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REVIEW ARTICLE

Current Guidelines and Considerations on the Use of Tranexamic Acid (TXA) in Pediatric and Obstetric Trauma: A Review

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ABSTRACT

Tranexamic acid (TXA), an antifibrinolytic agent, has shown significant promise in reducing hemorrhage-related morbidity and mortality, particularly in adult trauma and postpartum hemorrhage. However, its role in pediatric and obstetric trauma remains less clearly defined due to limited high-quality evidence and the unique physiological characteristics of these populations. This review examines current guidelines, clinical trials, and observational data supporting tranexamic acid use in pediatric and obstetric trauma settings. In pediatric trauma, studies like Pediatric Trauma and Tranexamic Acid Study (PED-TRAX) and Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC) suggest potential mortality benefits with low thromboembolic risk, although data are primarily observational and dosing strategies remain inconsistent. In obstetric trauma, robust evidence—especially from the World Maternal Antifibrinolytic (WOMAN) Trial—supports early tranexamic acid administration for postpartum hemorrhage, leading to international guideline endorsements. Despite these advancements, concerns persist regarding optimal dosing, long-term safety, fetal outcomes, and real-world implementation. Addressing these gaps through pediatric- and obstetric-specific randomized trials, standardized protocols, and system-level interventions is essential to optimizing the safe and effective use of tranexamic acid in these vulnerable populations.

1. Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent that has gained significant attention for its role in reducing bleeding and transfusion requirements in various clinical settings, including pediatric and obstetric trauma. Originally directed for hemophilia blood disorders or heavy menstrual bleeding, its use has been expanded with the application in trauma settings, surgery, or obstetrics care. The potential of TXA to lower mortality and transfusion needs in pediatric and obstetric trauma, two populations with distinct physiological considerations and frequently sparse evidence-based guidelines, has drawn a lot of attention.[1-2]

For instance, the Pediatric Trauma and Tranexamic Acid Study (PED-TRAX) found that TXA administration was independently associated with decreased mortality in pediatric trauma patients, without a significant increase in thromboembolic complications.[3] Additionally, the Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC) confirmed the feasibility of conducting large-scale trials to evaluate TXA's efficacy in severely injured children.[4]

In obstetric trauma, TXA has been shown to reduce maternal mortality due to postpartum hemorrhage. The American College of Obstetricians and Gynecologists, along with the Society for Maternal-Fetal Medicine, recommend the use of TXA in cases of postpartum hemorrhage, with a dose of 1 g intravenously within 3 hours of birth.[5] This recommendation is based on evidence from large, multicenter, international randomized clinical trials demonstrating the efficacy and safety of TXA in this context.[5] Furthermore, a systematic review highlighted the efficacy and safety of antifibrinolytic drugs, including TXA, in pediatric surgery, suggesting TXA as the drug of choice based on its level of evidence and safety profile.[6]

The optimal dosing regimen for TXA in pediatric trauma remains an area of ongoing research. Current recommendations suggest a loading dose of 10 to 30 mg/kg followed by a maintenance infusion of 5 to 10 mg/kg/h.[5] In obstetric settings, a dose of 1 g intravenously is recommended, with a second dose if bleeding persists.[3] A recent study proposed an optimal dose of 600 mg for future TXA efficacy studies to prevent postpartum hemorrhage.[8]

Overall, the use of TXA in pediatric and obstetric trauma is supported by evidence indicating its efficacy in reducing bleeding and improving survival outcomes. Nonetheless, some gaps remain in terms of it's safety and specific population dosing. The objectives of this review are to highlight current debates and research directions in the use of TXA for pediatric and obstetric trauma, as well as to summarize current guidelines and examine important clinical studies.

2. Tranexamic acid mechanism of action:

Tranexamic acid is a synthetic derivative of the amino acid lysine, which functions as an antifibrinolytic agent by inhibiting the activation of plasminogen to plasmin, the enzyme responsible for fibrin degradation. Tranexamic acid binds to the lysine-binding sites on plasminogen, preventing its conversion to plasmin and thereby stabilizing the fibrin matrix and reducing fibrinolysis and bleeding.[9-11]

The antifibrinolytic effects of TXA are mediated through reversible interactions at multiple binding sites within plasminogen. Native human plasminogen contains several lysine binding sites with varying affinities for TXA. The high-affinity lysine site is crucial for plasminogen binding to fibrin, and TXA's saturation of this site displaces plasminogen from the fibrin surface, inhibiting fibrinolysis.[11]

Tranexamic acid 's efficacy in trauma extends beyond its antifibrinolytic properties. It has been reported to suppress post-traumatic inflammation and edema, protect endothelial and epithelial monolayers, and stimulate mitochondrial respiration. Early administration of TXA is crucial, as delayed administration (beyond 3 hours post-injury) may increase the risk of death.[9-10, 12]

3a. Current Guidelines of the use of Tranexamic acid in Pediatric Trauma:

Current clinical guidelines regarding the use of TXA in pediatric trauma remain limited. The Advanced Trauma Life Support (ATLS) program does not provide specific recommendations for pediatric patients, as its focus is primarily on adult trauma care. Similarly, the Eastern Association for the Surgery of Trauma (EAST) does not specifically support TXA use in pediatric trauma. Its guidelines address adult populations, recommending TXA as a hemostatic adjunct in severely injured adult trauma patients when administered within three hours of injury to maximize efficacy and reduce mortality. [13]

On the other hand, TXA is recommended for use in pediatric trauma by the American College of Surgeons–Pediatric Trauma Society (ACS-PTS). This is supported by data from studies like the Pediatric Trauma and Tranexamic Acid Study (PED-TRAX), which showed a favorable safety profile and a decrease in mortality without a discernible rise in thromboembolic complications.[3] Recent evidence supports an intravenous loading dose of 15 mg/kg given over 10 minutes and a maintenance infusion of 2 mg/kg/h over 8. The Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC), which validated the safety and viability of administering TXA to childhood patients with severe injuries, supports this dosage approach.[3]

The American College of Surgeons–Pediatric Trauma Society endorses the use of TXA in pediatric trauma based on clinical evidence, despite the fact that ATLS and EAST do not offer pediatric-specific recommendations. Although more research is required to improve these recommendations and create firm, pediatric-specific guidelines, a standardized dosing regimen is becoming more and more popular.

3b. Current Guidelines of the use of Tranexamic acid in Obstetric Trauma:

Obstetric and maternal health organizations' recommendations offer the strongest evidence base for the use of TXA in this population, despite the fact that

specific trauma guidelines for pregnant patients are still in development, with organizations like ATLS and EAST concentrating primarily on general adult trauma care.[13] Based on data from pivotal studies like the World Maternal Antifibrinolytic (WOMAN) trial, which demonstrated a significant reduction in bleeding-related mortality when TXA was administered within three hours of the onset of postpartum hemorrhage, the ACS-PTS supports the administration of TXA in obstetric trauma.[15]

Tranexamic acid is also a part of the World Health Organization's (WHO) standard PPH treatment regimen. According to their guidelines, if bleeding persists after 30 minutes or recurs within 24 hours, a second dose of 1 gram should be administered intravenously as soon as possible after the bleeding starts. [16] Expert consensus and data from clinical trials have led to the widespread adoption of this dosage schedule.[15-16] Apart from the WOMAN trial, Ker et al.'s systematic review and meta-analysis came to the conclusion that TXA lowers the risk of potentially fatal postpartum hemorrhage without raising the risk of thromboembolic complications.[13] Furthermore, prophylactic TXA may not significantly reduce blood loss ≥500 mL or ≥1000 mL following vaginal birth, according to a Cochrane review by Rohwer et al., but it reduces the need for extra uterotonics in women without anemia and lowers the risk of serious morbidity.[17]

In the context of pregnancy, there is a paucity of trauma-specific randomized data; however, extrapolation from obstetric hemorrhage guidelines and general trauma data has informed current practice. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have issued recommendations supporting the use of TXA in the management of obstetric hemorrhage, particularly postpartum hemorrhage, which remains a leading cause of maternal mortality worldwide.[1] These recommendations are based on robust evidence, including findings from the WOMAN trial, which demonstrated that TXA administration reduces mortality due to bleeding in women with postpartum hemorrhage.

Importantly, current recommendations emphasize individualized clinical judgment when considering TXA administration in pregnant trauma patients. The decision to use TXA should weigh the maternal benefits of reduced hemorrhage and mortality against the potential fetal risks, which are not well defined due to limited data in this population. Nevertheless, no teratogenic effects or adverse fetal outcomes directly attributable to TXA have been conclusively demonstrated in the available literature.

4. Adverse effects and safety considerations:

The safety profile of tranexamic acid in pediatric trauma patients has been well-supported by studies such as the PED-TRAX trial and systematic reviews. The PED-TRAX study and subsequent trials have consistently reported that TXA is well tolerated in pediatric trauma patients. Moreover, studies evaluating perioperative TXA use in children have corroborated these findings, further supporting its safety profile. [3, 6-7]

Specific side effects of TXA in pregnant trauma patients are not extensively documented in the literature, primarily due to the lack of large-scale, trauma-specific studies in this population. However, potential adverse effects can be extrapolated from broader data derived from the general trauma population, as well as from the use of TXA in obstetric hemorrhage management and perioperative settings.

One of the primary concerns associated with TXA use is the potential for thromboembolic events. As an antifibrinolytic agent, TXA inhibits fibrinolysis and stabilizes clot formation, raising theoretical concerns regarding an increased risk of venous thromboembolism (VTE), arterial thrombosis, or disseminated intravascular coagulation (DIC). Nevertheless, large randomized controlled trials such as the CRASH-2 trial and the WOMAN trial have not demonstrated a statistically significant increase in thromboembolic events when TXA is administered within the recommended time frame and dosing parameters.[15, 18] Despite these reassuring findings, caution is warranted in pregnant trauma patients, as pregnancy itself is a hypercoagulable state, and the additive risk of thromboembolism with TXA use cannot be entirely excluded.

Gastrointestinal symptoms are among the most commonly reported side effects associated with TXA administration. These typically include mild and transient symptoms such as nausea, vomiting, and diarrhea, which may be attributed to the drug's systemic effects and are generally self-limited.[19] A less frequent but noteworthy adverse effect of TXA is the occurrence of seizure, particularly at higher doses or with prolonged use. Although seizures are rarely reported with standard dosing regimens, the risk may increase in patients receiving higher cumulative doses or those with underlying neurological risk factors.[19]

Renal complications, specifically renal cortical necrosis, have been reported in isolated cases associated with TXA administration. This adverse event is rare and has primarily been linked to high-dose TXA use, exceeding current dosing recommendations. The exact pathophysiological mechanism remains unclear but may involve intravascular coagulation and microthrombi formation in the renal vasculature.[20]

Another important consideration in pregnant trauma patients is the potential impact of TXA on fetal and neonatal outcomes. Tranexamic acid readily crosses the placental barrier; however, current data do not suggest teratogenicity. Nonetheless, observational studies have reported neonatal complications, including low Apgar scores, neonatal sepsis, and low birth weight, following TXA administration. These outcomes may be multifactorial, reflecting the severity of maternal hemorrhage and trauma rather than a direct causal relationship with TXA. However, the potential association underscores the need for careful risk-benefit assessment when considering TXA use in pregnant trauma patients.[21]

In summary, while TXA is generally well tolerated and has been shown to improve survival in trauma and obstetric

hemorrhage without a significant increase in thromboembolic risk, its use in pregnant trauma patients necessitates caution. Potential adverse effects include thromboembolic events, gastrointestinal symptoms, seizures, and rare renal complications. Additionally, consideration of fetal and neonatal outcomes is essential. A thorough risk-benefit evaluation should guide the decision to administer TXA in this population, and further research is warranted to establish the safety profile of TXA specifically in pregnant trauma patients.[19, 21]

5a. Key trials and observational studies on the use of Tranexamic acid TXA in pediatric trauma

Several studies have examined the use of TXA in pediatric trauma patients, with varying findings depending on the context. The PED-TRAX study, a retrospective review conducted in a combat setting, reported that TXA administration was associated with decreased mortality and did not result in a significant increase in thromboembolic complications.[3] In contrast, a systematic review and meta-analysis by Kornelsen et al. found that TXA use did not significantly improve overall survival in pediatric trauma patients, except in combat environments, where a survival benefit was observed.[22] Similarly, a study based on the Israeli Defense Forces registry by Gendler et al. found no significant association between prehospital TXA administration and reduced mortality among pediatric trauma patients.[23] Lastly, the TIC-TOC pilot randomized trial by Nishijima et al. demonstrated the feasibility of conducting a larger trial to evaluate TXA in this population, though it did not reveal significant differences in clinical outcomes in its preliminary phase. [4]

However, current research on TXA in pediatric trauma is limited by several methodological and contextual factors. The majority of existing studies are retrospective and observational in nature, which restricts the ability to draw causal inferences.[3, 23-24] Additionally, many investigations are conducted in specific settings, such as combat zones, which limits the generalizability of their findings to civilian trauma populations.[3, 23] Another significant gap in the literature is the lack of consensus on the optimal dosing and timing of TXA administration in pediatric trauma, highlighting the need for further pharmacologic and clinical research.[4, 25] Finally, while pilot studies have demonstrated the feasibility of conducting trials in this area, there remains a critical need for large-scale randomized controlled trials to establish definitive evidence regarding the efficacy and safety of TXA in the pediatric trauma population.[4, 25]

5b. Key trials and observational studies on the use of Tranexamic acid in obstetric trauma

The WOMAN Trial is a pivotal study in the use of TXA for obstetric trauma, specifically postpartum hemorrhage (PPH). This large, randomized controlled trial demonstrated that TXA significantly reduced the risk of death due to bleeding when administered within 3 hours of delivery, without increasing the risk of thromboembolic events.[15]

In trauma settings, the CRASH-2 Trial is a key study that evaluated TXA in bleeding trauma patients. This trial showed that TXA reduced all-cause mortality and death due to bleeding when administered within 3 hours of injury. The CRASH-3 Trial extended these findings to patients with traumatic brain injury, showing a reduction in head injury-related deaths. [22-23]

Extrapolation to Trauma: The efficacy of TXA in reducing mortality in trauma patients, as demonstrated in the CRASH trials, supports its use in obstetric trauma where hemorrhage is a critical concern. The pharmacological rationale is similar, given TXA's antifibrinolytic properties.

Registries and Observational Studies: The MATTERs and MATTERs II studies, conducted in military settings, also support the use of TXA in trauma, showing reduced mortality in patients receiving TXA. The PATCH-Trauma trial evaluated prehospital TXA administration and found no significant difference in functional outcomes at 6 months, highlighting the need for further research in advanced trauma systems.[25]

FETAL OUTCOMES

Evidence regarding fetal outcomes with maternal TXA use in trauma is very limited, as no trial has tracked fetal status in detail. The primary fetal concern is whether TXA or prolonged maternal hypercoagulability could compromise placental circulation. TXA does cross the placenta to some extent, but it is classified as FDA pregnancy category B, which means no known teratogenic effects in animal studies or human case reports.[26] In the context of trauma, the most significant threats to the fetus are maternal shock and placental abruption from the injury itself, rather than TXA.[27] None of the included studies documented any adverse fetal effects directly linked to TXA. In fact, prompt TXA use to control maternal hemorrhage would be expected to improve fetal outcomes indirectly by stabilizing maternal hemodynamics and maintaining uteroplacental perfusion.

A 2023 systematic review on pregnant trauma management recommended that TXA be given to hemorrhaging pregnant trauma patients as part of maternal resuscitation; this implies that the potential benefit to both mother and fetus (through improved maternal survival) outweighs any theoretical fetal risk.[28] Some case studies have noted successful fetal deliveries after maternal TXA use in trauma resuscitation, though these are anecdotal. Placental abruption is a common consequence of blunt trauma; while TXA will not reattach the placenta, it may reduce maternal bleeding from the uterine wound. Fetal mortality in trauma is largely driven by the severity of maternal injury (e.g. anoxic brain injury or exsanguination) and by abruption. By preventing maternal exsanguination, TXA could reduce secondary fetal loss. No increase in miscarriage, stillbirth, or congenital anomalies has been reported with TXA use during pregnancy in the trauma or obstetric literature to date. Overall, TXA is considered safe for the fetus in trauma settings, and ongoing fetal monitoring and usual trauma obstetric care (e.g. continuous fetal heart rate monitoring in viable pregnancies, urgent delivery if needed) remain paramount.[27] High-quality data on long-term fetal outcomes (neurodevelopment, etc.) after in

utero TXA exposure are lacking, so this remains an area for further study.

Many studies investigating the use of TXA in trauma are retrospective or observational in design, which limits the ability to establish causal relationships. Furthermore, findings derived from combat settings may not be fully generalizable to civilian trauma populations due to differences in injury patterns, resources, and clinical contexts. A critical gap in the current literature involves the lack of clarity surrounding the optimal dosing and timing of TXA administration across diverse trauma scenarios, underscoring the need for further targeted research. Overall, although TXA has demonstrated benefits in both obstetric and general trauma care, continued investigation is essential to overcome existing limitations and optimize its clinical application.

6. Clinical considerations and controversies surrounding the use of Tranexamic acid in trauma

The use of TXA in pediatric and obstetric trauma presents several clinical and ethical challenges that require further investigation. One major area of uncertainty is the optimal dosing regimen for pediatric patients. The TIC-TOC trial examined weight-based dosing strategies—such as a 15 mg/kg bolus followed by a 2 mg/kg/h infusion versus a higher 30 mg/kg bolus with a 4 mg/kg/h infusion—though age-based dosing has not been adequately studied, and weight-based dosing is generally preferred due to variability in pharmacokinetics. [4,14, 29] Despite these dosing uncertainties, the risk of thromboembolic events in pediatric trauma patients receiving TXA appears to be low; meta-analyses and observational studies have not demonstrated a significant increase in thromboembolic complications.[3, 22]

TXA has also been evaluated in a range of trauma contexts, including both polytrauma and isolated bleeding. The PED-TRAX study suggested a benefit in polytrauma scenarios, particularly in combat settings, while the efficacy of TXA in isolated bleeding remains less clear and warrants further investigation. [3] Additionally, trauma-induced coagulopathy in children differs markedly from that seen in pregnant patients. Pediatric patients exhibit diverse fibrinolytic phenotypes—such as hyperfibrinolysis, physiologic fibrinolysis, and fibrinolytic shutdown—that may influence TXA's effectiveness, whereas pregnant individuals, as evidenced in the WOMAN trial, benefit from TXA due to distinct coagulopathy mechanisms related to postpartum hemorrhage.[2] Ethical considerations also arise in the administration of TXA to vulnerable populations such as children and pregnant patients. The TIC-TOC trial addressed these issues by employing federal exception from informed consent (EFIC) procedures.[4, 14] Finally, a significant limitation in the existing literature is the lack of large-scale randomized controlled trials (RCTs) evaluating TXA in pediatric and obstetric trauma. Much of the current evidence is derived from retrospective studies and pilot trials, underscoring the need for robust RCTs to establish definitive conclusions regarding safety and efficacy.[2, 4, 22]

Extrapolating Data from Adult Studies: Extrapolation from adult studies, such as CRASH-2 and CRASH-3, is problematic due to differences in physiology and coagulopathy between adults and children. Pediatric-specific trials are essential to determine appropriate dosing and efficacy.[2,4,22] While TXA shows promise in pediatric and obstetric trauma, significant challenges and controversies remain, particularly regarding dosing, thromboembolic risks, and the need for pediatric-specific RCTs.

7. Future Directions and research needs

Although the use of TXA has been well established in adult trauma and postpartum hemorrhage, its role in pediatric and obstetric trauma remains insufficiently defined. One of the most pressing needs is the development of pediatric-specific randomized controlled trials (RCTs), as current recommendations for TXA use in children are primarily extrapolated from adult studies, which may not accurately reflect the unique physiological and coagulopathic profiles of pediatric patients. Similarly, in the obstetric population, while TXA has demonstrated efficacy in postpartum hemorrhage, there is a lack of high-quality data evaluating its use in the setting of obstetric trauma. The creation of obstetric trauma registries would allow for the systematic collection of data regarding maternal and fetal outcomes, dosing practices, and potential adverse effects, thereby contributing to the development of evidence-based guidelines.

In both pediatric and obstetric trauma, there is also a clear need for standardized dosing protocols. Currently, dosing strategies vary widely, particularly in pediatric patients where weight-based dosing is utilized without universal consensus. In pregnant patients, the physiological changes of pregnancy—including increased plasma volume and altered renal clearance—further complicate the determination of optimal dosing regimens. Establishing consistent, validated dosing protocols would enhance the safety and efficacy of TXA administration in these vulnerable populations.

Another critical consideration is the long-term safety of TXA use. Although generally regarded as safe, concerns persist regarding thromboembolic events, particularly in populations at increased baseline risk, such as pregnant patients. Longitudinal studies evaluating the incidence of venous thromboembolism, seizures, and other adverse outcomes following TXA administration in pediatric and obstetric trauma patients are warranted. Additionally, implementing robust safety monitoring and pharmacovigilance systems within trauma care networks would facilitate early detection of potential complications.

Finally, addressing the real-world barriers to TXA implementation in trauma systems is essential. Despite guideline recommendations, TXA use remains inconsistent, often limited by a lack of awareness among healthcare providers, logistical challenges in resource-limited settings, and medico-legal concerns, particularly in obstetric trauma. Future research should focus on identifying and mitigating these barriers through system-level interventions, including protocol-driven

administration, education and simulation training, and the integration of decision-support tools. By addressing these knowledge gaps and implementation challenges, future efforts can improve the safe and effective use of TXA in pediatric and obstetric trauma care.

8. Conclusion

Tranexamic acid has emerged as a potentially life-saving intervention in pediatric and obstetric trauma, demonstrating efficacy in reducing hemorrhage and improving survival. Yet, its application in these populations remains inconsistent and under-researched. There is a critical need for pediatric- and obstetric-specific randomized controlled trials to establish clear, evidence-based guidelines. Furthermore, consistent dosing protocols, robust safety data, and real-world implementation strategies are necessary to translate promising findings into standard practice. Bridging these knowledge gaps will be essential to optimize trauma care for some of the most vulnerable patient populations—children and pregnant women.

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