

The Role of Tranexamic Acid in the Prevention of Perioperative Hemorrhage

Iqra Imtiaz, Sana Fatima, Abu Haraira Sabir, Hira Ashraf

IMPORTANCE Significant blood loss can occur as a result of trauma, surgery, anticoagulation, obstetric complications, and hemostatic disorders. As there are many diverse causes of hemorrhage, the availability of a clinically safe and effective hemostatic agent is the need of the hour. Tranexamic acid is one of the most commonly used and widely researched anti-fibrinolytic agents. Its role in trauma-associated, postoperative, and postpartum hemorrhage has been well recognized. However, the utility of tranexamic acid goes farther than these common indications, supported by accruing data suggesting its ability to reduce blood loss along with improvement in clinical outcomes in many hemostatic challenges without increasing thromboembolic risk.

OBJECTIVE To review the clinical application and effectiveness of tranexamic acid in the prevention of intraoperative hemorrhage.

METHODS: Secondary data were selected by utilizing three steps; identification of 490 articles, recruitment of 116 articles, and selection of 61 articles for the systematic review. Inclusion and exclusion criteria were designed according to PRISMA protocol.

RESULTS Tranexamic acid has reduced perioperative hemorrhage and blood transfusion requirements in elective surgical procedures. Many studies established the efficacy of tranexamic acid and its safety without raising thromboembolic risk, precipitating kidney failure, or their complications.

CONCLUSION In multiple clinical scenarios, tranexamic acid has proven to prevent hemorrhage without increasing thromboembolic risk and has broad-spectrum clinical indications. However more caution and regulatory guidelines need to be established to prevent the rare incidence of complications so as thromboembolism and seizures.

KEYWORDS Tranexamic acid, Prevention of haemorrhage, Intraoperative, General surgery, Anti fibrinolytic

HOW TO CITE Imtiaz I. The Role of Tranexamic Acid in the Prevention of Perioperative Hemorrhage. *Archives of Surgical Research*. 2022, 3 (2):19-28. <https://doi.org/10.48111/2022.02.04>

Systematic Literature Review

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author:

Sana Fatima, Shalamar Medical and Dental College, Lahore. sanafatima2225@gmail.com <https://doi.org/10.48111/2022.02.04>

Tranexamic acid, a synthetic amino acid has shown to be effective at preventing complications of bleeding in various hemostatic challenges due to its antifibrinolytic activities and reducing mortality rate with negligible side effects.¹⁻⁷ In one study, tranexamic acid has shown to decrease bleeding by nearly one-third as compared to placebo.⁸ A hemostatic agent, such as tranexamic acid, with wide-ranging applicability and insignificant side effects is desirable as a part of supportive care protocol for hemorrhage.³

Massive blood loss following severe trauma or surgical intervention remains one of the most common life-threatening emergencies.⁹⁻¹¹ Haemorrhagic shock associated with trauma is the recurrent cause of preventable

mortality, along with hyper-fibrinolysis at the time of hospitalization is a well-known predictor of mortality.¹²⁻¹⁴ Tranexamic acid has been extensively used for the prevention and treatment of hemorrhages and hyper-fibrinolysis. Clinical data has shown that timely administration of tranexamic acid following severe trauma can significantly improve the rate of survival. Studies are focused on the intravenous administration of tranexamic acid. However oral preparations have the same efficacy and safety.¹⁵⁻¹⁸

The decrease in intraoperative hemorrhage and the consequential decline in blood transfusion requirement has prompted the European Society of Anaesthesiology and Task Force for Advanced Bleeding Care in Trauma to issue a 1A recommendation in their guidelines for use of tranexamic

acid in the event of perioperative and trauma-associated hemorrhage.^{10,11}

METHODS

Search engines employed to obtain scientific data for this review were; PubMed and Google Scholar. After recruitment, data were carefully chosen based on the inclusion criteria.

Search Strategy, Data Extraction, and Inclusion Criteria:

We searched the Pubmed database using the terms: Search: (tranexamic acid) AND (perioperative hemorrhage) Filters: Free full text, from 2018 - 2022 Sort by: Most Recent. The Google Scholar database was also searched using the term: "tranexamic acid and perioperative hemorrhage." PRISMA

guidelines were used for the inclusion of data in this systematic review. For inclusion, the procedure was divided into three steps; identification, primary selection, and final selection. In the first step, 490 articles were identified. 16 articles were selected in the second step. In the final step, 11 most relevant and admissible articles were selected. The selected articles, based on randomized trials, contained clear abstracts, and no older than five years, and were peer-reviewed.

Exclusion Criteria: Articles published more than five years ago and articles without any abstract or background information were excluded. Articles with fewer references and a lack of proper author information and affiliation were also excluded.

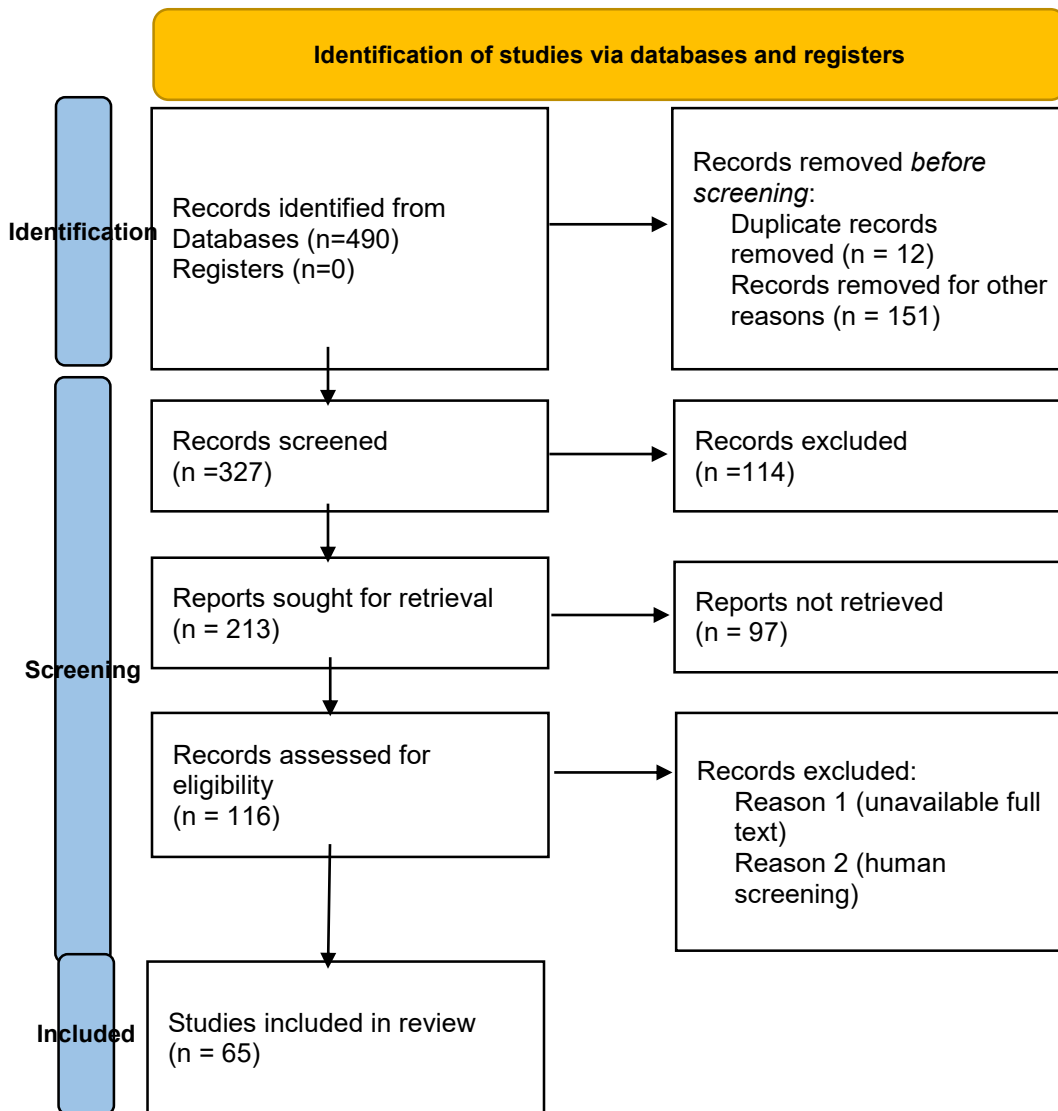


Figure 1: Article selection process through PRISMA flowchart; (From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71)

RESULTS

Bleeding remains one of the top perioperative complications in many surgical operations, including liver surgery. It has reduced the blood transfusion requirement and reoperation

rate following hemorrhage. Tranexamic acid has been used intraoperatively in different surgical fields to reduce blood loss and maintain hemostasis. The potential of tranexamic acid in avoiding bleeding during and after surgery has been a subject of interest. The most important benefit of treatment is the absence of deaths. Delayed administration of tranexamic acid reduces treatment benefits.³

Year	Author	Country	Research Method	Themes Identified
2022	SJ (SJ et al., 2022)	India	Cohort	Administration of tranexamic acid effectively reduces the need for blood transfusion.
2022	Zha (Zha et al., 2022)	People's Republic of China	Observational study	Preoperative administration of tranexamic acid reduces the need for blood transfusion without an increase in risk for DVT.
2022	Kukreja (Kukreja et al., 2022)	USA	Cohort	The use of a tourniquet to control hemorrhage in a limb is superior to using tranexamic acid peri-operatively.
2022	Koh (Koh et al., 2022)	UK	Systematic review and meta-analysis	Administration of tranexamic acid effectively reduces the need for blood transfusion in elective extrahepatic abdominopelvic surgery.
2022	Ek (Ek et al., 2022)	Australia	Cohort	Administration of tranexamic acid effectively reduces bleeding without any change in postoperative pain or range of motion.
2022	Compton (Compton et al., 2022)	USA	Comparative study	Administration of tranexamic acid effectively reduces the need for blood transfusion.
2022	Regan et al.	USA	Expert analysis	Tranexamic acid is highly effective in reducing bleeding but increases cardiovascular risk, due which an individualized approach should be used mind while administering it.
2021	Liu (Liu et al., 2022)	People's Republic of China	Cohort	There are various fibrinolytic phenotypes, only some of which demonstrate a response to tranexamic acid transfusion.
2021	Huynh (Huynh et al., 2021)	USA	Retrospective Chart Review	Administration of tranexamic acid effectively reduces the need for blood transfusion.
2021	Pinsornsak et al.	Thailand	RCT	Peri-articular injection of tranexamic acid in total knee arthroplasty is better for high risk patients in terms of adverse effects as compared to intravenous injection.
2021	Xie (Xie et al., 2021)	People's Republic of China	Case Report	Perioperative tranexamic acid transfusion may increase the risk of thromboembolism.
2021	Wei et al.	China	Systematic review and meta-analysis	Prophylactic tranexamic acid administration reduces blood loss during primary shoulder paediatric surgery.
2020	Kang et al.	China	RCT	Perioperative use of tranexamic acid in three doses during total knee arthroplasty reduces fibrinolytic response and inflammation safely.
2020	Monaco et al.	Italy	RCT	Infusion of tranexamic acid prophylactically in abdominal aorta aneurysm repair does not reduce intraoperative blood loss.
2020	Gao et al.	China	Clinical Study	Topical use of tranexamic acid during arthroscopic shoulder surgery reduces tissue swelling safely.
2020	Yoon et al.	Republic of Korea	RCT	Haemorrhage does not differ among different routes of tranexamic acid administration during reverse total shoulder arthroplasty. Topical administration has a better safety profile and should be preferred.
2020	Hurley	Ireland	RCT	Perioperative use of tranexamic acid during Latarjet procedure decreases post-operative bleeding, pain, swelling, hematoma formation and opioid use.

2020	Meissner et al.	Germany	Cohort Study	Perioperative use of tranexamic acid does not reduce haemorrhage after open –heart surgery. Its use should be confined to patients at risk of massive blood loss and hyperfibrinolysis.
2020	Khadanga et al.	India	Cohort Study	Tranexamic acid administration reduces blood loss during Off Pump Coronary Artery Bypass Grafting.
2019	Abdul et al	Nigeria	RCT	Adjunctive use of tranexamic acid with tourniquet during myomectomy reduces haemorrhage.
2019	Zhang et al.	People's Republic of China	RCT	Both peri and intra articular injections of tranexamic acid safely reduce bleeding in total knee arthroplasty.
2019	Liu et al.	Taiwan	RCT	Parenteral tranexamic acid administration reduces perioperative haemorrhage, pain and analgesia requirement during and after arthroscopic shoulder surgery
2019	Hirose et al.	Japan	Case series	Tranexamic acid is effective in improving range of motion after total knee arthroplasty.
2019	Fenger-Eriksen et al.	Denmark	RCT	Intraoperative and postoperative tranexamic acid administration reduces bleeding and need for blood transfusion.
2018	Kim et al.	Republic of Korea	Clinical Trial	Prophylactic tranexamic acid administration safely reduces blood loss during craniostylosis surgery.
2018	Saleh et al.	Egypt	RCT	Perioperative use of tranexamic acid during posterior spinal fusion surgery increases the need analgesia, indicating increased nociception.
2018	Sallam and Shady	Egypt	RCT	Parenteral and topical tranexamic acid administration safely reduces blood loss during abdominal hysterectomy.
2018	Prasad et al.	India	RCT	In abdominal tumour resection surgery, tranexamic acid bolus followed by infusion is superior to a single bolus in reducing haemorrhage.
2018	Shady et al	Egypt	RCT	Parenteral and topical tranexamic acid administration safely reduces blood loss during abdominal myomectomy
2018	Yozawa et al.	Japan	Observational study	Peri-articular injection of tranexamic acid in total knee arthroplasty is better for high risk patients in terms of adverse effects as compared to intravenous injection.
2018	Abbas et al.	Egypt	RCT	Perioperative use of tranexamic acid results in decreased haemorrhage during cesarean section for placenta accreta.
2018	Cvetanovich et al.	USA	RCT	Prophylactic tranexamic acid administration reduces blood loss during primary shoulder arthroplasty.
2017	Vara et al.	USA	RCT	Tranexamic acid administration in reverse total shoulder arthroplasty reduces bleeding and reduction in haemoglobin.
2017	Pauzenberger et al.	Austria	RCT	Intraoperative tranexamic acid administration reduces bleeding and need for blood transfusion, pain and hematoma formation in total shoulder arthroplasty.
2016	Sujata et al.	India	RCT	Preoperative intravenous tranexamic acid administration reduces the need for additional uterotonics in women at risk for post-partum haemorrhage.
2016	Topsoee et al.	Denmark	RCT	Prophylactic tranexamic acid administration safely reduces blood loss during elective benign hysterectomy.
2016	Mao et al.	People's Republic of China	Comparative Study	Both peri and intra articular injections of tranexamic acid reduce bleeding in total knee arthroplasty. However, peri-articular injection shows superiority in reducing haemorrhage.
2016	Alhomoud	Kuwait	Prospective randomized study	Tranexamic acid administration before laparoscopic sleeve gastrectomy reduces intraoperative bleeding without any side effects.
2015	Gillespie et al.	USA	RCT	Tranexamic acid reduces haemorrhage in total shoulder arthroplasty.
2014	Lundin et al.	Sweden	RCT	Prophylactic tranexamic acid bolus reduces blood loss during advanced ovarian cancer surgery
2013	Goswami et al.	India	RCT	Perioperative use of tranexamic acid during lower section caesarean section reduces the need for blood transfusions, especially in anaemic patients.
2013	Sentürk et al.	Turkey	RCT	Prophylactic administration of tranexamic acid before caesarean section safely helps reduce haemorrhage.

2013	Shahid and Khan	Pakistan	RCT	Perioperative use of tranexamic acid during lower section caesarean section reduces bleeding during surgery, but not after it.
2013	Xu et al.	China	RCT	Perioperative use of tranexamic acid safely results in decreased haemorrhage during cesarean section.
2013	Eldaba et al.	Egypt	RCT	Adjunctive use of single bolus tranexamic acid during functional endoscopic sinus surgery reduces haemorrhage and duration of surgery.
2012	Pfizer	India	Interventional Clinical Trial	Administration of tranexamic acid reduces blood loss during surgery.
2012	Aggarwal et al.	India	RCT	Sonoclot analysis is a safe and useful tool to monitor fibrinolysis and clotting in patients going intra-cardiac repair for tetralogy of Falot.
2012	Kumar et al.	India	RCT	Parenteral tranexamic acid administration safely reduces perioperative haemorrhage in percutaneous nephrolithotomy.
2012	Brum et al.	Brazil	RCT	Parenteral tranexamic acid administration does not reduce perioperative haemorrhage.
2011	Goobie et al.	USA	RCT	Perioperative use of tranexamic acid in surgical correction of craniosynostosis results in decreased haemorrhage and need for blood transfusion.
2011	Dadure et al.	France	RCT	Perioperative use of tranexamic acid in surgical correction of craniosynostosis results in decreased haemorrhage and need for blood transfusion in children pre-treated with erythropoietin.
2011	Shimizu et al.	Japan	RCT	In paediatric cardiac surgery, tranexamic acid reduces haemorrhage but not transfusion rate.
2008	Allanki et al.	India	RCT	Perioperative use of aprotinin and tranexamic acid during orthotopic liver transplant may reduce the need for blood transfusions.
2006	Wu et al.	China	RCT	Parenteral tranexamic acid administration reduces perioperative haemorrhage.
2005	Bulutcu et al.	Turkey	RCT	Perioperative use of aprotinin and tranexamic acid during cardiopulmonary bypass reduces the need for blood transfusions.
2005	Sethna et al.	USA	Clinical trial	Tranexamic acid administration safely reduces blood loss during surgery for scoliosis.
2004	Chauhan et al.	India	Clinical Trial	Tranexamic acid bolus administration before skin incision, on bypass, and after giving protamine gives the best results to reduce bleeding during paediatric cardiac surgery.
2004	Chauhan et al.	India	Clinical Trial	Infusion of tranexamic acid and/or Epsilon Aminocaproic Acid prophylactically in surgery for cyanotic heart disease equally reduces intraoperative blood loss and need for transfusion.
2000	Dalmau et al.	Spain	RCT	Prophylactic administration of tranexamic acid before liver transplant helps reduce haemorrhage within the first 24 hours. However, adverse effects such as arterial thromboses need to be kept in mind.
1997	Kaspar et al.	USA	RCT	Small dose tranexamic acid infusion reduces fibrinolysis but not the need for blood transfusion in orthotopic liver transplant surgery.
1996	Boylan et al.	Canada	RCT	High dose tranexamic acid infusion during orthotopic liver transplant may reduce the need for blood products transfusions.
1996	Zonis et al.	Canada	Clinical trial	Tranexamic acid administration in children undergoing cardiac surgery reduces bleeding only in the first 6 hours of the surgery.
1993	Yassen et al.	UK	RCT	Perioperative tranexamic acid administration may result in serious adverse effects, blood loss, and transfusion requirements.

DISCUSSION

Patented for the first time in 1957 and approved in the US in 1986, tranexamic acid is a synthetic lysine derivative used as an antifibrinolytic. Tranexamic acid is 10 times more potent than epsilon-aminocaproic acid.¹⁹ Tranexamic acid competitively inhibits the activation of plasminogen to

plasmin, hence, inhibiting the pathway of fibrinolysis. The recommended dosage of Tranexamic acid after cervical conisation is 1.5 g thrice daily for up to 14 days postoperatively¹⁹; though administration of Tranexamic acid is not recommended for mild gynecological interventions e.g. myomectomies.^{11, 20} It does so by blocking the lysine sites of plasminogen completely,²¹ to keep in check the extension of coagulation and clot formation beyond the

injury.²² At higher doses, it can directly inhibit plasmin function.²³ By inhibiting the binding of plasmin to fibrin, it prevents the dissolution of fibrin, thereby, stabilizing clot and preventing hemorrhage.

The therapeutic indications for IV, topical or oral tranexamic acid depend on the severity of the clinical condition and physicians' assessment. Major indications include preoperative hemorrhagic prophylaxis and perioperative and postoperative hemorrhage management. It is especially useful in geriatric populations undergoing surgery who are more vulnerable to bleeding and other perioperative complications such as thrombosis mainly due to their comorbidities.⁷ Other indications include bleeding in gastrointestinal conditions, UTIs, menorrhagia, epistaxis, trauma, and coagulopathies. (Table 1) It is used perioperatively in cases where a decrease in hemoglobin drop, blood loss, drain output, and blood transfusion rate is highly desired without an increase in adverse effects such as DVT or infection.²⁴ Perioperative hemorrhage makes for problematic dissection, unclear surgical field, poor healing of surgical site, increased incidence of complications, and poor functional results.²⁵

It has been used and studied widely in orthopedic procedures with remarkable results^{26,27} Tranexamic acid has long been studied for its efficacy and safety. It has been used by clinicians due to its desired outcomes for years. It may be used intravenously or topically, both methods being remarkably advantageous.²² But its widespread and over-the-counter use deserves a safety and efficacy profile.

Intravenous administration

Prophylaxis and treatment of bleeding due to a local or systemic hyperfibrinolysis
Menorrhagia
Gastrointestinal bleeding
Bleeding in urinary tract infections, post-op bleeding following prostatectomy
Ear, nose, and throat surgery
Gynecological or obstetric hemorrhage
Abdominothoracic and cardiac surgery
Antidote in bleeding needing immediate treatment in patients on fibrinolytic treatment

Oral administration

Hypermenorrhoea (menorrhagia)
Prostatectomy
Epistaxis
Conisation of the cervix
Prophylaxis of recurrent traumatic bleeding
Mucosal bleeding in patients with coagulopathies
Hereditary angioneurotic edema

Table 1 : Indications for tranexamic acid

The role of tranexamic acid specifically in elective surgeries is reviewed in this article. Many studies support the use of

tranexamic acid in pre, peri, and postoperative bleeding. It reduces the incidence of hemorrhage, hence, theoretically reducing the blood transfusion requirement. Practically this is not always the case.²⁸ Blood transfusions themselves pose the threat of early recurrence of various neoplasia, the transmission of viral infections, hypersensitivity reactions, circulatory overload, bacterial contamination, and reduced immunogenicity.²⁹ But the real question is does this desired outcome of hemorrhage prevention come with undesired side effects? Does it increase the incidence of thromboembolism, ischemic organ damage, or disseminated intravascular coagulation?

The S3 guidelines of the German Society of Accident Surgery³⁰, Austrian Society for Anaesthesiology, Resuscitation and Intensive Care, and European guidelines^{10, 11} recommend early administration of tranexamic acid whenever hyper-fibrinolysis is suspected in polytrauma patients.³¹ The CRASH-2 study shows that administration of tranexamic acid later than 3 hours is associated with increased mortality,¹⁵ suggesting it should be used as early as possible.¹⁹ The use of tranexamic acid is well-known in acute bleeding following severe trauma due to this study.^{17,32-34} However, in some literature, it is not more effective than other measures to control hemorrhage.³⁵ Another systemic literature review demonstrates the advantage of using tranexamic acid for decreased bleeding risk in elective extrahepatic surgical operations.³⁶ This study also makes known no increased risk of thromboembolism.³² The WOMAN trial³⁷ also established that tranexamic acid should be administered as soon as possible after the initial onset of bleeding, and reported decreased incidence of deaths. The optimal timing and dosage of administration, however, remain debated.³⁸ It is to be extrapolated from the HALT-IT trial that bleeding from tranexamic acid has different effects on different populations and different pathophysiologies of hemorrhage.³⁶ Two important guidelines for anticoagulation management issued by the Society of Thoracic Surgeons (STS) and the European Association for Cardio-Thoracic Surgery (EACTS) deal with the intraoperative use of anti-fibrinolytic in cardiac surgeries: both Tranexamic acid and Epsilon-aminocaproic acid are consistently recommended to minimize hemorrhage and blood transfusion requirement.^{9, 39}

Many contraindications have been reported for tranexamic acid but no study reported an increased risk of thromboembolism, hypoxic tissue injury, and disseminated intravascular coagulation even with a longer duration of administration and higher dosages.⁴⁰ Data available continue to support the use of tranexamic acid in medical and surgical cases due to its strong safety profile with

minimal side effects and no increased thromboembolic risk.⁴¹ Caution should be taken when dealing with patients having kidney dysfunction as tranexamic acid clearance is dependent on renal creatinine levels so dosage should be reduced but it does not increase the risk of renal failure (Table 2).⁴²

Hypersensitivity to TXA	
Early pregnancy, in late pregnancy only when vitally indicated	
Disturbances of color vision	
Massive bleeding in the upper urinary tract (risk of ureter obstruction due to clot)	
Acute venous or arterial thrombosis	
Severe renal impairment	
History of convulsions	
Intrathecal and intraventricular injection, intracerebral administration	(risk of cerebral oedema and convulsions)
Disseminated intravascular coagulation (DIC)	

Table 2: Contraindications of tranexamic acid

Dosing regimens sometimes vary owing to the practitioner’s clinical assessment, deciding whether re-dosing is necessary. The prescribed regimen is 1 to 1.5 gm or 15 to 25 mg/kg up to four times daily⁴³, and 3g for topical use.⁴⁴ A dose of 15mg/kg was more efficacious as compared to 10mg/kg in one study.⁴⁵ Repeated doses have the disadvantage of non-uniform levels of tranexamic acid in the blood, which leads to unpredictable coagulopathic behavior in blood.⁴⁶ Nonetheless, the outcome supports its utility in preventing life-threatening blood loss with negligible adverse effects perioperatively.³ Since, tranexamic acid prevents the lysis of already formed fibrin deposits, it should increase the thromboembolic risk. However, the literature did not report any statistically significant incidence of thromboembolism with the use of tranexamic acid in major surgeries.^{37,47} Tranexamic acid has a well-known safety profile with no increase in the risk of thromboembolism, irrespective of its dosage. (Table 3)

Events	RR	95% CI
Myocardial infarction	0.96	0.48-1.90
Stroke	1.25	0.47-3.31
Deep venous thrombosis	0.77	0.37-1.61
Renal failure	0.73	0.16-3.32

Table 3 Side effects of Tranexamic acid

There is a growing literature body advocating for perioperative use of tranexamic acid for a remarkable reduction in hemorrhage with negligible adverse effects in different fields, especially in orthopedic surgery as suggested by SJ et al.⁷, Zha et al.⁴⁷, Liu et al.,²⁴ Ek et al.⁴⁸, Compton et al.³⁸, and Huynh et al.⁴⁹, with peri-articular injections having more potential benefits⁵⁰⁻⁵² Similar results have been observed in pelvic^{53,54}, extrahepatic, cardiac^{55,56} and liver^{57,58} surgery.^{4,36} It is also proven to be efficacious in the pediatric population.^{59,60} It is postulated that a blood transfusion-free hepatectomy may be possible with the adjunctive use of tranexamic acid.⁶¹ Tranexamic acid is found to be superior to ε-aminocaproic acid and other such antifibrinolytics in this regard in one study.⁶² Another study contradicts this finding and has found epsilon-amino caproic acid and tranexamic acid to be equally effective.⁶³

There may be multiple factors for explosive hemorrhage after liver transplant, some of which include mixing of tissue plasminogen activator, hypothermia, and residual heparin from the donor's liver.⁶⁴ Tissue plasminogen activators arise about 30 minutes after the start of surgery, which theoretically poses to be the best time for the administration.⁶⁵ Even topical irrigation with tranexamic acid in benign hysterectomy significantly reduces hemorrhage and postoperative hemoglobin decrease,⁶⁵ with the advantage of reduced postoperative complications, and comparable effect to intravenous injection on reduction in hemorrhage^{66,67} In one study, tranexamic acid did not reduce the transfusion rate, but it is thought to be due to the already minimal need of blood transfusion in benign hysterectomy.⁶⁸ However in gynecological malignancy cases, tranexamic acid reduced the rate of transfusion by almost 12% in another study.⁶⁹ It is associated with a safe reduction in perioperative bleeding.⁷⁰ The antifibrinolytic action can be deduced by measurement of blood loss, D-dimers, clot lysis assay, thromboelastometry, and Sonoclot assay.^{71,72} It is also found to be useful in cardiac surgery in the pediatric population, although the calculation of the dosing regimen in such patients is complicated.⁷³ Chauhan et al.⁷⁴ have put forward a regimen of dose of 10mg/kg thrice (at the time of induction, on cardiopulmonary bypass, and after administration of protamine sulfate) during pediatric cardiac surgery, with good results.⁷⁵ A similar three-dose regimen showed good results in total knee arthroplasty.⁷⁶ Tranexamic acid use is also associated with a decrease in operative time, post-operative respiratory complications⁷⁷, pain, hematoma formation, blood volume loss in drainage,⁷⁸ anemia induced infarction, blood or blood products transfusions⁷⁹, recovery time⁸⁰ and hospital stay.⁸¹ which in turn reduces blood loss and morbidity.⁸² It however does not show a decrease in

postoperative blood loss either after discontinuation⁸³ or additional dosing⁸⁴. In some studies it has only shown to reduce intra-operative bleeding, more often only during the first 6 hours.⁸⁵ In other cases, it has not shown a benefit at all.⁸⁶ Some literature suggests that tranexamic acid is useful in only some cases, and in cases where it is not, it may cause ominous side effects such as fibrinolytic shutdown and thromboembolism⁸⁷, resulting in mortality.^{22,88} It is also postulated to increase nociception and hence, analgesia requirement and opioid use post surgery.⁸⁹ Some studies contradict this as there is of decreased hematoma formation and pain after using tranexamic acid^{90,91}

Tranexamic acid can be used safely as an anti-fibrinolytic with minimal side effects in surgical patients prophylactically as well as postoperatively.⁹² It has significantly reduced morbidity and mortality rates associated with hemorrhage. It has particular significance in developing countries where it is conveniently available and cost-efficient as opposed to other means to control bleeding.^{93,94}

CONCLUSION

Hemorrhage is one of the most serious complications and the leading cause of high mortality rate in postoperative patients. Hemorrhages following abdominopelvic, gynecological, and trauma surgeries are unwanted and life-threatening complications. To avert or manage this outcome without considering reoperation would be a significant advancement in surgical fields. Antifibrinolytic drugs such as tranexamic acid and aminocaproic acid have proven to be a life-saving miracle.

In multiple clinical situations, tranexamic acid has proven to prevent bleeding without increasing thromboembolic risk and has broad-spectrum clinical indications. Dosing regimens occasionally depend on the practitioner, but outcomes support their utility in preventing life-threatening blood loss with minimal side effects intraoperatively as well as postoperatively. However, the side effects should be kept in mind, which although rare, can be disastrous. The data reviewed in this literature study have shown that tranexamic acid is very effective in preventing hemorrhage-related deaths when timely administered.

ARTICLE INFORMATION

Accepted for Publication: March 23, 2022,
Published Online: June 30, 2022.

<https://doi.org/10.48111/2022.02.04>

Open Access: This is an open-access article distributed under the terms of the CC-BY License. © 2022 Imtiaz et al ASR.

Author Affiliations. Shalamar Medical and Dental College, Lahore.

Financial Support and Sponsorship: Nil.

Conflicts of Interest: There are no conflicts of interest

REFERENCES

- Maddali MM, Rajakumar MC. Tranexamic acid and primary coronary artery bypass surgery: a prospective study. *Asian Cardiovasc Thorac Ann*. 2007;15(4):313-319. doi:10.1177/021849230701500410
- Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*. 2014;349. doi:10.1136/BMJ.G4829
- Cai J, Ribkoff J, Olson S, et al. HHS Public Access. 2020;104(2):79-87. doi:10.1111/ejh.13348.The
- Koh A, Adiamah A, Gomez D, Sanyal S. Safety and Efficacy of Tranexamic Acid to Minimise Perioperative Bleeding in Hepatic Surgery: A Systematic Review and Meta-Analysis. *World J Surg*. 2022;46(2):441-449. doi:10.1007/S00268-021-06355-2
- Hunt BJ. The current place of tranexamic acid in the management of bleeding. *Anaesthesia*. 2015;70 Suppl 1:e18-53. doi:10.1111/ANA.E.12910
- Chornenki NLJ, Um KJ, Mendoza PA, et al. Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis. *Thromb Res*. 2019;179:81-86. doi:10.1016/J.THROMRES.2019.05.003
- SJ K, Ethiraj P, Shanthappa AH, Vellingiri K. Is Tranexamic Acid Safe and Efficacious in Hip Surgeries? *Cureus*. 2022;14(1). doi:10.7759/CUREUS.21249
- Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg*. 2013;100(10):1271-1279. doi:10.1002/BJS.9193
- Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91(3):944-982. doi:10.1016/J.ATHORACSUR.2010.11.078
- Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20(1). doi:10.1186/S13054-016-1265-X
- Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270-382. doi:10.1097/EJA.0B013E32835F4D5B
- Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma*. 2008;65(4):748-754. doi:10.1097/TA.0B013E3181877A9C
- Schöchl H, Cadamuro J, Seidl S, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest: results from a prospective observational thromboelastometry study. *Resuscitation*. 2013;84(4):454-459. doi:10.1016/J.RESUSCITATION.2012.08.318
- Cotton BA, Harvin JA, Kostousov V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. *J Trauma Acute Care Surg*. 2012;73(2):365-370. doi:10.1097/TA.0B013E31825C1234

15. Oлдashi F, Kerçi M, Zhurda T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23-32. doi:10.1016/S0140-6736(10)60835-5
16. Sydenham E. Thousands of lives could be saved using tranexamic acid for patients with bleeding trauma. *Inj Prev*. 2011;17(3):211. doi:10.1136/INJURYPREV-2011-040059
17. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012;147(2):113-119. doi:10.1001/ARCHSURG.2011.287
18. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERS II Study. *JAMA Surg*. 2013;148(3):218-225. doi:10.1001/JAMASURG.2013.764
19. Rossaint R, Bouillon B, Cerny V, et al. Management of bleeding following major trauma: an updated European guideline. *Crit Care*. 2010;14(2). doi:10.1186/CC8943
20. Caglar GS, Tasci Y, Kayikcioglu F, Haberal A. Intravenous tranexamic acid use in myomectomy: a prospective randomized double-blind placebo controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2008;137(2):227-231. doi:10.1016/j.ejogrb.2007.04.003
21. Sujata N, Tobin R, Kaur R, Aneja A, Khanna M, Hanjoora VM. Randomized controlled trial of tranexamic acid among parturients at increased risk for postpartum hemorrhage undergoing cesarean delivery. *Int J Gynecol Obstet*. 2016;133(3):312-315. doi:10.1016/j.ijgo.2015.09.032
22. Liu J, Wang H, Wu X, Lei Y, Huang W. Not all patients benefit from the postoperative antifibrinolytic treatment: clinical evidence against the universal use of tranexamic acid following total knee arthroplasty. *J Orthop Surg Res*. 2022;17(1):59. doi:10.1186/S13018-022-02958-0
23. De Leede-van der Maarl MG, Hilkens P, Bosch F. The epileptogenic effect of tranexamic acid. *J Neurol*. 1999;246(9):843. doi:10.1007/S004150050466
24. Liu Y, Shan D, Tian P, Li Z, Xu G, Fu X. Peri-Articular Injection of Tranexamic Acid Reduce Blood Loss and Transfusion Requirement During Total Knee Arthroplasty: A Meta-analysis. *Geriatr Orthop Surg Rehabil*. 2022;13:215145932211012. doi:10.1177/21514593221101264
25. Balik M, Kosina J, Husek P, Pacovsky J, Brodak M, Cecka F. Can the prophylactic administration of tranexamic acid reduce the blood loss after robotic-assisted radical prostatectomy? Robotic Assisted Radical Prostatectomy with tranEXamic acid (RARPEX): study protocol for a randomized controlled trial. *Trials*. 2022;23(1):508. doi:10.1186/S13063-022-06447-X
26. Cvetanovich GL, Fillingham YA, O'Brien M, et al. Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial. *JSES Open Access*. 2018;2(1):23-27. doi:10.1016/J.JSES.2018.01.002
27. Gao HL, Zhang JC, He Y, Zhai WT, Xiao LB, Shi Q. [Clinical study on the control of intra-articular hemorrhage by tranexamic acid after shoulder arthroscopy]. *Zhongguo Gu Shang*. 2020;33(3):238-241. doi:10.12200/J.ISSN.1003-0034.2020.03.010
28. Shimizu K, Toda Y, Iwasaki T, et al. Effect of tranexamic acid on blood loss in pediatric cardiac surgery: A randomized trial. *J Anesth*. 2011;25(6):823-830. doi:10.1007/S00540-011-1235-Z
29. Karanicolas PJ, Lin Y, McCluskey S, et al. Protocol: Tranexamic acid versus placebo to reduce perioperative blood transfusion in patients undergoing liver resection: protocol for the haemorrhage during liver resection tranexamic acid (HeLiX) randomised controlled trial. *BMJ Open*. 2022;12(2):29. doi:10.1136/BMJOPEN-2021-058850
30. Nr A, Gesellschaft D, Luisenstr L, et al. S3 – Leitlinie Polytrauma / . (012).
31. Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten – Gesamtnovelle 2020.
32. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17(10):1-80. doi:10.3310/HTA17100
33. Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg*. 2015;261(2):390-394. doi:10.1097/SLA.0000000000000717
34. Nadler R, Gendler S, Benov A, Strugo R, Abramovich A, Glassberg E. Tranexamic acid at the point of injury: the Israeli combined civilian and military experience. *J Trauma Acute Care Surg*. 2014;77(3 Suppl 2). doi:10.1097/TA.0000000000000325
35. Kukreja P, Johnson BM, Traylor C, et al. Comparison of the Utilization of Tranexamic Acid and Tourniquet Use in Total Knee Arthroplasty: A Retrospective Case Series. *Cureus*. 2022;14(5). doi:10.7759/CUREUS.24842
36. Koh A, Adiamah A, Gomez D, Sanyal S. Safety and efficacy of tranexamic acid in minimizing perioperative bleeding in extrahepatic abdominal surgery: meta-analysis. *BJS Open*. 2021;5(2). doi:10.1093/BJSOPEN/ZRAB004
37. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane database Syst Rev*. 2007;(4). doi:10.1002/14651858.CD001886.PUB2
38. Compton E, Goldstein RY, Nazareth A, Shymon SJ, Andras L, Kay RM. Tranexamic acid use decreases transfusion rate in children with cerebral palsy undergoing proximal femoral varus derotational osteotomy. *Medicine (Baltimore)*. 2022;101(2). doi:10.1097/MD.00000000000028506
39. Dunning J, Versteegh M, Fabbri A, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. *Eur J Cardiothorac Surg*. 2008;34(1):73-92. doi:10.1016/J.EJCTS.2008.02.024
40. (PDF) Gerinnungstabilisierung bei Polytrauma: Immer Tranexamsäure?
41. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr*. 2017;129(9-10):303-316. doi:10.1007/S00508-017-1194-Y/TABLES/2
42. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr*. 2017;129(9):303. doi:10.1007/S00508-017-1194-Y
43. Alhomoud H. The Effect of Tranexamic Acid on Blood Loss during Laparoscopic Sleeve Gastrectomy. doi:10.5005/jp-journals-10033-1266
44. Zhang S, Wang C, Shi L, Xue Q. Multi-route applications of tranexamic acid to reduce blood loss after total knee arthroplasty: a randomized controlled trial. *Medicine (Baltimore)*. 2019;98(30). doi:10.1097/MD.00000000000016570
45. Goswami U, Sarangi S, Gupta S, Babbar S. Comparative evaluation of two doses of tranexamic acid used prophylactically in anemic parturients for lower segment cesarean section: A double-blind randomized case control prospective trial. *Saudi J Anaesth*. 2013;7(4):427-431. doi:10.4103/1658-354X.121077
46. Prasad R, Patki A, Padhy S, Ramchandran G.

- Single intravenous bolus versus perioperative continuous infusion of tranexamic acid to reduce blood loss in abdominal oncological procedures: A prospective randomized double-blind clinical study. *J Anaesthesiol Clin Pharmacol*. 2018;34(4):529. doi:10.4103/JOACP.JOACP_122_17
47. Zha GC, Zhu XR, Wang L, Li HW. Tranexamic acid reduces blood loss in primary total hip arthroplasty performed using the direct anterior approach: a one-center retrospective observational study. *J Orthop Traumatol*. 2022;23(1):12. doi:10.1186/S10195-022-00638-7
 48. Ek ET, Wang KK, Bohan CM, Goulding NJ, Jamieson RP. Role of Tranexamic Acid in Arthroscopic Osteocapsular Release of the Elbow for Degenerative Arthritis. *Orthop J Sport Med*. 2022;10(4). doi:10.1177/23259671221089608
 49. Huynh PAN, Miller M, Will R. Intravenous Tranexamic Acid Decreases Blood Transfusions and Blood Loss for Patients with Surgically Treated Hip Fractures. *Geriatr Orthop Surg Rehabil*. 2021;12:1-5. doi:10.1177/21514593211063668
 50. Mao Z, Yue B, Wang Y, Yan M, Dai K. A comparative, retrospective study of peri-articular and intra-articular injection of tranexamic acid for the management of postoperative blood loss after total knee arthroplasty. *BMC Musculoskelet Disord*. 2016;17(1). doi:10.1186/S12891-016-1293-3
 51. Pinsornsak P, Phunphakchit J, Boontanapibul K. Efficacy and Systemic Absorption of Peri-articular Versus Intra-articular Administration of Tranexamic Acid in Total Knee Arthroplasty: A Prospective Randomized Controlled Trial. *Arthroplast Today*. 2021;11:1. doi:10.1016/J.ARTD.2021.06.005
 52. Yozawa S, Ogawa H, Matsumoto K, Akiyama H. Periarticular Injection of Tranexamic Acid Reduces Blood Loss and the Necessity for Allogeneic Transfusion After Total Knee Arthroplasty Using Autologous Transfusion: A Retrospective Observational Study. *J Arthroplasty*. 2018;33(1):86-89. doi:10.1016/J.ARTH.2017.08.018
 53. Abbas AM, Shady NW, Sallam HF. Bilateral uterine artery ligation plus intravenous tranexamic acid during cesarean delivery for placenta previa: a randomized double-blind controlled trial. *J Gynecol Obstet Hum Reprod*. 2019;48(2):115-119. doi:10.1016/J.JOGOH.2018.10.023
 54. Abdul IF, Amadu MB, Adesina KT, Olarinoye AO, Omokanye LO. Adjunctive use of tranexamic acid to tourniquet in reducing haemorrhage during abdominal myomectomy - A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2019;242:150-158. doi:10.1016/J.EJOGRB.2019.09.010
 55. Boylan JF, Klinck JR, Sandler AN, et al. Tranexamic Acid Reduces Blood Loss, Transfusion Requirements, and Coagulation Factor Use in Primary Orthotopic Liver Transplantation. *Anesthesiology*. 1996;85(5):1043-1048. doi:10.1097/0000542-199611000-00012
 56. Monaco F, Nardelli P, Pasin L, et al. Tranexamic acid in open aortic aneurysm surgery: a randomised clinical trial. *Br J Anaesth*. 2020;124(1):35-43. doi:10.1016/J.BJA.2019.08.028/ATTACHMENT3/3E55FD8E-F683-40EB-955F-7DDA63AAE1B6/MMC1.DOCX
 57. A. SD, Kapoor D, Gopal PBN, Subrahmanyam M, Ravichandra RS. Effect of antifibrinolytic drugs on transfusion requirement and blood loss during orthotopic liver transplantation: Results from a single center. *Asian J Transfus Sci*. 2008;2(2):61. doi:10.4103/0973-6247.42693
 58. YASSEN K, BELLAMY MC, SADEK SA, WEBSTER NR. Tranexamic acid reduces blood loss during orthotopic liver transplantation. *Clin Transplant*. 1993;7(5).
 59. Goobie SM, Meier PM, Pereira LM, et al. Efficacy of Tranexamic Acid in Pediatric Craniosynostosis Surgery: A Double-blind, Placebo-controlled Trial. *Anesthesiology*. 2011;114(4):862-871. doi:10.1097/ALN.0B013E318210FD8F
 60. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F. Tranexamic Acid Reduces Intraoperative Blood Loss in Pediatric Patients Undergoing Scoliosis Surgery. *Anesthesiology*. 2005;102(4):727-732. doi:10.1097/0000542-200504000-00006
 61. Wu CC, Ho WM, Cheng S Bin, et al. Perioperative Parenteral Tranexamic Acid in Liver Tumor Resection: A Prospective Randomized Trial Toward a "Blood Transfusion"-Free Hepatectomy. *Ann Surg*. 2006;243(2):173. doi:10.1097/01.SLA.0000197561.70972.73
 62. Dalmau A, Sabaté A, Acosta F, et al. Tranexamic acid reduces red cell transfusion better than ε-aminocaproic acid or placebo in liver transplantation. *Anesth Analg*. 2000;91(1):29-34. doi:10.1213/00000539-200007000-00006
 63. Chauhan S, Das SN, Bisoi A, Kale S, Kiran U. Comparison of Epsilon Aminocaproic Acid and Tranexamic Acid in Pediatric Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2004;18(2):141-143. doi:10.1053/J.JVCA.2004.01.016
 64. Kaspar M, Ramsay MAE, Nguyen AT, Cogswell M, Hurst G, Ramsay KJ. Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. *Anesth Analg*. 1997;85(2):281-285. doi:10.1097/00000539-199708000-00007
 65. Sallam HF, Shady NW. Reducing Blood Loss During Abdominal Hysterectomy with Intravenous Versus Topical Tranexamic Acid: A Double-Blind Randomized Controlled Trial. *J Obstet Gynaecol India*. 2019;69(2):173. doi:10.1007/S13224-018-1149-X
 66. Yoon JY, Park JH, Kim YS, Shin SJ, Yoo JC, Oh JH. Effect of tranexamic acid on blood loss after reverse total shoulder arthroplasty according to the administration method: a prospective, multicenter, randomized, controlled study. *J Shoulder Elb Surg*. 2020;29(6):1087-1095. doi:10.1016/J.JSE.2020.02.013
 67. Gillespie R, Shishani Y, Joseph S, Streit JJ, Gobezie R. Neer Award 2015: A randomized, prospective evaluation on the effectiveness of tranexamic acid in reducing blood loss after total shoulder arthroplasty. *J Shoulder Elb Surg*. 2015;24(11):1679-1684. doi:10.1016/J.JSE.2015.07.029
 68. Topsoe MF, Bergholt T, Ravn P, et al. Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy - A double-blinded randomized placebo-controlled trial. *Am J Obstet Gynecol*. 2016;215(1):72.e1-72.e8. doi:10.1016/j.ajog.2016.01.184
 69. Lundin ES, Johansson T, Zachrisson H, et al. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study. *Acta Obstet Gynecol Scand*. 2014;93(4):335-344. doi:10.1111/AOGS.12333
 70. Shahid A, Khan A. Tranexamic acid in decreasing blood loss during and after caesarean section. *J Coll Physicians Surg Pak*. 2013;23(7):459-462. doi:10.7203/jcpsp.459462
 71. Aggarwal V, Kapoor PM, Choudhury M, Kiran U, Chowdhury U. Utility of Sonoclot analysis and tranexamic acid in tetralogy of Fallot patients undergoing intracardiac repair. *Ann Card Anaesth*. 2012;15(1):26. doi:10.4103/0971-9784.91477
 72. Fenger-Eriksen C, D'Amore Lindholm A, Nørholt SE, et al. Reduced perioperative blood loss in children undergoing craniosynostosis surgery using prolonged tranexamic acid infusion: a randomised trial. *Br J Anaesth*. 2019;122(6):760-766. doi:10.1016/J.BJA.2019.02.017
 73. Bulutcu FS, Özbek U, Polat B, Yalçın Y, Karaci AR, Bayindir O. Which may be effective to reduce blood loss after cardiac operations in cyanotic children: Tranexamic acid, aprotinin or a combination? *Paediatr Anaesth*. 2005;15(1):41-46. doi:10.1111/J.1460-9592.2004.01366.X
 74. Chauhan S, Bisoi A, Kumar N, et al. Dose

- comparison of tranexamic acid in pediatric cardiac surgery. *Asian Cardiovasc Thorac Ann.* 2004;12(2):121-124. doi:10.1177/021849230401200208
75. Eldaba AA, Amr YM, Albirmawy OA. Effects of tranexamic acid during endoscopic sinus surgery in children. *Saudi J Anaesth.* 2013;7(3):229. doi:10.4103/1658-354X.115314
76. Kang B xin, Li Y lin, Xu H, et al. Effect of Multiple Doses of Intravenous Tranexamic Acid on Perioperative Blood Loss in Total Knee Arthroplasty: A Randomized Controlled Study. *Orthop Surg.* 2021;13(1):126-133. doi:10.1111/OS.12850
77. Kim EJ, Kim YO, Shim KW, Ko BW, Lee JW, Koo BN. Effects of Tranexamic Acid Based on its Population Pharmacokinetics in Pediatric Patients Undergoing Distraction Osteogenesis for Craniosynostosis: Rotational Thromboelastometry (ROTEM) Analysis. *Int J Med Sci.* 2018;15(8):788. doi:10.7150/IJMS.25008
78. Pauzenberger L, Domej MA, Heuberger PR, et al. The effect of intravenous tranexamic acid on blood loss and early post-operative pain in total shoulder arthroplasty. *Bone Jt J.* 2017;99B(8):1073-1079. doi:10.1302/0301-620X.99B8.BJJ-2016-1205.R1/ASSET/IMAGES/LARGE/BJJ-2016-1205.R1-GALLEYFIG7.JPEG
79. Wei Y, Zhang Y, Jin T, Wang H, Li J, Zhang D. Effects of Tranexamic Acid on Bleeding in Pediatric Surgeries: A Systematic Review and Meta-Analysis. *Front Surg.* 2021;8:471. doi:10.3389/FSURG.2021.759937/BIBTEX
80. Hirose H, Ogawa H, Matsumoto K, Akiyama H. Periarticular injection of tranexamic acid promotes early recovery of the range of knee motion after total knee arthroplasty. *J Orthop Surg.* 2019;27(3). doi:10.1177/2309499019864693
81. Vara AD, Koueiter DM, Pinkas DE, Gowda A, Wiater BP, Wiater JM. Intravenous tranexamic acid reduces total blood loss in reverse total shoulder arthroplasty: a prospective, double-blinded, randomized, controlled trial. *J Shoulder Elb Surg.* 2017;26(8):1383-1389. doi:10.1016/J.JSE.2017.01.005
82. Kumar S, Randhawa MS, Ganesamoni R, Singh SK. Tranexamic acid reduces blood loss during percutaneous nephrolithotomy: A prospective randomized controlled study. *J Urol.* 2013;189(5):1757-1761. doi:10.1016/J.JURO.2012.10.115
83. Dadure C, Sauter M, Bringuier S, et al. Intraoperative Tranexamic Acid Reduces Blood Transfusion in Children Undergoing Craniosynostosis Surgery: A Randomized Double-blind Study. *Anesthesiology.* 2011;114(4):856-861. doi:10.1097/ALN.0B013E318210F9E3
84. Meissner F, Plätzke M, Matschke K, Waldow T. Postoperative administration of tranexamic acid as approach to reduce blood loss after open-heart surgery. *Clin Hemorheol Microcirc.* 2020;76(1):43-49. doi:10.3233/CH-200836
85. Zonis Z, Secar M, Reichert C, Sett S, Allen C. The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *J Thorac Cardiovasc Surg.* 1996;111(5):982-987. doi:10.1016/S0022-5223(96)70374-4
86. Brum MR, Miura MS, Castro SF de, Machado GM, Lima LH, Neto JFL. Tranexamic acid in adenotonsillectomy in children: A double-blind randomized clinical trial. *Int J Pediatr Otorhinolaryngol.* 2012;76(10):1401-1405. doi:10.1016/J.IJPORL.2012.04.028
87. Xie Q, Huang CJ, Gu KP, Yao YX. Circulation collapse caused by intracardiac thrombosis associated with tranexamic acid administration: A case report. *Medicine (Baltimore).* 2021;100(47):E27997. doi:10.1097/MD.00000000000027997
88. Tranexamic Acid For the Prevention of Perioperative Bleeding - American College of Cardiology. Accessed July 10, 2022. <https://www.acc.org/Latest-in-Cardiology/Articles/2022/06/28/17/48/Tranexamic-Acid-For-the-Prevention-of-Perioperative-Bleeding>
89. Saleh AN, Mostafa RH. Increased Nociception Following Administration of Different Doses of Tranexamic Acid in Adolescent Idiopathic Scoliosis Surgery. *Open Anesth J.* 2018;12(1):61-68. doi:10.2174/2589645801812010061
90. Hurley ET, Lim Fat D, Pauzenberger L, Mullett H. Tranexamic acid for the Latarjet procedure: a randomized controlled trial. *J Shoulder Elb Surg.* 2020;29(5):882-885. doi:10.1016/J.JSE.2020.01.066
91. Liu YF, Hong CK, Hsu KL, et al. Intravenous Administration of Tranexamic Acid Significantly Improved Clarity of the Visual Field in Arthroscopic Shoulder Surgery. A Prospective, Double-Blind, and Randomized Controlled Trial. *Arthrosc - J Arthrosc Relat Surg.* 2020;36(3):640-647. doi:10.1016/J.ARTHRO.2019.10.020
92. Study Of Tranexamic Acid For The Reduction Of Blood Loss In Patients Undergoing Major Abdominal Surgery - Study Results - ClinicalTrials.gov. Accessed July 10, 2022. <https://clinicaltrials.gov/ct2/show/results/NC00827931>
93. Sentürk MB, Cakmak Y, Yildiz G, Yildiz P. Tranexamic acid for cesarean section: A double-blind, placebo-controlled, randomized clinical trial. *Arch Gynecol Obstet.* 2013;287(4):641-645. doi:10.1007/S00404-012-2624-8
94. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: A double-blind randomization trial. *Arch Gynecol Obstet.* 2013;287(3):463-468. doi:10.1007/S00404-012-2593-Y