Comparative Efficacy of Tranexamic Acid vs. Epsilon-Aminocaproic Acid in Reducing Surgical Bleeding: A Comprehensive Review

Dr. N. Junior Sundresh [1], M.S., FRCS., FACS., Ph.D., R. Pavithra [2], S. Murugan [3], R. Mukesh Kumar [4]

[1] Medical Superintendent and Professor, Department of Surgery, Government Cuddalore Medical College and Hospital, Annamalainagar, Chidambaram.
[2,3,4] Pharm. D, Department of Pharmacy, Annamalai University, Annamalainagar, Chidambaram.

ABSTRACT

A major clinical issue that raises morbidity, death, and medical expenses is excessive bleeding during surgery. Antifibrinolytic drugs, particularly tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), are crucial in minimizing surgical blood loss and the need for transfusions. The effectiveness, safety, pharmacology, dosage methods, and cost-efficiency of TXA versus EACA in a variety of surgical specialties are all included in this review. It shows that although both medications successfully reduce perioperative bleeding, their efficacy, risk profiles, and clinical value are very different. TXA has superior haemostatic efficacy, notably in cardiac and orthopaedic procedures, and is around 2-3 times more potent than EACA. In some situations, EACA is more economical and just as effective as TXA. In orthopaedic surgery in elderly patients both have same safety and blood loss notes. Both drugs have been associated to thromboembolic problems and neurological events, with TXA having a particularly strong relationship with seizures in cardiac patients where as EACA have chance of renal injury. The review goes into the mechanisms of action, pharmacokinetics, clinical outcomes in a variety of surgical populations, safety concerns, dosing recommendations, economic implications, and novel formulations. It advocates for tailored antifibrinolytic options based on surgical setting, patient characteristics, drug availability, and economic considerations, as well as recommendations for future research to advance evidence-based clinical practices.

Keywords— Tranexamic acid; epsilon-aminocaproic acid; antifibrinolytic agents; surgical hemostasis; blood loss; perioperative transfusion; cardiac surgery; orthopedic surgery; pharmacoeconomics; adverse events.

1. INTRODUCTION

Perioperative bleeding is a major concern in surgery, increasing morbidity, death, and healthcare costs. Antifibrinolytic medicines such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are critical for restoring hemostasis and lowering the need for

transfusions, especially in situations of hyperfibrinolysis caused by surgical trauma or cardiopulmonary bypass. While both TXA and EACA block plasminogen activation, research shows significant differences in their efficacy, safety, and cost-effectiveness. TXA has shown superior efficacy in minimizing postoperative bleeding during cardiac procedures compared to EACA, and it may produce better results at lower doses in hip arthroplasty. However, TXA has been linked to an increased incidence of seizures in pediatric cardiac operations.

As a result, a thorough comparison of TXA and EACA across multiple surgical specialties is required, with this study seeking to systematically analyze their respective effectiveness, safety, dosage, and cost in perioperative care. Excessive perioperative bleeding is not only a common surgical complication that leads to increased morbidity and longer hospital stays, but it also raises healthcare costs, particularly for major procedures such as cardiac, orthopedic, and neurological surgery. While allogeneic blood transfusions can save lives, they can include dangers such as disease transmission and consequences. As a result, managing perioperative bleeding has a significant impact on surgical outcomes, necessitating the increasing importance of blood conservation treatments, such as pharmacological medicines and cell salvage procedures, especially since the discontinuance of aprotinin in 2007.

1.1 COMPARATIVE STUDY

While individual agents like Tranexamic Acid (TXA) and Ethamsylate (EACA) have been studied, there is a lack of high-quality comparative data between them. Previous studies often involve small sample sizes or retrospective designs, which may limit the applicability of their findings. Additionally, clinical practices vary between regions and healthcare systems, with some hospitals preferring TXA while others stick to EACA due to cost issues and traditional methods. This gap in comparative research has important clinical ramifications, as healthcare professionals often do not have clear guidelines for selecting between these medications, despite uncertainties regarding their equivalence and factors guiding antifibrinolytic choices. Concerns regarding the safety of both medications, particularly the risk of seizures associated with TXA and economic implications, highlight the need for a thorough, objective evaluation to support evidence-based decision-making in clinical settings.

1.2 OBJECTIVE

This review compares the efficacy, safety, pharmacology, and clinical utility of tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).

Objectives include,

- Detailed pharmacological comparison, including mechanisms, structural differences, and pharmacokinetic/pharmacodynamic properties.
- Evaluation of clinical efficacy in various surgical specialties such as cardiac, orthopedic, neurosurgery, and trauma.

- Critical assessment of safety profiles, focusing on thromboembolic risks, neurological effects, and organ-specific considerations.
- Review of dosing regimens and administration strategies across different surgical contexts.
- Pharmacoeconomic analysis comparing cost-effectiveness and accessibility.
- Synthesis of evidence from systematic reviews and meta-analyses on comparative effectiveness.
- Identification of research gaps and suggestions for future investigations.
- Evidence-based recommendations for clinical practice.

I. PHARMACOLOGIC OVERVIEW

- Both tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are antifibrinolytic agents that inhibit fibrinolysis by blocking lysine-binding sites on plasminogen and plasmin, preventing clotdegradation.
- TXA and EACA stabilize formed clots, promoting hemostasis, especially during surgical procedures where coagulation and fibrinolytic activities are activated.
- EACA is a mono aminomonocarboxylic acid with a molecular weight of 131.17 g/mol, while TXA is a cyclized derivative with a molecular weight of 157.21 g/mol, offering greater antifibrinolytic potency(2-10times) than EACA.
- TXA has rapid absorption, a shorter plasma half-life (~2 hours), and longer tissue retention (up to 17 hours), enabling less frequent dosing compared to EACA's slower absorption and shorter retention.
- TXA achieves peak plasma concentrations within 30 minutes post-intravenous administration, while EACA peaks in 1-2 hours, leading to different dosing strategies: TXA is given in 10-30 mg/kg boluses, whereas EACA usually starts with 100-150 mg/kg loading doses.
- The pharmacodynamics effects of TXA are demonstrated through more significant suppression of fibrinolytic markers compared to EACA in laboratory tests such as thromboelastographic (TEG) and rotational thromboelastometry (ROTEM).

Table 1 Comparative pharmacology of TXA vs EACA

Feature	TXA (Tranexamic Acid)	EACA (Epsilon-Aminocaproic Acid)
Mechanism of Action	Blocks lysine-binding sites on plasminogen/plasmin → prevents fibrin degradation.	Binds plasminogen kringle domains → inhibits binding to fibrin and plasmin conversion.
Relative Potency	Approximately 2-10 × higher than EACA.	Lower potency; older lysine analogue.
Absorption / Peak Time	Rapid absorption; oral bioavailability ~30-50%.	Slower absorption; peak plasma ~1-2 h (IV/oral).
Half-life	~2 h plasma half-life; renal excretion >95% unchanged.	~2 h half-life; renal elimination ~60-80% unchanged.
Dosing Implications	Lower required dose; less frequent dosing often sufficient.	Higher dose or more frequent dosing needed for similar effect.
Clinical Considerations	Preferred for high-bleed-risk surgeries; watch for seizure risk, renal impairment.	Good alternative when TXA cost/availability is an issue; effective in many settings.

II. CLINICAL EFFICACY COMPARISON

Cardiac surgery utilizes antifibrinolytic therapy, with TXA shown to reduce perioperative blood loss and transfusion needs, particularly in procedures involving cardiopulmonary bypass. High-dose TXA modestly reduces transfusion requirements, while low-dose strategies reduce blood loss by 30-40%. Direct comparisons with EACA indicate similar efficacy in specific contexts, but TXA shows slightly better hemostatic effects. Orthopedic surgeries, especially TKA and THA, benefit from TXA therapy, reducing intraoperative blood loss by 30-50% and transfusion requirements significantly. Limited evidence for EACA suggests comparable effectiveness at a lower cost. In neurosurgery and spine surgery, antifibrinolytics like TXA effectively manage blood loss during procedures, with high-dose TXA showing superior safety profiles. In trauma care, early TXA administration greatly reduces mortality rates, establishing it as a key intervention, while EACA lacks substantial supportive evidence in trauma settings. Other specialties, including urological and thoracic surgery, have shown TXA's effectiveness in reducing bleeding. However, the evidence for general surgical contexts remains variable and patient-specific.

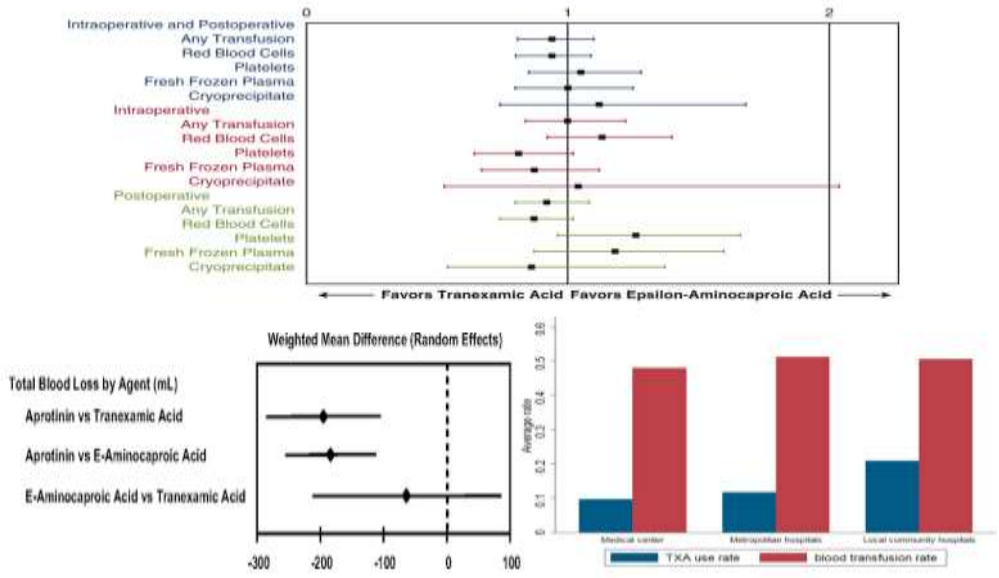

Figure 1 Comparative efficacy of TXA vs EACA in reducing perioperative bleeding.

- Tranexamic acid (TXA) and Epsilon-aminocaproic acid (EACA) effectively reduce perioperative blood loss and transfusion requirements.
- In total knee arthroplasty, TXA shows a slight advantage over EACA, with a reduction of approximately 175 mL in total blood loss.
- Both TXA and EACA demonstrate comparable transfusion rates.
- In cardiac surgery, outcomes for bleeding and transfusion rates are similar, but TXA is often preferred for slightly better hemostatic efficacy.
- EACA is a viable, cost-effective alternative when TXA is not readily available.

III. SAFTEY AND ADVERSE EVENTS

The section details the safety and adverse events associated with antifibrinolytic agents, focusing on tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).

1. THROMBOEMBOLIC RISKS: Concerns about thrombotic complications from antifibrinolytic agents arise from the excessive suppression of fibrinolysis, with risks including deep venous thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction, and cerebrovascular accidents. Systematic reviews indicate that TXA does not significantly increase these risks compared to controls. However, specific surgical populations, particularly those undergoing cardiac surgery, may experience elevated stroke risks with TXA. Evidence is insufficient for EACA's thromboembolic risk, but studies suggest similar profiles between TXA and EACA. The proposed mechanism for increased thrombotic risk involves excessive fibrinolysis inhibition, although large trials have not consistently shown increased complications. Care is advised for patients with pre-existing thrombotic conditions.
2. NEUROLOGIC EFFECTS: Seizures are a notable neurological complication linked to TXA, with incidences of 1.0% in high-dose regimens versus 0.4% in low-dose ones. High doses may influence glycine receptors, increasing neuronal excitability and leading to possible vasospasm. Risk factors for seizures include high doses, existing cerebrovascular issues, and renal dysfunction. Seizures appear to be manageable without lasting neurological consequences. Limited evidence exists regarding EACA's neurological effects, but it may carry a lower seizure risk.

3. RENAL AND HEPATIC CONSIDERATIONS: Both TXA and EACA are primarily really excreted, necessitating adjustments in patients with renal impairment. Normal dosing does not typically cause nephrotoxicity; however, patients with renal dysfunction may experience drug accumulation, increasing adverse event risks. Studies indicate that EACA may impact renal microcirculation more significantly than TXA. Hepatic function is not significantly involved in the excretion of either agent, so no routine adjustments for hepatic impairment are usually required.

4. ALLERGIC AND HYPERSENSITIVITY REACTIONS: Allergic reactions to TXA and EACA are rare, with occasional mild hypersensitivity cases reported. Serious reactions such as anaphylaxis are exceptional, and from a clinical standpoint, these agents do not pose substantial immunogenicity risks, allowing for their use without significant concern for allergic reactions in patients without documented sensitivities.

					P-Value*			
Variable	DriveTrain= All (N=92)	DriveTrain= Front (N=226)	DriveTrain= Rear (N=110)	All (N=428)	All	DriveTrain= All vs DriveTrain= Front	DriveTrain= All vs DriveTrain= Rear	DriveTrain= Front vs DriveTrain= Rear
Cylinders(N=426)	6.217±1.481	5.195±1.322	6.741±1.512	5.808±1.558	<.0001†	<.0001§	0.0147§	<.0001§
	N=92	N=226	N=108	N=426				
MPG (City)(N=428)	16.978±2.972	22.257±5.924	18.127±2.424	20.061±5.238	<.0001†	<.0001§	0.0034§	<.0001§
	N=92	N=226	N=110	N=428				
Origin				N=428	<.0001	<.0001	0.0799	<.0001
ASIA(N=158)	34(36.96%)	99(43.81%)	25(22.73%)	158(36.92%)				
EUROPE(N=123)	36(39.13%)	37(16.37%)	50(45.45%)	123(28.74%)				
USA; United States(N=147)	22(23.91%)	90(39.82%)	35(31.82%)	147(34.35%)				
Type_				N=428	0.4279*	0.5594*	N/A	0.5537*
HYBRID(N=3)	0(0.00%)	3(1.33%)	0(0.00%)	3(0.70%)				
OTHERS(N=425)	92(100.0%)	223(98.67%)	110(100.0%)	425(99.30%)				

Note: * † by ANOVA; § by t-test; # by Kruskal-Wallis Test ; $ by Wilcoxon rank-sum Test; * by Fisher's Exact Test; Otherwise by Chi-Square Test;

	Total N = 39		Nivolumab plus SOX n = 21		Nivolumab plus CapeOX n = 18	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE	39 (100.0)	24 (61.5)	21 (100.0)	12 (57.1)	18 (100.0)	12 (66.7)
Treatment-related SAEs	10 (25.6)	6 (15.4)	4 (19.0)	3 (14.3)	6 (33.3)	3 (16.7)
TRAEs leading to discontinuation*	5 (12.8)	2 (5.1)	3 (14.3)	1 (4.8)	2 (11.1)	1 (5.6)
TRAEs leading to dose delay or reduction	37 (94.9)	18 (46.2)	20 (95.2)	10 (47.6)	17 (94.4)	8 (44.4)
TRAEs (≥20%)						
Neutropenia*	25 (64.1)	6 (15.4)	13 (61.9)	3 (14.3)	12 (66.7)	3 (16.7)
Peripheral sensory neuropathy	24 (61.5)	3 (7.7)	12 (57.1)	1 (4.8)	12 (66.7)	2 (11.1)
Decreased appetite	23 (59.0)	2 (5.1)	12 (57.1)	0	11 (61.1)	2 (11.1)
Diarrhea	22 (56.4)	3 (7.7)	14 (66.7)	2 (9.5)	8 (44.4)	1 (5.6)
Nausea	20 (51.3)	2 (5.1)	11 (52.4)	0	9 (50.0)	2 (11.1)
Thrombocytopenia*	18 (46.2)	1 (2.6)	14 (66.7)	0	4 (22.2)	1 (5.6)
Fatigue	13 (33.3)	1 (2.6)	7 (33.3)	0	6 (33.3)	1 (5.6)
Vomiting	11 (28.2)	0	5 (23.8)	0	6 (33.3)	0
Constipation	10 (25.6)	0	5 (23.8)	0	5 (27.8)	0
Abdominal pain	8 (20.5)	3 (7.7)	4 (19.0)	2 (9.5)	4 (22.2)	1 (5.6)
Dysgeusia	8 (20.5)	0	3 (14.3)	0	5 (27.8)	0
Palmar-plantar erythrodysesthesia syndrome	8 (20.5)	0	0	0	8 (44.4)	0
Peripheral neuropathy	8 (20.5)	1 (2.6)	6 (28.6)	1 (4.8)	2 (11.1)	0
Pyrexia	8 (20.5)	0	4 (19.0)	0	4 (22.2)	0
Peripheral edema	7 (17.9)	0	6 (28.6)	0	1 (5.6)	0
Stomatitis	7 (17.9)	0	3 (14.3)	0	4 (22.2)	0
Anemia	6 (15.4)	2 (5.1)	2 (9.5)	0	4 (22.2)	2 (11.1)
Decreased white blood cell count	6 (15.4)	0	2 (9.5)	0	4 (22.2)	0

Figure 2 Sample Statistical output

IV. DOSING

Tranexamic Acid (TXA)

- Standard dose: 10-15 mg/kg bolus, followed by 1-2 mg/kg/hour infusion or repeated boluses during anesthesia induction and cardiopulmonary bypass.
- High-dose: 30 mg/kg bolus and 16 mg/kg/hour infusion, with an additional bolus at cardiopulmonary bypass commencement;improved hemostasis but higher neurological risks.
- Topical application: 500 mg to 2 grams directly at surgical sites; effective in orthopedic surgery without systemic absorption concerns.

Epsilon-Aminocaproic Acid (EACA)

- Standard dose: 100-150 mg/kg bolus, followed by 15 mg/kg/hour infusion.
- Alternative regimen: 4-5 grams loading dose and 1-1.5 grams/hour infusion; highlights significant dosing discrepancies due to EACA's lower potency.

Timing of Administration

- Preoperatively: Start antifibrinolytic therapy post-anesthesia induction and pre-incision for optimal hemostasis.
- Intraoperative: Re-dose during lengthy procedures to maintain plasma concentrations.
- Postoperatively: Early administration in trauma cases within 3 hours of injury is critical.

Comparative Dose Adjustments

Renal Impairment

- TXA doses reduced by 50% for creatinine clearance < 50 mL/min; EACA by 75% in significant renal impairment.

Body Weight: Total body weight versus ideal body weight considerations for TXA dosing in obese patients are debated.
Age: Some centers reduce TXA doses in elderly patients to minimize seizure risk; specific EACA adjustments are less common.
Topical Administration: No systemic dose adjustments required, though large volume applications may raise absorption concerns.

Drug	Typical Loading / Bolus Dose	Maintenance / Infusion Dose	Special Notes & Adjustments
TXA	10-15 mg/kg bolus (standard)	1-2 mg/kg/hour infusion	High-dose regimens (e.g., 30 mg/kg bolus + 16 mg/kg/hr.) used for high-bleed risk; topical dose 500 mg-2 g.
			In renal impairment: reduce dose (e.g., for eGFR < 60)
EACA	100-150 mg/kg bolus	~15 mg/kg/hour infusion	Lower potency vs TXA → needs larger dose; dose adjustments needed in renal impairment.

Figure 3 key dose regimens for Tranexamic Acid (TXA) and Epsilon-Aminocaproic Acid (EACA)

V. DISCUSSION

Comparative evaluation of tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) shows both effective antifibrinolytic therapy with differences in potency, application, adverse effects, and costs.

• **Efficacy:** TXA is more potent (2-10 times greater antifibrinolytic potency) with strong results in blood loss and transfusion reductions in cardiac and orthopedic surgeries. In trauma, TXA has been shown to reduce mortality effectively. Some orthopedic studies show comparable outcomes between TXA and EACA, indicating that EACA can achieve meaningful hemostasis if properly dosed.
• **Safety Profile**: Both agents have thromboembolic risks, but TXA has a higher risk of perioperative seizures. EACA has lower neurological risks. Both require dose adjustments for renal impairment.
• **Cost-effectiveness:** EACA is 5-10 times cheaper than TXA, making it a preferable option in resource-limited settings,particularly in orthopedic surgery.
• **Clinical Selection:** TXA is preferred in trauma for its mortality reduction; either agent can be used in cardiac surgery based on local practices. EACA is often the first choice in orthopedic contexts due to cost.
• **Implementation:** Successful use of antifibrinolytics demands clear protocols regarding indications, dosing, and adherence with regular review to enhance safety and effectiveness.
• **Emerging Directions:** Future strategies involve topical formulations, personalized medicine, and combination therapies to improve outcomes and minimize adverse events.

VI. FUTURE PERSPECTIVES

Novel Formulations	• Topical/gel/hydrogel TXA systems for localized hemostasis • Liposomal or depot TXA delivery for sustained effect
Personalized Medicine	• Real-time coagulation monitoring (TEG/ROTEM)-guided antifibrinolytic use • Pharmacogenomic profiling to tailor agent/dose
Combined Haemostatic Approaches	• Antifibrinolytics + transfusion/platelet/Factor concentrates for synergy • IV + topical agent combinations explored in network-analyses
Research & Implementation	• Large randomized trials comparing TXA vs EACA in various surgeries • Mechanistic studies on adverse events and pharmacoeconomics • Predictive models for individualized therapy • Implementation science: protocol adherence, real-world barriers

VII. CONCLUSION

Tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are important antifibrinolytic agents used to reduce surgical bleeding. TXA is generally more potent, but EACA can achieve effective hemostasis at a lower cost. Clinical selection of these agents should consider the specific surgical context, patient characteristics, and available resources. TXA is favored in trauma due to evidence of reduced mortality, while both agents perform similarly in cardiac surgery, allowing for cost-based choice. In orthopedic contexts, EACA is a reasonable first-line treatment. Clinicians should be knowledgeable about each agent's pharmacology and adverse effects to make informed decisions. Future research should focus on addressing evidence gaps to further enhance patient outcomes. The choice between these agents should reflect their context-specific advantages rather than seeking a single superior option.

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