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Pharmacology of Tranexamic Acid: Mechanisms and Applications in Modern Medicine

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Abstract

Tranexamic acid (TXA) is a synthetic lysine-analogue antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin, preventing the dissolution and degradation of fibrin clots. TXA has demonstrated efficacy in reducing blood loss and transfusion requirements across various clinical contexts, including cardiac surgery, trauma, liver surgery, and orthopedic procedures. In cardiac surgery, TXA inhibits plasmin-induced platelet activation during cardiopulmonary bypass, attenuates the inflammatory response, and interacts beneficially with desmopressin. Robust evidence supports TXA use in trauma, with the CRASH-2 trial showing reduced all-cause mortality and death due to bleeding. In liver transplantation, TXA exhibits similar efficacy to aprotinin in reducing blood loss and transfusion needs. TXA is also effective in treating menorrhagia and reducing blood loss in obstetric and gynecological surgeries. Topical TXA application achieves lower plasma concentrations while maintaining effectiveness in reducing bleeding. Adverse effects include dose-dependent seizures, particularly in cardiac surgery, potentially due to TXA's inhibition of GABA and glycine receptors. Despite no definitive evidence of increased thromboembolic risk, judicious use is advised, especially with prothrombotic medications. Optimal dosing regimens and the impact on renal-impaired patients require further research. Ongoing trials, such as CRASH-3, WOMAN, and ATACUS, are expected to provide insights into TXA's role in improving morbidity and mortality across diverse clinical settings.

Keywords: Tranexamic acid (TXA), Pharmacology, Antifibrinolytic agent, Mechanism of action, Plasmin inhibition

Introduction

Blood loss and subsequent transfusion are strongly associated with significant morbidity and mortality. The administration of antifibrinolytic agents has demonstrated the ability to reduce blood loss in various clinical contexts, including cardiac surgery, trauma, liver surgery, solid organ transplantation, and some non-surgical conditions. Evidence supporting the efficacy of these agents has been accumulating for several years. The synthetic lysine analogue tranexamic acid (TXA, trans-4-aminomethylcyclohexane-1-carboxylic acid) and e-aminocaproic acid (e-ACA) were first patented by S. Okamoto (Ker & Roberts, 2014). Despite this progress, questions remain regarding TXA's broader clinical effects, including its potential anti-inflammatory response to cardiopulmonary bypass (CPB), the risk of thromboembolic events, neurologic adverse effects such as seizures,

and its overall impact on morbidity and mortality. These unresolved issues necessitate further clinical trials to evaluate TXA's safety and effectiveness across various medical settings. This review aims to guide acute care physicians in interpreting the existing clinical evidence on TXA, optimizing dosing regimens to minimize harm, and understanding its expanding range of applications.

Tranexamic acid (AMCA) is a potent antifibrinolytic drug, with its efficacy attributed to the trans-isomer. It blocks lysine-binding sites on plasminogen, preventing fibrin binding and activation by plasminogen activators. Administered orally or intravenously, AMCA is excreted via urine, distributes into tissues and fluids, and crosses the placenta. While it does not induce thrombogenesis, it delays fibrin deposit dissolution. AMCA is highly valuable for managing bleeding caused by systemic and local fibrinolysis.

Mechanisms of Action

TXA is a synthetic lysine-analogue antifibrinolytic that functions by competitively inhibiting the activation of plasminogen to plasmin. At higher concentrations, it acts non-competitively to block plasmin directly. Consequently, TXA prevents the dissolution and degradation of fibrin clots by plasmin. TXA's binding to plasminogen is six to ten times more potent than that of e-ACA. In animal models, TXA has been shown to enhance thrombus formation in a dose-dependent manner, a property in contrast to aprotinin, which inhibits thrombus formation.

Evidence from numerous studies demonstrates that TXA inhibits plasmin-induced platelet activation during extracorporeal circulation, such as CPB in cardiac surgery. Bleeding following CPB results from multiple factors, but fibrinolysis is one of the few that can be addressed pharmacologically. TXA reduces excessive bleeding after CPB through several mechanisms. First, plasmin-platelet interactions result in the selective release of ADP granules from platelets, triggered by platelet surface contact with the extracorporeal circuit. Soslau et al. observed that platelet dense-granule ADP content was higher in patients receiving pre-CPB TXA compared to those receiving TXA post-CPB, with a strong inverse relationship to blood loss. Their study estimated the EC50 (half-maximal effective concentration) of TXA for inhibiting plasmin-induced platelet aggregation during CPB to be ≤ 15 μg mL-1 in vitro, and they noted that thrombin-induced platelet activation was also inhibited by plasmin-TXA binding to platelet receptors. This suggests several mechanisms through which TXA preserves platelet function during CPB.

Second, TXA appears to attenuate the inflammatory response and related hemodynamic instability in CPB patients. Hyperfibrinolysis may play a significant role in this inflammatory response. In a randomized controlled trial (RCT) involving 50 CPB patients, TXA significantly reduced biochemical markers of the inflammatory response, including IL-6, fibrin degradation products, creatine kinase (CK), and plasminogen activator inhibitor. Patients treated with TXA experienced fewer inflammatory episodes, reduced vasoplegic shock, fewer hours of norepinephrine use (1.2 vs. 25.4 hours), and shorter durations of mechanical ventilation (6.5 vs. 12 hours) in intensive care units post-CPB. In a larger RCT, IL-6 levels correlated with temperature, D-dimer, troponin I, CK, and lactic acid after CPB. Post-CPB administration of TXA significantly reduced the relative risk (RR 2.5) of inflammatory response compared to pre-CPB administration alone.

Third, hyperfibrinolysis is a known contributor to trauma-related coagulopathy, with an estimated incidence of 15%. Tissue damage in trauma induces the release of tissue plasminogen activator due to ischemia and endothelial injury. Rapid identification of hyperfibrinolysis in trauma patients using point-of-care rotational thromboelastometry has revealed associations with greater INR derangements, lower fibrinogen levels, and higher mortality rates compared to physiologic fibrinolysis. The physiological rationale for TXA use in trauma is well-founded, though diagnosing hyperfibrinolysis is essential before initiating treatment.

Finally, TXA has a beneficial interaction with desmopressin. TXA abolishes the transient fibrinolytic activity of desmopressin, mediated by the release of tissue plasminogen activators. This interaction allows desmopressin to enhance platelet activation and significantly reduce postoperative blood loss and transfusion requirements.

Clinical Usage and Efficacy

The primary purpose of TXA is to minimize perioperative bleeding and transfusion requirements in both cardiac and non-cardiac surgeries. TXA provides clear benefits in terms of reducing morbidity, mortality, and economic costs. A recent meta-analysis of over 100 RCTs involving more than 10,000 surgical patients compared TXA with no TXA or placebo and demonstrated a 38% reduction in the probability of transfusion. Cumulative meta-analysis indicated that this evidence has been available for over a decade. Although the study observed fewer deaths in the TXA group (RR 0.61, 95% CI 0.38 to 0.98), this finding became less certain when restricted to trials with adequate concealment. Similarly, a Cochrane review evaluating antifibrinolytics' impact on blood loss and allogeneic blood transfusion found that TXA reduced blood transfusion rates by 39%, corresponding to an absolute risk reduction of 18%. However, TXA was not consistently associated with reduced mortality across all surgeries.

Cardiac Surgery

Following studies by Mangano et al. and Karkouti et al. the use of antifibrinolytics in cardiac surgery has shifted from aprotinin to TXA and e-ACA due to concerns over aprotinin's association with increased risks of

cardiovascular or cerebrovascular events, as well as renal dysfunction or failure. A propensity-score matched analysis of 10,870 high-risk cardiac surgery patients by Karkouti et al. found that aprotinin posed a higher risk of renal toxicity compared to TXA, potentially increasing mortality, despite both agents demonstrating similar hemostatic effectiveness. Similarly, in a 5-year follow-up study involving 4,374 patients undergoing CABG surgery, Mangano et al. reported higher mortality with aprotinin compared to controls, TXA, and e-ACA.

The BART trial (Blood Conservation Using Antifibrinolytics in a Randomized Trial) conducted by Fergusson et al. further cemented this shift by comparing aprotinin, TXA, and e-ACA in high-risk cardiac surgery patients. The 30-day mortality rate was 6% for the aprotinin group, compared to 3.9% for TXA (RR 1.55) and 4.0% for e-ACA (RR 1.52). Although aprotinin modestly reduced the risk of massive bleeding compared to the lysine analogues, these findings led to the withdrawal of aprotinin's approval by the FDA and Health Canada. Critics of the BART trial argued that aprotinin might have a more favorable benefit/risk profile in certain high-risk patient subgroups, a perspective supported by a propensity-score matched study involving 1,544 patients conducted by Karkouti et al.

The efficacy of tranexamic acid (TXA) compared to a control group in reducing blood loss and transfusion requirements during cardiac surgery has been documented for decades. Recent meta-analyses reinforce this understanding. Henry et al. reported a relative risk reduction in blood transfusion with TXA of 0.68, corresponding to an average of approximately 300 mL of blood conserved, while Ngaage et al. indicated an odds ratio of 0.53, saving around 298 mL of blood. Although comparisons between TXA and placebo demonstrated a reduction in reoperations due to blood loss, the reduction in reoperation numbers is more substantial with high-dose aprotinin. While TXA is approximately seven times more potent than epsilon-aminocaproic acid (e-ACA), both were comparable in terms of relative risk and actual blood loss volume in cardiac surgery. However, the aforementioned meta-analyses did not show a reduction in mortality risk with TXA use during cardiac surgery.

The high-dose TXA regimen described in the BART protocol—comprising a 30 mg/kg loading dose followed by a 16 mg/kg/h infusion during surgery, with an additional 2 mg/kg in the circuit—has been widely adopted in many cardiac surgical centers since the BART study was published (Dhir, 2013). Earlier dose-response studies in cardiac surgery conducted by Horrow et al. identified an optimal prophylactic loading dose of 10 mg/kg followed by a 1 mg/kg/h infusion. This conclusion was drawn from comparisons among six incremental loading doses ranging from 2.5 to 40 mg/kg and infusions from 0.25 to 4 mg/kg/h. Subsequent research, however, highlighted inconsistencies in plasma concentrations when the Horrow regimen was analyzed with the inclusion of circuit pharmacokinetics and patient renal function. A recent randomized controlled trial (RCT) compared the Horrow regimen with the higher-dose BART regimen in cardiac surgery patients (Sigaut et al., 2014), revealing that although high-dose TXA does not significantly reduce blood product transfusion incidence up to seven days postoperatively (63% for low dose vs. 60% for high dose), it is more effective in reducing transfusion volumes (2.5 vs. 4.1 units), blood loss (590 vs. 820 mL), and reoperation rates (2.5% vs. 6%). Subgroup analysis of high-risk patients receiving dual antiplatelet therapy or undergoing complex surgeries further supported the superiority of high-dose TXA in reducing transfusion incidence.

Patients undergoing cardiac surgery frequently receive aspirin and/or clopidogrel preoperatively. Evidence suggests that TXA partially mitigates platelet aggregation defects induced by arachidonic acid (aspirin) and ADP (clopidogrel), as detected by multiple electrode aggregometry. This aligns with findings of plasmin-induced platelet inhibition via redistribution and degradation of glycoprotein Ib and IIb/IIIa receptors.

Pediatric Cardiac and Non-Cardiac Surgery

The efficacy of TXA in major pediatric surgeries mirrors findings in adult populations. A meta-analysis of over 2,000 pediatric patients undergoing cardiac or scoliosis surgeries found no evidence of TXA's inferiority compared to aprotinin in reducing blood loss at 24 hours. TXA decreased blood loss by 11 mL/kg (95% CI: 9–13 mL/kg) and packed red cell transfusion by 4 mL/kg (95% CI: 2–7 mL/kg). In scoliosis surgeries, TXA reduced blood loss significantly by 682 mL (95% CI: 214–1,149 mL). An RCT involving pediatric cardiac surgery patients (n = 150) reported reduced blood loss at 24 hours but no significant change in blood transfusion volumes. Similarly, a retrospective study (n = 231) on pediatric cardiac surgery found TXA to significantly lower blood loss, intraoperative transfusion volumes, and 48-hour transfusion requirements, with fewer patients requiring transfusion (45/103 vs. 77/127, $P = 0.012$). Both studies noted no differences between cyanotic and acyanotic patient subgroups. A meta-analysis by Faraoni et al. identified heterogeneity in data from pediatric RCTs, with variability in transfusion policies, TXA regimens, and morbidity/mortality data. Nonetheless, among 848 analyzed patients, TXA use showed decreasing trends in transfusion of red cells, platelets, and fresh frozen plasma. Despite advances in pediatric pharmacokinetic studies (Goobie et al., 2013), the optimal TXA dose regimen for pediatric cardiac surgery remains undefined (Faraoni & Goobie, 2013). In vitro studies have shown lower plasma concentrations (~6.5 μg/mL vs. ~17 μg/mL) required to prevent hyperfibrinolysis in neonates compared to adults, guiding future trials on dosing and risk-benefit analysis.

Faraoni and Goobie's systematic review on antifibrinolytic use in pediatric non-cardiac surgery concluded that TXA effectively reduces blood loss and transfusion requirements in pediatric spine (mainly scoliosis correction)

and craniosynostosis surgeries(Faraoni & Goobie, 2014). An earlier Cochrane meta-analysis found that antifibrinolytics reduced blood loss by 426 mL and transfusion volumes by 327 mL in scoliosis surgery, though TXA-specific analysis was not conducted. Limited RCTs addressing TXA in pediatric scoliosis surgery leave its safety profile unresolved.

Basta et al. conducted a systematic review on antifibrinolytic use in major pediatric surgeries (cardiac, spinal, craniofacial) and found reductions in blood loss and transfusion volumes, especially in craniofacial surgery. Craniosynostosis, often requiring early surgical intervention, is associated with substantial blood loss. Two RCTs compared TXA with control in craniosynostosis surgery: Goobie et al. reported reduced blood loss by 54 mL/kg and transfusion volumes by 23 mL/kg, while Dadure et al. observed an 85% intraoperative transfusion reduction (11 to 1.6 mL/kg) and a 57% postoperative reduction (16.6 to 7.2 mL/kg). Goobie et al. proposed a dosing regimen for craniosynostosis using a two-compartment model, suggesting a 10 mg/kg TXA loading dose followed by a 5 mg/kg/h infusion to maintain a plasma concentration threshold of 16 µg/mL.

Orthopedic Surgery

The minimization of blood loss is a critical consideration in orthopedic procedures, particularly in hip or knee arthroplasty and spinal surgery. The pharmacological application of TXA has seen renewed interest in this field. Evidence from a meta-analysis by Kagoma et al. indicates that TXA reduces blood loss, lowers the relative risk of transfusion (RR 0.52), and does not increase thromboembolism risk, with dosing ranging between 10–15 mg kg^{-1}. Additionally, a comprehensive retrospective study by Poeran et al. on perioperative TXA use in hip and knee arthroplasty (n = 872,416) demonstrated lower rates of blood transfusion (7.7% vs. 20.1%), thromboembolic events (0.6% vs. 0.8%), acute renal failure (1.6% vs. 1.8%), and overall complications (1.9% vs. 2.6%). With escalating TXA doses (none, <1 g, ~2 g, and >3 g), the odds of transfusion decreased significantly (OR 0.31–0.38) without a corresponding increase in complications(Poeran et al., 2014).

The safety and efficacy of TXA in orthopedic surgery are corroborated by meta-analyses in primary hip and knee arthroplasty. In hip arthroplasty, Sukeik et al. reported reduced intraoperative blood loss by 104 mL and postoperative loss by 172 mL (n = 350), alongside a proportional reduction in transfusion requirements (risk difference −0.20). Similarly, in knee arthroplasty, Alshryda et al. observed a significant reduction in blood loss by 591 mL (n = 763). Although there was notable heterogeneity in trials, a subgroup analysis of high-dose TXA (>4 g) revealed a consistent reduction in transfusion needs. Both studies found no evidence of increased thromboembolism risk with TXA. Additionally, the activation of local fibrinolysis due to tourniquet use in knee arthroplasty further justifies TXA use in such cases. Yang et al. conducted a meta-analysis on intravenous TXA in spinal surgery (n = 581), reporting reductions in postoperative blood loss by 389.21 mL and transfusion volume by 134.55 mL, findings consistent with those in pediatric scoliosis surgery(B. Yang et al., 2013). A randomized controlled trial (RCT) on intravenous TXA in cervical laminoplasty showed a reduction in total blood loss (264 mL) but not intraoperative blood loss, with no increase in complications.

Topical Use

Topical application of TXA has been reviewed in a Cochrane study by Ker et al., which found strong evidence for its effectiveness in reducing bleeding and transfusion needs in surgical patients(Perel et al., 2013). However, the risk of thromboembolism remains unclear as many studies lacked sufficient power to address this complication. Topical TXA achieves approximately tenfold lower plasma concentrations compared to intravenous administration, potentially mitigating adverse effects. Its topical application has been studied in cardiothoracic, orthopedic, otorhinolaryngologic, and orthognathic surgeries, though high-quality trials are still limited.

In knee arthroplasty, a meta-analysis highlighted the efficacy of topical TXA in reducing postoperative drain output (−268 mL), total blood loss (−220 mL), hemoglobin drop (−0.94 g dL^{-1}), and transfusion risk (RR 0.47, 95% CI 0.26–0.84), without an increase in thromboembolic events. Subgroup analysis of doses >2 g revealed a marked reduction in transfusion risk (RR 0.41, P = 0.05). Similarly, Zhang et al., in a separate RCT review, found that intra-articular TXA in knee arthroplasty reduced blood loss (396 mL), transfusion risk (RR 0.22), drainage output, and hemoglobin drop without raising thromboembolism risk, despite heterogeneity in trial designs(Zhang et al., 2014). RCTs by Alshryda et al. on intra-articular TXA in primary hip (n = 161) and knee (n = 157) arthroplasties reported reduced absolute transfusion risk (19.6% and 15.4%, respectively), blood loss, hemoglobindrops, and costs per episode (£305 and £333, respectively). The findings also showed a decreased hospital stay by 1.2 days in knee surgeries with no increased thromboembolic events. Collectively, these results support the use of topical TXA in orthopedic procedures.

A meta-analysis of topical antifibrinolytic agents in cardiac surgery (n = 622) by Abrishami et al. demonstrated reductions in postoperative blood loss and transfusion needs in on-pump procedures. Mahaffey et al. (n = 160) observed decreased chest drain output at 3, 6, and 12 hours postoperatively when combining intravenous and topical TXA(Mahaffey et al., 2013). Despite higher overall TXA amounts in the combined group, less TXA was administered intravenously (4.1 g vs. 5.1 g), with no increase in adverse events. Spegar et al. evaluated systemic TXA augmented with topical application (2.5 g in 250 mL saline into the pericardial cavity) during valvular surgery (n = 100) and found non-significant reductions in blood loss and fresh frozen plasma usage. In contrast,

Fawzy et al., in an RCT (n = 38), reported decreased postoperative blood loss (−626 mL vs. −1,040 mL) and platelet transfusion requirements (median units 0 vs. 2) using 1 g TXA in 100 mL saline. Other RCTs with similar regimens confirmed reduced postoperative blood loss in cardiac surgeries without additional adverse events.

Trauma

Robust clinical evidence supports the use of TXA in trauma. The CRASH-2 trial, a large multicenter RCT, compared TXA to a placebo in over 20,000 trauma patients. Participants received either a placebo or an IV TXA loading dose of 1 g within 8 hours of trauma, followed by an 8-hour infusion of 1 g TXA. Results showed a reduction in all-cause mortality in the TXA group (RR 0.91) and a significant reduction in death due to bleeding (RR 0.85). Further analysis revealed that early treatment (≤1 hour from injury) decreased the risk of death from bleeding (RR 0.68), whereas administration after 3 hours increased this risk.

It is critical to recognize that trauma patients may exhibit physiological fibrinolysis, fibrinolytic shutdown, or hyperfibrinolysis. A recent study (n = 180) of individuals with an Injury Severity Score ≥15 identified fibrinolytic shutdown in 64% of patients, as assessed by thromboelastometry at 30 minutes (Moore et al., 2014). Mortality distribution followed a U-shaped curve: the physiologic fibrinolysis group had the lowest mortality (5%), while the hyperfibrinolysis (44%) and shutdown (26%) groups experienced higher mortality rates. These findings underscore the importance of patient selection and judicious use of exogenous fibrinolytic inhibitors like TXA. Employing thromboelastometry can help mitigate indiscriminate TXA administration.

Neurosurgery

The application of antifibrinolytics in intracranial hemorrhage (ICH), particularly aneurysmal subarachnoid hemorrhage (SAH), has been a subject of investigation for decades. Early studies identified reduced re-bleeding rates but reported an increased risk of stroke. Subsequently, shorter antifibrinolytic intervention periods were introduced to address cerebral vasospasm prevention (Meier & Hoesch, 2013). Renewed interest has emerged in the use of tranexamic acid (TXA) and epsilon-aminocaproic acid (e-ACA) for these patients. A review by the Cochrane Stroke Group examined antifibrinolytics versus control in ICH, concluding that treatment did not improve patient outcomes or reduce mortality but did lower the risk of re-bleeding (OR 0.55) with notable heterogeneity among the trials. However, an increased risk of ischemic stroke (OR 1.39) was observed, leading the authors to advise against the routine use of antifibrinolytics in aneurysmal SAH. In contrast, a study by Roos et al. reported no increase in ischemic stroke rates, likely due to concurrent administration of nimodipine and hypervolemic therapy.

Since the meta-analysis, newer strategies involving short-duration antifibrinolytic use have demonstrated a reduction in re-bleeding with fewer adverse events. The multifactorial mechanism of re-bleeding includes heightened fibrinolysis and decreased platelet-plug stability (Larsen & Astrup, 2013). Re-bleeding risk peaks within the first six hours post-aneurysmal SAH, correlating with poor outcomes, including a Glasgow Outcome Scale reduction of 40% to 80% and mortality rates of 20% to 60%. An RCT by Hillman et al. involving 505 participants compared early intravenous TXA administration with a control group for up to 72 hours, observing a significant reduction in early re-bleeding (from 10.8% to 2.4%) and an 80% decrease in mortality among early re-bleeders. Evidence from transcranial Doppler and clinical studies supports the incorporation of TXA into protocol-based acute-phase aneurysm SAH therapy, in conjunction with other vasospasm prevention strategies, before aneurysm closure.

Regarding traumatic ICH, which includes epidural, subdural, and subarachnoid hemorrhages, TXA use has gained attention following the CRASH-2 trial. A nested RCT within CRASH-2 by Perel et al. assessed ICH growth in 270 patients, finding no significant benefits or harms regarding hemorrhage expansion or new ischemic lesions in traumatic brain injury. Sprigg et al. later conducted a pilot RCT comparing TXA with a control in spontaneous intracerebral hemorrhage, marking the first study in this application(Sprigg et al., 2014). They found early intravenous TXA feasible and well-tolerated. Consequently, two large multicenter trials, TICH-2 (International) and STOP-2 (Australia), are underway to evaluate TXA's efficacy and safety in spontaneous intracerebral hemorrhage.

Hepatic Surgery

Orthotopic liver transplantation (OLT) is associated with substantial blood loss and a frequent need for transfusion of blood products, with fibrinolysis playing a significant role. Clinical evidence supporting antifibrinolytic use in OLT has existed for over three decades, with aprotinin historically favored over TXA due to its additional antioxidant and anti-inflammatory properties. A meta-analysis by Molenaar et al. encompassing 1,407 patients, demonstrated that both drugs reduced intraoperative blood and fresh frozen plasma requirements. Several studies have compared TXA's efficacy with aprotinin in OLT. One RCT involving 127 participants found similar efficacy for prophylactic TXA and aprotinin in reducing intraoperative and 24-hour blood and component transfusions. No differences in mortality, complications, or intraoperative coagulation parameters, except aPTT, were observed. Similar results were reported by Ickx et al. in a study of 51 patients, showing that both TXA and aprotinin inhibited fibrinolysis compared to controls. A Cochrane review by Gurusamy et al. on strategies to decrease blood loss in OLT identified biases in clinical trials but reported no differences in 60-day

mortality, retransplantation risk, or thromboembolic events between TXA and control groups, nor between aprotinin and TXA.

Massicotte et al. analyzed data from 400 OLT patients treated with antifibrinolytics, finding no significant differences between TXA and aprotinin regarding blood loss (1,082 vs. 1,007 mL), blood transfusions per patient (0.5 vs. 0.5 U), final hemoglobin levels (93 vs. 95 g/L), transfusion-free case percentages (80% vs. 82%), or one-year survival rates (85.1% vs. 87.4%). Interestingly, preoperative hemoglobin levels correlated with one-year survival and transfusion requirements. Görlingeranalyzed 642 OLTs using rotational thromboelastometry (ROTEM®) and recommended prophylactic antifibrinolytics only for patients with fulminant liver failure or reduced maximal clot firmness, indicating a high risk of hyperfibrinolysis. Although 60% of patients exhibited hyperfibrinolysis during OLT, only 40% required antifibrinolytics during the prehepatic and anhepatic phases, with treatment in the neohepatic phase limited to patients with clinical bleeding and increased fibrinolysis.

TXA's role in blood conservation during hepatectomy for tumor resection has also been explored. An RCT by Wu et al. involving 214 participants, showed promising efficacy. Although a Cochrane review on pharmacological interventions for blood conservation in liver resection found that aprotinin and TXA significantly reduced allogeneic blood transfusion risk compared to controls, the review included only a few small RCTs. A survey of Canadian hepatobiliary surgeons indicated frequent use of low central venous pressure strategies during liver resection, while other strategies, including TXA, were seldom employed (Truong et al., 2014). High-quality RCTs are required to evaluate the perioperative morbidity and mortality associated with pharmacological interventions for blood conservation in hepatectomy.

OBSTETRICS AND GYNECOLOGY

Menorrhagia is a prevalent condition that significantly impacts women's health and quality of life. Tranexamic acid (TXA) has been utilized as a treatment for this condition for over four decades. Recent reviews indicate that TXA effectively reduces menstrual blood loss by 34% to 59%. An earlier Cochrane review comparing antifibrinolytics (including TXA and its precursor) to placebo demonstrated a significant reduction in mean blood loss with TXA (mean difference −94 mL). TXA also proved superior to mefenamic acid, norethisterone, and etamsylate in reducing blood loss, with no significant differences in adverse effects between TXA and the other agents. A recent randomized controlled trial (RCT) highlighted a new oral TXA formulation that reduced menstrual blood loss by more than 50 mL at doses exceeding 3.9 g/day for up to 5 days, with results both statistically and clinically significant. These findings align with earlier research, which revealed improved quality of life among women with menorrhagia treated with TXA, as assessed by a questionnaire adapted from Edlund et al..

A Cochrane review encompassing two RCTs (n = 453) comparing TXA to controls during cesarean section or vaginal delivery reported reduced rates of significant blood loss (>400 mL) and lower mean blood loss in the TXA group (mean difference −75 mL). A meta-analysis on TXA in pregnancy and postpartum settings by Peisidis et al. included several quasi-blinded trials excluded from the earlier Cochrane review, demonstrating a combined estimated reduction in blood loss by 32.5 mL with TXA administration before cesarean section(Gobbur et al., 2014). Ferrer et al. conducted a separate meta-analysis that showed TXA reduced postpartum blood loss by 92 mL compared to controls.

In a study by Ducloy-Bouthers et al. involving high-dose TXA (4 g infusion over 1 hour followed by 1 g/hour for 6 hours) in cases of postpartum hemorrhage exceeding 800 mL, TXA reduced blood loss (173 vs. 221 mL), shortened hemorrhage duration, decreased progression to severe postpartum hemorrhage, and reduced transfusion incidence. However, the study lacked sufficient power to identify rare adverse effects. Another RCT by Gungorduk et al. demonstrated that administering 1 g of intravenous TXA during the delivery of the anterior shoulder significantly reduced blood loss during the third and fourth stages of labor (261.5 vs. 349.98 mL), with no major complications observed during three-week follow-up. In another RCT (n = 660), Gungorduk et al. found that pre-cesarean intravenous TXA reduced mean blood loss, the proportion of women experiencing severe postpartum hemorrhage (>1,000 mL), and the need for additional uterotonics.

Three additional RCTs examining pre-cesarean section intravenous TXA versus controls confirmed reduced intraoperative and post-cesarean blood loss without increased adverse events, such as thromboembolism. Further research is required to determine the optimal obstetric and gynecological scenarios where TXA proves beneficial(Movafegh et al., 2011; Sentürk et al., 2013; Xu et al., 2013).

OTHER APPLICATIONS

In tonsillectomy, post-operative bleeding is a significant concern. A meta-analysis of TXA use in tonsillectomy (n = 180) revealed reduced blood loss volume but no significant effect on the number of patients experiencing post-tonsillectomy hemorrhage. Albirmawy et al. found that post-resection topical TXA in pediatric adenoidectomy reduced intraoperative blood loss, postoperative bleeding, and transfusion rates.

Several older studies support TXA's role in hereditary angioneurotic edema. TXA's biological mechanism involves complement system inhibition in C1 esterase deficiency and partial normalization of plasma kinin activation. In Japan, TXA is approved for treating urticarial swelling, eczema, itch, drug eruptions, and toxicoderma, conditions linked to local hyperfibrinolysis and inflammation.

For upper gastrointestinal bleeding, a Cochrane meta-analysis found TXA reduced mortality risk compared to controls. However, this effect was negated in subgroup analyses accounting for bias control and sequential analysis. TXA demonstrated no benefit over other anti-ulcer therapies, with no statistically significant differences in thromboembolic event incidence. No RCTs have examined TXA for upper gastrointestinal bleeding in liver disease. In hemoptysis, a Cochrane review revealed that TXA significantly shortened bleeding duration (mean difference −19.47 hours) without differences in side effects compared to controls.

ADVERSE EFFECTS AND DOSING

Animal studies have demonstrated dose-dependent seizures following topical TXA administration to the central nervous system. Similar outcomes have been reported in humans following accidental intrathecal TXA injections. High TXA doses in cardiac surgery are now recognized as a seizure risk factor. TXA crosses the blood-brain barrier, achieving cerebrospinal fluid concentrations approximately 10% of plasma levels. It also diffuses into joint fluid and synovial membranes.

Studies indicate moderate to high TXA doses during cardiac surgery are associated with increased postoperative seizures. A multivariate analysis of over 11,000 cardiac surgery patients identified TXA as a strong predictor of postoperative seizures (odds ratio 14.3), with associated higher mortality rates (Sharma et al., 2014). Propensity-score-adjusted analysis (n = 4,883) corroborated these findings, linking moderate TXA doses to doubled post-cardiopulmonary bypass (CPB) seizure rates and increased in-hospital mortality (Koster et al., 2013). In pediatric cardiac surgery, concerns about seizure risks have prompted some European centers to substitute TXA with e-aminocaproic acid (e-ACA).

Mechanistically, TXA binds to $GABA_A$ receptors, inhibiting GABA-mediated CNS activity. TXA's structural similarity to glycine also enables it to competitively inhibit glycine receptors, heightening excitatory synaptic activity. Late-onset seizures post-CPB align with peak cerebrospinal TXA levels occurring after infusion cessation. Conversely, e-ACA exhibits 10-fold lower glycine receptor inhibition, while aprotinin lacks this inhibitory effect.

Effective TXA plasma concentrations for antifibrinolysis range from 5−10 μg/mL to 10−16 μg/mL. The BART study dosing regimen includes a 30 mg/kg loading dose, a 16 mg/kg/hour maintenance infusion, and an additional 2 mg/kg in the circuit. Pharmacokinetic studies confirm sustained TXA plasma levels achieving complete fibrinolysis inhibition postoperatively. Approximately 95% of TXA is excreted unchanged via urine, necessitating dosage adjustments for patients with renal impairment (Q. J. Yang et al., 2015). Further research is needed to optimize dosing protocols.

Although TXA undergoes minimal metabolism within the body, it is advised to exercise caution when used in conjunction with prothrombotic medications. According to the Cyklokapron® product information, such medications include combination hormonal contraceptives, factor IX, Xa, and VIIa complex concentrates, anti-inhibitor coagulant concentrates, thrombin, batroxobin, or hemocoagulase. However, there is no current clinical evidence indicating that TXA increases the risk of thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis, or pulmonary embolism, as reported in meta-analyses and clinical trials across various settings, including general, trauma, orthopedic, cardiac, and obstetric and gynecological contexts. Nevertheless, there are case reports of catastrophic intracardiac or intrapulmonary thromboses linked to antifibrinolytic agents, though none specifically involved TXA.

A meta-analysis on antifibrinolytics in orthotopic liver transplantation (OLT) (n = 1,407) conducted by Molenaar et al. found no increased incidence of hepatic artery thrombosis or thromboembolism. Similarly, Ngaage et al. in their meta-analysis of TXA in cardiac surgery, observed that while thromboembolic events (myocardial infarction and neurological complications) and mortality were rare, they did not significantly differ between the TXA and control groups. Despite this, the authors advised against the indiscriminate use of TXA. In patients with menorrhagia, TXA was not associated with an elevated thromboembolism risk in a nested case-control study (n = 686), while other treatment groups displayed a significantly increased risk, suggesting that menorrhagia itself may have prothrombotic properties. Lastly, a Cochrane review by Perel et al. on TXA in emergency surgery noted uncertainty about the increased risks of thromboembolism and stroke, as only three trials met inclusion criteria, and the number of events was small.

Overall, available evidence suggests that TXA is a well-tolerated drug, whether administered orally, intravenously, or topically. Commonly reported adverse effects include gastrointestinal disturbances, allergic skin reactions, and visual disturbances, while seizures occur less frequently and are typically associated with high plasma concentrations.

Despite significant progress, important questions regarding TXA's impact on morbidity and mortality in surgical settings remain unanswered. A reduction in transfusion requirements might be expected to translate into reduced mortality and morbidity. However, as previously noted, Ker et al. observed fewer deaths in the TXA group (RR 0.61) in their meta-analysis, albeit with concerns about adequate concealment. Similarly, the potential for an increased thromboembolism risk with TXA remains unresolved. The safety profile and optimal dosing regimens of TXA, particularly in pediatric populations undergoing cardiac and non-cardiac surgeries, warrant further exploration as prior studies have been underpowered to detect significant adverse effects.

Dose adjustments for TXA in cases of renal impairment also require additional research, particularly given the high-risk patient cohort undergoing cardiac surgery. Despite known seizure risks associated with high-dose TXA, no universally accepted dosing regimens have been established.

The interplay between the inflammatory response and coagulation-fibrinolysis systems, as well as TXA's role in mitigating inflammatory responses during CPB, suggests the need to identify at-risk patients who might benefit most from TXA therapy. Reports have emerged of ischemic cerebral events in young, healthy individuals following TXA administration, particularly among those with heterozygous MTFR C677T gene mutations (methylene tetrahydrofolate reductase). While the risk of stroke, pulmonary embolism, and deep vein thrombosis remains uncertain in meta-analyses and large clinical trials, the pharmacological interactions with genetic predispositions present an intriguing avenue for further research.

Several ongoing multicenter RCTs on TXA hold promise for answering these outstanding questions. The STOP-AUST trial investigates the efficacy of early (≤ 4.5 hours post-stroke onset) intravenous TXA administration compared to placebo in patients with confirmed intracerebral hemorrhage as identified by CT angiography contrast extravasation, a biomarker for potential hematoma expansion. This trial hypothesizes that TXA will reduce hematoma growth within 24 hours.

The CRASH-3 trial is an international pragmatic study evaluating the effect of early TXA (using the same regimen as CRASH-2) on mortality and morbidity in 10,000 patients with traumatic brain injury. Additionally, Shakur et al. are conducting the WOMAN trial, an international pragmatic study assessing TXA use in 15,000 women diagnosed with postpartum hemorrhage. This trial hypothesizes a reduction in mortality and/or the need for hysterectomy and includes a substantial representation from low- and middle-income countries, highlighting its contextual relevance.

In the context of cardiac surgery and its associated thrombotic and hemorrhagic complications, Myles et al. are leading the ATACUS trial, a multicenter RCT with 4,600 participants, to evaluate the efficacy of aspirin and TXA in CABG surgery. Employing a 2 × 2 factorial design, this trial assesses whether aspirin, TXA, or their combination reduces mortality and/or morbidity following elective CABG. Secondary endpoints include ischemic complications such as renal, cerebral, or bowel ischemia, offering critical insights into TXA's role in cardiac surgery.

Conclusion

Tranexamic acid (TXA) has emerged as a pivotal antifibrinolytic agent across a broad spectrum of clinical settings, from surgery and trauma to obstetric, gynecological, and non-surgical applications. Its pharmacological ability to inhibit plasminogen activation and stabilize fibrin clots underpins its efficacy in reducing blood loss and transfusion requirements. Despite its generally favorable safety profile and minimal metabolic demands, questions remain regarding its potential association with thromboembolic risks, particularly in prothrombotic contexts or at higher doses. Adverse effects such as seizures, gastrointestinal disturbances, and visual impairments require cautious administration, especially in vulnerable populations.

Critical gaps persist, particularly in defining optimal dosing regimens, understanding its impact on renal-impaired patients, and elucidating genetic predispositions that may influence outcomes. The interplay between TXA's anti-inflammatory effects and its role in modulating coagulation warrants further exploration to identify patient subsets likely to derive the most benefit.

Ongoing large-scale trials, such as STOP-AUST, CRASH-3, WOMAN, and ATACUS, are expected to shed light on these unanswered questions, enhancing our understanding of TXA’s role in improving morbidity and mortality across diverse clinical settings. Through continued research, TXA has the potential to further cement its place as a cornerstone of modern pharmacological interventions in hemostasis.

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