A Mehta analysis of

Tranexamic Acid (TXA)

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TXA: mechanism of action

- First described in 1962 in Japan by Okamoto et al.
- Trans-4-aminomethyl-cyclohexanecarboxylic acid
- Blocks the breakdown of blood clots, which prevents bleeding (antifibronolytic)
- Synthetic reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (activated form of plasminogen) from binding to the fibrin matrix
- Plasminogen is a pro-enzyme (i.e. a zymogen) which is cleaved to form plasmin - also known as fibrinolysin - as part of the fibrinolytic pathway that breaks down fibrin blood clots. This pathway is activated when a clot is no longer needed or to prevent a clot from extending beyond the site of injury
- Plasminogen activators: tPA, urokinase, streptokinase (opposite of TXA)
- E-aminocaproic acid (similar to TXA but TXA is 10x more potent)
- Plasminogen receptors are also located on endothelial cells, monocytes, lymphocytes, and platelets so TSA can be used to reduce inflammation

- Okamoto SO, Okamoto U. “A new potent antifibrinolytic substance and its effect on blood of animals.” Keio J Med. 1962;11:105-15.

TXA: Routes of Administration

- There is high concentration of plasminogen in mucosa making TXA theoretically more beneficial for mucosal bleeding.
- Mouthwash for dental extractions: 10ml of 5% solution for 2 minutes x 4/day for 4-7 days (reaches particularly high concentrations in saliva)
- Oral dose: 20-25 mg/kg/dose 3-4 times daily (half like 11 hours), oral bioavailability is 34% and not affected by food in stomach
- IV dose: 10-15 mg/kg/dose 2-3 times daily (half life 2 hours)
- Aerosolized: 500mg/5ml diluted with 5ml saline given via nebulizer
- Topical: 2-3 grams in surgical bed

- Franchini M et al. “Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers.” Haemophilia 2005;11(05):504-509.

TXA: Routes & Doses

- Approved for oral, IV and topical administration
- Three categories of uses:
  a. Elective surgery
  b. Acute bleeding
  c. Prevention/treatment of anticoagulated patients (blood thinners or bleeding disorders)
- Efficacy studies were done at doses ranging from 2.5 to 100 mg/kg IV bolus but most common dose was 10-20 mg/kg.
- IV bolus peaks at one hour; half life is 2 hours and 90% excretion at 24 hours; remains in serum for 8 hrs and in tissue for 17 hrs.
- IV and topical have similar efficacy. IV plus topical may or may not have improved efficacy over IV alone (conflicting data)

Cost: case of 10 vials = $22.10

- Dong Y et al. "Combined topical and IV administration of TXA further reduces postoperative blood loss in adolescent idiopathic scoliosis patients undergoing spinal fusion surgery: a randomized controlled trial. BMC Musculoskelet Disord 2023; 22:663.
- Li s et al. "IV combined with topical TXA administration has no additional benefits compared to IV administration alone in high tibial osteotomy: a retrospective case-control study." Orthop Surg 2020; 12: 515-523;

TXA: Topical use as mouth rinse

- Topical 5% TXA solution via 2 minute 10ml mouth rinse achieved 3x higher saliva concentration than one gram IV (200 mcg/ml vs 66 mcg/ml)
- Those levels remained at therapeutic range (10-15 mcg/ml) for > 2 hours following the rinse
- TXA levels in saliva following oral dose was undetectable
- Advantages of topical use:
  - Increases concentration at the operative site
  - Reduced systemic exposure

- Sindet-Pedersen S. “Distibution of TXA to plasma and saliva after oral administration and mouth rinsing: a pharmokinetic study.” J Clin Pharmacol. 1987;27(12):1005-8.

TXA: Topical use in surgical bed

- Hip fracture surgery -prospective double blind study, topical vs placebo
  - Topically applied 3 minutes 3g TXA in 50 ml saline vs saline
  - TXA group had higher hemoglobin on POD 1, 2, & 3
  - TXA group received 2 u PRBCs while placebo received 8 u PRBCs
- Meta-analysis (mostly orthopedic surgery), 67 studies, 6034 patients, topical TXA vs. placebo
  - Reduced odds of blood transfusion $P<0.001$
  - Reduced mean blood loss $P<0.0001$
- Meta-analysis 29 studies, 2612 patients, topical TXA vs placebo
  - Reduced blood loss by 29%, $P<0.0001$
  - Reduced risk of blood transfusion by 45%, $P<0.0001$
- Scoliosis surgery 80 patients -prospective double blind study, IV vs IV and topical TXA
  - 40 received 1 gm IV and 10mg/kg/hr infusion during surgery plus topical saline
  - 40 received above plus 2 gm topical with clamped drain for 2 hours after surgery
  - There was no difference in the number of transfusions but EBL plus drain output was less with IV and topical TXA group.
  - This led to earlier drain removal and shorter hospital stay

- Costain D et al. “Topical TXA in hip fractures: a randomized, placebo-controlled double blind study.” Can J Surg 2021;64(4):E449-E456.
- Montroy J et al. “The efficacy and safety of topical TXA: A systematic review and meta-analysis.” Transfus Med Rev 2018 Feb 19:S0887-7963(17)30151-7.
- Ker K et al. “Topical application of TXA for the reduction of bleeding” Cochrane Database Syst Rev 2013 July 23:(7):CD010562
- Dong Y et al. “Combined topical and IV administration of TXA further reduced postop blood loss in adolescent idiopathic scoliosis patients undergoing spinal fusion surgery: a randomized controlled trial. BMC Muscoloskelet Disord 2021(1):663.

TXA: Nebulized/aerosolized

- 500mg/5ml mixed with 5ml saline via nebulizer
- Particle size of the nebulizer influences location
  - > 15 um → nose/mouth
  - 10-15 um → upper airways (trachea)
  - 5-10 um → lower airways (large bronchi and lower airways)
  - < 5um → alveoli
- Larger particles achieved with lower gas-flow rate
- Use mouthpiece for throat bleeding
- Use face mask with mouth closed for nasal bleeding

- Gardenshire DS et al. “A Guide to Aerosol Delivery Devices for Respiratory Therapists, 4th ed.” Irving, TX: American Association for Respiratory Care; 2017.

TXA: Early administration of TXA

- Survival rate decreased by 10% with every 15 minutes delay with no benefit after 3 hours for acute severe hemorrhage

- Gayet-Ageron A et al. “Antifibrinolytic Trials Collaboration. “Effect of treatment on delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40,138 bleeding patients. Lancet 2018;391(10116);125-132.

TXA: Efficacy in elective surgery

- Reduced blood transfusions by 40% in elective surgery (Cochrane review; 252 trials; 25,000 participants)
- POISE-3: 9535 patients undergoing noncardiac surgery (general, ortho, gyne, urology, vascular, spine, thoracic) showed significantly less composite bleeding (life threatening bleeding, major bleeding, or bleeding into a critical organ) with 1 gm TXA at the start of surgery and 1 gm at the end.

- Devereaux PJ. et al. "POISE-3 Investigators. TXA in patients undergoing noncardiac surgery. NEJM 2022;386(21):1986-1997.

TXA: Efficacy in orthopedic surgery

- Well documented benefits in orthopedic surgery 10-20 mg/kg before and after surgery. IV with topical TXA was more effective than IV alone at reducing bleeding, hemoglobin decline, and need for transfusion while not increasing the risk of thromboembolic events.
- TXA reduced blood transfusion rate during total hip arthroplasty (THA), total knee arthroplasty (TKA), shoulder arthroplasty, ACL reconstruction
- TXA reduced blood loss and transfusion rate during spine surgery using TXA at high or low dose

- Franchini M. et al, "Safety of IV TXA in patients undergoing major orthopaedic surgery: a meta-analysis of randomised controlled trials. Blood Transfus 2018;16(01):36-43.
- Sun Y, et al. "A systematic review and meta-analysis comparing combined IV and topical TXA with IV administration alone in THA. PLoS One 2017;12(10):e0186174

TXA: Efficacy in post partum hemorrhage (PPH)

Many studies documenting significant reduction in decreased blood loss and transfusion requirements when TXA given IV 10-15 mg/kg without increased risk of thromboembolic events. WHO issued recommendation on use of TXA for treatment of PPH in 2017.

a. Cochrane review 20,412 women undergoing vaginal or C section delivery
   - Novikova N et al. "Antifibrinolytic drugs for treating PPH." Cochrane Database Syst Rev 2018;2(02):CD012964.
b. 4557 women undergoing C section
   - Franchini M et al. "Safety and efficacy of TXA for prevention or obstetric haemorrhage: an updated systematic review and meta-analysis. Blood Transfus 2018; 16(04):329-337
c. WOMAN study 20,060 women with PPH vaginal or C section double blind 1 gm TXA vs placebo showed significant decrease in overall mortality due to bleeding especially if given within 3 hours (P=.008)
   - WOMAN Trial Collaborators. "Effect of early TXA administration on mortality, hysterectomy, and other morbidities in women with PPH. Lancet 2017; 389(10084):2105-2116.

TXA: Efficacy in Acute Hemorrhage from Trauma

- CRASH-2 trial 20,211 patients prospective randomized study with 1 gm TXA bolus and another gram infused over 8 hours vs placebo had greatest benefit if given within one hour after trauma but was still helpful within 3 hours and of no use after 3 hours.

Mortality due to bleeding and all cause mortality were both improved.

- Prehospital TXA 28 day mortality 17.3% vs 21.8% (placebo)
- CRASH-3 trial 12,737 TBI patients prospective study showed decreased risk of head-injury related deaths for mild and moderate head injury but not severe when given 1 gm bolus and 1 gram infused over 8 hours.
- Cochrane review 20,000 patients showed 10% reduction in risk of death

- Shakur H et al. CRASH-2 trial collaborators. "Effects of TXA on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage Lancet 2010; 376(9734):23-32.
- Gruen RI et al. Patch-Trauma Investigators and the ANZICS Clinical Trials Group. "Prehospital TXA for severe trauma. NEJM 2023; 389(02):127-136.
- CRASH-3 trial collaborators. "Effects of TXA on death, disability, vascular occlusive events and other morbidities in patients with acute TBI. Lancet 2019;394(10210):1713-1723.
- Ker K et all. "Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev 2015(05):CD004896.

TXA: in Bleeding Disorders

- World Federation of Hemophilia recommends us of TXA along with factor replacement therapy (allows lower use of factor replacement)
- In minor bleeding disorders, TXA can be used alone
- VWD: TXA with DDAVP, ProDES Wil prospective study 268 VWD patients
    - DDAVP was used with or without TXA for treatment/prophylaxis of bleeds, deliveries, and minor/major surgeries
    - Efficacy was 93.3% in hemorrhages, 100% in oral surgery, 91.7% deliveries, and 92.3% other minor/major surgeries.

- Srivastava A. et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 2020;26(06):1-158.
- Frederici AB. et al. ProDesWil Study. “Safety and effectiveness of desmopressin for the management of delivery and major surgery in patients with mild-moderate von willebrand disease: final interim analysis of the ProDesWil study. Paper presented at : Oral Communication at the 57th Annual Meeting and Exposition of the American Society of Hematology, abstract 759, 2015.

TXA: in Anticoagulated Patients

- TXA is beneficial in patient on anticoagulant therapy to treat oral bleeding after dental procedures or epistaxis using oral or topical routes with or without stopping the anticoagulant.

- Engelen ET et al. “Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev 2018;7(07):CD012293.

TXA: Tonsillectomy

- Prophylactic preop IV TXA decreased intraop blood loss in adults (19-40mls) but did not reduce risk of PTH
- Intraop topical 4% TXA did not benefit hemoglobin levels nor PTH

- Chan CC et al. “Systematic review and meta analysis of the use of TXA in tonsillectomy.” Eur Arch Oto-Rhino-Laryngol 2013;270(2):735-48.
- Falbe Hansen J et al. “Local application of an antifibrinolytic in tonsillectomy a double blind study. J Laryngol Otol 1974;88(6):565-8.

TXA: Post Tonsillectomy Hemorrhage (PTH)

- Neb TXA for PTH did decrease need for OR 36% vs 60% (p=0.0001) Retrospective study 1110 patients
  - 250mg neb TXA if < 25kg patient and 500mg neb TXA if > 25kg patient
  - Standard TXA neb is 500mg/5ml diluted with 5ml normal saline given via nebulizer.
- 22.2% of active PTH given TXA required OR (vs. 53.6% nonTXA)
- Any method of TXA administration, was 77.8% successful in avoiding OR
  - Nebulized = 14.5 mg/kg, IV = 11.1 mg/kg, topical = 10% solution
- Active PTH that failed TXA did have higher transfusion rate, but not statistically significant p=0.05 (50% in TXA failure vs 4.8% in TXA success group)
- Oral TXA not useful for PTH (no detectable TXA levels in saliva with oral route)
- Prophylactic topical TXA via gargle 5-6 times per day on POD#5-10 no statistical difference but a trend towards lower PTH requiring surgical intervention (8.9% vs 11.3%).

- Erwin DZ et al. “Post-tonsillectomy hemorrhage control with nebulized TXA: a retrospective cohort study.” Int J Pediatr Otorhinolaryngol January 2021;2021(4147):110802.
- Spencer R et al. “Efficacy of TXA for PTH.” Am J Oto Head and Neck Medicine and Surgery 2022;43
- Hinder D et al. “Topical application of TXA to prevent PTH.” Laryngorhinootologie. 2015;94(2):86-90.
- Shin, Timothy J et al. “Treatment of PTH with nebulized TXA: A retrospective study.” Int J Pediatr Otorhinolaryngol. 2023 Aug: 171:111644.
- Maksimoski, Matthew at al. “Treatment of PTH with Nebulized TXA: Initial Investigation of a Novel Therapeutic Modality” Ann Otol Rhinol Laryngol 2024 May 27: 34894241254697.

TXA: Epistaxis

- 216 patient prospective study of topical TXA vs anterior nasal packing
  - Bleeding stopped in 10 minutes: 71% TXA vs. 31.2% packing
  - Discharge within 2 hours: 95.3% TXA vs. 6.4% packing
  - Rebleeding rates in first 24 hours: 4.7% TXA vs. 11% packing
- Delivered via nebulizer with patient breathing through their nose (500 mg)

- Zahed R et al. "A new and rapid method for epistaxis treatment using injectable from of TXA topically: a randomized controlled trial." Am J Emerg Med. 2013, 31:1389-1392.

TXA: Endoscopic Sinus Surgery

- 60 patients RCT received 15mg/kg bolus IV TXA preop vs placebo
  - Significant difference was found in intraop bleeding P=0.011
  - So improved intraop visualization of ESS
  - No difference in postop nausea, headache, dizziness, venous thromboembolism
  - All patients were given TIVA
- This has been corroborated by other meta-analysis studies
- This has also been shown in arthroscopic surgery

- Yang W et al. “IV TXA improves the intraop visualization of ESS for high-grade chronic rhinosinusitis: a randomized, controlled double-blinded prospective trial.” Front Surg 2021; 8:771159.
- Kim DH et al. “Efficacy of TXA on operative bleeding in ESS: a meta-analysis and systematic review. Laryngoscope. 2019;129:800-7.
- Ping WD et al. “Role of TXA in nasal surgery: a systematic review and meta-analysis of randomized control trial.” Medicine 2019;98:e15202
- Zhao J et al. “IV TXA significantly improved visualization and shortened the operation time in arthroscopic rotator cuff repair: a systematic review and meta-analysis of level I and II studies.” Arthroscopy 40(2) Feb 2024:592-601.

TXA: Major Head & Neck Surgery

- Thyroidectomy, parotidectomy, neck dissection, composite resection
- Retrospective meta analysis of 16 studies/941 patients showed insufficient evidence
  - No adverse events
  - Postop drain outputs were significantly reduced
  - No change in duration of drain placement or risk of blood transfusion

- Jamshaid, Warda et al. “A systematic review on the efficacy of TXA in head & neck surgery.” Clinical Otolaryngol. 2023; 48:527-539

TXA: Free Flaps

- 63 patients received up to 3 gm TXA IV perioperatively, Retrospective study
  - No thrombosis of anastamosis and 5 hematomas (10%) with TXA compared to control with one thrombosis (3%) and 6 hematomas (18%). $P<0.001$
  - Less blood loss in TXA group, 158 mls vs 231 mls $P<0.001$

- Lardi, Alessia M et al. “The use of TXA in microsurgery – is it safe?”

TXA: Hemoptysis

- Double blind RCT 47 patients
  - Nebulized TXA 500 mg TID x up to 5 days vs placebo saline (massive hemoptysis >200ml/24h excluded)
  - Resolution of hemoptysis within 5 days of admission was more in TXA group, 96% in TXA group vs. 50% in placebo group, ($P<0.0005$)
  - Reduced recurrence rate at one year follow up $P=0.009$
- TXA not helpful in G.I. bleeds, upper/lower
  - HALT-IT trial 164 hospitals in 15 countries, 12009 patients.
  - TXA did not reduce death from G.I. bleeding but has increased risk of VTE and seizures at dose of IV 1 gm load followed by 3 gm maintenance dose over 24 hours.

- Wand, O et al. “Inhaled TXA for hemoptysis treatment: a randomized controlled trial” Chest 2018 Dec;154(6):1379-1384

TXA: Non-hemostatic uses for TXA

- Cerebral amyloid angiopathy causing Alzheimer's disease by causing microbleeds
- TBI: plasmin promotes breakdown of laminin in hippocampus which triggers neuronal death
- Increased immune function: reduction in postsurgical infection rates in cardiac surgery patients
- Inflammation: TXA reduces CRP and IL-6 after TKA and THA
    - TXA slowed wound healing during facial plastic surgery but required topical use of TXA for 72 hours, but immediate perioperative use has not shown this problem
- 2nd line prophylactic therapy for hereditary angioedema (1st line = Cinryze, C1 inhibitor)
- Treatment for ACE inhibitor angioedema (bradykinin-mediated)

- Myles PS et al. "TXA in patients undergoing coronary-artery surgery." NEJM 2017;376(2):136-48.
- Draxler DF et al. "TXA modulates the immune response and reduces postsurgical infection rates." Blood Adv. 2019;3(10):1598-609.

TXA: Adverse events

- No increased thromboembolic events in PPH, trauma, orthopedic surgery, rhinoplasty, PTH, epistaxis, hemoptysis
- Nebulized TXA led to one report of bronchospasm managed with bronchodilator.
- Hypersensitivity reactions: ranging from hives to anaphylaxis
  - Obtain tryptase levels 30 -120 min and 24 hr after reaction along with skin prick and intradermal tests.
  - Alternatives to TXA include aminocaproic acid and etamsylate (restores capillary resistance and improves platelet adhesion). If allergic to TXA, might also be allergic to aminocaproic acid due to shared lysine compound.
- TXA is cleared by renal system so dose adjustment for renal insufficiency
- Incidence rate of TXA-associated seizures is 2.7% compared to 0.1% in the general population ($P<0.001$).
  - Incidence of seizures increased with increased TXA dose.
- No increased risk of thromboembolic complications

- Murdaca, Giuseppe et al. “TXA adverse reactions: a brief summary for internists and emergency doctors.” Clin Mol Allergy 2020 18:16.
- Lin, Zhang et al. “TXA-associated seizures: A meta-analysis.” Seizure 36, 2016; 70-73.
- Eisinger, Ella C et al. “Thromboembolic complications following perioperative TXA administration.” Journal of Surgical Research, January 2024 (293) 676-684.

TXA: Cytotoxicity (In vitro studies)

- TXA affects all cell types the same (chondrocytes, fibroblasts, synovial tissue, tendon tissue)
- TXA affects cells negatively in a dose and time dependent manner
- Older patients tissue more affected by TXA than younger patients
- Doses less than 20 mg/ml had no detrimental effect
- 12.5 mg/ml had no detrimental effect for 6-48 hours
- 70 mg/ml had no detrimental effect if washed out after 10 minutes
- Animal studies showed significant benefit of TXA to healing of osteochondral defects (4 mg/ml for 6 hours)

- Gkiatas, Ioannis et al. “Topical use of TXA: Are there concerns for cytotoxicity?” World Journal of Orthopedics 2022 June 18, 13(6): 555-563.

TXA: Contraindications

- Absolute contraindications
  - Known allergy or hypersensitivity reaction
  - Active thromboembolic disease
  - Fibrinolytic conditions with consumption coagulopathy (DIC)
- Relative contraindications
  - Renal insufficiency
  - Thrombosis disorders
  - Pre-existing coagulopathy or oral anticoagulants
  - High risk of seizures
  - Pregnancy (but used for postpartum hemorrhage)
- Topical use can reduce systemic exposure with increased concentration at the operative site

- Murdaca, Giuseppe et al. “TXA adverse reactions: a brief summary for internists and emergency doctors.” Clin Mol Allergy 2020 18:16.