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TRANEXAMIC ACID IN PEDIATRIC CARDIAC SURGERY: A COMPREHENSIVE REVIEW OF EFFICACY, SAFETY, AND CURRENT CONTROVERSIES

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ABSTRACT

Pediatric patients undergoing cardiac surgery, particularly with cardiopulmonary bypass (CPB), are at high risk for significant bleeding and allogeneic blood transfusions due to their unique hemostatic profile. Tranexamic acid (TXA) is the primary antifibrinolytic agent used to mitigate this risk, but its efficacy, safety, and optimal administration in this population remain topics of debate. This article provides a comprehensive review and to synthesize the available evidence and identify critical knowledge gaps. Our analysis confirms that TXA significantly reduces postoperative blood loss and the need for allogeneic red blood cell and fresh frozen plasma transfusions. This effect was particularly notable in high-risk subgroups such as infants and cyanotic patients. Substantial heterogeneity was found across studies, primarily related to varying TXA dosing regimens and differing transfusion protocols, which limited the ability to define a single optimal dose. TXA is an effective agent for reducing bleeding and transfusion needs in pediatric cardiac surgery, but its use is associated with a potential, dose-dependent risk of seizures. The wide variability in dosing regimens and the lack of robust data on long-term neurological outcomes highlight a critical need for future large-scale, prospective trials. These studies should aim to standardize dosing protocols and definitively assess the true benefit-to-risk ratio of TXA in specific pediatric subgroups.

KEYWORDS

Tranexamic Acid, Pediatric Cardiac Surgery, Antifibrinolytics, Cardiopulmonary Bypass, Seizures

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1. Introduction

Pediatric cardiac surgery presents unique challenges in the context of hemostasis.

Children undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at significant risk of bleeding due to hemodilution, hemostatic disturbances such as platelet dysfunction, systemic inflammation, and hypothermia. The occurrence of bleeding and the child's critical clinical condition are associated with poorer outcomes, including increased need for blood product transfusions, prolonged stays in the intensive care unit, and higher mortality rates(Bartucca et al., 2023).

Neonates are particularly vulnerable to bleeding after CPB. This susceptibility is due to the immaturity of their coagulation system, substantial hemodilution from the priming volume of the CPB circuit, prolonged bypass times at low temperatures, and extensive suture lines. Perioperative bleeding may lead to serious complications, including hypotension, metabolic acidosis, infection, acute respiratory distress syndrome, and multiorgan damage(Guzzetta et al., 2015).

Congenital heart defects are frequently associated with coagulation abnormalities, such as reduced fibrinogen levels and impaired platelet function. Due to significant physiological differences between children and adults, pediatric patients should be approached separately in surgical settings. Children have a much smaller total blood volume, meaning that even minor blood loss — tolerable in adults — can be clinically significant in pediatric patients. Moreover, children possess highly effective compensatory mechanisms, which allow them to maintain normotension until substantial blood loss has occurred(Zou et al., 2022).

To reduce perioperative and post-traumatic blood loss and transfusion requirements, antifibrinolytic agents are commonly used. These drugs work by inhibiting fibrin clot breakdown. Historically, aprotinin — a serine protease inhibitor that suppresses kallikrein activity and the conversion of plasminogen to plasmin — was used to reduce bleeding in pediatric cardiac surgery. However, in 2006, a retrospective study revealed an association between aprotinin use and increased risks of renal failure, myocardial infarction, and stroke, prompting reevaluation of its clinical use At that time, aprotinin was replaced by tranexamic acid (TXA)(Breuer et al., 2009; Schindler et al., 2011).

Tranexamic acid, a synthetic lysine analog, exerts antifibrinolytic effects by competitively binding to plasminogen receptor sites on fibrin and by inhibiting plasmin-induced platelet activation(Giordano et al., 2012). The use of TXA represents a significant advancement in pediatric cardiac surgery by reducing perioperative and postoperative blood loss and decreasing the need for transfusions. TXA has been associated with lower mortality compared to aprotinin; however, emerging studies have revealed a dose-dependent relationship between TXA and the risk of seizures in pediatric patients undergoing cardiac surgery(Zhang, Zhang, et al., 2019).

This review summarizes the current evidence on the efficacy, safety, and optimal use of TXA in pediatric cardiac surgery, while addressing ongoing controversies and identifying key gaps in knowledge.

2. Methodology of the Review

A comprehensive and systematic search was performed across multiple electronic databases to identify relevant studies published up to July 2025. The databases searched included: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, Scopus.

The search strategy combined Medical Subject Headings (MeSH terms) and keywords related to the intervention (Tranexamic Acid, TXA, antifibrinolytic), population (pediatric, child, infant, neonate, congenital heart disease, cardiac surgery), and outcomes (bleeding, hemorrhage, blood transfusion, adverse events, seizures, thrombosis). Boolean operators (AND, OR) and truncation symbols were used to broaden the search. Additionally, the reference lists of included studies and relevant review articles were manually screened for any additional pertinent studies.

Inclusion Criteria:

- Original research articles (randomized controlled trials, quasi-randomized trials, cohort studies, case-control studies).
- Studies investigating the use of tranexamic acid in pediatric patients (defined as <18 years of age, or specific age groups like neonates/infants/children/adolescents as relevant to the study's scope) undergoing cardiac surgery
- Studies reporting on relevant outcomes such as blood loss, blood transfusion requirements, re-exploration for bleeding, or adverse events (e.g., seizures, thrombotic events).
- Studies published in English.
- Studies with a control group (placebo, no antifibrinolytic, or another antifibrinolytic like EACA for comparative analyses).

Exclusion Criteria:

- Case reports, letters to the editor, editorials, conference abstracts without full publication, opinion pieces.
- Studies not involving pediatric patients or cardiac surgery with CPB.
- Studies solely on adult populations.
- Studies where TXA was used for non-cardiac indications.
- Studies lacking a control group for comparative analysis.
- Studies with insufficient data to extract relevant outcomes.

For outcomes or questions where meta-analysis was not appropriate due to significant heterogeneity, diverse study designs, or insufficient data, a comprehensive narrative synthesis was provided. This involved critically discussing the findings of individual studies, highlighting consistent trends, contradictory results, and plausible explanations for variations.

The overall certainty of evidence for key outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. This provides a structured framework for judging the strength of recommendations based on the body of evidence.

3. Efficacy of Tranexamic Acid

Reduction in blood loss

TXA is a crucial component of blood conservation strategies in adult cardiac surgery. It is endorsed by guidelines as a class I level A recommendation aimed at reducing both blood loss and the need for blood transfusions during cardiac procedures(Tibi et al., 2021), although there are no guidelines for pediatric cardiac patients, the use of TXA is considered standard practice in pediatric procedures.

Researchers should also pay attention to infants weighing less than 10 kg (or 8 kg, according to some authors), as they are particularly vulnerable due to their immature coagulation systems and the significant hemodilution up to 150% due to their limited blood volume(Siemens et al., 2018).

TXA has long been a subject of interest for researchers in pediatric cardiac surgery. In 2005, in his paper on blood conservation in pediatric cardiac surgery, Pouard identified TXA as one of the antifibrinolytic agents capable of reducing both postoperative blood loss and need for transfusions(Pouard, 2008). Since then, numerous original studies on this topic have been published. Consequently, this section will focus only on recent findings, as much of the earlier literature has been comprehensively reviewed and presented in both reviews and meta-analyses.

In a 2019 single-center study, Zhang et al. found that the use of TXA significantly reduced postoperative bleeding (both at the 12-hour mark and in total) in children undergoing cardiac surgery compared to those receiving a placebo. The study further compared children under 10 kg with those over 10 kg, revealing a statistically significant difference in favour of children under 10 kg. As well as cyanotic and acyanotic patients, with a statistical difference in favour of cyanotic patients(Zhang, Zhang, et al., 2019).

A 2022 meta-analysis by Zou et al. conducted on a total of 1421 pediatric patients in China demonstrated a reduction of postoperative bleeding within the first 24 hours in both cyanotic, acyanotic, and combined cyanotic and acyanotic patients. It's worth noting that this meta-analysis did not include a distinct section addressing infants under 10 kg(Zou et al., 2022).

A noteworthy study by Hasegawa et al. in 2014 examined not only blood loss through chest drainage but also the duration of drainage, discovering a significant difference in both when comparing TXA to placebo(Hasegawa et al., 2014). It may be beneficial to incorporate drainage time as a parameter in future studies, as prolonged drainage can result in postoperative pain(Mueller et al., 2000).

In summary, recent research consistently emphasizes the critical role of TXA in pediatric cardiac surgery. It significantly reduces blood loss among high-risk populations, including infants weighing less than 10 kg and cyanotic patients, as well as older children.

Reduction in Blood Transfusion Requirements

While tranexamic acid (TXA) often reduces blood loss, its impact on the requirement for allogeneic blood products (red blood cells, fresh frozen plasma, platelets) varies across studies. Some reviews report a significant reduction in transfusion volume or incidence, while others note decreased total blood product exposure without a corresponding change in the number of transfused patients. This variability likely stems from institutional differences in transfusion thresholds and patient complexity.

The study by Zonis et al. demonstrated that a single TXA dose (50 mg/kg) significantly reduced the need for both red blood cell and platelet transfusions in cyanotic patients. In the non-TXA group, 7 of 10 patients required blood transfusions, compared to only 1 of 8 in the TXA group. Platelet transfusion was necessary in 6 of 10 patients in the non-TXA group, while none in the TXA group required them(Zonis et al., 1996).

Reid's study found a significant reduction in the total transfusion volume (whole blood, packed red cells, or reconstituted blood) in the TXA group. However, categories like"total red cell exposure" and"non-red cell exposure" did not show statistically significant differences, though"total red cell exposure" approached significance ($p = 0.06$), with an average of 2.0 units transfused in the TXA group vs. 3.0 units in the placebo group(Reid et al., 1997).

Chauhan's study from 2004, which included five groups (control, single-dose TXA 50 mg/kg, bolus of 10 mg/kg followed by continuous infusion of 1 mg/kg/h, triple-dose TXA at 10 mg/kg each, and double-dose TXA at 20 mg/kg), revealed that the triple-dose TXA group experienced significantly the least blood loss and the lowest requirement for red blood cell transfusion, followed closely by the group that received the double dose of 20 mg/kg each(Chauhan et al., 2004). Faraoni, in a letter to the editor in 2011, emphasized that while initial findings support TXA effectiveness, varying dosages prevent definitive conclusions(Faraoni et al., 2012).

Giordano's study applied TXA at 20 mg/kg after induction of anesthesia and after protamine administration. The TXA group received fewer intraoperative erythrocyte transfusions compared to placebo. Although the control group exhibited greater blood loss, there was no significant difference in postoperative blood product requirements(Giordano et al., 2012).

In a retrospective analysis conducted by Zhang, which included over 2, 000 patients who either received TXA or did not, no statistically significant differences were observed in intraoperative blood loss or postoperative allogeneic transfusion rates between the TXA and non-TXA groups(Zhang, Zhang, et al., 2019). A study by Baser compared three groups: no medication, TXA alone, and TXA with ethamsylate. TXA alone reduced transfusion

needs compared to control, and the combined therapy group showed an even greater reduction(El Baser et al., 2021). In the 2021 study by Madathil, which included 124 patients and compared two triple-dose TXA regimens (10 mg/kg vs. 25 mg/kg), no statistically significant differences were observed between the groups in the transfusion of red blood cells, plasma, platelets, or cryoprecipitate(Madathil et al., 2021).

Zou's 2022 meta-analysis, conducted in the Chinese pediatric population and including randomized studies comparing tranexamic acid (TXA) to placebo, confirmed that TXA reduces red blood cell (RBC) transfusion in both cyanotic and non-cyanotic patients. It also significantly decreases plasma use in non-cyanotic and mixed patient groups. The researchers compared their findings with data from the Caucasian pediatric population, allowing them to conclude that although TXA similarly reduces blood loss in both populations, its effect on transfusion requirements differs. Specifically, in the Caucasian population, TXA reduces RBC transfusions primarily in non-cyanotic patients, while it decreases fresh frozen plasma (FFP) use in cyanotic patients(Zou et al., 2022). In Patel's 2017 study, patients were divided into three subgroups: those who did not receive any medication, those who received intravenous TXA twice at a dose of 20 mg/kg, and those who received TXA both intravenously and intrapericardially. The group that received both intravenous and intrapericardial TXA ultimately required the least amount of blood products(Patel et al., 2017). However Hatami's randomized trial showed no differences in blood product usage among patients receiving TXA via different administration routes (pericardial, intravenous, or none)(Hatami et al., 2020). A study by Muthialu, comparing TXA and aprotinin in children showed higher use of whole blood and fresh frozen plasma in the aprotinin group, with no differences in intraoperative red blood cell or platelet transfusion(Muthialu et al., 2015). Willems reported similar findings—greater blood product exposure in the aprotinin group than the TXA group(Willems et al., 2019). Conversely, Lin found that patients receiving aprotinin (with or without TXA) needed fewer transfusions than those on TXA alone(Lin et al., 2015). Turaga's systematic review from 2023 of 20 studies concluded that TXA effectively reduces blood transfusion requirements(Turaga, 2023).

Re-exploration for Bleeding

Several studies and meta-analyses suggest that the use of tranexamic acid (TXA) is associated with a reduction in the need for re-operations due to bleeding. However, this outcome often shows substantial heterogeneity across studies, likely reflecting differences in study design, patient populations, dosing regimens, timing of administration, and surgical procedures involved. Despite this variability, the overall trend indicates a potential benefit of TXA in decreasing the likelihood of bleeding-related surgical re-interventions.

In the study by Zonis et al., among the six patients excluded from the main analysis, three required reoperations — all of whom were from the group that did not receive tranexamic acid (TXA)(Zonis et al., 1996). This finding suggests that the absence of TXA treatment may be associated with a higher risk of needing surgical re-intervention, highlighting the potential effectiveness of TXA in preventing bleeding-related complications. In the study conducted by Chauhan, none of the patients receiving either double-dose or triple-dose TXA required surgical re-exploration. In contrast, 16% of patients in the control group, who did not receive TXA, underwent re-operation(Chauhan et al., 2004). Giordano's study demonstrated similar results—two patients in the control group required early reoperation due to bleeding, whereas no patients in the TXA group needed such intervention (Giordano et al., 2012). In Pasquali's extensive comparative analysis, patients treated with TXA had a lower incidence of reoperations due to bleeding—1.3% in the TXA group compared to 2.1% in both the aprotinin and aminocaproic acid groups(Pasquali et al., 2012). In Muthialu's study comparing TXA and aprotinin, fewer patients in the TXA group required reoperation (2 out of 26) compared to the aprotinin group (5 out of 24)(Muthialu et al., 2015).

These results further support the potential benefit of TXA in reducing the need for additional surgical interventions due to bleeding.However, Lin's study presents contradictory findings. In his comparison of three groups—patients who did not receive antifibrinolytics, those treated with TXA alone, and those receiving aprotinin (with or without TXA)—no statistically significant differences were found in the rates of surgical re-exploration(Lin et al., 2015). Madathil's study similarly found no significant difference in re-exploration rates between groups receiving varying dosages TXA (10 mg/kg vs. 25 mg/kg)(Madathil et al., 2021). A systematic review and meta-analysis conducted by Szarpak comparing tranexamic acid (TXA) and ε-aminocaproic acid found no significant differences in the rates of reoperation due to uncontrolled bleeding(Szarpak et al., 2024).

Length of ICU Stay / Ventilation

There is no consistent or strong evidence suggesting that TXA significantly reduces ICU length of stay or duration of mechanical ventilation. However, some individual studies report beneficial trends. Reid's 1997 study demonstrated that surgical procedures were shorter in patients treated with TXA, although no significant difference was observed in the duration of ICU ventilation between the TXA and placebo groups(Reid et al., 1997). Pasquali's study indicated that patients treated with TXA experienced shorter ICU stays—3.3 days compared to 3.9 days in patients treated with aprotinin and 4.3 days in those receiving aminocaproic acid(Pasquali et al., 2012). Hasegawa's study found a significant difference between patients treated with tranexamic acid (TXA) and the control group. Administration of a 100 mg/kg bolus followed by a continuous infusion of 10 mg/kg/h was associated with significantly shorter intubation times (5.8 ± 1.6 hours vs. 7.9 ± 4.1 hours) and a reduced overall length of hospital stay (6.3 ± 1.4 days vs. 8.0 ± 2.7 days)(Hasegawa et al., 2014).

In Muthialu's study, postoperative ventilation duration was significantly shorter in the TXA group compared to the aprotinin group (1.1 days versus 3.5 days), and the length of ICU stay was also markedly reduced (2.0 days versus 6.35 days)(Muthialu et al., 2015). However, Lin did not observe any statistically significant differences in hospitalization duration among the groups receiving no treatment, TXA alone, or aprotinin—with or without TXA(Lin et al., 2015)]. Patel also reported no significant differences in ICU stay or ventilation duration between different methods of TXA administration—intravenous, intrapericardial, or a combination of both(Patel et al., 2017).

In the 2021 study by Baser, no statistically significant differences were observed between subgroups receiving no treatment, TXA alone, or TXA combined with ethamsylate in terms of ICU stay length(El Baser et al., 2021). Bigdelian's 2023 trial demonstrated that intravenous administration of TXA resulted in significantly shorter intubation times compared to intrapericardial administration(Bigdelian et al., 2023).

Topical TXA

The topical use of TXA has been studied in the adult population since the notable study conducted by De Bonis et al. in 2000. This study paved the way for a variety of subsequent randomized controlled trials, reviews, and meta-analyses. In recent years, researchers have expanded their focus to conduct trials on the use of topical TXA in pediatric patients. The concept of topical TXA use arises from the reports of complications associated with TXA, such as seizures, thromboembolism, and renal impairment, which are detailed in a dedicated section of this paper. The previously mentioned De Bonis' study found no detectable TXA blood concentration following topical application. This finding indicates that such a mode of application is likely to mitigate the risk of systemic complications(De Bonis et al., 2000).

In 2017, Patel et al. conducted a study involving 75 patients, comparing the efficacy of IV TXA (group A) compared to topical TXA (group B) and a combination of topical and IV TXA (group C). The results revealed that blood loss and transfusion rate were lowest in group C. However, the study did not indicate whether these differences were statistically significant. Furthermore, serum urea and creatinine levels were significantly lower in group B, compared to groups A and C(Patel et al., 2017).

The 2020 study by Hatami et al. presents similar findings when comparing topical TXA with low-dose IV TXA and placebo. Involving 117 children aged 1 month to 14 years, the study revealed that both topical and IV TXA groups had lower blood loss and transfusion rate when compared to placebo. Furthermore, there was no statistically significant difference between the IV and topical group in blood loss, raising the question of whether topical TXA can be effectively administered on its own, without the IV form. Finally, the study found no differences in the occurrence of neurological events among the groups(Hatami et al., 2020).

Finally, the 2023 study by Bigdelian et al. examined 50 patients who received either IV or topical TXA. The results were consistent with previous studies, showing that bleeding was significantly lower in the topical group up to 24 hours, but not at 48 hours. However, contrary to Patel's results, Bigdelian found no difference in post-operative serum urea and creatinine levels. Additionally, there were no reported incidents of seizures in either group(Bigdelian et al., 2023).

In summary, the studies presented raise an important question: considering controversies surrounding the adverse effects of the TXA, can topical TXA be used as an alternative? A straightforward answer might be yes, as no statistical difference has been identified between these two routes of administration. However, the presented studies were conducted on small groups of patients, and the authors observed no additional benefits from the use of topical TXA instead of IV TXA(Murkin et al., 2010). Given the effectiveness of current low dose IV TXA regimens in reducing adverse effects, further investigation into topical TXA is needed on a larger group of patients to determine whether topical TXA offers any advantages over IV TXA.

Table 1. Topical TXA studies comparison.

Author, year	Number of patients	TXA dose (topical)	Comparison group(s)	Primary outcome	Result	Statistically significant
(Patel et al., 2017)	75	50mg/kg	IV (20mg/kg + IV 20mg/kg); IV (20mg/kg) + topical (50mg/kg)	Postoperative chest drainage	Lowest in IV + topical group	Not indicated
(Hatami et al., 2020)	117	50mg/kg	IV (20mg/kg + 20mg/kg); placebo	Total blood loss	Lowest in topical group	NO
(Bigdelian et al., 2023)	50	50mg/kg	IV 50mg/kg	Postoperative bleeding	Lower in topical group	YES

4. Safety of Tranexamic Acid

Seizures

In pediatric cardiac surgery, this is one of the most frequently discussed and thoroughly investigated adverse events associated with TXA(Giordano et al., 2012). The pathogenesis of seizures associated with tranexamic acid administration remains incompletely understood. Research has suggested that TXA enhances neuronal excitation by antagonizing inhibitory γ-aminobutyric acid (GABA) neurotransmission(Kratzer et al., 2014). By contrast, another study has shown that TXA inhibits neural glycine receptors, and the inhibition of the neurotransmitter glycine is a known cause of seizures(Lecker et al., 2012).

A compelling observation is that the peak concentration of TXA in the cerebral spinal fluid occurred approximately five hours after the plasma peak concentration. This finding may account for the reported delay between TXA administration and the onset of clinical seizures following cardiac surgery(Faraoni et al., 2019). Prolonging anaesthetic delivery during the immediate postoperative period may represent a simple yet effective strategy for mitigating the risk of seizures(Maeda et al., 2017). Furthermore, the occurrence of seizures following cardiac surgery can elevate operative mortality and adversely affect the neurodevelopmental outcomes and quality of life in pediatric patients(Wesley et al., 2015; Zhang, Jia, et al., 2019).

Investigations suggest that the incidence of seizures may be related to the dosage of TXA administered. The retrospective research by (Couture et al., 2017) demonstrated that the risk of seizures linked to TXA use in cardiac surgery was elevated with higher doses and diminished with lower doses(Couture et al., 2017). Based on another investigation recommended that a low dose of TXA should be administered via either the systemic or topical route in pediatric cardiac surgery patients to prevent seizures(Hatami et al., 2020).

Future investigations are warranted to elucidate the optimal TXA dosage that provides the most favorable benefit-to-risk ratio, balancing hemostatic efficacy with the minimization of adverse events such as seizures(Martin et al., 2011a).

Renal dysfunction:

Kidney injury is common in pediatric cardiac surgery, with a reported prevalence of up to 33% (Cardoso et al., 2016). The risk is particularly high in newborns, with some studies suggesting that the incidence of acute kidney injury (AKI) may reach 50–60% in this population(Suieubekov et al., 2023).

Standard perioperative dosing of TXA is generally considered safe and effective in patients with a creatinine clearance above 30 mL/min; however, its safety and efficacy in those with more severe renal impairment remain uncertain(Liu et al., 2024).

The kidneys eliminate TXA; therefore, in kidney dysfunction, the elimination half-life of TXA increases. As a result, the risk of TXA-induced seizures and other adverse effects also increases, even at doses considered safe for patients without kidney disease. Some studies suggest that thrombotic risk in patients with renal impairment is also higher. Moreover, kidney disease is associated with dysfunction in platelet aggregation and interaction with vessel walls, along with hypofibrinolysis. All of these factors can influence the antihemorrhagic properties of TXA, potentially making it less effective in reducing bleeding(Liu et al., 2024).

In addition to TXA, epsilon-aminocaproic acid (EACA) is also used to reduce bleeding in pediatric cardiac surgery. Aprotinin was eventually replaced by EACA, which, according to studies, was associated with a lower incidence of AKI(Leyvi et al., 2011)https://doi.org/10.1053/j.jvca.2011.01.015. However, a systematic

review and meta-analysis comparing EACA with TXA found that EACA was associated with a higher mortality rate and an increased risk of renal injury compared to TXA (Szarpak et al., 2024).

It is worth noting that TXA, due to its antifibrinolytic properties, can promote blood clot formation in the kidneys, potentially leading to renal cortical necrosis(Radhakrishnan & Mehra, 2020). Patients with hematuria are at the highest risk for this complication; however, case reports have also documented TXA-induced renal cortical necrosis in individuals without hematuria(Berri et al., 2025).

Thrombotic events:

Considering the TXA mechanism of action, it is reasonable to suspect that it may increase the risk of thrombosis(Nishida et al., 2017). Nonetheless, multiple large randomized controlled trials and meta-analyses have demonstrated that TXA is not associated with a higher risk of pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, or other thrombotic complications when compared to placebo(Ivasyk et al., 2022; Murao et al., 2021).

Mortality and major morbidity

Numerous trials have investigated blood loss and transfusion rates associated with TXA use in pediatric cardiac surgery and beyond. However, studies assessing long-term outcomes—specifically morbidity and mortality—are limited. A recent meta-analysis including both pediatric and adult populations undergoing cardiac surgeries (such as valve replacements, coronary artery bypass grafting, abdominal aortic aneurysm repair, etc.) reported favourable outcomes. Neither TXA nor EACA was found to negatively affect morbidity or mortality (Casares et al., 2024). Furthermore, a randomized trial with a 7-year follow-up suggested that TXA use in cardiac surgery can potentially reduce the risk of myocardial infarction; however, this study involved only an adult population(Zhang et al., 2018).

5. Controversies and Knowledge Gaps

Despite the widespread incorporation of TXA into pediatric cardiac surgical practice, significant controversies persist regarding its optimal use, particularly in neonates and infants. Central to these disputes are unresolved issues in dosing strategies, the risk of neurologic toxicity—especially postoperative seizures—and the extrapolation of adult-derived evidence to pediatric populations lacking robust randomized data.

The question of dose standardization is among the most contentious. In the absence of universally accepted protocols, clinical practice varies markedly, with bolus doses ranging from 10 to 100 mg/kg and maintenance infusions inconsistently applied. This variability stems from limited pharmacokinetic data across age strata and was underscored in the systematic review by Faraoni et al., who noted heterogeneity not only in TXA administration but also in transfusion thresholds and definitions of bleeding endpoints(Faraoni et al., 2012). Similarly, a single-center analysis by Zhang et al. documented seizure occurrences predominantly in patients receiving higher cumulative doses of TXA, reinforcing dose-related neurotoxicity concerns (Zhang, Zhang, et al., 2019). These findings align with pharmacologic models suggesting that TXA crosses the immature blood-brain barrier in neonates, potentially inhibiting GABAergic transmission and predisposing to cortical hyperexcitability(Schertz et al., 2022; Taam et al., 2020).

Another area of controversy involves the risk–benefit ratio of TXA use in neonates and complex congenital heart repairs. While Schertz et al. systematically reviewed prophylactic antifibrinolytic use during pediatric cardiac surgery and reported reduced bleeding and transfusion requirements, they cautioned against definitive conclusions due to the overall low quality and pediatric specificity of available trials(Schertz et al., 2022). Notably, Siemens et al. echoed these concerns in their scoping review, highlighting the absence of pediatric-defined bleeding scores or validated transfusion algorithms as critical gaps(Siemens et al., 2018).

Further complexity arises from conflicting institutional practices and the lack of harmonized clinical guidelines. Although TXA is recommended by various expert panels as part of blood conservation strategies, formal pediatric-specific recommendations remain lacking. Moynihan et al., in their Pediatric ECMO Anticoagulation Consensus Conference, called for rigorous multicenter trials to clarify appropriate hemostatic strategies including TXA in bypass and extracorporeal circuits(Moynihan et al., 2024).

Despite growing acceptance of TXA's role in reducing bleeding, there remains insufficient clarity on long-term outcomes, including neurodevelopmental implications in vulnerable populations such as preterm neonates and children with cyanotic heart disease. Aran et al. and Cholette et al. both point to these areas as urgent priorities for prospective surveillance and biomarker-informed investigations(Aran et al., 2021; Cholette et al., 2018).

Significant heterogeneity in TXA dosing (bolus, infusion, single vs. multiple doses, mg/kg) across studies makes it difficult to define a universally optimal regimen for all pediatric cardiac patients. The ideal balance between efficacy and minimizing seizure risk remains under debate. While overall trends are clear, the precise benefit-to-risk ratio may vary in specific subgroups (e.g., neonates, those with single ventricle physiology, or specific types of defects).

The potential for tranexamic acid (TXA) to induce postoperative seizures is a significant concern, necessitating careful neurological monitoring, though the precise incidence and clinical relevance of subtle neurologic effects remain under-investigated(Breuer et al., 2009; Gertler et al., 2014). Clinical reports document cases of grand-mal seizures in infants during the early postoperative period following TXA administration(Gertler et al., 2014). This neurotoxicity may be mediated by TXA's competitive antagonism at cerebral GABA-A receptors, a mechanism that could be exacerbated by the increased permeability of the blood-brain barrier following cardiopulmonary bypass(Breuer et al., 2009; Gertler et al., 2014). While some prospective studies did not observe any postoperative seizures, the authors still considered it a key safety outcome to monitor(Madathil et al., 2021). Other analyses have noted a non-significant trend toward a higher incidence of seizures in patients receiving TXA(Breuer et al., 2009). Conversely, one pharmacokinetic study involving 55 young children reported no seizures, hypothesizing that the high doses of concomitant anesthetics such as midazolam and fentanyl may have provided a neuroprotective effect against the high plasma levels of TXA achieved(Wesley et al., 2015). Given these findings, there is a clear need for age-appropriate dosing regimens and potentially enhanced neurological surveillance to mitigate seizure risk(Gertler et al., 2014).

The link between TXA and seizures is strongly substantiated by a large, nationwide, retrospective cohort study in Japan, which included 3, 739 propensity-score-matched pairs of pediatric cardiac surgery patients. This analysis found that the proportion of postoperative seizures was significantly higher in the group receiving TXA compared to the non-TXA group (1.6% vs. 0.2%, respectively). Despite this increased seizure risk, the study found no associated increase in in-hospital mortality, thromboembolism, or renal dysfunction(Maeda et al., 2017). Another study comparing TXA to EACA also observed a non-significant, fourfold higher incidence of seizures with TXA (3.5% vs. 0.8%), but the authors noted their study was significantly underpowered to detect a true difference in such a rare event (Martin et al., 2011b). The potential mechanisms for this neurotoxicity are thought to involve the structural similarity of TXA to GABA, allowing it to act as an antagonist on GABA-A receptors, and its ability to inhibit glycine receptors, both of which can lead to enhanced neuronal excitation(Faraoni et al., 2019).

Long-Term Outcomes

Data on the long-term outcomes following TXA exposure in pediatric cardiac surgery are sparse, particularly concerning neurodevelopmental status and thrombotic events(Breuer et al., 2009; Reid et al., 1997). While several studies recorded in-hospital and 30-day outcomes, follow-up extending to one year or more is rare(Breuer et al., 2009; Graham et al., 2012). One study that assessed all-cause mortality one year after surgery found no significant difference between patients who received TXA and those who received aprotinin(Breuer et al., 2009). A critical, albeit indirect, concern for long-term morbidity stems from the established association between postoperative seizures in infancy and worsened neurodevelopmental outcomes; this is particularly alarming given the tendency for increased seizure rates with TXA use reported in some cohorts(Breuer et al., 2009; Wesley et al., 2015). Regarding thrombotic complications, multiple studies have reported a lack of overt thrombotic events or shunt thrombosis associated with TXA during the observation period(Graham et al., 2012; Reid et al., 1997). However, it has been acknowledged that a properly powered prospective study designed to detect subtle or devastating complications from TXA has not been conducted(Reid et al., 1997). The short-term follow-up available, such as one case report noting no further seizures four months after the initial event, does not provide sufficient data to assess long-term safety profiles(Gertler et al., 2014).

A comprehensive scoping review of the literature highlights the significant limitations in the existing evidence base, noting that most controlled trials are small, single-center studies that are likely underpowered to detect differences in rare but critical outcomes The review also identified marked heterogeneity in how outcomes are defined and reported; for instance, postoperative blood loss was reported over nine different time periods across various studies, making direct comparisons and meta-analyses challenging. This lack of standardized outcomes is a major barrier to understanding the true long-term impact of TXA and other hemostatic interventions. The review also identified marked heterogeneity in how outcomes are defined and reported; for instance, postoperative blood loss was reported over nine different time periods across various studies, making direct comparisons and meta-analyses challenging. This lack of standardized outcomes is a

major barrier to understanding the true long-term impact of TXA and other hemostatic interventions(Siemens et al., 2018). Consequently, while large database studies provide valuable insight into short-term safety events like in-hospital mortality, they often lack the granularity and follow-up duration to assess long-term morbidities(Maeda et al., 2017). There remains an urgent need for large, multicenter studies with standardized core outcome sets to properly evaluate the long-term safety and efficacy of TXA in this vulnerable population(Siemens et al., 2018).

Comparison with Other Agents

The efficacy of TXA has been evaluated against placebo and other antifibrinolytic agents like aprotinin and aminocaproic acid (ACA), yielding a complex and at times contradictory body of evidence(Breuer et al., 2009; Bulutcu et al., 2005; Pasquali et al., 2012). In prospective, randomized, placebo-controlled trials, TXA has been shown to reduce blood loss and transfusion requirements, with its effects being most pronounced in high-risk populations such as children with cyanotic heart disease or those undergoing repeat sternotomy(Reid et al., 1997; Zonis et al., 1996). When compared with aprotinin, results are inconsistent. Some studies suggest aprotinin has a superior blood-sparing effect, demonstrating significantly lower postoperative blood loss, reduced red blood cell transfusion, and fewer re-thoracotomies for bleeding(Breuer et al., 2009). In neonates, aprotinin use was associated with diminished use of nearly all blood products and attenuated cytokine activation compared to TXA(Graham et al., 2012). In contrast, a large multicenter database analysis found that TXA was associated with significantly reduced mortality and bleeding requiring surgical intervention when compared with aprotinin, particularly in neonates(Pasquali et al., 2012). Another study in cyanotic children found both agents were similarly effective at reducing blood loss compared to a control group, with no additional benefit from their combined use (Bulutcu et al., 2005). Limited comparative data exist for TXA versus ACA, though one large analysis found no significant difference in outcomes between aprotinin and ACA, which, when coupled with its finding that TXA was superior to aprotinin, suggests a potential advantage for TXA(Pasquali et al., 2012).

Direct comparisons between TXA and epsilon-aminocaproic acid (EACA) have produced nuanced and evolving findings. An earlier non-randomized study of 234 pediatric patients found TXA and EACA to be comparable in their effect on postoperative blood loss, transfusion requirements, and major clinical outcomes. However, this study noted a concerning, albeit non-significant, fourfold increase in seizure risk with TXA, prompting the institution to switch to EACA as its standard of care(Martin et al., 2011b). In contrast, a more recent and larger systematic review and meta-analysis encompassing 3, 487 patients found that TXA was associated with significantly lower in-hospital mortality and a reduced risk of renal failure requiring dialysis when compared to EACA. This same meta-analysis, however, also identified a non-significant trend towards a higher incidence of neurologic deficits with TXA(Szarpak et al., 2024). This highlights a potential trade-off between improved survival and renal outcomes with TXA versus a possibly more favorable neurological safety profile with EACA. These contrasting results underscore the difficulty in drawing definitive conclusions from a heterogeneous body of literature, much of which consists of small, single-center trials(Siemens et al., 2018). Following safety concerns in adult cardiac surgery that led to the market withdrawal of aprotinin, lysine analogs like TXA and EACA became the preferred agents, although aprotinin was later reintroduced with restrictions(Faraoni et al., 2019). Due to the remaining safety questions surrounding aprotinin in the pediatric population, lysine analogs are generally recommended as the first-line antifibrinolytic choice

6. Conclusion and Future Directions

Tranexamic acid (TXA) has become a standard component of hemostatic management in pediatric cardiac surgery. A systematic review of the literature indicates its effectiveness in reducing perioperative bleeding and potentially reducing the need for blood transfusions and reoperations due to bleeding, as well as postoperative drainage time. However, the reports reveal considerable heterogeneity and often contradictory findings. TXA may be particularly beneficial in high-risk groups such as newborns, children weighing <10 kg, and cyanotic patients. TXA, both intravenously and topically, exhibits significant antifibrinolytic effects, but the differences in efficacy and advantages between these forms of administration are unclear.

Despite the widespread use of TXA, many aspects of its use remain controversial. Despite its generally good safety profile, potential adverse effects remain controversial. The most frequently discussed of these concerns remains the increased risk of postoperative seizures and their association with neurotoxicity, which is particularly concerning in pediatric patients. This risk is likely dose-dependent. Renal excretion of TXA highlights the need to determine its safety and dosage in patients with low creatinine clearance. Discrepancies

in studies may result from differences in local procedures, such as different transfusion thresholds, as well as from differences in study conduct or population differences.

TXA remains a recommended expert element of the blood loss reduction strategy in pediatric cardiac surgery. However, the lack of uniform, formal pediatric guidelines regarding dosage, administration format, and measures to reduce adverse effects should prompt clinicians to exercise caution during treatment and postoperative monitoring.

Further research on TXA should include randomized trials in large patient groups, the results of which could serve as a basis for standardizing the use of TXA in pediatric patients. A systematic review shows that studying various aspects of TXA efficacy simultaneously could be beneficial. Research should also focus on ways to minimize the risks associated with TXA use and develop a dosing regimen with the most favorable clinical benefit-to-risk ratio. Long-term studies should also be conducted to exclude potential long-term effects, including neurodevelopmental effects. Research should aim to enable clinicians to personalize therapy according to individual patient characteristics and risk factors.

REFERENCES

1. Aran, A. A., Karam, O., & Nellis, M. E. (2021). Bleeding in Critically Ill Children-Review of Literature, Knowledge Gaps, and Suggestions for Future Investigation. *Front Pediatr*, *9*, 611680. https://doi.org/10.3389/fped.2021.611680
2. Bartucca, L. M., Shaykh, R., Stock, A., Dayton, J. D., Bacha, E., Haque, K. D., & Nellis, M. E. (2023). Epidemiology of severe bleeding in children following cardiac surgery involving cardiopulmonary bypass: use of Bleeding Assessment Scale for critically Ill Children (BASIC). *Cardiology in the Young*, *33*(10), 1913-1919. https://doi.org/10.1017/S1047951122003493
3. Berri, J., Quintrec Donnette, M. L., Millet, I., Chenine, L., Serre, J. E., & Mazloum, M. (2025). Tranexamic acid-induced acute bilateral renal cortical necrosis in a young trauma patient: a case report and literature review. *BMC Nephrology*, *26*(1), 95. https://doi.org/10.1186/s12882-025-03982-y
4. Bigdelian, H., Montazeri, M., Sedighi, M., Mansouri, M., & Amanollahi, A. (2023). Topical and Intravenous Tranexamic Acid in Acyanotic Children Undergoing Congenital Heart Surgery: A Randomized Clinical Trial. *Journal of Surgical Research*, *288*, 64-70. https://doi.org/10.1016/j.jss.2023.02.029
5. Breuer, T., Martin, K., Wilhelm, M., Wiesner, G., Schreiber, C., Hess, J., Lange, R., & Tassani, P. (2009). The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. *European Journal of Cardio-Thoracic Surgery*, *35*(1), 167-171; author reply 171. https://doi.org/10.1016/j.ejcts.2008.09.038
6. Bulutcu, F. S., Ozbek, U., Polat, B., Yalcin, Y., Karaci, A. R., & Bayindir, O. (2005). Which may be effective to reduce blood loss after cardiac operations in cyanotic children: tranexamic acid, aprotinin or a combination? *Paediatric Anaesthesia*, *15*(1), 41-46. https://doi.org/10.1111/j.1460-9592.2004.01366.x
7. Cardoso, B., Laranjo, S., Gomes, I., Freitas, I., Trigo, C., Fragata, I., Fragata, J., & Pinto, F. (2016). [Acute kidney injury after pediatric cardiac surgery: risk factors and outcomes. Proposal for a predictive model]. *Revista Portuguesa de Cardiologia*, *35*(2), 99-104. https://doi.org/10.1016/j.repc.2015.06.006 (Insuficiencia renal aguda no contexto de cirurgia cardiaca pediatrica: fatores de risco e prognostico. Proposta de um modelo preditivo.)
8. Casares, J. A., Jaramillo, A. P., Nizamudeen, S., Valenzuela, A., Abdul Samad, S. K., & Rincon Gomez, A. S. (2024). Evaluating the Effectiveness of Tranexamic Acid vs. Placebo in Cardiac Surgery: A Systematic Review and Meta-Analysis. *Cureus*, *16*(6), e63089. https://doi.org/10.7759/cureus.63089
9. Chauhan, S., Bisoi, A., Kumar, N., Mittal, D., Kale, S., Kiran, U., & Venugopal, P. (2004). Dose comparison of tranexamic acid in pediatric cardiac surgery. *Asian Cardiovascular & Thoracic Annals*, *12*(2), 121-124. https://doi.org/10.1177/021849230401200208
10. Cholette, J. M., Faraoni, D., Goobie, S. M., Ferraris, V., & Hassan, N. (2018). Patient Blood Management in Pediatric Cardiac Surgery: A Review. *Anesthesia and Analgesia*, *127*(4), 1002-1016. https://doi.org/10.1213/ANE.0000000000002504
11. Couture, P., Lebon, J. S., Laliberté, É., Desjardins, G., Chamberland, M., Ayoub, C., Rochon, A., Cogan, J., Denault, A., & Deschamps, A. (2017). Low-Dose Versus High-Dose Tranexamic Acid Reduces the Risk of Nonischemic Seizures After Cardiac Surgery With Cardiopulmonary Bypass. *J Cardiothorac Vasc Anesth*, *31*(5), 1611-1617. https://doi.org/10.1053/j.jvca.2017.04.026
12. De Bonis, M., Cavaliere, F., Alessandrini, F., Lapenna, E., Santarelli, F., Moscato, U., Schiavello, R., & Possati, G. F. (2000). Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *Journal of Thoracic and Cardiovascular Surgery*, *119*(3), 575-580. https://doi.org/10.1016/s0022-5223(00)70139-5
13. El Baser, I. I. A., ElBendary, H. M., & ElDerie, A. (2021). The synergistic effect of tranexamic acid and ethamsylate combination on blood loss in pediatric cardiac surgery. *Annals of Cardiac Anaesthesia*, *24*(1), 17-23. https://doi.org/10.4103/aca.ACA_84_19

14. Faraoni, D., Rahe, C., & Cybulski, K. A. (2019). Use of antifibrinolytics in pediatric cardiac surgery: Where are we now? *Paediatric Anaesthesia*, *29*(5), 435-440. https://doi.org/10.1111/pan.13533
15. Faraoni, D., Willems, A., Melot, C., De Hert, S., & Van der Linden, P. (2012). Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. *European Journal of Cardio-Thoracic Surgery*, *42*(5), 781-786. https://doi.org/10.1093/ejcts/ezs127
16. Gertler, R., Wiesner, G., Tassani-Prell, P., Martin, K., & Gruber, M. (2014). Measurement of tranexamic acid serum concentrations in a 7-month-old infant with clinical seizures after open heart surgery. *Pediatric Neurology*, *51*(2), e1-2. https://doi.org/10.1016/j.pediatrneurol.2014.04.003
17. Giordano, R., Palma, G., Poli, V., Palumbo, S., Russolillo, V., Cioffi, S., Mucerino, M., Mannacio, V. A., & Vosa, C. (2012). Tranexamic acid therapy in pediatric cardiac surgery: a single-center study. *Annals of Thoracic Surgery*, *94*(4), 1302-1306. https://doi.org/10.1016/j.athoracsur.2012.04.078
18. Graham, E. M., Atz, A. M., Gillis, J., Desantis, S. M., Haney, A. L., Deardorff, R. L., Uber, W. E., Reeves, S. T., McGowan, F. X., Jr., Bradley, S. M., & Spinale, F. G. (2012). Differential effects of aprotinin and tranexamic acid on outcomes and cytokine profiles in neonates undergoing cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery*, *143*(5), 1069-1076. https://doi.org/10.1016/j.jtcvs.2011.08.051
19. Guzzetta, N. A., Allen, N. N., Wilson, E. C., Foster, G. S., Ehrlich, A. C., & Miller, B. E. (2015). Excessive postoperative bleeding and outcomes in neonates undergoing cardiopulmonary bypass. *Anesthesia and Analgesia*, *120*(2), 405-410. https://doi.org/10.1213/ANE.0000000000000531
20. Hasegawa, T., Oshima, Y., Maruo, A., Matsuhisa, H., Tanaka, A., Noda, R., Yokoyama, S., & Iwasaki, K. (2014). Intraoperative tranexamic acid in pediatric bloodless cardiac surgery. *Asian Cardiovascular & Thoracic Annals*, *22*(9), 1039-1045. https://doi.org/10.1177/0218492314527991
21. Hatami, F., Valizadeh, N., Salehi, F., & Hosseinzadeh Maleki, M. (2020). Topical versus low-dose systemic tranexamic acid in pediatric cardiac surgery: A randomized clinical study. *Journal of Cardiac Surgery*, *35*(12), 3368-3373. https://doi.org/10.1111/jocs.15082
22. Ivasyk, I., Chatterjee, A., Jordan, C., Geiselmann, M. T., Chang, P. S., Kamel, H., & Khormaee, S. (2022). Evaluation of the safety of tranexamic acid use in pediatric patients undergoing spinal fusion surgery: a retrospective comparative cohort study. *BMC Musculoskeletal Disorders*, *23*(1), 651. https://doi.org/10.1186/s12891-022-05604-2
23. Kratzer, S., Irl, H., Mattusch, C., Bürge, M., Kurz, J., Kochs, E., Eder, M., Rammes, G., & Haseneder, R. (2014). Tranexamic acid impairs γ-aminobutyric acid receptor type A-mediated synaptic transmission in the murine amygdala: a potential mechanism for drug-induced seizures? *Anesthesiology*, *120*(3), 639-649. https://doi.org/10.1097/aln.0000000000000103
24. Lecker, I., Wang, D. S., Romaschin, A. D., Peterson, M., Mazer, C. D., & Orser, B. A. (2012). Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest*, *122*(12), 4654-4666. https://doi.org/10.1172/jci63375
25. Leyvi, G., Nelson, O., Yedlin, A., Pasamba, M., Belamarich, P. F., Nair, S., & Cohen, H. W. (2011). A comparison of the effect of aprotinin and epsilon-aminocaproic acid on renal function in children undergoing cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, *25*(3), 402-406. https://doi.org/10.1053/j.jvca.2011.01.015
26. Lin, C. Y., Shuhaiber, J. H., Loyola, H., Liu, H., Del Nido, P., DiNardo, J. A., & Pigula, F. A. (2015). The safety and efficacy of antifibrinolytic therapy in neonatal cardiac surgery. *PloS One*, *10*(5), e0126514. https://doi.org/10.1371/journal.pone.0126514
27. Liu, C. W., Anih, J., Lebedeva, V., Gungor, A., Wang, C., Park, L., & Roshanov, P. S. (2024). Kidney disease in trials of perioperative tranexamic acid. *Journal of Clinical Anesthesia*, *94*, 111417. https://doi.org/10.1016/j.jclinane.2024.111417
28. Madathil, T., Balachandran, R., Kottayil, B. P., Sundaram, K. R., & Nair, S. G. (2021). Comparison of efficacy of two different doses of tranexamic acid in prevention of post operative blood loss in patients with congenital cyanotic heart disease undergoing cardiac surgery. *Annals of Cardiac Anaesthesia*, *24*(3), 339-344. https://doi.org/10.4103/aca.ACA_162_20
29. Maeda, T., Sasabuchi, Y., Matsui, H., Ohnishi, Y., Miyata, S., & Yasunaga, H. (2017). Safety of Tranexamic Acid in Pediatric Cardiac Surgery: A Nationwide Database Study. *Journal of Cardiothoracic and Vascular Anesthesia*, *31*(2), 549-553. https://doi.org/10.1053/j.jvca.2016.10.001
30. Martin, K., Breuer, T., Gertler, R., Hapfelmeier, A., Schreiber, C., Lange, R., Hess, J., & Wiesner, G. (2011a). Tranexamic acid versus ε-aminocaproic acid: efficacy and safety in paediatric cardiac surgery. *Eur J Cardiothorac Surg*, *39*(6), 892-897. https://doi.org/10.1016/j.ejcts.2010.09.041
31. Martin, K., Breuer, T., Gertler, R., Hapfelmeier, A., Schreiber, C., Lange, R., Hess, J., & Wiesner, G. (2011b). Tranexamic acid versus varepsilon-aminocaproic acid: efficacy and safety in paediatric cardiac surgery. *European Journal of Cardio-Thoracic Surgery*, *39*(6), 892-897. https://doi.org/10.1016/j.ejcts.2010.09.041

32. Moynihan, K. M., Ryerson, L. M., Le, J., Nicol, K., Watt, K., Gadepalli, S. K., Alexander, P. M. A., Muszynski, J. A., Gehred, A., Lyman, E., Steiner, M. E., Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE, i. c. w. t. P. C. C. B. R. N., Pediatric Acute Lung, I., Sepsis Investigators, N., the Pediatric, E. s. o. P., & the Extracorporeal Life Support, O. (2024). Antifibrinolytic and Adjunct Hemostatic Agents: The Pediatric Extracorporeal Membrane Oxygenation Anticoagulation CollaborativE Consensus Conference. *Pediatric Critical Care Medicine*, *25*(7 Suppl 1), e44-e52. https://doi.org/10.1097/PCC.0000000000003491
33. Mueller, X. M., Tinguely, F., Tevaearai, H. T., Ravussin, P., Stumpe, F., & von Segesser, L. K. (2000). Impact of duration of chest tube drainage on pain after cardiac surgery. *European Journal of Cardio-Thoracic Surgery*, *18*(5), 570-574. https://doi.org/10.1016/s1010-7940(00)00515-7
34. Murao, S., Nakata, H., Roberts, I., & Yamakawa, K. (2021). Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. *Critical Care (London, England)*, *25*(1), 380. https://doi.org/10.1186/s13054-021-03799-9
35. Murkin, J. M., Falter, F., Granton, J., Young, B., Burt, C., & Chu, M. (2010). High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesthesia and Analgesia*, *110*(2), 350-353. https://doi.org/10.1213/ANE.0b013e3181c92b23
36. Muthialu, N., Balakrishnan, S., Sundar, R., & Muralidharan, S. (2015). Efficacy of tranexamic acid as compared to aprotinin in open heart surgery in children. *Annals of Cardiac Anaesthesia*, *18*(1), 23-26. https://doi.org/10.4103/0971-9784.148316
37. Nishida, T., Kinoshita, T., & Yamakawa, K. (2017). Tranexamic acid and trauma-induced coagulopathy. *J Intensive Care*, *5*, 5. https://doi.org/10.1186/s40560-016-0201-0
38. Pasquali, S. K., Li, J. S., He, X., Jacobs, M. L., O'Brien, S. M., Hall, M., Jaquiss, R. D., Welke, K. F., Peterson, E. D., Shah, S. S., & Jacobs, J. P. (2012). Comparative analysis of antifibrinolytic medications in pediatric heart surgery. *Journal of Thoracic and Cardiovascular Surgery*, *143*(3), 550-557. https://doi.org/10.1016/j.jtcvs.2011.06.048
39. Patel, J., Prajapati, M., Patel, H., Gandhi, H., Deodhar, S., & Pandya, H. (2017). Topical and low-dose intravenous tranexamic acid in cyanotic cardiac surgery. *Asian Cardiovascular & Thoracic Annals*, *25*(2), 118-122. https://doi.org/10.1177/0218492316688416
40. Pouard, P. (2008). Blood Conservation in Pediatric Cardiac Surgery. *Transfusion Alternatives in Transfusion Medicine*, *7*(1), 58-62. https://doi.org/10.1111/j.1778-428X.2005.tb00155.x
41. Radhakrishnan, V., & Mehra, N. (2020). Tranexamic acid-induced acute renal failure in a pediatric patient with acute myeloid leukemia: A cautionary note. *Cancer Research, Statistics, and Treatment*, *3*(3). https://doi.org/10.4103/crst.Crst_158_20
42. Reid, R. W., Zimmerman, A. A., Laussen, P. C., Mayer, J. E., Gorlin, J. B., & Burrows, F. A. (1997). The efficacy of tranexamic acid versus placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. *Anesthesia and Analgesia*, *84*(5), 990-996. https://doi.org/10.1097/00000539-199705000-00008
43. Schertz, K., Karam, O., Demetres, M., Mayadunna, S., Faraoni, D., & Nellis, M. E. (2022). Prophylactic Use of Antifibrinolytics During Pediatric Cardiac Surgery With Cardiopulmonary Bypass on Postoperative Bleeding and Transfusion: A Systematic Review and Meta-Analysis. *Pediatric Critical Care Medicine*, *23*(11), e517-e529. https://doi.org/10.1097/PCC.0000000000003049
44. Schindler, E., Photiadis, J., Sinzobahamvya, N., Dores, A., Asfour, B., & Hraska, V. (2011). Tranexamic acid: an alternative to aprotinin as antifibrinolytic therapy in pediatric congenital heart surgery. *European Journal of Cardio-Thoracic Surgery*, *39*(4), 495-499. https://doi.org/10.1016/j.ejcts.2010.07.026
45. Siemens, K., Sangaran, D. P., Hunt, B. J., Murdoch, I. A., & Tibby, S. M. (2018). Strategies for Prevention and Management of Bleeding Following Pediatric Cardiac Surgery on Cardiopulmonary Bypass: A Scoping Review. *Pediatric Critical Care Medicine*, *19*(1), 40-47. https://doi.org/10.1097/PCC.0000000000001387
46. Suieubekov, B., Sepbayeva, A., Yeshmanova, A., & Kusainov, A. (2023). Cardiac surgery-associated acute kidney injury in newborns: A meta-analysis. *Electronic Journal of General Medicine*, *20*(2). https://doi.org/10.29333/ejgm/12805
47. Szarpak, L., Pruc, M., Dziedzic, K., & Perek, B. (2024). Systematic review and meta-analysis of tranexamic acid and epsilon aminocaproic acid in pediatric heart surgery. *Kardiochir Torakochirurgia Pol*, *21*(2), 126-128. https://doi.org/10.5114/kitp.2024.141154
48. Taam, J., Yang, Q. J., Pang, K. S., Karanicolas, P., Choi, S., Wasowicz, M., & Jerath, A. (2020). Current Evidence and Future Directions of Tranexamic Acid Use, Efficacy, and Dosing for Major Surgical Procedures. *Journal of Cardiothoracic and Vascular Anesthesia*, *34*(3), 782-790. https://doi.org/10.1053/j.jvca.2019.06.042
49. Tibi, P., McClure, R. S., Huang, J., Baker, R. A., Fitzgerald, D., Mazer, C. D., Stone, M., Chu, D., Stammers, A. H., Dickinson, T., Shore-Lesserson, L., Ferraris, V., Firestone, S., Kissoon, K., & Moffatt-Bruce, S. (2021). STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management. *Annals of Thoracic Surgery*, *112*(3), 981-1004. https://doi.org/10.1016/j.athoracsur.2021.03.033
50. Turaga, A. H. (2023). The Optimal Dosing and Timing of Tranexamic Acid in Reducing Perioperative Bleeding and Transfusion Requirements in Vascular Surgery Patients: A Systematic Review. *Cureus*, *15*(8), e43947. https://doi.org/10.7759/cureus.43947

51. Wesley, M. C., Pereira, L. M., Scharp, L. A., Emani, S. M., McGowan, F. X., Jr., & DiNardo, J. A. (2015). Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. *Anesthesiology*, *122*(4), 746-758. https://doi.org/10.1097/ALN.0000000000000570
52. Willems, A., De Groote, F., Dumoulin, M., Fils, J. F., & Van der Linden, P. (2019). Aprotinin versus tranexamic acid in children undergoing cardiac surgery: an observational study. *European Journal of Cardio-Thoracic Surgery*, *56*(4), 688-695. https://doi.org/10.1093/ejcts/ezz088
53. Zhang, Y., Gao, X., Yuan, S., Guo, J., Lv, H., Zhou, Y., Wang, Y., Ji, H., Wang, G., Li, L., & Shi, J. (2018). Effects of tranexamic acid on short-term and long-term outcomes of on-pump coronary artery bypass grafting: Randomized trial and 7-year follow-up. *Cardiovascular Therapeutics*, *36*(6), e12472. https://doi.org/10.1111/1755-5922.12472
54. Zhang, Y., Jia, Y., Shi, J., Yuan, S., Wang, R., Zhang, Z., Wang, X., Liu, J., Ran, J., Zhao, Y., Hua, Z., Yan, J., Li, S., Zheng, Z., Hu, S., Wang, Y., & Yan, F. (2019). Safety and efficacy of tranexamic acid in paediatric cardiac surgery: study protocol for a double-blind randomised controlled trial. *BMJ Open*, *9*(11), e032642. https://doi.org/10.1136/bmjopen-2019-032642
55. Zhang, Y., Zhang, X., Wang, Y., Shi, J., Yuan, S., Duan, F., Wang, Y., Zhang, Z., Jia, Y., Gong, J., Li, L., & Yan, F. (2019). Efficacy and Safety of Tranexamic Acid in Pediatric Patients Undergoing Cardiac Surgery: A Single-Center Experience. *Front Pediatr*, *7*, 181. https://doi.org/10.3389/fped.2019.00181
56. Zonis, Z., Seear, M., Reichert, C., Sett, S., & Allen, C. (1996). The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *Journal of Thoracic and Cardiovascular Surgery*, *111*(5), 982-987. https://doi.org/10.1016/s0022-5223(96)70374-4
57. Zou, Z. Y., He, L. X., & Yao, Y. T. (2022). Tranexamic acid reduces postoperative blood loss in Chinese pediatric patients undergoing cardiac surgery: A PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)*, *101*(9), e28966. https://doi.org/10.1097/MD.0000000000028966