total number of blood product units transfused was nearly halved in the TXA group (4,331 units) compared to the placebo group (7,994 units). Furthermore, reoperation due to major hemorrhage or cardiac tamponade was significantly lower in the TXA group (1.4%) than in the placebo group (2.8%). There was no significant difference in the composite outcome of death and thrombotic complications within 30 days of surgery. However, the use of TXA was associated with a significantly higher risk of postoperative seizures (0.7% vs. 0.1%; RR 7.8; 95%CI,1.8-34.1; P=0.002).

The 2024 EACTS/EACTAIC guidelines on patient blood management in adult cardiac surgery [50] recommend antifibrinolytic therapy to reduce bleeding, blood product transfusions, and reoperations for hemorrhage.

5.2 Non-cardiac surgery (NCS)

The POISE-3 (Peri-Operative Ischemic Evaluation-3) trial [51], a multicenter RCT, enrolled 9,535 patients undergoing NCS at risk for bleeding and cardiovascular complications (known atherosclerotic disease, undergoing major surgery, age ≥70 years, or serum creatinine level >2 mg/dL). Exclusion criteria included intracranial surgery, creatinine clearance of <30 mL/minute, or long-term dialysis. The trial compared a 1 g intravenous bolus of TXA at the start and end of surgery with a placebo. TXA significantly reduced the composite bleeding outcome (9.1% vs. 11.7; P<0.001). However, TXA did not meet the non-inferiority criterion for the composite cardiovascular safety outcome (HR 1.02; 95%CI, 0.92–1.14; non-inferiority margin 1.125).

The 2016 NICE guidelines [52] recommend TXA for adults expected to have moderate blood loss (>500 mL) during surgery. Similarly, the 2015 ASA guidelines advise prophylactic antifibrinolytic therapy for patients at risk for excessive bleeding and also recommend considering its use for patients who develop excessive bleeding during or after surgery. The 2022 European Society of Cardiology (ESC) guidelines [53], published after the POISE-3 trial, focus on treatment, recommending that in patients undergoing NCS and experiencing major bleeding, administration of TXA should be immediately considered.

The recent 2023 meta-analysis [54] of 191 RCTs in NCS (n=40,621) supported that prophylactic intravenous TXA reduced blood transfusions (9.9% vs. 19.4%; RR 0.46; 95%CI, 0.41–0.51; P<0.0001) without a significant increase in composite cardiovascular thromboembolic events, seizures, and 30-day mortality. The authors concluded that the evidence remains insufficient to definitively confirm the drug's thromboembolic safety, as the analysis was underpowered.

5.2.1 General surgery

A subsequent analysis of 3,260 POISE-3 participants undergoing general surgery found prophylactic TXA to be both safe and effective. TXA significantly reduced the composite bleeding outcome (life-threatening, major, or critical organ bleeding) (8.0% vs. 10.5%; P=0.01) without increasing cardiovascular risk [55].

A 2025 meta-analysis [56] of 26 RCTs in general surgery compared prophylactic TXA with placebo using heterogeneous dosing regimens, most commonly a single 1 g IV bolus pre-incision or weight-based dosing (10–15 mg/kg). TXA significantly reduced intraoperative blood loss (−35.85 mL; 95%CI, −57.20 to −14.51 mL), transfusion requirements (RR 0.75; 95%CI, 0.60–0.94; P=0.01), and major bleeding events (RR 0.72; 95%CI, 0.59–0.89; P=0.002), without increasing venous thromboembolism. No differences were observed in mortality or length of hospital stay. Subgroup analysis showed no consistent benefit across all procedures; however, TXA reduced major bleeding in hepatobiliary surgery (RR 0.59; 95%CI, 0.39–0.90; P=0.01). Overall, prophylactic TXA appears beneficial in general surgical procedures; however, the magnitude of benefit varies by procedure type, suggesting that TXA administration should be individualized based on surgical context and patient characteristics.

5.2.2 Urological surgery and hematuria

In urological surgery, TXA has shown efficacy in reducing blood loss. For percutaneous nephrolithotomy (PCNL), both systemic (1 g IV at induction, then 500 mg PO x 3 doses) [57] and local TXA (0.1% TXA in irrigation fluid during surgery) [58] reduce hemoglobin drop and transfusion rates. However, systemic administration is associated with a potential, though not statistically significant, risk of ureteric clot obstruction requiring stenting. A 2024 meta-analysis [59] further supports systemic TXA in PCNL for reducing transfusions without increasing thromboembolic events. Similarly, multiple RCTs confirm that both intravenous [60] and intravesical TXA [61] decrease bleeding and operative time in transurethral resection of the prostate (TURP).

For hematuria management, the evidence is less conclusive. In lower urinary tract hematuria, including bleeding from the bladder and urethra [62], a pilot RCT [63] suggests local bladder instillation of TXA may reduce the need for saline irrigation but does not impact hemoglobin levels. Crucially, TXA is not currently recommended for upper tract hematuria involving the kidneys and ureters [62]. Although case reports (primarily in autosomal dominant polycystic kidney disease) [64] describe its use for severe cases, the risk of severe complications, including ureteric clot obstruction and urinary tract perforation [65], is a significant deterrent.

5.2.3 Orthopedic surgery

In a subgroup analysis of the POISE-3 trial [51] focused on orthopedic surgery, the administration of intravenous TXA led to a significant reduction in the composite bleeding outcome (10.9% vs. 14.7%; P<0.001), although no similar benefit was observed for the composite cardiovascular outcome.

Regarding the optimal route of administration, several studies focusing on total knee and hip arthroplasty established that both intravenous and topical TXA are similarly safe and effective [66]. However, evidence from other meta-analyses indicates that a dual-route approach (combination of intravenous and topical administration) is more effective than either method used in isolation. This combined strategy has been shown to achieve a greater reduction in transfusion requirements [67,68], postoperative hemoglobin drop [68,69], and blood loss [67,69] in total hip arthroplasty. Importantly, these benefits were not associated with an increase in thromboembolic events. However, higher-quality RCTs are needed to solidify the recommendation for combined delivery.

6. Systemic and hematologic conditions: Hematologic malignancy

The 2022 a-TREAT [70] RCT investigated prophylactic TXA in patients with hematologic malignancy or aplasia who were undergoing chemotherapy, immunotherapy, or hematopoietic stem cell transplant and had developed severe thrombocytopenia (platelet count ≤10,000/μL for 5 days). Participants received either TXA (1.3 g orally or 1 g intravenously every 8 hours) or a placebo. The study found that TXA failed to reduce WHO grade ≥2 bleeding (50.3% vs. 54.2%, P=0.44) or the need for platelet transfusions. Subsequently, the 2025 TREATT (Trial to Evaluate Tranexamic Acid Therapy in Thrombocytopenia) [71] trial, a multicenter RCT, recruited a similar patient population and also found no benefit with prophylactic TXA (1.5 g orally or 1 g intravenously every 8 hours) in reducing WHO grade 2 or higher bleeding compared to placebo (31.7% vs. 34.2%, P=0.62). Notably, neither trial demonstrated an increased risk of thromboembolic events with TXA.

Therefore, current evidence does not recommend prophylactic TXA for the prevention of bleeding in patients with thrombocytopenia associated with hematological malignancies undergoing intensive chemotherapy.

DOSAGE AND ADMINISTRATION OF TXA

TXA has a wide range of clinical indications. The recommended dosages and routes of administration vary according to different trials and guidelines, as summarized in Table 1.

TXA is primarily renally eliminated; therefore, dose adjustment should follow recommended guidelines when renal function is known (Table 2). However, in emergency bleeding, treatment should not be delayed for creatinine assessment. Major studies did not exclude patients with renal impairment, excluding only those with known severe renal failure without specific creatinine thresholds. Overall, administration of a single initial dose of tranexamic acid is considered safe in emergency bleeding, even when renal function is unknown.

SAFETY PROFILE OF TXA

The administration of TXA is associated with several potential adverse reactions. Common side effects include nausea, vomiting, and diarrhea. Other documented reactions are allergic dermatitis and hypotension, the latter occurring if the intravenous infusion is too rapid. Hypersensitivity reactions can range from fixed drug eruption to anaphylaxis. Although the incidence is low, caution is warranted in patients with a history of multidrug hypersensitivity [76]. Visual disturbances secondary to focal retinal degeneration are another concern, though this has been observed in animal studies using very high doses (1.6-22 times the recommended human dose) [74].

However, the most clinically significant adverse events are thromboembolic events and seizures.

Table 1. Dose and route of TXA per indications.

Condition	Suggestion	Trials	Guidelines	Dose and route of TXA
Trauma with significant hemorrhage	✓	CRASH-2[8] STAAMP[12] PATCH[14]	ATLS 11th edition[16] PHTLS 10th edition[15]	Within 3 hours of injury - 1 g infusion over 10 min then 1 g infusion over 8 hours - 2 g infusion over 10 min
Traumatic brain injury	✓	CRASH-3[17]	ATLS 11th edition[16] PHTLS 10th edition[15]	Within 3 hours of injury - 1 g infusion over 10 min then 1 g infusion over 8 hours - 2 g infusion over 10 min
			NICE 2022[18]	Within 2 hours of injury - 2 g intravenous bolus - Age < 16 years old :15-30 mg/kg (up to 2 g) intravenous bolus
Postpartum hemorrhage	✓	WOMAN[29] TRAAP[30] TRAAP-2[31] WOMAN-2[32]	WHO 2017[33]	1 g infusion over 10 min within 3 hours of birth then 1 g infusion if bleeding continues after 30 minutes or restarts within 24 hours
Coronary surgery	✓	ATACAS[49]	EACTS/EACTAIC 2024[50]	50 mg/kg over 30 minutes after the induction of anesthesia
Non-cardiac surgery	✓	POISE-3[51,55]	NICE 2015[52] ASA 2016[72]	1 g intravenous bolus at the start and end of surgery for patients at risk for excessive bleeding
			ASA 2016[72] ESC 2022[53]	Consider TXA intravenous for patient with excessive bleeding
Orthopedic surgery	✓	POISE-3[51,55]		1 g intravenous bolus at the start and end of surgery
Hemoptysis	✓	Gopinath et al[48] Wand et al[47]		500 mg nebulized on arrival and tid
Percutaneous nephrolithotomy	✓	Kumar et al[57] Cleveland et al[59]		1 g infusion at induction then 500 mg orally every 8 hours for 24 hours
		Bansal et al[58]		1 g in 1 L of irrigant solution
Transurethral resection of the prostate	✓	Kumsar et al[60]		10 mg/kg infusion during the first half hour of the operation
		Tawfick et al[61]		1 g in 1 L of irrigant solution
Heavy menstrual bleeding	-	Lukes et al[34]		1.3 g oral tid at the onset of HMB f or 5 days
Epistaxis	-	Zahed et al[41,42] Janapala et al[45]		Topical application of cotton pledget soaked in TXA 500 mg/5 mL

Condition	Suggestion	Trials	Guidelines	Dose and route of TXA
Lower tract hematuria (bladder and urethra)	-	Moharamzadeh et al[63]		500 mg dissolved in 100 mL of NSS intravesical
Non-traumatic intracerebral hemorrhage	-	TICH-2[19] STOP-AUST[20] TRAIGE[21] TICH-NOAC[22] STOP-MSU[23]	ESO 2025[24]	Uncertainty about the balance of clinical benefits and adverse effects
Thrombocytopenia associated with hematological malignancies undergoing intensive chemotherapy	×	a-TREAT[70] TREATT[71]		Not recommend prophylactic TXA for the prevention of bleeding
Aneurysmal subarachnoid hemorrhage	×	ULTRA[25] Germans et al[26]	AHA/ASA 2023[27]	Not recommend the routine use
			NCS 2023[28]	Recommends against the administration of antifibrinolytic therapy
Gastrointestinal bleeding	×	HALT-IT[37]	ESGE 2021[38,73]	Not recommend TXA for NVUGIH or LGIB.
			ACG 2022[40]	Recommends against the administration of antifibrinolytic agents for LGIB.
Upper tract hematuria (kidneys and ureters)	×	Alameel et al[64] Maresca et al[65]		Not recommended due to risk of ureteric clot

Table 2. Recommended dose based on serum creatinine level [74,75].

Serum creatinine (mg/dL)	Intravenous dosage	Oral dosage
1.36-2.83	10 mg/kg twice daily	15 mg/kg twice daily
2.83-5.66	10 mg/kg daily	15 mg/kg daily
>5.66	10 mg/kg every 48 hours or 5 mg/kg daily	7.5 mg/kg daily

Thromboembolic events

A primary safety concern with TXA is the risk of thromboembolic events, including deep vein thrombosis (DVT), PE, MI, or stroke. While numerous RCTs have affirmed TXA's safety in acute hemorrhage [8,12,14,17,19,22,25,29,31,32,55], the HALT-IT trial [37] presented a significant counterpoint. Investigating GIB, HALT-IT was the first large RCT to demonstrate clear thromboembolic harm, showing an increased risk of VTE (0.8% vs. 0.4%; RR 1.85; 95%CI,1.15-2.98). However, the HALT-IT patient population differed from those in the CRASH-2 and WOMAN trials, they were older, had more comorbidities, and presented with pathologies like cirrhosis. Administering TXA to this high-risk population, with a different coagulopathic profile, is a plausible explanation for the increased thrombotic events.

This outlier finding is explained by broad meta-analytic data. A 2021 meta-analysis by Taeuber et al.[77] (192 RCTs, 125,550 patients) found no link between intravenous TXA and total thromboembolic events, while confirming a significant mortality reduction. A meta-analysis by Murao et al.[78] including 234 studies and 102,681 patients, found no increased risk of thrombotic events with tranexamic acid. No dose-response relationship was observed. Thrombotic risk was not increased at doses of 2 g per day or less (RR 0.94, 95%CI 0.84 to 1.05), while uncertainty remained at doses greater than 2 g per day (RR 1.18, 95%CI, 0.98–1.43). Meta regression showed no significant association between higher tranexamic acid dose and thrombotic events (P=0.122).

In summary, the current evidence indicates that for short-term use in acute hyperfibrinolytic conditions, the thrombotic risk is minimal and substantially outweighed by the survival benefit. Conversely, the risk may be amplified in patients with a high baseline thrombotic propensity or those receiving prolonged or high-dose therapy.

Seizure

The primary mechanism of TXA-associated seizures involves reduced inhibitory neurotransmission within the central nervous system. This disinhibition occurs as TXA acts as a competitive antagonist at γ-aminobutyric acid type A (GABAa) receptors. Secondly, due to its structural similarity to glycine, TXA also competitively inhibits glycine receptors. These two inhibitions lead to neuronal hyperexcitability and a lowered seizure threshold. A study has found that after discontinuing a TXA infusion, its cerebrospinal fluid concentration declines more slowly than in plasma. Therefore, persistently high brain concentrations during the early postoperative period may contribute to seizure genesis [79].

Several risk factors for TXA-associated seizures have been identified. Higher doses [34,80,81] are a primary concern. A meta-analysis [78] found that patients receiving more than 2 g/day have an increased risk of seizure (RR 3.05; **95%CI**, 1.01–9.20). Patient-specific factors include female gender, advanced age, poor health, renal dysfunction, and a history of neurological or cardiovascular disorders. The clinical setting is also critical, with seizures most frequently reported following cardiac surgery. The risk is further elevated in procedures involving deep hypothermic circulatory arrest or prolonged bypass/aortic cross-clamp time [34,79,81].

In postoperative cardiac surgery, TXA-associated seizures typically manifest as generalized tonic-clonic events, with approximately 20% of patients exhibiting myoclonic activity. Onset is typically within the first 5-8 hours post-surgery as patients are weaned from sedation. While seizures are brief, persisting for only a few minutes without progressing to status epilepticus, recurrences are common (30-60%) within the first 24-48 hours [79].

General anesthetic drugs (e.g., propofol, inhalation agents) may be considered first-line treatment. They enhance glycine receptor activity, directly counteracting the seizure mechanism. Second-line treatment includes benzodiazepines that upregulate $GABA_A$ receptor activity. However, the optimal strategy is prevention through dose adjustment, particularly in patients with renal impairment [79].

CONCLUSION

Current evidence and guidelines delineate a clear framework for using TXA across various clinical scenarios. A consensus supports its administration in trauma with significant hemorrhage, moderate to severe TBI, and PPH. Its role is also well-established for prophylaxis and treatment in non-cardiac and coronary artery surgery. In these acute hemorrhagic settings, timing is critical. TXA should be administered as early as possible within 3 hours of onset, as its efficacy decreases over time.

While TXA shows considerable utility in other conditions like specific urological and orthopedic surgeries, non-massive hemoptysis, and epistaxis, formal guideline recommendations are still pending. The evidence is more uncertain for HMB, spontaneous ICH, and lower tract hematuria. For prophylactic use in patients with thrombocytopenia secondary to hematological malignancies, TXA has been shown to be ineffective at reducing bleeding. In contrast, for aSAH, GIB, and upper tract hematuria, TXA is not recommended due to a risk-benefit profile favoring harm. Regarding safety, the thromboembolic risk of short-term use is minimal and outweighed by the mortality benefit. Although caution is needed in patients with a high baseline thrombotic risk. Furthermore, the risk of seizures is preventable with appropriate TXA doses and adjustments for renal function.

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