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# Tranexamic acid: a clinical review

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**Abstract**

Blood loss and subsequent transfusions are associated with major morbidity and mortality. The use of antifibrinolytics can reduce blood loss in cardiac surgery, trauma, orthopedic surgery, liver surgery and solid organ transplantation, obstetrics and gynecology, neurosurgery and non-surgical diseases. The evidence of their efficacy has been mounting for years. Tranexamic acid (TXA), a synthetic lysine-analogue antifibrinolytic, was first patented in 1957 and its use has been increasing in contrast to aprotinin, a serine protease inhibitor antifibrinolytic. This review aims to help acute care physicians navigate through the clinical evidence available for TXA therapy, develop appropriate dose regimens whilst minimizing harm, as well as understand its broadening scope of applications. Many questions remain unanswered regarding other clinical effects of TXA such as anti-inflammatory response to cardiopulmonary bypass, the risk of thromboembolic events, adverse neurological effects such as seizures, and its morbidity and mortality, all of which necessitate further clinical trials on its usage and safety in various clinical settings.

**Key words:** anesthesia, tranexamic acid, antifibrinolytic, blood conservation

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Blood loss and subsequent transfusions are associated with major morbidity and mortality [1, 2]. The use of antifibrinolytics can reduce blood loss in cardiac surgery, trauma, liver surgery and solid organ transplantation and non-surgical diseases. The evidence of their efficacy has been mounting for years [3, 4]. Synthetic lysine-analogue tranexamic acid (TXA, trans-4-aminomethylcyclohexane-1-carboxylic acid), along with $\varepsilon$-aminocaproic acid ($\varepsilon$-ACA), were first patented by S. Okamoto in 1957 [5]. Many questions remain unanswered regarding other clinical effects of TXA such as anti-inflammatory response to cardiopulmonary bypass (CPB), the risk of thromboembolic events and adverse neurologic effects (seizures), as well as the morbidity and mortality of TXA, all of which necessitate further clinical trials on its usage and safety in various clinical settings. Therefore, this review aims to help acute care physicians navigate through the clinical evidence available for TXA treatment, develop appropriate dose regimens whilst minimizing harm, as well as understand its broadening scope of applications [5].

## MECHANISMS OF ACTION

TXA is a synthetic lysine-analogue antifibrinolytic [6] that competitively inhibits the activation of plasminogen to plasmin; at high concentrations it non-competitively blocks plasmin, thus TXA inhibits the dissolution and degradation of fibrin clots by plasmin. The binding of TXA to plasminogen is 6 to 10 times more potent that of $\varepsilon$-ACA [7]. TXA has been shown to increase thrombus formation in a dose-dependent fashion in animal models, in contrast to aprotinin, which inhibits thrombus formation [8].

Evidence from numerous studies show that TXA inhibits plasmin-induced platelet activation during extracorporeal circulation, such as cardiopulmonary bypass (CPB) used in cardiac surgery [9–12]. There are multiple factors that lead to bleeding following CPB, and fibrinolysis is one of the few that can be mitigated by pharmacological intervention. TXA also reduces excessive bleeding after CPB by several other mechanisms. Firstly, plasmin-platelet interaction leads to the selective release of ADP-granules from platelets,

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which is triggered by platelet surface contact with the extracorporeal circuit. Soslau *et al*. [13] found that platelet dense-granule ADP content in patients loaded with TXA pre-CPB were higher compared to those loaded with TXA post-CPB, with a strong inverse relationship to blood loss. The same investigators estimated the EC50 (half maximal effective concentration) of TXA required for the inactivation of plasmin-induced platelet aggregation during CPB to be ≤ 15 μg $mL^{-1}$ *in vitro*; thrombin activation of platelets was also inhibited by plasmin-TXA binding to platelet receptors. Thus, one may conclude that there are several pathways explaining the preservation of platelet function by TXA during CPB.

Secondly, TXA possibly attenuates the inflammatory response and related hemodynamic instability in patients undergoing CPB. Hyperfibrinolysis probably plays a significant role in this inflammatory response. In a randomized controlled trial (RCT) of 50 patients undergoing CPB, TXA reduced significantly several of the biochemical markers of inflammatory response [14]: IL-6, fibrin separation products, creatine-kinase (CK) and plasminogen activator inhibitor. Patients receiving TXA had reduced incidences of inflammatory response and vasoplegic shock, fewer mean hours of norepinephrine use (1.2 vs 25.4 h) and fewer hours of mechanical ventilation (6.5 vs 12 h) in intensive care after CPB. In a larger RCT, IL-6 had a direct relationship with temperature, D-dimer, troponin I, CK, and lactic acid after CPB [15]. Furthermore, giving additional post-CPB TXA significantly reduced the relative risk (RR 2.5) of inflammatory response compared to pre-CPB TXA dosing alone.

Thirdly, hyperfibrinolysis contributes to coagulopathy in trauma and has an estimated incidence of 15% [16]. In trauma, tissue damage causes the release of tissue plasminogen activator induced by tissue ischemia and endothelial injury [17]. Point-of-care testing by rotational thromboelastometry allows rapid identification of patients with hyperfibrinolysis in trauma — a state associated with greater INR derangements, lower fibrinogen and higher mortality rates [18, 19] when compared to physiologic fibrinolysis. TXA use in trauma thus has physiologic justification, but the diagnosis of hyperfibrinolysis is crucial before initiating treatment.

Lastly, there is a beneficial interaction of TXA with desmopressin: if the fibrinolytic activity of desmopressin via the transient release of tissue plasminogen activators [11, 20] is abolished by TXA preparation, desmopressin exerts salutary effect on platelet activation, significantly reducing postoperative blood loss and transfusion [21].

## CLINICAL USAGE AND EFFICACY

The main purpose of TXA is the reduction of perioperative bleeding and transfusion requirements in both cardiac and non-cardiac surgery. There are clear benefits both from the mortality-morbidity and economic-cost perspectives. In a recent meta-analysis of over 100 RCTs that compared TXA vs no TXA or a placebo in more than 10,000 patients undergoing surgery [22], there was overwhelming evidence that TXA reduces the probability of transfusion by 38%. Moreover, a cumulative meta-analysis suggests that this evidence has been available for more than 10 years. Although the same study showed that fewer deaths occurred in the TXA group (RR 0.61, 95% CI 0.38 to 0.98), this became uncertain when analysis was restricted to the trials with adequate concealment. Similarly, the Cochrane Review of the effect of antifibrinolytics on blood-loss and transfusion of allogeneic blood [3] found that TXA significantly reduced blood transfusion by 39%, representing an absolute risk reduction of 18%. However, TXA was not associated with decreased mortality in all surgeries.

## CARDIAC SURGERY

Since the publication of findings by Mangano *et al*. [23] and Karkouti *et al*. antifibrinolytic choice in cardiac surgery has shifted from aprotinin to TXA and ε-ACA. This was due to the concern that aprotinin may be associated with an increased risk of cardiovascular or cerebral vascular events, as well as renal dysfunction or failure. In a propensity-score matched analysis (n = 10,870) of patients at high risk of blood loss in cardiac surgery, Karkouti *et al*. [2] reported an increased risk of renal toxicity of aprotinin when compared with TXA with a potential increase in mortality, whilst both antifibrinolytics had similar hemostatic effectiveness. Subsequently, in a 5-year follow-up of (n = 4,374) patients having CABG surgery [24], Mangano *et al*. found aprotinin to be associated with increased mortality compared with a control, TXA and ε-ACA.

The use of TXA was further propelled by the BART [25] trial (**B**lood Conservation Using **A**ntifibrinolytics in a **R**andomized **T**rial) published by Fergusson *et al*. [25], who compared the use of aprotinin, TXA and ε-ACA in high-risk cardiac surgery patients. Alarmingly, the 30-day mortality rate, was 6% for the aprotinin group vs 3.9% for TXA (RR 1.55) and 4.0% for ε-ACA (RR 1.52); however, there was a modest reduction in the risk of massive bleeding in the aprotinin group compared with the two lysine-analogues. This led to the withdrawal of FDA and Health Canada approvals for aprotinin [26]. On the other hand, critics of BART have noted that in the high-risk patient subset, aprotinin may possibly have a better benefit/risk profile [27]. Indeed, this is supported by the propensity-score (n = 1,544) matched study by Karkouti *et al*. [28]

Knowledge of the efficacy of TXA vs a control in reducing blood loss and transfusion in cardiac surgery has been available for decades [29, 30]. Recent meta-analyses confirm this notion. A report by Henry *et al*. [31] stated a relative risk of blood transfusion with TXA of 0.68 with ~300 mL of blood

saved while Ngaage *et al*. [32] reported an odds ratio of 0.53 with ~298 mL of blood saved. Although a comparison of TXA with a placebo showed a reduction in the number of reoperations caused by blood loss [3, 32], once again the benefit of reduced reoperation numbers due to blood loss is even more convincing with high-dose aprotinin [3, 31]. Even though TXA is approximately 7-times more potent than $\varepsilon$-ACA, they were comparable in relative risk and actual volume of blood loss in cardiac surgery [3]. Moreover, TXA did not show a decreased risk of mortality in cardiac surgery in the aforementioned meta-analyses.

While the BART protocol TXA regimen — 30 mg $kg^{-1}$ loading dose followed by 16 mg $kg^{-1}$ $h^{-1}$ infusion during surgery with an added 2 mg $kg^{-1}$ in the circuit is in the high-dose range [33, 34], it has been nevertheless widely adopted by many cardiac surgical centers since the publication of BART. Early dose-response studies in cardiac surgery by Horrow *et al*. [35] found that a prophylactic loading dose of 10 mg $kg^{-1}$ with infusion at 1 mg $kg^{-1}$ $h^{-1}$ was optimal, when compared to six incremental loading doses from 2.5 to 40 mg $kg^{-1}$ followed by 0.25 mg to 4 mg $kg^{-1}$ $h^{-1}$ infusion. Later, several authors found inconsistent plasma concentrations [36, 37] with the Horrow regimen when the pharmacokinetic influence of the circuit and patient renal function were included in analysis. A recent RCT pitted the Horrow regimen against the higher BART regimen in cardiac surgery patients [38], and it found that although a high dose of TXA does not reduce the incidence of blood product transfusion up to day 7 (63% low dose vs 60% high dose), it is more effective than a low dose of TXA in decreasing transfusion (2.5 vs 4.1 U), blood loss (590 vs 820 mL), and repeat surgery (2.5% vs 6%). A subgroup analysis of high-risk patients with dual antiplatelet therapy or having complex surgery showed a further reduced incidence of transfusion and suggests that a high dose of TXA may be better in that group.

Many patients undergoing cardiac surgery receive aspirin and/or clopidogrel preoperatively. There is evidence that TXA partially corrects arachidonic acid-induced (aspirin) and ADP-induced (clopidogrel) platelet aggregation defects [39] detected by multiple electrode aggregometry, in patients on dual-antiplatelet therapy, concurring with the plasmin-induced platelet inhibition [10] by the redistribution and degradation of glycoprotein Ib and IIb/IIIa receptors.

## PPEDIATRIC CARDIAC AND NON-CARDIAC SURGERY

The efficacy of TXA in major pediatric surgery reproduces what was found in the adult population. In a meta-analysis of over 2,000 pediatric patients undergoing cardiac or scoliosis surgery the authors found no evidence that TXA was inferior in the reduction of blood loss vs aprotinin at 24 h. Indeed, TXA reduced blood loss by 11 mL $kg^{-1}$ (95% CI 9 to 13 mL $kg^{-1}$), and reduced packed red cell transfusion by 4 mL $kg^{-1}$ (95% CI 2 to 7 mL $kg^{-1}$). In scoliosis surgery, TXA significantly reduced blood loss by 682 mL (95% CI 214 to 1,149 mL). A recent RCT comparing TXA with a control (n = 150) in pediatric patients undergoing cardiac surgery [41] demonstrated a reduction of blood loss but not the units of blood transfused at 24 h. Similarly, a retrospective study (n = 231) of pediatric patients having cardiac surgery [42] found that TXA significantly reduced blood loss and reduced the amount of blood transfused intraoperatively, as well as at 48 h. Moreover, the authors found a reduction in the number of patients requiring blood transfusion (45/103 vs 77/127, $P$ = 0.012) at 48 hours. Interestingly, both studies did not find differences between cyanotic and acyanotic subgroups. However, according to Faraoni *et al*. [43] in their meta-analysis of pediatric cardiac surgery and TXA, there is much heterogeneity in the data from RCTs: transfusion policies were ill-defined, with variability in regimens and data on TXA effect on morbidity and mortality. However, these authors found that in the 848 patients included in the analysis, the amount of red cells, platelet and fresh frozen plasma transfused showed decreasing trends between TXA and the control. Despite recent pharmacokinetic studies on pediatric populations [44, 45] the ideal dose regimen of TXA in pediatric cardiac surgery is still unknown [46]. *In vitro* studies in neonates have shown a significantly lower plasma concentration (~6.5 µg $mL^{-1}$ vs ~17 µg $mL^{-1}$) required to prevent hyperfibrinolysis when compared to adults [45]; this would set the basis of future clinical trials on dosing regimens and risk-benefit balance.

Faraoni and Goobie also performed a systematic review [47] on the use of antifibrinolytics in pediatric non-cardiac surgery and concluded that in pediatric spine surgery (mainly scoliosis correction) and craniosynostosis surgery, TXA did decrease blood loss and transfusion requirements. An older Cochrane meta-analysis [48] found antifibrinolytics as a class in scoliosis surgery reduced blood loss by 426 mL and the amount of blood transfused by 327 mL; no subgroup analysis on the effect of TXA alone was carried out. There are few RCTs [49–51] on TXA use in pediatric scoliosis surgery. Thus, the safety profile of TXA use in pediatric spinal surgery remains unresolved.

Basta *et al*. [52] conducted a separate systematic review on major pediatric surgery (cardiac, spinal and craniofacial) and found that antifibrinolytics reduced blood loss and transfusion volumes, particularly in craniofacial surgery. Craniosynostosis is not an uncommon pediatric disease requiring early surgical intervention and is associated with considerable blood loss [53]. There are two RCTs of TXA vs control in craniosynostosis surgery [54, 55]: Goobie *et al.* showed significant decrease in blood loss of 54 mL kg-1 and decreased volume of blood transfused by 23 mL $kg^{-1}$; Dadure

*et al.* [55] found a decrease in transfusion requirement by 85% (11 to 1.6 mL $kg^{-1}$) intraoperatively and by 57% (16.6 to 7.2 mL $kg^{-1}$) postoperatively. Moreover, Goobie *et al*. [44] describes a dose regimen for craniosynostosis using a two-compartment model, suggesting a 10 mg $kg^{-1}$ loading TXA followed by a 5 mg $kg^{-1}$ $h^{-1}$ infusion to produce a threshold plasma concentration of 16 µg $mL^{-1}$.

## ORTHOPEDIC SURGERY

The reduction of blood loss in orthopedic surgery is of great importance, especially in hip or knee arthoplasty and spinal surgery. Pharmacological treatment with TXA is making a resurgence in orthopedic surgery. Indeed, antifibrinolytic use in orthopedic surgery is supported by a meta-analysis by Kagoma *et al*. [56], which found a reduction in blood loss, relative risk of transfusion (RR 0.52) and no increased risk of thromboembolism; the dose of TXA administered ranged between 10–15 mg $kg^{-1}$. A large retrospective analysis by Poeran *et al*. [57] studied the perioperative use of TXA in knee or hip arthroplasty (n = 872,416). Patients who received TXA had lower rates of blood transfusion (7.7 vs 20.1%), fewer thromboembolic events (0.6 vs 0.8%), and reduced incidence of acute renal failure (1.6 vs 1.8%) as well as combined complications (1.9 vs 2.6%). With an increasing dose of TXA (none, < 1 g, ~ 2 g and > 3 g), there were decreasing odds (OR 0.31 to 0.38) of blood transfusion, and no significant increased risk of complications.

Moreover, its efficacy and safety profile in orthopedic surgery is further supported by two meta-analyses of TXA use in primary hip [58] and knee [59] arthoplasty. In hip surgery, Sukeik *et al*. [58] found that TXA reduced intraoperative blood loss by 104 mL and postoperative blood loss by 172 mL (n = 350). There was also a proportional reduction of patients requiring blood transfusion (risk difference –0.20). In total knee replacement, Alshryda *et al.* [59] found significant reduction in blood loss by 591 mL (n = 763). It should be noted that there was significant heterogeneity in the trials. Subgroup analysis of high dose TXA (> 4 g) showed a reduction in transfusion requirements with homogeneity. In both meta-analyses there was no evidence of increased risk of thromboembolic events due to TXA. In addition, the use of the tourniquet in knee arthroplasty can activate local fibrinolysis apart from standard tissue trauma [60] and adds justification for TXA use. A meta-analysis of intravenous TXA use (n = 581) in spinal surgery by Yang *et al*. [61] had comparable findings to pediatric scoliosis surgery: there was reduction in postoperative blood loss by 389.21 mL and the amount of blood transfused by 134.55 mL with TXA. A RCT of intravenous TXA use in cervical laminoplasty also found a decrease in blood loss (264 mL) but not intraoperative blood loss [62]; again there was no increase in complications.

## TOPICAL USE

The topical use of TXA has been examined in a Cochrane review by Ker *et al*. [63] Although the authors found reliable evidence that topical TXA reduces bleeding and blood transfusion in surgical patients, the risk of thromboembolism is unclear, as many studies do not report this complication or are underpowered. Topical administration results in a ten-fold less plasma concentration of TXA when compared to intravenous administration [8, 64], with a potential reduction in adverse effects. Although topical TXA has been studied in cardiothoracic [65–68], orthopedic [64, 69–72], otorhinolaryngologic [73, 74] and orthognathic [75–77] surgeries, high-quality trials are lacking.

Topical TXA in knee arthoplasty has been reviewed in a meta-analysis [78] while Panteli *et al*. showed that topical TXA reduced 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 to 0.84); there was no increase in thromboembolisms. The authors examined the subgroup using > 2 g of topical TXA and found that these patients had a significantly less transfusion requirement (RR 0.41, $P = 0.05$). Similarly in a separate review of RCTs [72], Zhang *et al*. [72] also found the intra-articular injection of TXA in knee arthroplasty found a reduction of blood loss (396 mL), relative transfusion risk (RR 0.22), drainage output and hemoglobin drop; there was no increased risk of thromboembolism. Once again there was significant heterogeneity in these trials. Two RCTs [69, 70] by Alshryda *et al*. found that intra-articular injection of TXA in primary total hip (n = 161) and knee (n = 157) arthroplasty reduced the absolute risk of blood transfusion by 19.6% and 15.4%, respectively, and reduced blood loss, hemoglobin drop, as well as decreased the cost per episode by £ 305 and £ 333 respectively. Moreover, there was decreased length of stay in knee surgery by 1.2 days without increased in thromboembolic events. All these findings cumulatively support the topical use of TXA in orthopedic surgery.

In a meta-analysis of topical antifibrinolytic use in cardiac surgery (n = 622), Abrishami *et al*. [79] found reduced postoperative blood loss and transfusion requirements in patients undergoing on-pump cardiac surgery. Mahaffey *et al*. [80] (n = 160) found that combined intravenous and topical TXA was associated with decreased chest drain output at 3, 6 and 12 h postoperatively. Even though the total amount of TXA was higher in the combined group, less TXA (4.1 g vs 5.1 g) was given intravenously compared with the control. In addition, there was no increase in adverse events. Spegar *et al.* [81] studied the augmentation of systemic TXA by topical application (2.5 g in 250 mL saline into pericardial cavity) in valvular surgery (n = 100) and found intergroup variance on blood loss and fresh frozen plasma but a non-significant decrease in the volume of blood loss in the augmented

group. In contrast, Fawzy *et al*. [66] in their RCT (n = 38) found a decrease in postoperative blood loss (–626 mL vs –1,040 mL) and platelet transfusion (median units 0 vs 2) using 1 g TXA in 100 mL saline into the pericardial cavity. Similar regimens used in two other RCTs found that topical TXA did reduce postoperative blood loss in cardiac surgery without increased risk of adverse events [67, 68].

## TRAUMA

TXA application in trauma is supported by firm clinical evidence. The most convincing multicenter RCT in trauma [82] to date is the comparison of TXA vs placebo in over 20,000 patients by the CRASH-2 collaborators. Patients were assigned to a placebo or IV loading of 1 g TXA within 8 h of trauma then followed by IV infusion of 1 g TXA over 8 h. It showed that all-cause mortality was reduced in the TXA group (RR 0.91), and death due to bleeding was significantly reduced (RR 0.85). Subsequent analysis showed that early treatment (≤ 1 h from injury) reduced the risk of death from bleeding (RR 0.68), while treatment given after 3h of injury seemed to increase the risk of death due to bleeding [83].

It is important to remember that physiologic fibrinolysis and even fibrinolytic shutdown occurs in trauma, and not just hyperfibrinolysis. In a recent study (n = 180) of patients with an Injury Severity Score of ≥ 15, there was a sizeable portion (64%) of patients with fibrinolysis shutdown per thromboelastometry at 30 min [84]. The distribution of mortality was U-shaped relative to the fibrinolysis system, the physiologic group had lowest mortality (5%), and the hyperfibrinolysis (44%) and shutdown (26%) groups had higher mortality. This supports the employment of careful patient selection when using exogenous inhibition of fibrinolytic system. The use of thromboelastometry will help prevent indiscriminate TXA therapy.

## NEUROSURGERY

The use of antifibrinolytics in intracranial hemorrhage (ICH) and particularly aneurysmal subarachnoid hemorrhage (SAH) has been investigated for decades, with earlier findings of decreased re-bleeding rates but increased risk of stroke. New strategies were introduced for the prevention of cerebral vasospasm with shorter antifibrinolytic intervention periods [85]. There is renewed interest in TXA and $\varepsilon$-ACA for these patients. The earlier position is outlined in the review of antifibrinolytics vs a control in ICH by the Cochrane Stroke Group [86]: the treatment did not benefit patient outcome and death was not reduced. Treatment did reduce risk of re-bleeding (OR 0.55) with some heterogeneity across the trials. However, there was an increased risk of ischemic stroke (OR 1.39), again with heterogeneity in the trials. In drawing conclusions from these results, the authors did not support the routine use of antifibrinolytics in aneurysmal SAH. In contrast, a study [87] by Roos *et al*. [87] did not show rates of increased ischemic stroke, namely delayed cerebral ischemia from vasospasm, probably because patients in this trial were given calcium channel antagonist nimodipine and hypervolemic therapy concurrently.

Since this meta-analysis, new strategies using antifibrinolytics in short duration have shown promise of reduced re-bleeding with fewer adverse events [88–91]. Although the mechanism for re-bleeding is multifactorial, increased fibrinolysis and decreased platelet-plug stability are implicated [92]. The risk of rebleeding is highest in the first 6 h after aneurysmal SAH, with a poor prognosis as assessed by a reduction of the Glasgow Outcome Scale from 40% to 80% and a mortality rate of 20% to 60% [92]. Hillman *et al*. [91] in their RCT (n = 505) compared early intravenous TXA with a control in patients with SAH for short duration (up to 72 h) and found a significant reduction of early re-bleeding from 10.8% to 2.4% and an 80% reduction in the mortality rate in the early rebleeders. Using evidence from transcranial Doppler and clinical measurements, recent literature shows a resurgence of TXA as a part of protocol therapy alongside other preventative strategies for vasospasm in the acute phase of aneurysm SAH, prior to aneurysm closure [88, 93].

As traumatic ICH includes epidural, subdural and subarachnoid hemorrhage, the use of TXA has been gaining increasing interest since CRASH-2 [82]. A nested RCT within CRASH-2 by Perel *et al*. [94] reviewed the rate of ICH growth in 270 patients, and they found no moderate benefits (total hemorrhage growth and/or new ischemic lesions) nor harmful effects with certainty in traumatic brain injury. More recently, Sprigg *et al*. [95] performed a pilot RCT comparing TXA vs a control in spontaneous intracerebral hemorrhage — the first trial studying this application — and found it feasible to use intravenous TXA early with good tolerability. As a result, two large multicenter trials — namely TICH-2 (International) [95] and STOP-2 (Australia) [97] — are in progress to evaluate the efficacy and safety of TXA in the setting of spontaneous intracerebral hemorrhage.

## HEPATIC SURGERY

Orthotopic liver transplantation (OLT) is associated with significant blood loss and the need for transfusion of blood products, with fibrinolysis being a major player in this [98, 99]. There has been clinical evidence for the use of antifibrinolytics in OLT for over three decades; previously aprotinin was commonly used in OLT and trials demonstrated potential advantages (antioxidant, anti-inflammatory) of aprotinin over TXA [100]. There is one meta-analysis which has studied the use of antifibrinolytics including TXA and aprotinin in OLT (n = 1,407), while Molenaar *et al*. [101] found that both drugs reduced intraoperative blood and fresh frozen plasma requirements.

There are several studies which have compared the efficacy of TXA with aprotinin in OLT. In one RCT (n = 127), prophylactic TXA had similar efficacy to aprotinin [102] in terms of blood and component transfusions both intraoperatively and at 24 h. There were neither differences in mortality and complications nor in coagulation laboratory data collected intraoperatively, except aPTT. Similar results were found by Ickx *et al*. [103] (n = 51), with the additional finding of inhibition of fibrinolysis by both TXA and aprotinin vs a control. Gurusamy *et al*. [104] addressed different strategies of decreasing blood loss in OLT in their Cochrane review. Although with respect to aprotinin and TXA, they concluded that the clinical trials had been biased, there were no differences in 60-day mortality rates, re-transplantation risk or thromboembolic events in the TXA group vs the control and no difference between aprotinin and TXA in mortality or thromboembolism risk. Massicotte *et al*. [105] analyzed 400 patients undergoing OLT who had received antifibrinolytics and found no difference between TXA and aprotinin in blood loss (1082 vs 1007 mL), blood transfused per patient (0.5 vs 0.5 U), final hemoglobin (93 vs 95 g $L^{-1}$), percentage of transfusion-free cases (80 vs 82%) or the 1-year survival rate (85.1 vs 87.4%). Interestingly, preoperative hemoglobin correlated with 1-year survival and transfusion requirements.

Görlinger [106] analyzed ROTEM® (rotational thromboelastometry) in 642 OLTs and suggests using prophylactic administration only in fulminant liver failure or reduced maximal clot firmness, which indicates a high-risk for hyperfibrinolysis. Although 60% of patients displayed hyperfibrinolysis during OLT, only 40% who showed early hyperfibrinolysis during prehepatic and anhepatic phases, required antifibrinolytics. In the neohepatic phase, only patients with increased fibrinolysis and clinical bleeding were treated. This selection by point-of-care testing is aimed at reducing iatrogenic prothrombotic risk.

TXA use has also been investigated for blood conservation in hepatectomy performed for tumor resection. These studies showed promising efficacy, according to a RCT by Wu *et al*. [107] (n = 214). Although a Cochrane review addressed use of pharmacological intervention for blood conservation in liver resection, and found that aprotinin and TXA significantly reduced the risk of allogeneic blood transfusion compared with a control [108], this review included a few small RCTs. A survey of Canadian hepatobiliary surgeons showed that even though low central venous pressure strategy was used commonly during liver resection, other conservation strategies including TXA were rarely employed [109]. High quality RCTs on perioperative morbidity and mortality are needed to assess pharmacological intervention for blood conservation in hepatectomy.

## OBSTETRIC AND GYNECOLOGY

As menorrhagia is a common illness affecting women's health and quality of life, TXA has been used as a form of treatment for over four decades. A recent review [110] placed its efficacy in the reduction of menstrual blood loss by 34 to 59%. An earlier Cochrane review [111] on the use of antifibrinolytics (TXA and its precursor) in heavy menstrual bleeding found that TXA vs a placebo significantly reduced mean blood loss (mean difference –94 mL). TXA also significantly reduced blood loss when compared to mefenamic acid, norethisterone and etamsylate; there was no difference in adverse effects between TXA and the other agents. A recent RCT also found reductions in menstrual blood loss by a new oral formulation of TXA that was both statistically significant (> 50 mL) and clinically meaningful to patients, at doses > 3.9 g $day^{-1}$ for up to 5 days of the cycle [112]. This reinforced the findings of a greater quality of life with TXA use in women with menorrhagia in an early uncontrolled study [113] (n = 849), who were assessed by a questionnaire based on one designed by Edlund *et al*. [114].

A Cochrane review [115] analyzed two RCTs (n = 453) comparing TXA vs a control in women having a caesarean section or vaginal delivery [116, 117], and the authors found that blood loss of > 400 mL was less common and mean blood loss was lower in the TXA group vs the control (mean difference –75 mL). A recent meta-analysis on TXA in pregnancy and postpartum [118] by Peisidis *et al*. [118] included several quasi-blinded trials [119–121] excluded from the above Cochrane review, and found a combined estimated decrease of blood loss by 32.5 mL in TXA pre-caesarean section vs a control. A similar effect of TXA was found in a separate meta-analysis by Ferrer *et al*. [122] in a reduction of postpartum blood loss by 92 mL compared with the control.

Ducloy-Bouthers *et al*. [123] (n = 144) demonstrated that a high-dose TXA (4 g infusion over 1 h followed by 1 g $h^{-1}$ for 6 h) vs a control — in women with greater than 800 mL postpartum hemorrhage — was effective in reducing blood loss (173 vs 221 mL). Moreover, the TXA group had a shorter duration of hemorrhage, less progression to severe postpartum hemorrhage and less incidence of transfusion. This trial was underpowered to detect rare adverse effects. A RCT (n = 439) by Gungorduk *et al*. [124] showed that TXA — 1 g given intravenously over 5 min at the delivery of the anterior shoulder — reduced blood loss during the 3rd and 4th stage of labor compared to the control (261.5 vs 349.98 mL), significantly higher hematocrit and hemoglobin levels on day one, with no major complications at a three week follow-up. Gungorduk *et al*. [125] also performed a RCT (n = 660) of pre-caesarean intravenous TXA vs control, and found a significantly lower mean blood loss, a lower proportion of

women with severe postpartum hemorrhage (> 1,000 mL blood loss) and a lower risk of additional uterotonics used. Finally, three new RCTs [126–128] comparing pre-caesarean section intravenous TXA vs a control have shown a reduction of intraoperative and post-caesarean blood loss without increased adverse events such as thromboembolism. Determining the different obstetric and gynecological settings in which TXA may be beneficial remains a critical question for future research.

## OTHER USAGES

A common minor surgery where post-operative bleeding remains a big issue is tonsillectomy. A meta-analysis of the use of TXA in tonsillectomy [129] (n = 180), showed a reduced volume of blood loss but not the number of patients with post-tonsillectomy hemorrhage. Albirmawy *et al*. [73] found that post-resection topical TXA in pediatric adenoidectomy led to a reduction of blood loss during surgery, decreased postoperative bleeding and transfusion.

Lastly, several old trials support the use of TXA in hereditary angioneurotic edema [130, 131]. The biological mechanism involves the inhibition of the complement system by TXA in the presence C1 esterase deficiency and partial normalization of plasma kinin activation [130]. In Japan, TXA is approved for conditions such as urticarial swelling, itch, eczema, drug eruptions or toxicoderma [8], in which local hyperfibrinolysis and inflammation are involved [131].

The use of TXA in upper gastrointestinal bleeding was reviewed in a Cochrane meta-analysis, and although TXA use vs a control reduced mortality risk, the effect was lost in a subgroup analysis stratified for bias control and in an sequential analysis [132]. No such benefit was demonstrated in TXA vs other anti-ulcer therapy. Although five serious cases of thromboembolic events occurred in the TXA group, this was not statistically significant. No RCTs were found assessing TXA use in upper gastrointestinal bleeding in liver disease [133]. The use of TXA in hemoptysis from any cause was reviewed by the Cochrane Collaboration [134], and TXA vs a control significantly reduced bleeding time (mean difference –19.47 h), without any difference in side-effects.

## ADVERSE EFFECTS AND DOSING

Topical administration of TXA to the central nervous system of animals has been shown to cause seizures in a dose-related fashion [135, 136], this correlates with human reports of seizures induced by accidental intrathecal injections of TXA [136–138]. Recently a dose-response relationship of TXA has been proposed as a modifiable risk factor for seizures for patients undergoing cardiac surgery [139]. TXA crosses the blood-brain barrier and penetrates the eye, and produces cerebrospinal fluid concentration levels around 10% of the plasma concentration [8]. Likewise, it diffuses into and out of synovial membranes and joint fluid. It is now clear from current literature that moderate to high doses of TXA in cardiac surgery are associated with an increased risk of seizures [139, 140]. In a multivariate analysis of over 11,000 patients after cardiac surgery, Sharma *et al*. [142] found TXA to be a strong independent predictor for the development of postoperative generalized seizures [141] (OR 14.3); in addition, patients with seizures had a 2.5 times higher mortality rate. Similarly, in a propensity-score adjusted analysis (n = 4883) Koster *et al*. [143] showed that moderate dosing of TXA in cardiac surgery doubled the rate of post-CPB seizure and in-hospital mortality. Similar concerns over the increasing trend of post-CPB seizure in pediatric patients have led to the substitution of TXA by $\varepsilon$-ACA in a major European center for pediatric cardiac surgery.

The postulated mechanism was TXA binding to $GABA_A$ receptors, subsequently blocking $GABA_A$-mediated inhibition in the CNS [144, 145]. Recently, Lecker *et al.* [145] have demonstrated that TXA is structurally similar to glycine, and competitively inhibits glycine inhibitory receptors in the cortical and spinal cord neurons in rats; TXA also inhibited the $GABA_A$ receptors in cortical and spinal cord neurons. Both TXA dis-inhibitory pathways cause increased excitatory synaptic drive evidenced by seizure-like events in cortical slices induced at TXA concentrations of 31 μg $mL^{-1}$ (200 μM), similar to that measured in CSF of patients undergoing CPB. Finally, peak CSF TXA concentrations occurred when the infusions were stopped after CPB, later than peak serum levels. When taken together, this explains the late-onset of unexpected seizures in patients emerging from anesthesia after CPB. Moreover, $\varepsilon$-ACA had 10-fold less potency in glycine receptor inhibition, and aprotinin had no inhibitory potency.

There are various dose regimens for different indications cited by clinical trials; initially an effective plasma concentration of TXA for antifibrinolysis was reported to be 5–10 μg $mL^{-1}$ [147] or 10–16 μg $mL^{-1}$ [13, 147, 148]. Subsequently, Dowd *et al*. [37] proposed the dosing scheme later adopted in the BART study, in order to ensure plasma levels which would achieve complete inhibition of fibrinolysis for cardiac patients undergoing CPB, namely a loading dose 30 mg $kg^{-1}$, maintenance infusion at 16 mg $kg^{-1}$ $h^{-1}$with an additional 2 mg $kg^{-1}$ in the circuit [25, 37]. Sharma *et al*. [150] conducted a pharmacokinetic study of the BART regimen in cardiac surgery and demonstrated that plasma TXA concentrations were consistently higher than suggested levels aiming to achieve 100% (> 100 ug $mL^{-1}$) and 80% inhibition (> 10 μg $mL^{-1}$) of tissue plasminogen activator and these levels remained high for up to 6 hours postoperatively. Approximately 95% of TXA is excreted via the urine unchanged, and excretion decreases with increasing plasma creatinine levels. The dosage adjustment for renal-impaired patients remains an unknown; Jang *et al*. [151]used the 2 compartment model to guide

a simulated reduction of the maintenance infusion rate according to the GFR of patients during CPB to achieve > 100 μg $mL^{-1}$ threshold plasma concentrations. Please see full paper, which just got published. It would be beneficial for readers to have access to it.

Despite the fact that TXA is minimally metabolized in the body, precautions should be taken with prothrombotic medications [152] used concomitantly. According to the Cyklokapron® product information [6], these medications include combination hormone contraceptives, factor IX, Xa and VIIa complex concentrates, anti-inhibitor coagulant concentrates, thrombin, batroxobin or hemocoagulase.

There is currently no clinical evidence that the use of TXA increases the risk of thromboembolic events, namely myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism according to meta-analyses and clinical trials cited in the general [22, 63], trauma [82], orthopedic [48, 56, 58, 59, 78], cardiac [25, 32, 153] or obstetric & gynecological [111, 112, 119, 123] settings. However, there are reports of catastrophic intracardiac or intrapulmonary thromboses [154], whose putative cause was antifibrinolytic use, albeit none involved TXA. The meta-analysis of antifibrinolytics in OLT (n = 1,407) by Molenaar *et al*. [101] found no increased risk of hepatic artery thromboses or thromboembolism. Ngaage *et al*. [32] in their meta-analysis of TXA in cardiac surgery noted that thromboembolic events (myocardial infarction and neurologic complication) and mortality observed were few but not increased compared to non-treatment groups; the authors still warn against the indiscriminate use of TXA. In patients with menorrhagia, TXA was not associated with an increased thromboembolism risk in a nested case-control study [155] (n = 686), whereas other therapy groups had a significantly increased risk, suggesting that menorrhagia is prothrombotic. Finally, Perel *et al*. [63] were uncertain about the increased risk of thromboembolism and stroke in a Cochrane review of TXA in emergency surgery; only three trials met the criteria for inclusion and the number of events observed were small.

Overall, the cumulative evidence shows that TXA is a well-tolerated drug when delivered orally, intravenously and/or topically. Gastrointestinal disturbance, allergic skin reaction, visual disturbance occur more commonly [8] and seizures less commonly at high concentrations.

## UNANSWERED QUESTIONS

There are still important questions of mortality and morbidity of TXA use in surgery. One may expect that a reduction of transfusion would translate into reduction in mortality and morbidity. As mentioned above, Ker *et al*. [22] found fewer deaths (RR 0.61) occurred in the TXA group in their meta-analysis, albeit with uncertainty of adequate concealment. The overall potential for increased thromboembolism risk with TXA remains uncertain. The safety profile and dose regimens of TXA in cardiac and non-cardiac surgeries in the pediatric population requires further investigation, as previous studies are underpowered to detect differences in adverse effects [47].

The adjustment of TXA in renal impairment warrants further investigation, especially given the at-risk patient group undergoing cardiac surgery. There is no universally accepted dose regimen despite definite concerns of seizure risk of high-dose TXA.

Given the link between inflammatory response and coagulation-fibrinolysis systems and the likely attenuation of inflammatory response by TXA in CPB [14, 15], clinicians ought to identify at-risk patients who may benefit from its treatment.

There are several case reports of young, healthy individuals developing ischemic cerebral events after TXA use, especially those with heterozygous MTFR C677T genes (methylene tetrafolate transferase) [156]. In the meta-analyses and large clinical trials, the risk of stroke, pulmonary thromboembolism and deep venous thrombosis with TXA use remains uncertain. The interaction of pharmacology with genetic factors is an exciting field for research.

Several ongoing multicenter RCTs on TXA are worth following. The STOP-AUST trial [98] is comparing early (≤ 4.5 h of stroke onset) intravenous TXA use with a placebo in patients with confirmed intracerebral hemorrhage by CT angiography contrast extravasation — a biomarker of likely hematoma growth. The hypothesis is that TXA will reduce intracerebral hematoma growth at 24 h. CRASH-3 is an international pragmatic trial quantifying the effect of early TXA (the same regimen as CRASH-2) on mortality and morbidity in 10,000 patients with traumatic brain injury [157]. Lastly, Shakur *et al*. [158] is leading an international pragmatic trial, a.k.a. the WOMAN trial, on the use of TXA in 15,000 women with a clinical diagnosis of postpartum hemorrhage, with the authors hypothesizing a reduction of mortality and/or hysterectomy. This trial has a large third world representation with an obvious contextual relevance. In view of the thrombotic and bleeding complications of cardiac surgery [5], Myles *et al.* is leading a multicenter RCT (ATACUS, n = 4,600) investigating aspirin and TXA in CABG surgery [159]. It is a 2 × 2 factorial trial assessing whether aspirin, TXA, or both can reduce mortality and/or morbidity after elective CABG. Ischemic (renal, cerebral, bowel) complication is a secondary endpoint. This will yield important data on TXA in cardiac surgery.

## SUMMARY

TXA as an antifibrinolytic treatment applied in a perioperative setting has strong pharmacological and clinical grounds. Although there are other situations in which the use of TXA is desirable, these require definitive trials on morbidity and mortality. TXA administration should be based on clinical judgment, guided by patient history, thromboelastometry, laboratory and radiologic investigation, and tailored

to the treatment location and capacity for intervention and transfusion. Future reviews should include guidelines on TXA dose regimens minimizing seizure risk, and conclusions regarding the thromboembolic risk. The ongoing research outlined will help answer these questions.

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