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LETTER TO THE EDITOR

Tranexamic acid vs. epsilon-aminocaproic acid: Evidence gaps and practical implications

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ABSTRACT:

Antifibrinolytic agents, particularly tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), are widely used to reduce perioperative bleeding. Although both drugs share a similar mechanism—competitive inhibition of plasminogen activation—they differ in pharmacologic potency, dosing requirements, and clinical evidence. TXA demonstrates 6–10 times greater affinity for plasminogen, resulting in stronger antifibrinolytic effects at lower doses. Evidence from randomized trials and meta-analyses, primarily in orthopedic surgery, suggests TXA may reduce blood loss more effectively than EACA; however, differences in transfusion rates and thromboembolic complications are generally not significant. In cardiac surgery, limited data show no clear superiority of either agent. TXA has robust evidence supporting its use in trauma and obstetrics, while comparable high-quality data for EACA remain lacking. Both agents appear safe, though high doses—especially in renal impairment—may increase seizure risk. Importantly, EACA may achieve similar clinical outcomes when administered at appropriately higher doses. Current evidence is limited by heterogeneous study designs, variable dosing regimens, and underpowered trials. Overall, while TXA is more potent and better studied, definitive clinical superiority over EACA remains unproven. Drug selection should therefore consider patient factors, institutional protocols, and resource availability pending further large-scale comparative trials.

Keywords: Tranexamic acid; Epsilon-aminocaproic acid; Antifibrinolytic therapy; Perioperative bleeding; Blood conservation

To editor,

Antifibrinolytic therapy has become a cornerstone of modern perioperative blood conservation. Among the synthetic lysine analogs, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are the two most widely used drugs. Both agents competitively inhibit plasminogen activation by blocking its lysine-binding sites, thereby preventing the conversion to plasmin and stabilizing the fibrin clot. Despite sharing this mechanism of action, they differ in pharmacological potency, pharmacokinetic properties, and perhaps in clinical effectiveness. Given their widespread use in orthopedic, cardiac, and trauma surgery, a critical comparison of TXA and EACA remains clinically relevant [1]. This letter aims to highlight unresolved clinical uncertainties and practical decision-making considerations relevant to intensivists and perioperative clinicians who frequently encounter bleeding complications and transfusion decisions in the critical care setting.

Key randomized trials and meta-analyses cited in this letter were identified through a focused narrative review of major perioperative and critical care literature. Evidence levels are indicated where relevant, including randomized controlled trials (RCTs), meta-analyses, and retrospective observational studies.

Chemically, TXA is a trans-4-aminomethylcyclohexane carboxylic acid, while EACA is a straight-chain analog of lysine. However, TXA binds plasminogen with substantially higher affinity, estimated to be six to ten times greater than EACA, which translates into stronger antifibrinolytic potency at lower molar concentrations [2,3].

Most comparative trials between TXA and EACA derive from orthopedic literature. Several randomized controlled trials (RCTs) and meta-analyses suggest that TXA achieves a greater reduction in calculated blood loss and postoperative hemoglobin decline than EACA. For instance, Bradley et al. conducted an RCT in total joint arthroplasty using intravenous TXA 1 g before incision followed by 1 g at wound closure, compared with EACA administered as a 5 g intravenous loading dose followed by intraoperative infusion, and reported superior reductions in blood loss with TXA, though transfusion rates did not differ significantly. Similarly, a recent meta-analysis by Li et al. pooled randomized trials in total knee arthroplasty and concluded that TXA was more effective than EACA in lowering blood loss, but again no clear differences were seen in transfusion requirements or thromboembolic complications [4].

Contrasting evidence, however, has also emerged. Boese et al., in a randomized trial of total knee arthroplasty, administered TXA 10–15 mg/kg intravenously prior to incision compared with EACA 100 mg/kg loading followed by infusion and found that blood conservation with TXA was not superior to EACA, with no significant differences observed in transfusion rates or venous thromboembolism [5]. Other retrospective analyses in hip arthroplasty have similarly suggested that when EACA is administered in sufficiently high doses, clinical outcomes may approximate those achieved with TXA. This dose–response relationship is important: TXA's greater potency implies that equivalent ant fibrinolysis may require substantially higher doses of EACA, as confirmed by in vitro models. Typical perioperative regimens include TXA 10–20 mg/kg IV at induction with optional repeat dosing or infusion, whereas EACA protocols often require 100–150 mg/kg loading doses followed by continuous infusion. Indeed, some authors have proposed that effective EACA dosing may need to be approximately fivefold higher than TXA to achieve comparable clinical efficacy [5].

Cardiac surgery represents another important field for antifibrinolytic therapy. Routine use of these agents has long been standard practice to reduce bleeding, transfusion requirements, and reoperation for bleeding. However, few well-powered trials have directly compared TXA and EACA in this setting. Leff et al. conducted a randomized, double-blind trial in 114 patients undergoing coronary artery bypass grafting (CABG) and/or valve surgery under cardiopulmonary bypass, assigning patients to weight-based dosing of TXA or EACA. In this study, TXA was administered as a 10 mg/kg loading dose followed by infusion, whereas EACA was given as approximately 100 mg/kg loading followed by infusion. The investigators found no difference in chest tube output at 24 hours but intriguingly reported higher rates of blood product transfusion in the TXA group compared with EACA. Safety outcomes, including renal dysfunction, stroke, seizures, and death, did not differ.

From an intensive care perspective, the choice between TXA and EACA may influence early postoperative bleeding, transfusion burden, and resource utilization in the ICU. Excessive postoperative bleeding is associated with prolonged mechanical ventilation, renal dysfunction, and longer ICU stays. Therefore, even modest differences in antifibrinolytic efficacy may translate into meaningful downstream critical care outcomes. Although limited by single-center design and small sample size, this trial underscores the lack of definitive evidence supporting the superiority of one agent over the other in cardiac surgery [1].

Beyond orthopedics and cardiac surgery, TXA has been studied in trauma, spine surgery, obstetrics, and liver transplantation. In trauma, large multicenter trials such as CRASH-2 (RCT, >20,000 patients) demonstrated that TXA administered within three hours of injury (1 g IV followed by 1 g infusion over 8 hours) significantly reduced mortality from bleeding. However, no equivalent high-quality evidence exists for EACA in trauma populations. In obstetrics, the WOMAN Trial (2017, Lancet) demonstrated reduced mortality from postpartum hemorrhage with early TXA administration, leading to guideline recommendations for its use in postpartum hemorrhage management. In liver transplantation, antifibrinolytic therapy (whether TXA or EACA) is generally reserved for patients with documented hyperfibrinolysis due to concern for hepatic artery thrombosis. Comparative trials of TXA and EACA in these diverse surgical contexts are lacking, limiting our ability to generalize beyond orthopedics and cardiac surgery [1]. It is also important to recognize clinical scenarios in which antifibrinolytic therapy has not consistently demonstrated benefit. For example, trials in gastrointestinal bleeding have shown inconsistent results regarding mortality reduction, highlighting that the efficacy of antifibrinolytic therapy may depend strongly on the underlying pathophysiology of bleeding. Key phase III randomized trials evaluating antifibrinolytic therapy across different clinical settings are summarized in Table 1.

KEY MESSAGES:

- TXA is pharmacologically more potent than EACA and has stronger evidence from large, randomized trials in trauma and perioperative medicine.
- However, when adequately dosed, EACA may achieve comparable clinical outcomes in several surgical settings, particularly orthopedics and cardiac surgery.
- Current evidence gaps highlight the need for large multicenter non-inferiority trials with standardized dosing strategies to guide optimal antifibrinolytic selection.

Table 1. Landmark TXA trials

Trial	Population	Key finding
CRASH-2	Trauma	Reduced mortality if given <3h
WOMAN	Postpartum hemorrhage	Reduced death due to bleeding
POISE-3	Non-cardiac surgery	Reduced major bleeding

Table 2. Typical TXA and EACA dosing strategies

Clinical setting	TXA typical dosing	EACA typical dosing	Timing
Total knee arthroplasty	10–20 mg/kg IV or 1 g IV	100–150 mg/kg IV	Before incision
Hip arthroplasty	1 g IV ± repeat dose	5 g loading + infusion	Pre-incision
Cardiac surgery	10 mg/kg load + infusion	100 mg/kg load + infusion	Before CPB
Trauma	1 g IV + 1 g over 8h	Not established	Within 3 h injury
Postpartum hemorrhage	1 g IV	Limited evidence	Early bleeding

Both TXA and EACA are generally considered safe, with low rates of thromboembolic complications across trials and meta-analyses [6].

However, arterial thrombotic events such as myocardial ischemia, limb ischemia, and bowel ischemia have been reported rarely in association with antifibrinolytic therapy, particularly in patients with high baseline thrombotic risk. Both agents have also been associated with seizures when administered in very high doses, likely due to their antagonism of inhibitory neurotransmitter receptors, but this is more consistently documented with TXA in the context of high-dose cardiac surgery [4].

Both TXA and EACA are predominantly renally cleared; therefore, drug accumulation may occur in patients with renal impairment, potentially increasing the risk of neurotoxicity and seizures. Dose adjustment in renal dysfunction is therefore recommended in several clinical guidelines. Importantly, there is no specific pharmacologic antidote for TXA or EACA; management of overdose or complications relies on supportive care and discontinuation of the drug.

The optimal dosing strategies for both drugs remain incompletely defined, with current regimens largely empirical and not derived from dose–response studies. This represents a key limitation of the literature and a barrier to definitive comparison [4]. Typical dosing regimens and timing strategies reported in major clinical settings are summarized in Table 2.

Several limitations characterize the existing evidence base. First, most comparative trials are single-center and underpowered to detect differences in rare but clinically important outcomes such as thromboembolism, stroke, seizures, or mortality. Second, dosing regimens vary substantially between studies, with intravenous, topical, intra-articular, and combined strategies employed, making pooled analyses heterogeneous and difficult to interpret. Third, meta-analyses may also be affected by publication bias, differences in transfusion thresholds, and variability in surgical techniques across studies. The choice of primary endpoint varies, ranging from laboratory or surrogate measures such as drain output or hemoglobin decline to clinical outcomes such as transfusion requirements, leading to different interpretations of "superiority." Finally, most systematic reviews conclude that while TXA appears more potent, the clinical relevance of this advantage remains uncertain in the absence of large non-inferiority or equivalence trials.

From a clinical standpoint, TXA offers stronger antifibrinolytic potency at lower doses and has been more extensively studied, including in large pragmatic trials such as POISE-3, which confirmed its ability to reduce major bleeding in non-cardiac surgery without increasing thrombotic events. EACA, by contrast, has a more limited evidence base, but available data suggest it can be an effective and safe alternative, particularly when cost or regional availability is a deciding factor. Importantly, given the dose–response relationship, clinicians must ensure that EACA is administered in sufficiently high doses to achieve comparable efficacy.

In summary, while tranexamic acid is pharmacologically more potent than epsilon-aminocaproic acid and has shown favorable results in some randomized trials, the overall evidence base remains inconclusive regarding clinical superiority. Transfusion requirements and thromboembolic risks appear broadly similar between agents. Existing studies are limited by heterogeneity, small sample sizes, and variable endpoints, precluding firm recommendations. Until definitive comparative trials are available, agent selection should prioritize institutional protocols, patient-specific risk factors, renal function, and resource stewardship in the perioperative and critical care setting.

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