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The Final thesis

Recommendations for the Use of Tranexamic Acid and the Risk in the Management of Acute Bleeding During Anesthesia

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Summary

This narrative review will focus mainly on the indications and recommendations for the use of tranexamic acid and its use in the management of acute bleeding without evaluating the risk in the management of acute bleeding.

Excessive bleeding and blood loss are among the leading causes of mortality.

In the management of acute bleeding, one drug seems to be widely used among anesthesiologists and surgeons all around the world - tranexamic acid.

Tranexamic acid belongs to the antifibrinolytic drug group, as it prevents the degradation and dissolution of fibrin clots and helps maintain homeostasis.

However, tranexamic acid carries the risk of serious adverse effects.

Over the past decade, tranexamic acid has been extensively studied in various major clinical trials that have demonstrated its important role, efficacy, and effectiveness in preventing excessive blood loss and reducing blood transfusion requirements in various settings such as trauma, surgeries, traumatic brain injuries, and postpartum hemorrhages among others, leading the world health organization to include it in its essential drug list.

Tranexamic acid was found to be most effective when used in proximity to the time of injury and within three hours from the initial injury time in trauma settings.

The optimal dosage and route of administration differ between various settings, and more studies are needed in order to optimize its use in the future.

Key words : tranexamic acid, antifibrinolytic, acute bleeding, hemorrhage, trauma, surgery, cardiac surgery, traumatic brain injury, orthopedic surgery, adverse effect, CRASH trial, postpartum hemorrhage, TICH2 trial, WOMEN trial.

Literature search strategy:

This narrative review is based on a systematic search for relevant studies, randomized controlled trials (RCT), systemic reviews, meta-analyses, clinical practice guidelines, and articles published on tranexamic acid and acute bleeding over the past decade.

I used PubMed National Library, Google Scholar, The New England Journal of Medicine, and ScienceDirect to conduct my literature search.

In addition, I have scanned the reference lists of identified articles and related reviews for relevant studies.

Abbreviations :

TXA - Tranexamic Acid

tPA- Tissue Plasmin Activator

CRASH - Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage

Cal-PAT -California Prehospital Antifibrinolytic Therapy

WOMEN- World Maternal Antifibrinolytic

NATA- Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis

TICH-2- tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage

GI - Gastrointestinal

WHO - World Health Organization

PPH - Post Partum Hemorrhage

TBI - Traumatic Brain Injury

ICH - Intra Cranial Hemorrhage

GCS - Glasgow Coma Scale

RCT- Randomized Control Trial

CSF - Cerebro Spinal Fluid

RR- Risk Ratio

CI - Confidence Interval

TKA- Total Knee Arthroplasty

THA - Total Hip Arthroplasty

Introduction

The usage of tranexamic acid has become popular among anesthesiologists and within operating rooms since it was first introduced in 1969.
It is widely used as an anti-fibrinolytic agent in order to minimize bleeding and reduce the need for blood transfusion due to blood loss in different settings. (1)

Tranexamic acid is a synthetic derivative of the amino acid lysine.
The pharmacologic mechanism behind it is that it acts competitively and reversibly to inhibit the activation of plasminogen to plasmin.
Plasminogen is a proenzyme produced by the liver and is converted to its active form plasmin by several enzymes such as tissue plasmin activator (tPA) and other enzymes such as urokinase, factor XIIa and XIa and kallikrein.
Plasmin is a proteolytic enzyme, used to break clots as it binds to fibrin and degrades the clotting meshwork.
The binding of plasmin to fibrin induces fibrinolysis.
Tranexamic acid binds to lysine receptors on plasminogen, by occupying binding sites it prevents fibrin dissolution, thereby stabilizing the clot and preventing bleeding. (2,3)
In higher doses, tranexamic acid can also directly inhibit plasmin and reduce its formation. (4)
Tranexamic acid is said to be six to ten times more potent than the same class antifibrinolytic drug which is also a derivative of the amino acid lysine called aminocaproic acid. (1)

There are several indications for the use of tranexamic acid, as an antifibrinolytic agent it is mostly used to prevent severe bleeding in the settings of surgery and trauma when there is a high risk for hemorrhages, by so it reduces mortality risk from bleeding and reduces the need for blood transfusions due to blood loss. (5)
In addition, it can be used outside the settings of operations or trauma for the treatment of various bleeding disorders.
Significant bleeding may occur as a result of surgery, trauma, obstetric complications, or various hemostatic disorders. In recent years several trials investigated the effect of TXA within the mentioned settings, such trials as CRASH2, CRASH3, WOMEN, TICH-2 and others have demonstrated that tranexamic acid was found to be effective in preventing bleeding complications and reducing mortality in certain circumstances, with minimal risk of side effects.(6-8)
Following these trials, in 2011 WHO (World Health Organization) added TXA to its essential drug list for the treatment of hemorrhages and in 2017 has recommended its usage for postpartum hemorrhage treatment.
TXA is indicated for use in a variety of conditions : (1)

- Acute trauma
- Cardiothoracic surgeries
- Orthopedic surgeries

- Traumatic brain injuries
- Dental interventions
- Obstetrical complications such as postpartum hemorrhage and abnormal uterine bleeding
- Epistaxis
- Hemophilia
- Hereditary angioedema.

TXA can be taken orally, topically, and intravenously depending on the purpose for which it is used and recommended guidelines.
When taken as an oral dose it is usually indicated for hereditary angioedema and heavy menstrual bleeding. (1)
Taken by the intravenous route it is indicated for short-term usage and in the setting of surgical procedures, hemorrhages, and trauma.
The dosage depends on the case for which it is used for, the administration route, and patient factors such as weight, age, and the presence of renal insufficiency.
The usual dosage for adult patients is approximately 1 to 2g in trauma cases. (9)
Intravenous tranexamic acid usually comes in ampules containing 5ml, while oral formulation is sold in tablets of 650mg.
The route of elimination is by renal clearance, about 95% of TXA is excreted as an unchanged drug.
The excretion rate depends on the route of administration - approximately 90% of an intravenous dose is excreted within 24 hours, while an oral dose is excreted only by 39% within 24 hours, oral bioavailability ranges from 30 to 50 %.
The half-life of tranexamic acid is 2 to 3 hours when taken IV and the mean terminal half-life is estimated to be 11 hours, however half-life at the tissue level can be much longer, up to 17 h.(10)
Rate of administration of tranexamic acid injection is 100 mg/mL, by slow IV injection at a rate no faster than 1 mL/minute in order to avoid hypotension. (9)
Follow-up infusion can be administered if needed.
It is believed that the optimal time for administration of tranexamic acid in the setting of a trauma event is within 1 to 3 hours, while the most optimal results were shown when it was given during the first hour.
Studies have indicated that the administration of tranexamic acid to trauma patients has been shown to decrease mortality due to bleeding by 32% if the first bolus was given early within the first hour, and by 21% if given between the first and third hour following trauma. (5,11-15)

Common adverse effects in the usage of TXA are:
Thromboembolic events, seizures, hypotension, nausea, vomiting, diarrhea and allergic dermatitis, visual disturbances, headache, and malaise (16)

The contraindications for the use of tranexamic acid are specified as:(9)

- Allergy to TXA.
- Patients with active or a history of thromboembolic diseases
- Defective color vision.
- In combination with oral contraceptives
- Initial administration of TXA after more than 3 hours have passed since the traumatic injury.

Despite its promising effects, TXA should be used with caution since it may be related to the risk of developing thromboembolic events, and a risk of dose-dependent seizures in cardiac surgery or death when administered by neuraxial route.
Since TXA is eliminated by the kidney, patients with renal impairment may have higher concentrations in plasma hence they should be closely monitored and dosage should be adjusted in order to prevent adverse effects associated with high concentrations of the drug. (16)

Tranexamic acid use in Trauma

One of the major complications in trauma cases leading to death is bleeding.
Several trials have proven that tranexamic acid has been effective at reducing mortality rates among patients presenting with traumatic bleeding and blood loss, without increasing the risk of morbidity or mortality.
The largest trial to examine the effect of TXA on trauma patients is the CRASH2(Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) trial- a randomized, multicentered, placebo-controlled trial conducted on 20,211 trauma patients across 40 countries. With inclusion criteria of adult patients with prominent hemorrhage, systolic blood pressure lower than 90 mmHg, and heart rate over 110 beats per minute, within 8 hours of the occurrence of trauma injury, who were to receive either 1g of IV TXA over 10 minutes, followed by additional infusion of 1g over 8 hours, or placebo.
The results of the trial presented that mortality rates within 28 days were significantly reduced in the TXA group (14.5% vs 16%) compared to the placebo group, as well as a decrease in the risk of death due to bleeding (4.9% vs 5.7%). (17)
The incidence of thromboembolic events did not seem to be higher in the TXA group in comparison to the control group (1.7% vs. 2.0%). (17)
In order to achieve its beneficial effect TXA has to be administered within 3 hours of initiation of bleeding, with the most favorable result when it is administered within the first hour.
Any administration later than the 3 hours time window has been shown to have the opposite effect by increasing the risk of mortality due to bleeding. (18,19)(Fig.1)
Yet there are a few limitations to this trial, half of the participants in this trial received blood transfusions but no blood transfusion protocol was used as well missing data on additional blood products administered and the severity of the injury.
Another rising question is whether thrombotic complications were followed and recorded correctly since the trial was conducted in developing countries where transfusion protocols and detection of adverse events may differ compared to developed countries. (20)

Fig.1 Timing of administration of TXA as an effect on mortality in hemorrhage. (19)

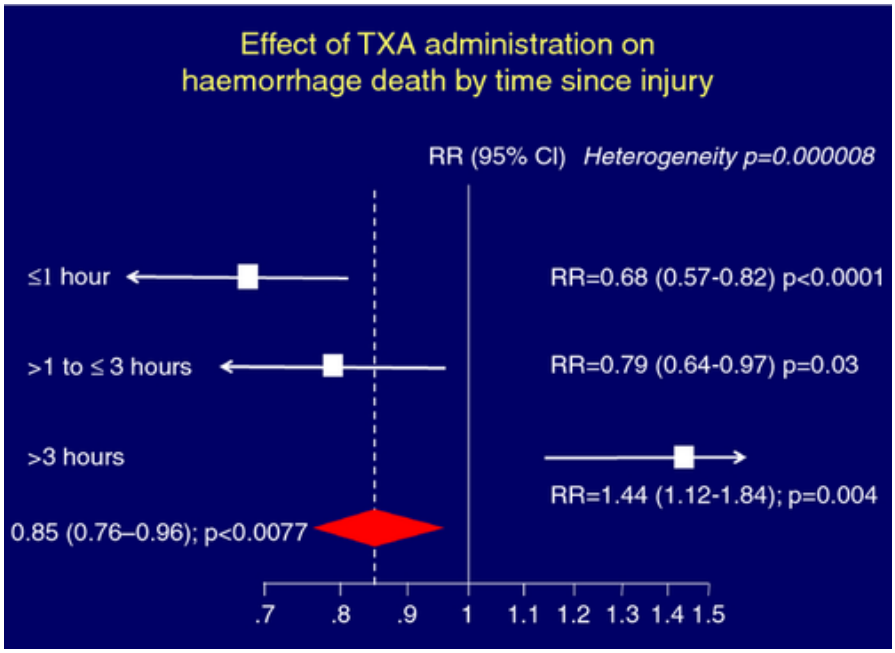


Fig. 1 shows the impact of the administration of tranexamic acid (TXA) on death as an interval of time in patients with hemorrhage, RR(risk ratio) CI (confidence interval)

Additional study carried out by Cal-PAT (California Prehospital Antifibrinolytic Therapy), has investigated the outcomes of pre-hospital administration of TXA in patients presenting with hemorrhagic shock.
The trial included 724 patients, divided equally to receive prehospital TXA or none.
Trial results recommend the pre-hospital application of TXA as it may improve survival outcomes in patients presenting with signs of hemorrhagic shock (21) by Stabilizing blood clots and reducing fibrinolytic activity leading to a reduction in D-dimer levels. (22)
This study also demonstrated a decrease in mortality over 24, 48 hours, and 28 days time periods, blood transfusion needs and length of hospital stay among patients receiving prehospital TXA (fig 2).
There was no difference in the incidence of occurrence of adverse effects such as thromboembolism, myocardial infarction, or neurologic events among the two groups. (21)

Fig 2. Patient outcomes in Cal-PAT study. (21)

Table 1. Patient outcomes for the control and TXA groups.

	TXA (n=362)	Control (n=362)	Statistic with 95% CI*
Mortality at 24 hours	7 (1.9%)	13 (3.6%)	0.53 (0.21, 1.34)
Mortality at 48 hours	10 (2.8%)	16 (4.4%)	0.61 (0.27, 1.37)
Mortality at 28 days	13 (3.6%)	30 (8.3%)	0.41 (0.21, 0.8)
Total blood products transfused (in units), median (Q1, Q3)	1 (0, 6)	3 (2, 8)	2 (1.14, 2.86)
Hospital LOS (in days), median (Q1, Q3)	4 (1, 12)	8 (5, 15)	4 (2.35,5.64)
ICU LOS (in days), median (Q1, Q3)	4 (2, 8)	5 (3, 8)	1(0.65, 2.25)
Adverse events			
Thromboembolic events	2	2	Not Applicable
Myocardial infarction events	0	0	Not Applicable
Neurologic events	0	0	Not Applicable
Penetrating trauma	228 (63%)	228 (63%)	1 (0.74,1.35)
Male	293 (80.9%)	293 (80.9%)	1 (0.69, 1.45)
Age, years, mean ± SD	37.96 ± 16.11	37.64 ± 16.33	0.32 (-2.05, 2.69)
ISS, mean ± SD	16.08 ± 10.69	17.15 ± 11.71	-1.07 (-2.86, 0.72)
SBP, mmHg, mean ± SD	78.42 ± 16.17	83.66 ± 14.13	-5.24 (-8.48, -2)
GCS, mean ± SD	12.78 ± 3.71	13 ± 3.4	-0.22 (-1.01, 0.57)

TXA, tranexamic acid; *LOS*, length of stay; *ICU*, intensive care unit; *ISS*, Injury Severity Score; *SD*, standard deviation; *SBP*, systolic blood pressure; *GCS*, Glasgow Coma Scale Score; *OR*, odds ratio; *CI*, confidence interval; *Q1*, 25th percentile; *Q3*, 75th percentile.
*Reported as odds ratio and the corresponding 95% confidence interval or difference in median or mean between TXA and control groups, depending on the variable type.

Fig. 2 Trauma patient's factors and outcomes in the Cal-PAT study among tranexamic acid(TXA) and control groups. CI(confidence interval), ICU(intensive care unit), LOS(length of stay), ISS(injury severity score), SD(standard deviation), SBP(systolic blood pressure), GCS(Glasgow coma scale).

In conclusion, the current protocol in trauma suggests the administration of a total of 2 grams of TXA, given as a loading dose of 1g followed by an infusion of 1g over 8 hours within 3 hours in trauma patients.

The use of tranexamic acid in obstetrics

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide.
PPH is defined as blood loss of more than 500 mL in the first 24 hours after vaginal labor or 1000 mL after cesarean section, or any blood loss that is sufficient to compromise hemodynamic stability. (23)
According to the WOMAN (World Maternal Antifibrinolytic) trial, which was published in 2017, consisted of women diagnosed with postpartum hemorrhage after vaginal birth or cesarean delivery from 193 hospitals in 21 countries, tranexamic acid was found to reduce deaths due to bleeding with no major increase in thromboembolic events, while the greatest effect was seen when women received tranexamic acid within 3 h of PPH (fig.3).
In the trial, women were to receive either 1g IV tranexamic acid or a matching placebo. If bleeding continued after 30 min or stopped and restarted within 24 hours of the first dose, a second dose of 1g of TXA or placebo was given.
However, TXA did not seem to show a reduction in death from all causes, or a decrease in rates of hysterectomies, the occurrence of adverse effects between the groups did not differ as well.(24)
Following the WOMEN trial, WHO has updated its recommendations for women with PPH to

receive 1 g tranexamic acid intravenously as soon as possible, followed by a second dose if bleeding continues after 30 min or restarts within 24 h since the first dose-1B level recommendation. (25)(26)
A recent review that analyzed the efficacy of pre-incisional TXA in cesarean section and the use of TXA after vaginal delivery, with uterotonic co-administration, showed a decrease in bleeding, blood transfusion, and medical interventions among women who received TXA. (27)
Yet the NATA (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis) consensus guidelines, do not recommend the routine use of tranexamic acid as prophylaxis to prevent PPH and advise to reserve its use for antepartum bleeding and in women at increased risk for developing PPH, with the administration of TXA at doses of 0.5 to 1g, in addition to oxytocin in patients with high risk of PPH. (26)
It should be noted that tranexamic acid should be given in addition to the usual treatments for the management of postpartum hemorrhage including the administration of medical (uterotonics), and surgical interventions, regardless of the cause of hemorrhage or the mode of delivery. (23)
TXA should be administered slowly as an IV injection over 10 min because bolus injection carries a potential risk of lowering blood pressure. (28)

Overall there may be a debate regarding the prophylactic administration of TXA in order to prevent PPH in vaginal and cesarean deliveries, however, there are no official recommendations for its use as a prophylactic agent.

Fig. 3: The effects of early administration of TXA on death in PPH.(24)

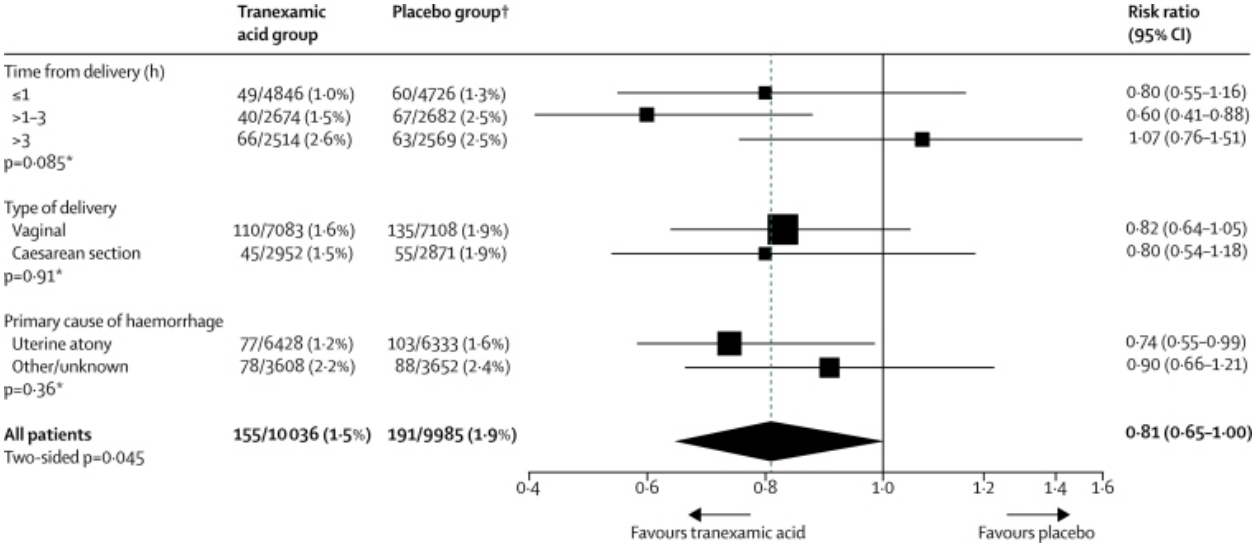


Fig.3 Death from postpartum hemorrhage by subgroup, showing a favorable outcome in women treated with tranexamic acid within 3 hours.

Tranexamic acid use in traumatic brain injuries

The use of TXA in traumatic brain injuries (TBI) has been recently studied in CRASH 3 trials. CRASH3 trial is a randomized, multicentered, placebo-controlled trial investigating the effects of TXA on patients suffering from TBI.
The trial enrolled 9202 patients within 3 hours of injury with a GCS score ≤ 12, or evidence of intracranial bleeding seen on CT scan with no extracranial bleeding, to receive TXA (loading dose of 1g over 10 min followed by 1g infusion over 8 hours) or placebo. (29)
Trial results have shown that patients in the TXA group had a lower incidence of death related to brain injury in comparison to the patients treated with a placebo (18.5% vs 19.8%)
A significant reduction in the risk of head injury-related death was seen in patients with mild to moderate TBI, while the risk for thrombotic complications or seizures did not differ between the TXA and the placebo groups. (30)
A different meta-analysis done on the impact of TXA on TBI indicated that administration of a loading dose of 1g TXA diluted with 100 ml normal saline within 10 to 30 minutes after admission may reduce the growth of hemorrhagic mass in the brain and thus reduce mortality.(31)
An additional randomized controlled trial TICH2 (tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage) studied 2307 patients with intracerebral hemorrhage who were treated within 8 hours of initiation of bleeding with TXA over placebo.
TXA was given at a rate of 1 g of an IV TXA bolus followed by an 8-hour 1g infusion or matching placebo.
The results of the trial showed reduced mortality within 7 days and fewer adverse effects in the TXA group in addition to reduction of the hematoma expansion and volume of the bleeding. However the functional status of the patients after 90 days did not differ between the placebo and tranexamic acid recipients. (32)

Tranexamic acid in cardiology

Cardiac surgeries carry a high risk for blood loss and blood transfusions.
Since some surgical procedures require the patients to be connected to the cardiopulmonary bypass machine (CPB) Coagulopathy is a common complication among them, resulting from hemodilution, platelet degradation, and thrombin formation which increase overall fibrinolytic activity, as well as the administration of anticoagulants prior to the surgery. (33)

The Aspirin And Tranexamic Acid For Coronary Artery Surgery (ATACAS) RCT
Has compared TXA with placebo in patients undergoing coronary artery surgery,
A dose of 100 mg per kg or placebo was given intravenously 30 min after the induction of anesthesia.
During the trial several incidences of seizures has been reported, it was believed to be dosage dependent and thus the dosage was reduced by half to 50 mg per kg.
The trial reported that the group receiving TXA over a placebo had a reduced risk for bleeding, blood transfusion, and reoperation due to hemorrhages, with no increased risk for thrombotic complications.

However, patients receiving TXA had a higher incidence of postsurgical seizures in comparison to the placebo. (34)
The European Association of cardiothoracic anesthesiology has recommended the use of TXA in cardiac surgery as an A1-level recommendation. (35)

Table.1: Recommendation level for the use of TXA in cardiac surgery. (35)

Recommendations	Class[a]	Level[b]
Antifibrinolytic therapy (TXA, aprotinin and EACA) is recommended to reduce bleeding and transfusions of blood products and reoperations for bleeding (TXA and aprotinin).	I	A

Recommendation of the European Association of cardiothoracic anesthesiology to use tranexamic acid (TXA) as antifibrinolytic therapy - A1 level recommendation.

According to the cardiac surgery transfusion risk scale, the suggested TXA in cardiac surgeries is as follows:

- Low-risk patients, a bolus of 10 mg per kg, before sternotomy and additionally 1 mg/kg-1.h-1 perfusion throughout the surgery.
- High-risk patients, a bolus of 30 mg per kg, before sternotomy in addition to 10mg.kg-1.h-1 perfusion throughout the surgery. (35)(33)

Tranexamic acid in orthopedic surgery

TXA has been widely utilized in Orthopedic Surgery, given the fact that orthopedic surgeries involve significant amounts of blood loss and sequentially increased needs for blood transfusions.
One of the most studied fields in the use of TXA in orthopedics is its use in total joint arthroplasty (TJA), total hip arthroplasty (THA) and total knee arthroplasty (TKA) surgeries.
Up to 37% of patients having THA and 21% of patients having TKA will require blood transfusion (36), It is estimated that the average blood loss in THA and TKA can reach up to 1-2 Liters. (37)(38)
Numerous studies have tried to establish the optimal amount and route of administration of TXA, it was found that all routes of administration were helpful in reducing blood loss compared to placebo(39)(40), yet the best dosage and route are yet to be determined.
A network meta-analysis studied 32 RCTs, comparing different routes of administration of

TXA(IV, oral and topical), have found out that the IV route had the best outcomes regarding reduction of blood loss and transfusion rates. (41)
According to the guidelines published by The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society and Knee Society (THS, TKS), and The American Society of Regional Anesthesia and Pain Medicine (ASRA), TXA has been proven to be effective in reducing bleeding in TJA compared to placebo.
IV and topical administration were found to reduce the risk of transfusion compared to placebo by 60% and 71%, respectively in TKA.
Regarding the route of administration whether multiple or single doses of IV or oral TXA reduce the risk for blood loss or transfusion the guidelines state that no significant differences were found in order to conclude that one way is preferred over the other.
However, the guideline suggests that in primary TJA the application of TXA would most benefit when applied before the incision.
In a meta-analysis included in the guidelines it was determined that low dose (≤ 1.5g) and high dose (> 1.5g) of topical TXA had no difference regarding reduction of blood loss and transfusion rates in hip and knee arthroplasties thus higher dose of topical TXA is effective as a low dose.
Regarding the IV route, no additional reduction in blood loss was reached in a hip or knee arthroplasty with high dose IV (≥ 20mg/kg or > 1g) TXA compared to low dose IV (< 20mg/kg or ≤ 1g) TXA.(39)

Fig .4 Summary of Current Evidence on Use of TXA in Orthopedic Surgery (42)

	Name of Study	OP	Type	Population	Methods	Conclusion
Arthroplasty	Lei et al, 2020[14]	TKA	RCT	132 patients	Patients groups: (A) no TXA (B) before incision, 3, 6, and 12 h later (C) before incision, 3, 6, 12, and 18 h later (D) before incision, 3, 6, 12, 18, and 24 h later	- A high initial-dose (60 mg/kg) IV-TXA before surgery followed by five doses is an effective approach to reduce blood loss, provide additional fibrinolysis and inflammation control, and ameliorate postoperative pain following TKA. - This will not increase the risk of treatment-related complications.
	Zhang et al, 2021[18]	TKA	RCT	175 patients	Patients groups (A) placebo (B) a single preoperative dose of 20 mg/kg IV-TXA (C) six-dose IV-TXA from the beginning of the procedure to subsequent 24 hours with the total dosage more than 6 g	The administration of six-dose IV-TXA during the first 24 hours resulted in reduced HBL following TKA without a measured increase in thromboembolic events.
	Zhao et al, 2019[20]	THA	Meta analysis	32 RCTs 2476 patients		Intravenous TXA may be the best way to reduce the need for transfusion and total blood loss.
	Xie et al, 2017[24]	TKA THA	RCT	18 RCTs involving TKA and 4 RCTs involving THA 2260 patients		- Topical and intravenous tranexamic acid have similar transfusion requirements and safety in THA and TKA. - Intravenous injection is associated with a smaller maximum drop in hemoglobin.
	Zhang et al, 2017[25]	THA	Meta analysis	7 RCTs 1762 patients	Combined application versus individual topical and intravenous application of tranexamic acid	The combined application showed lower transfusion rates, hemoglobin decline and total blood loss compared to the individual administrations.
	Yu et al 2017 [38]	SA	Meta analysis	Two RCTs and 2 non-RCTs 580 patients		TXA in SA decreases postoperative hemoglobin reduction, drainage volume, and total blood loss and does not increase the risk of complications

Fig.4 demonstrates several RCT and meta-analyses done in recent years in the field of arthroplasty and the use of TXA, different regimes and doses were tested, yet all the studies have proven that TXA was successful in minimizing blood loss and transfusion rates with no reports of increased complications such as thromboembolic events. (42)
In a meta-analysis of 73 RCTs, which included 4,174 patients and 2,779 controls done on the safety of TXA in patients undergoing orthopedic surgeries, TXA has been found to be safe in

terms of venous thromboembolism with no significant differences between the occurrence among patients in the controlled and TXA groups(43)
Additional meta-analysis regarding complications of TXA in lower limb orthopedic surgeries, done on 140 articles and a total of 9067 patients, undergoing various types of lower limbs surgeries(TKA, THA, and others) with different regimes of TXA (IV, IM, oral) have indicated that TXA was safe and did not increase the risk for thromboembolic complications compared to control (2.4% and 2.8%, respectively). (44)
Thus it may be concluded that the usage of TXA in orthopedic surgery does not increase the risk of developing thromboembolic complications when used on patients who are not contraindicated to be treated with TXA.

Tranexamic acid complications

Despite TXA being considered a safe drug when used as indicated, there have been reports on the dangerous effects it may implicit when misused.
Several cases in the literature have reported incidents in which TXA has been accidentally injected intrathecally in spinal anesthesia.
In a narrative review of 22 case reports, between the time period of July 2018 to September 2022, TXA was administered accidentally intrathecally by anesthesiologists.
The majority of the patients underwent orthopedics or cesarean surgeries.
Among the 22 patients, 8 have died, and 4 have suffered from long-term consequences,
19 patients have developed status epilepticus, and some have developed ventricular arrhythmias which resulted in death eventually. (45)
The common side effects reported were back pain radiating to the gluteal region and lower extremities, generalized tonic-clonic seizures, hypertension, tachycardia, ventricular arrhythmias, and death. (46)
An additional article examined 21 incidences of accidental intrathecal injection of TXA between the years 1960 to 2018, has reported that all patients suffered from neurological or cardiac complications which required resuscitation or intensive care, death been reported in 10 patients.(47)
A high concentration of TXA in CSF causes neurotoxicity, the proposed mechanism behind it is that TXA inhibits GABA and glycine receptors, leading to increased glutamate release causing increased excitability.
TXA suppresses GABA-A inhibitory receptors in the cortex leading to decreased neuronal depolarization threshold, moreover, TXA is a structural analogue of glycine receptors it competitively inhibits them, contributing to its neurotoxic effect and possible outcome of convolution and seizures, hypertension and ventricular arrhythmias may be followed by sympathetic activation due to seizures. (48)
Up to date, there is no official guideline for reversing TXA-induced neurotoxicity.
Inhalational anesthetics such as desflurane, sevoflurane, and isoflurane as well as IV propofol increase glycine receptor function and may be effective in treating seizures induced by TXA,

another suggestion is to use benzodiazepines (lorazepam, midazolam, diazepam, and clonazepam) in order to increase GABA-A receptor activity. (49)
several case reports demonstrated favorable outcomes when CSF lavage was performed to dilute and replace TXA in CSF. (46)

Tranexamic acid safety

Some concerns have arisen regarding the safety of tranexamic acid and the possible side effects it may induce as an antifibrinolytic drug.
Studies have investigated the correlation between thromboembolic events and the use of tranexamic acid as well as other adverse effects.
In a meta-analysis and systematic review published by Taeuber, I on the Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality, examined 216 studies involving 125,550 patients undergoing surgical procedures who received IV TXA, placebo or no treatment, has reported 1020 (2.1%) thromboembolic events occurred in the tranexamic acid group and 900 (2.0%) thromboembolic events in the control group.
These results suggest that there was no significant difference between thromboembolic events between the two groups regardless of the dosing of TXA, concluding that TXA does not increase the risk of thromboembolic events.
However the findings in patients undergoing neurological surgical interventions who received TXA were inconclusive, hence the authors suggest more trials are needed within this group in order to establish whether TXA increased the risk of side effects.
The authors mention several limitations to their study that could have affected the result of their study such as asymptomatic thrombosis and the use of postoperative thrombosis prophylaxis.(50)
An additional systematic review and meta-analyses done on the effect of tranexamic acid on thrombotic events and seizures in bleeding patients included 234 studies with 102,681 patients. This review included 124 trials in orthopedic surgery, 47 trials in cardiac surgery, 22 trials in obstetric and gynecological surgery, 7 trauma trials (including traumatic brain injury), 9 trials in non-traumatic intracranial hemorrhage, and 3 trials on gastrointestinal bleeding.
The review found that overall TXA did not increase the risk of developing thromboembolism in comparison to a placebo.
Yet the risk of stroke appeared higher in the TXA group than in the control group in patients presenting with intracranial hemorrhage. (Fig.5)
It was also reported that cardiac patients treated with TXA had an increased risk of developing seizures when TXA was given at a dose higher than 2g/day. (51)

Fig.5: Forest plot comparing tranexamic acid and control for primary outcome. (51)

	Studies	Events, No. / total TXA	Control	RR (95% CI)
Thrombotic events	230	1342/52103	1278/50211	1.00 (0.93-1.08)
Seizures	40	404/30351	351/29847	1.18 (0.91-1.53)
Venous thromboembolism	208	532/50037	454/48447	1.04 (0.92-1.17)
Acute coronary syndrome	107	421/42763	476/41663	0.88 (0.78-1.00)
Stroke	106	446/42924	389/42014	1.12 (0.98-1.27)

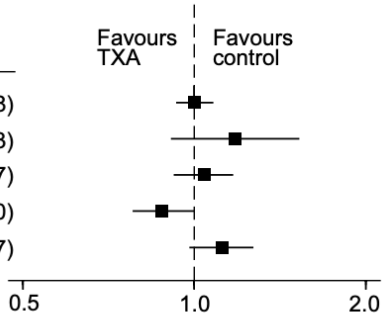


Fig. 2 Forest plot comparing tranexamic acid and control for primary outcome. TXA, tranexamic acid. RR, risk ratio. CI, confidence interval

The incidence of adverse events in the tranexamic acid (TXA) group in comparison to the incidence of the same adverse effects in the control group in multiple studies. RR(risk ratio), CI(confidence interval), with a remark incidence of seizures among patients receiving tranexamic acid.

Discussion

Mechanisms of action of tranexamic acid on the coagulation system :

In trauma patients or any other conditions which involve major bleeding the coagulation process may be disturbed due to several factors such as endothelial dysfunction, platelet dysfunction(52) inflammatory responses, trauma-induced coagulopathy and others, thus bleeding may continue and external interventions are needed in order to stop the bleeding.

The most studied pharmacological agent to stop fibrinolysis is tranexamic acid.

In order to understand the effect of tranexamic acid on the coagulation system it is essential to realize its role within the coagulation system.

Tranexamic acid is an anti-fibrinolytic agent.

The importance of antifibrinolysis lies within its inhibition of fibrin degradation (a key protein in blood clotting).

Upon bleeding the coagulation system takes place.

The coagulation system consists of primary and secondary hemostasis and fibrinolysis.

In order to stay on the topic and not go deep into the physiology of hemostasis and the coagulation process the focus will remain on the role of fibrin within the coagulation system and its link to tranexamic acid.

Once bleeding occurs the coagulation system is activated to form a clot to stop the bleeding.

Fibrinogen is a protein produced by the liver which circulates in the bloodstream and is converted to fibrin by the enzyme thrombin, to form a meshwork of fibers that traps platelets and blood cells to stabilize and form a clot that will prevent the continuation of the bleeding.

Once the clot is formed and stabilized it is degraded in a process called fibrinolysis.

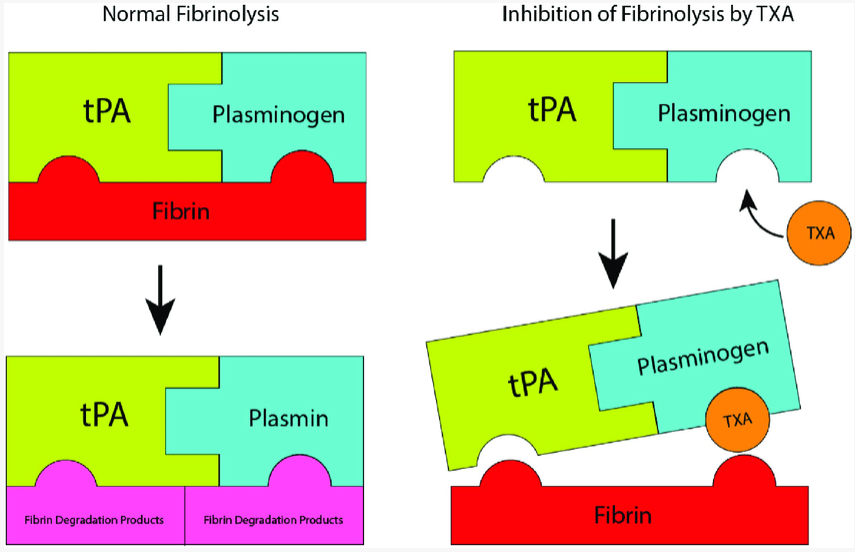
Plasminogen is a protein synthesized by the liver and converted by the enzymes tissue plasminogen activator (tPA), factor 9a, factor 12a, and kallikrein into its active form plasmin.

Plasmin in turn cleaves fibrin, this process degrades the meshwork and the clot dissolves.

Plasminogen has binding sites for lysine and since TXA is an analogue of lysine molecules it

competitively binds to its binding sites preventing tissue plasminogen activator from binding to it and converting into plasmin, hence preventing the binding of plasmin to fibrin and the clot dissolution and degradation. (53,54)(fig.5)

Figure 5: normal fibrinolysis vs TXA mechanism of action (55)



Demonstration of initiation of a normal fibrinolytic process and the yielded degradation products as shown in the left side, vs the inhibition of fibrinolysis by tranexamic acid (TXA) preventing the interaction between plasminogen and fibrin as shown in the right side. tPA (Tissue Plasmin Activator).

Conclusion :

As has been previously discussed tranexamic acid plays a pivotal role in the management of acute bleedings, as an antifibrinolytic drug tranexamic acid halts the transformation of plasminogen to plasmin and thereby prevents the breakdown of fibrin clots and promotes hemostasis.

Several major trials investigating the impact of tranexamic acid on acute bleeding, have concluded that tranexamic acid reduces bleeding and blood transfusion rates among trauma patients and in various surgical procedures.

In trauma patients, early administration of tranexamic acid has been found to reduce mortality rates by reducing hyperfibrinolysis and minimizing excessive blood loss.

Similarly, in surgical procedures, tranexamic acid has demonstrated efficacy in reducing blood loss and blood transfusion requirements.

Concerns have arisen regarding its safety, since thromboembolic events and seizures were reported among patients treated with tranexamic acid, although the major trials have stated that

thrombotic events were not increased in the tranexamic group, further and deeper investigation of its adverse effects are needed in order to determine its safety.

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