TXA SAVES THE DAY? AN UPDATE ON TRANEXAMIC ACID USE FOR VARIOUS INDICATIONS

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Off-label Uses Tranexamic Acid

- Trauma associated hemorrhage
- Traumatic brain injury
- Post-partum hemorrhage
- Epistaxis
- Hemoptysis
- Gastrointestinal hemorrhage
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td>Confidence interval</td>
<td>CI</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>GI</td>
</tr>
<tr>
<td>Emergency department</td>
<td>ED</td>
</tr>
<tr>
<td>Relative risk</td>
<td>RR</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>TPA</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>TXA</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>TBI</td>
</tr>
</tbody>
</table>
OBJECTIVES

- Discuss the role of tranexamic acid across different indications
- Evaluate the literature supporting tranexamic acid for off-label use
- Describe the preparation and administration of tranexamic acid for novel indications
For acute traumatic hemorrhage, tranexamic has shown to reduce death due to bleeding if given within what time frame?

A. Greater than 8 hours after injury
B. Between 3 and 4.5 hours of injury
C. Within 3 hours of injury
D. 24 to 48 hours after injury
Tranexamic use in the setting of symptomatic intracerebral hemorrhage after tissue plasminogen activator is based on what type of published evidence?

A. Case reports
B. Retrospective studies
C. Randomized controlled trials
D. Meta-analyses
Which modes of administration of tranexamic acid have been studied in the setting of epistaxis?

A. Nasal atomization
B. Topical solution
C. Sublingual
D. Both A & B
More than 60,000 deaths per year from hemorrhage in the U.S.

Approximately 1.9 million deaths worldwide, 1.5 million of which are from physical trauma
WHAT HAPPENS WHEN WE’RE BLEEDING?

Cellular Level

Tissue Level

Maladaptive Changes
PHARMACOLOGIC AGENTS FOR BLEEDING CONTROL

Anticoagulant Reversal/Factor Products

Antifibrinolytics
PHARMACOLOGIC AGENTS FOR BLEEDING CONTROL

- Anticoagulant Reversal/Factor Products
- Antifibrinolytics
TRANEXAMIC ACID: BACKGROUND

- Mechanism of action:
  - Forms a complex that displaces plasminogen from fibrin
  - Also inhibits the proteolytic activity of plasmin
  - Results in inhibition of fibrinolysis
TRANEXAMIC ACID: PHARMACOKINETICS

- Onset:
  - Oral: ~2.5 hours
- Half life of elimination
  - ~2 to 11 hours
- Excretion:
  - 95% unchanged drug in the urine
Ocular Effects

- Includes → changes in color vision, general visual loss
- Cases of retinal venous and arterial occlusions have been reported

Seizures

- Case reports, mostly associated with intraoperative use
- Most reports involve older patients
- Mechanism may be secondary to GABA inhibition
Thrombotic Events

- Due to mechanism, patients are at higher risk of thrombosis
- Use with caution in patients with thromboembolic disease

Ureteral Obstruction

- Caution in patients with upper urinary tract bleeding
- Ureteral obstruction may occur due to blood clot formation
Only two labeled indications

- Treatment of cyclic heavy menstrual bleeding
- Tooth extraction in patients with hemostatic defects
TRANEXAMIC ACID: OFF-LABEL INDICATIONS

Laundry list of off-label uses:

- Trauma associated hemorrhage
- Subarachnoid hemorrhage
- Intracranial bleeding associated with thrombolytics
- Hemoptysis
- Epistaxis
- Post-partum hemorrhage
- Hereditary angioedema
- Perioperative prevention of blood loss
ROADMAP

- Trauma
- Traumatic Brain Injury
- Epistaxis
- Hemoptysis
- Gastrointestinal Hemorrhage
- Post-partum Hemorrhage
ROADMAP

- Trauma
- Traumatic Brain Injury
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- Post-partum Hemorrhage
Many preventable deaths in trauma occur due to uncontrolled hemorrhage.

Resuscitation for acute traumatic hemorrhage involves addressing the lethal trauma triad:

- Hypothermia
- Acidosis
- Coagulopathy
**Coagulopathy** can occur in multiple ways:

- Dilutional from fluid administration
- Activation of protein C pathway with acute depletion of plasminogen activators

Rationale for TXA use in these patients is to stabilize clot formation due to hypocoagulability.
LANDMARK TRIALS IN TRAUMATIC HEMORRHAGE

CRASH-2

MATTERS

CRASH-2: subgroup analysis of death due to bleeding
CRASH-2: DATA

**Study Design**
- Multicenter randomized placebo controlled trial
- Compared tranexamic acid 1 gm over 10 min then 1 gm over 8 hours (n=10,060) vs placebo (n=10,067) in trauma patients with acute traumatic hemorrhage

**Outcomes**
- Lower in hospital death at 28 days: 14.5% in TXA group vs 16% in placebo group [RR 0.91 (0.85 – 0.97)]
- No difference in vascular occlusive events or receipt of blood transfusion

**Conclusions and limitations**
- Author: TXA significantly reduced risk of death in trauma patients without increased risk of vascular occlusive events
- Limitations: Only 50% of patients actually received transfusions, only ~32% of patients had SBP < 90mmHg on admission

SHAKUR H, ET AL. . LANCET. 2010
CRASH-2: ANALYSIS OF DEATH DUE TO BLEEDING

Exploratory analysis of CRASH-2

- Re-examined data for death due to bleeding
- Found significant interaction between TXA and time from injury to treatment ($p<0.0001$)

Conclusions:

- TXA given < 3 hours of from injury showed benefit
- TXA given > 3 hours from injury showed harm

### Risk of Death Due to Bleeding After TXA

<table>
<thead>
<tr>
<th>Time from Injury</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 hour</td>
<td>0.68 (0.57 – 0.82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>1 - 3 hours</td>
<td>0.79 (0.64 – 0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt; 3 hours</td>
<td>1.44 (1.12 – 1.84)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
In CRASH2 trial, only ~32% of patients had penetrating injuries which may not be applicable to wartime injuries.

MATTERs trial: single center retrospective observational study that compared TXA with no TXA in patients receiving at least 1 unit of packed red blood cells in a hospital in Southern Afghanistan.

Total of 896 patients (TXA = 293) with combat related injuries.
Outcomes: mortality at 24 hours, 48 hours, and 30 days, thromboembolic complications, and influence of TXA on coagulopathy.
MATTERS TRIAL: OUTCOMES

**Mortality**
- Lower in TXA group vs no TXA group
- 17.4% vs 23.9% (P = 0.03)

**Massive Transfusion**
- Greatest mortality benefit for TXA seen in patients that received massive transfusion
- 14.4% vs 28.1% (P = 0.004)

**Thrombosis**
- Significantly more patients with deep vein thrombosis in TXA group
- 2.4% vs 0.2% (P = 0.001)
SUMMARY OF RESULTS FOR TRAUMATIC HEMORRHAGE

CRASH2

• Established mortality benefit for TXA in trauma patients
• Demonstrated that benefit is seen if TXA given within 3 hours of injury and there is potential for harm if administered > 3 hours from injury

MATTERS

• Determined that patients undergoing massive transfusion derive the greatest benefit from TXA administration
CURRENT CLINICAL PRACTICE

Acute or imminent massive blood loss

Initiate massive transfusion protocol

If injury < 3 hours: Give TXA
ROADMAP

- Trauma
- Traumatic Brain Injury
- Epistaxis
- Hemoptysis
- Gastrointestinal Hemorrhage
- Post-partum Hemorrhage
ROADMAP

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Intracranial bleeding is a common complication of traumatic brain injury.

Bleeding often starts at the moment of impact.

Continued bleeding can lead to increased intracranial pressure, brain herniation, and death.
CRASH-3 TRIAL

Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial

The CRASH-3 trial collaborators*
CRASH-3 TRIAL

Study design: International multicenter randomized placebo controlled trial

Intervention: tranexamic acid vs placebo in patients with traumatic brain injury

Dose: 1 gm over 10 minutes followed by 1 gm over 8 hours or matching placebo
Inclusion

• Adults with TBI presenting within 3 hours of injury
• GCS ≤ 12 or any intracranial bleeding on CT scan

Exclusion

• Major extracranial bleeding
• Definite indication for tranexamic acid per the treating clinician
CRASH-3 TRIAL

Primary outcomes

• Head injury related death in hospital within 28 days of injury for patients randomized within 3 hours of injury
• Primary outcome reporting stratified by 3 baseline characteristics: severity of head injury, time to treatment, and age
• Pre-specified subgroup analysis excluding patients with GCS 3 and bilateral unreactive pupils

Secondary outcomes

• Early head injury related death (within 24 hours), all-cause mortality, disability, vascular occlusive events, seizures, complications, neurosurgery, days in ICU, adverse events within 28 days of randomization
CRASH-3 TRIAL

Total Patients Randomly Assigned

N = 12,737

Patients In Each Group

TXA
N = 6,406

Placebo
N = 6,331

Patients Assigned Within 3 Hours of Injury And With Outcome Data

N = 4,613

N = 4,514
CRASH-3 TRIAL

Total Patients Randomly Assigned: N = 12,737

Patients In Each Group:
- TXA: N = 6,406
- Placebo: N = 6,331

Patients Assigned Within 3 Hours of Injury And With Outcome Data:
- N = 4,613
- N = 4,514

13,000 patients for 90% power to detect 15% difference in mortality
**Primary Outcome**

- Risk of head injury-related death:
  - 18.5% in TXA group versus 19.8% in placebo group
  - RR 0.94 (95% CI 0.86 - 1.02)

**Prespecified Sensitivity Analysis**

- Excluded patients with GCS 3 and bilateral unreactive pupils
- Head injury related death:
  - 12.5% in TXA group versus 14.0% in placebo group
  - RR 0.89 (95% CI 0.80 – 1.00)
### Risk of Head Injury Related Death (Stratified by Severity)

<table>
<thead>
<tr>
<th>Severity of TBI</th>
<th>Tranexamic Acid</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild – moderate TBI (GCS 9–15)</td>
<td>166/2846 (5.8%)</td>
<td>207/2769 (7.5%)</td>
<td>0.78 (0.64 – 0.95)</td>
</tr>
<tr>
<td>Severe TBI (GCS 3–8)</td>
<td>689/1739 (39.6%)</td>
<td>685/1710 (40.1%)</td>
<td>0.99 (0.91 – 1.07)</td>
</tr>
</tbody>
</table>
### CRASH-3 TRIAL

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>RR of TXA vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early head injury related death</td>
<td>0.81 (0.69–0.95)</td>
</tr>
<tr>
<td>*Excluding GCS 3 and unreactive pupils</td>
<td><strong>0.72 (0.56 – 0.92)</strong></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.96 (0.89 – 1.04)</td>
</tr>
<tr>
<td>Disability</td>
<td>No difference across 6 reported measures</td>
</tr>
<tr>
<td>Vascular occlusive events</td>
<td>0.98 (0.74 – 1.28)</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.09 (0.90–1.33)</td>
</tr>
<tr>
<td>Adverse events within 28 days of randomization</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

CRASH-3 TRIAL COLLABORATORS. THE LANCET. 2019.
Author’s Key Conclusions:

- Provides evidence that TXA given within 3 hours of injury can reduced head injury related death in mild to moderate TBI patients
- No increased risk of adverse events (i.e. vasoclusive events)
CRASH-3 TRIAL

**Strengths:**
- Largest trial to assess use of TXA in TBI
- Few patients were lost to follow up
- Authors clearly explained reasons for changing timeframe for administration from 8 hours to 3 hours
- Prespecified sub group analysis that excluded patients with GCS 3 and bilateral unreactive pupils
Limitations:

- Primary outcome not significant
- Did not meet power criteria
- Wide confidence intervals despite large trial size
- Significant benefit was only seen in subgroup of patients
  - Absolute difference = 1.7% (5.8 vs 7.5%)
CRASH-3 TRIAL: SUMMARY

- Trial established safety of TXA in patients with traumatic brain injury
- Subgroup of patients that may benefit from therapy, although effect size is modest at best
- No benefit in terms of functional outcomes
- This data has yet to change clinical practice at our institution
PATIENT CASE
HM is a 72 year old female that initially presented to the ED as a code stroke and received TPA approximately 2 hours ago.

The patient is on a hold in the ED prior to receiving an ICU bed, and the nurse notices the patient has an acute decline in mental status.

A repeat CT scan shows intracerebral hemorrhage new from prior.
The neurologist asks if you have any recommendations for reversal of bleeding associated with tissue plasminogen activator?
TPA ASSOCIATED HEMORRHAGE

What do the ischemic stroke guidelines recommend?

- Stop infusion of tissue plasminogen activator
- 10 units cryoprecipitate
- Tranexamic acid 1000 mg IV infused over 10 min or
- Aminocaproic acid 4 – 5 g over 1 hour, followed by 1 g IV until bleeding is controlled

POWERS WJ, ET AL. STROKE. 2018
TPA ASSOCIATED HEMORRHAGE

TPA: converts plasminogen to plasmin *causing* fibrinolysis

TXA: removes plasminogen from fibrin *preventing* fibrinolysis
TPA ASSOCIATED HEMORRHAGE

- Best evidence from single case report available in the literature:
- Patient was a Jehovah’s witness and could not receive blood products
- Patient received TXA 1 gm over 10 minutes then a subsequent 675 mg IV dose (10 mg/kg)
- No further hematoma expansion seen on CT scan
TPA ASSOCIATED HEMORRHAGE

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| • Logical mechanism  
• Relatively low risk of adverse effects in large randomized trials  
• Can be readily available in automated dispensing cabinets | • Lack of quality data |
PATIENT CASE: HM

Recommendations for patient HM?
Can recommend TXA 1 gm IV over 10 minutes while waiting for cryoprecipitate

Continue to monitor patient and provide supportive care (blood pressure management, etc.)
Epistaxis (nose bleeds) are one of the most common ear, nose, and throat emergencies that present to the emergency room.

Approximately 60% of people have experienced epistaxis with only 10% of those requiring intervention.

Affects mostly children and elderly.

Can be either anterior or posterior.

Further divided into primary or secondary:

- Primary = spontaneous and idiopathic
- Secondary = trauma or anticoagulation use
EPISTAXIS: CAUSES

Local
- Digital manipulation
- Deviated septum
- Trauma
- Inhaled corticosteroids
- Chronic nasal cannula use

Systemic
- Alcoholism
- Hypertension
- Vascular malformations
- Coagulopathies
EPISTAXIS: CAUSES

Environmental
- Allergies or dryness during winter months

Medication Induced
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Anticoagulants
- Antiplatelets
- Supplements/alternative medications
EPISTAXIS: MANAGEMENT CONSIDERATIONS

Epistaxis

Assess airway, breathing, circulation

Apply nasal decongestants + direct pressure

ENT consult

Nasal packing

Cautery (silver nitrate)
WHERE DOES TXA FIT IN?

- Why use it?
  - Faster hemostasis can potentially lead to shorter length of stay and fewer invasive interventions (e.g. nasal packing)

- How do you administer it?
  - Trials vary considerably regarding administration
  - PO and various topical methods have been studied
  - Recent trials utilize the IV formulation applied topically

CME
Topical Tranexamic Acid Compared With Anterior Nasal Packing for Treatment of Epistaxis in Patients Taking Antiplatelet Drugs: Randomized Controlled Trial

Reza Zahed, MD, Mohammad Hossain Mousavi Jazayeri, MD, Asieh Naderi, PhD, Zeinab Naderpour, MD, and Morteza Saeedi, MD
TXA IN EPISTAXIS: PATIENTS ON ANTIPLATELET AGENTS

Study design
• Randomized parallel group study at two ED’s

Methods
• Compared topical TXA (n=62) vs anterior nasal packing (n=62) in patients taking aspirin, clopidogrel, or both and presenting with anterior epistaxis

Outcomes
• Primary: Bleeding cessation at 10 minutes
• Secondary: Recurrence of epistaxis at 24 hours and 7 days, ED length of stay (LOS), patient satisfaction scores (scale of 1-10, with higher numbers indicating greater satisfaction)
Inclusion
• Anterior epistaxis that persisted after 20 minutes of compression
• On aspirin, clopidogrel, or both

Exclusion
• Traumatic epistaxis
• Anticoagulant use
• Inherited bleeding or platelet disorder
• INR > 1.5
• Shock
• Visible bleeding vessel on exam
• History of renal disease
### Administration

<table>
<thead>
<tr>
<th>TXA Group</th>
<th>Nasal packing (ANP) Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 15 cm cotton pledget soaked in TXA (500 mg in 5 mL) inserted into affected nostril</td>
<td></td>
</tr>
<tr>
<td>- Removed when bleeding confirmed to have stopped</td>
<td></td>
</tr>
<tr>
<td>- Cotton pledget that had been soaked in epinephrine (1:100,000) + lidocaine (2%) inserted into the affected nostril and left in place for 10 minutes.</td>
<td></td>
</tr>
<tr>
<td>- ANP was subsequently performed with several cotton pledgets covered with tetracycline ointment.</td>
<td></td>
</tr>
</tbody>
</table>
## TXA IN EPISTAXIS: PATIENTS ON ANTIPLATELET AGENTS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TXA Group n (%)</th>
<th>ANP Group n (%)</th>
<th>% difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding cessation at 10 minutes</td>
<td>45 (73)</td>
<td>18 (29)</td>
<td>44 (26 to 57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recurrence of epistaxis at 24 hours</td>
<td>3 (5)</td>
<td>6 (10)</td>
<td>-</td>
<td>0.299</td>
</tr>
<tr>
<td>Recurrence of epistaxis at 7 days</td>
<td>3 (5)</td>
<td>13 (21)</td>
<td>-16 (-28 to -4)</td>
<td>0.007</td>
</tr>
<tr>
<td>% of patients discharged at 2 hours</td>
<td>60 (97)</td>
<td>8 (62)</td>
<td>84 (71 to 91)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median patient satisfaction score (interquartile range)</td>
<td>9 (8-9.25)</td>
<td>4 (3-5)</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Author’s conclusions:
- Topical TXA in epistaxis conferred faster bleeding cessation, less re-bleeding at 7 days, shorter ED LOS, and higher patient satisfaction scores

Considerations:
- Trial limited by small sample size
- Treating clinician’s not blinded due to nature of intervention
- No subgroup analysis for patients receiving dual antiplatelet therapy
Evaluating Effectiveness of Nasal Compression With Tranexamic Acid Compared With Simple Nasal Compression and Merocel Packing: A Randomized Controlled Trial

Sedat Akkan, MD; Şeref K. Çorbacıoğlu, MD*; Halit Aytar, MD; Emine Emektar, MD; Seda Dağar, MD; Yunsur Çevik, MD

*Corresponding Author. E-mail: serefkeremcorbaciglu@gmail.com, Twitter: @drserefkerem.
TXA IN EPISTAXIS: ATOMIZED TXA

Study Design

• Single center prospective randomized trial

Methods

• Compared three groups: TXA + compression (n=45) vs normal saline + compression (n=45) vs nasal packing (n=45)
• TXA administration: 500 mg (5 mL) administered in each nostril using nasal atomizer device

Outcomes

• Primary outcome: Cessation of bleeding within 15 minutes of administration of treatment
• Secondary outcome: Re-bleeding at 24 hours
<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &gt; 18 years old</td>
<td>• Current <em>anticoagulation</em> therapy (antiplatelet therapy ok)</td>
</tr>
<tr>
<td>• Active spontaneous <em>anterior</em> epistaxis</td>
<td>• Hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>• Altered mental status</td>
</tr>
<tr>
<td></td>
<td>• Traumatic epistaxis</td>
</tr>
<tr>
<td></td>
<td>• Resolved epistaxis on admission</td>
</tr>
<tr>
<td></td>
<td>• Patients with known bleeding disorder</td>
</tr>
</tbody>
</table>
Proportion of patients with bleeding cessation at 15 minutes:

- **No** significant difference between TXA group and nasal packing group
- Both nasal packing and TXA groups significantly better than normal saline (NS) group

<table>
<thead>
<tr>
<th>Group</th>
<th>Bleeding Cessation within 15 min. N (%)</th>
<th>% Difference compared to NS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Saline group</td>
<td>32 (71.1)</td>
<td>-</td>
</tr>
<tr>
<td>TXA group</td>
<td>41 (91.1)</td>
<td>20 (3.6 to 35.4)</td>
</tr>
<tr>
<td>Nasal packing group</td>
<td>42 (93.3)</td>
<td>22.2 (6.3 to 37.3)</td>
</tr>
</tbody>
</table>
Tranexamic acid had a higher proportion of patients **without** re-bleeding at 24 hours compared to normal saline and nasal packing groups.

Statistical significance only seen compared to normal saline (NS) group.

<table>
<thead>
<tr>
<th>Group</th>
<th>No re-bleeding at 24 hours</th>
<th>% Difference compared to NS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Saline group</td>
<td>27 (60)</td>
<td>-</td>
</tr>
<tr>
<td>TXA group</td>
<td>39 (86.7)</td>
<td>26.7 (8.4 to 42.8)</td>
</tr>
<tr>
<td>Nasal packing group</td>
<td>33 (73.3)</td>
<td>14 (-5 to 31.9)</td>
</tr>
</tbody>
</table>
TXA IN EPISTAXIS: ATOMIZED TXA

- Author’s conclusions:
  - Atomized TXA no different from nasal packing in regards to bleeding cessation within 15 minutes
  - TXA has numerically lower rates of re-bleeding at 24 hours compared to nasal packing and normal saline

- Limitations
  - Small trial size
  - Incomplete blinding of treatment groups
  - Results only to apply to specific nasal packing used

7 patients in nasal packing group mentioned severe pain and requested for intervention to be stopped (stopped in 1 patient)
FUTURE STUDIES

**NOPAC study:**
- Double-blind, parallel group, randomized, controlled trial comparing the use of topical intranasal TXA with placebo
- Primary outcome → subsequent need for anterior nasal packing in the ED
- Finished enrolling, awaiting publication
### TXA: ADMINISTRATION FOR EPISTAXIS

<table>
<thead>
<tr>
<th>Topical</th>
<th>Atomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1 to 5 mL of TXA 10% solution applied to cotton ball or pledget and then inserted into bleeding nostril</td>
<td>- 5 mL of TXA 10% (500 mg) administered to bleeding nostril using nasal atomizer</td>
</tr>
</tbody>
</table>
EPISTAXIS CONCLUSIONS

- Moderate quality evidence exists to support use of TXA for epistaxis
- Administration via topical or atomized routes may reduce the need for nasal packing
- A large amount of variability in practice exists with no clear consensus on best practice
- Future trials may elucidate the optimal administration and dosing method in addition to allowing standardization of care
ROADMAP

Trauma

Traumatic Brain Injury

Epistaxis

Hemoptysis

Gastrointestinal Hemorrhage

Post-partum Hemorrhage
ROADMAP

- Trauma
- Traumatic Brain Injury
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- Post-partum Hemorrhage
HEMOPTYSIS: BACKGROUND

- Highly variable presentation from blood-streaked sputum to life threatening hemorrhage
- Long list of potential etiologies including malignancy, bronchiectasis, tuberculosis, and airway trauma
- Definitive management of severe cases requires endobronchial intervention
- Currently no well defined medication therapies other than treatment of specific cause
HEMOPTYSIS: GENERAL MANAGEMENT

1. Hemoptysis
2. Assess airway, breathing, circulation
3. Obtain Chest X-ray
4. Bronchoscopy
5. CT scan if Chest X-ray undiagnostic
6. Treat underlying cause (infection, malignancy, etc.)
HEMOPTYSIS: TXA USE

- 2016 Cochrane review:
  - Two randomized controlled studies met criteria for inclusion with a total of 90 patients
  - One trial used IV therapy and one trial used oral therapy
  - Pooled results → reduction in bleeding time for patients versus placebo with a weighted mean difference (WMD) of -19.47 (95% CI -26.90 to -12.03 hours)
  - Concluded there was insignificant evidence to judge whether TXA was efficacious, though limited evidence exists that it reduces bleeding time

PRUTSKY G, ET AL. COCHRANE DATABASE SYST REV. 2012
Inhaled Tranexamic Acid for Hemoptyisis Treatment
A Randomized Controlled Trial

Ori Wand, MD; Elad Guber, MD; Alexander Guber, MD; Gali Epstein Shochet, PhD; Lilach Israeli-Shani, MD; and David Shitrit, MD
HEMOPTYSIS: INHALED TXA USE

Study Design

• Prospective, double-blind, randomized, placebo controlled trial
• Objective of the trial was to assess the effectiveness of inhaled TXA for hemoptysis

Methods

• Compared nebulized TXA (n=25) vs placebo (n=22) in patients admitted for hemoptysis of various etiologies
• Dosing: 500 mg/5 mL of nebulized TXA three times daily or a matching placebo using normal saline
• Inhaled therapy was given for up to five days

Outcomes

• Primary outcomes: Rate of patients with complete resolution of hemoptysis at 5 days and difference in volume of expectorated blood
• Secondary outcomes: Rates of procedural intervention and hospital length of stay
HEMOPTYSIS: INHALED TXA USE

Inclusion
• > 18 years old
• Admitted with hemoptysis within previous 24 hours

Exclusion
• Massive hemoptysis (>200 mL expectorated blood)
• Respiratory or hemodynamic instability
• Pregnancy
• Renal impairment
• Hepatic failure
• Coagulopathy
• Known hypersensitivity to TXA
HEMOPTYSIS: INHALED TXA USE

**Primary Outcomes**
- Resolution of bleeding at day 5:
  - 96% in TXA group vs 50% in placebo group (P<0.0005)
  - TXA associated with reduced amount of expectorated blood starting from day 2 through day 5 (P<0.01)

**Secondary Outcomes**
- Intervention to control bleeding:
  - 18.2% of the patients in the placebo group vs zero in the TXA group (P=0.041)
  - Average hospital length of stay: 7.8 days in the placebo group vs 5.7 days for the TXA group (P =0.046)

**Author conclusion:**
Nebulized TXA safe and effective for non-massive hemoptysis
# HEMOPTYSIS: INHALED TXA USE

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First prospective study</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Baseline characteristics balanced</td>
<td>Trial halted early</td>
</tr>
<tr>
<td>Included patients on anticoagulation</td>
<td>Exact time of resolution not documented</td>
</tr>
</tbody>
</table>
HEMOPTYSIS: INHALED TXA USE

- Limited data to support use of TXA in hemoptysis
- May consider use as an adjunct agent in stable patients with non-massive hemoptysis
- Dose: TXA 500 mg/ 5mL through nebulizer three times daily
- Unknown benefit after 5 days of use
ROADMAP

- Trauma
- Traumatic Brain Injury
- Epistaxis
- Hemoptysis
- Gastrointestinal Hemorrhage
- Post-partum Hemorrhage
ROADMAP

Trauma

Traumatic Brain Injury

Epistaxis

Hemoptysis

Gastrointestinal Hemorrhage

Post-partum Hemorrhage
GI HEMORRHAGE: BACKGROUND

- Upper gastrointestinal bleeding is responsible for ~350,000 hospital admissions per year in the U.S.
- Accounts for approximately 20,000 deaths annually
- Common etiologies include peptic/duodenal ulcers, esophageal varices, medication induced esophagitis
GI HEMORRHAGE: GENERAL PRINCIPLES OF MANAGEMENT

- Aggressive resuscitation
- Proton pump inhibitor +/- octreotide
- Endoscopic examination
GI HEMORRHAGE: GENERAL PRINCIPLES OF MANAGEMENT

- Aggressive resuscitation
- Proton pump inhibitor +/- octreotide
- TXA?
- Endoscopic examination
GI HEMORRHAGE: PREVIOUS LITERATURE

Historical literature:

- 8 clinical trials performed between 1973 – 2011
- Number of patients ranged from 47 to 216
- Cochrane review of data showed potential mortality benefit (P=0.007)
- Key source of bias was attrition rate
- Concluded that **high quality trials** are needed to confirm benefit

BENNETT C, ET AL. COCHRANE DATABASE SYST REV. 2014
Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial

The HALT-IT Trial Collaborators*
GI HEMORRHAGE: THE HALT-IT TRIAL

Study Design

• International, multicenter, randomized, placebo controlled trial
• Objective was to evaluate the effectiveness of TXA in patients with GI hemorrhage

Methods

• Compared TXA (n=5,956) 1 gm over 10 minutes followed by 3 gm continuously infused over 24 hours to matching placebo (n=5,981)

Outcomes

• Primary: Death due to bleeding within 5 days of randomization
• Secondary: death due to bleeding within 24 hours and within 28 days, all cause mortality, rebleeding within 24 hours, surgical intervention, transfusion requirements, thromboembolic events, seizures, ICU length of stay, functional outcomes

ROBERTS I, ET AL. THE LANCET. 2020
GI HEMORRHAGE: THE HALT-IT TRIAL

**Inclusion**
- At or above adulthood in respective country (16 or 18 years)
- Responsible clinician substantially uncertain if TXA indicated
- Clinical diagnosis of significant bleeding

**Exclusion**
- Failure to meet inclusion
- Receipt of TXA prior to randomization
- Withdrawal of consent

ROBERTS I, ET AL. THE LANCET. 2020
## GI HEMORRHAGE: THE HALT-IT TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TXA group</th>
<th>Placebo group</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death due to bleeding within 5 days</strong></td>
<td>222 (3.7%)</td>
<td>226 (3.8%)</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td>564 (9.5%)</td>
<td>548 (9.2%)</td>
<td>1.03 (0.92-1.16)</td>
</tr>
<tr>
<td><strong>Rebleeding within 24 hours</strong></td>
<td>41 (0.7%)</td>
<td>41 (0.7%)</td>
<td>1 (0.65-1.55)</td>
</tr>
<tr>
<td><strong>Venous thromboembolism</strong></td>
<td>48/5952 (0.8%)</td>
<td>26/5977 (0.4%)</td>
<td>1.85 (1.15-2.98)</td>
</tr>
<tr>
<td><strong>Any transfusion</strong></td>
<td>4076/5951 (68.5%)</td>
<td>4129/5978 (69.1%)</td>
<td>0.99 (0.97-1.02)</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td>38/5952 (0.6%)</td>
<td>22/5977 (0.4%)</td>
<td>1.73 (1.03-2.93)</td>
</tr>
</tbody>
</table>
Author’s conclusions:

- TXA did not reduce death due to bleeding in patients with GI hemorrhage
- Patients that received TXA were at higher risk of venous thromboembolism and seizure

Other Key points

- Over 500 patients in each group on anticoagulation
- >40% in each group with signs of shock
- Included both upper and lower GI bleeds
- 45% of patients with suspected variceal bleeding
Pending trials:

- EXARHOSE trial
- Multicenter, randomized, double-blind, placebo-controlled trial, for adult patients with cirrhosis presenting with an acute upper gastrointestinal bleed
- TXA dosing same as HALT-IT trial
- Status: still recruiting
GI HEMORRHAGE: SUMMARY

- Although meta-analyses of small trials suggested some mortality benefit, results from larger trials demonstrate otherwise.
- HALT-IT trial provides higher quality data that TXA does not provide benefit in patients with acute GI hemorrhage.
- TXA is NOT recommended for routine use at this time in this patient population.
ROADMAP

- Trauma
- Traumatic Brain Injury
- Epistaxis
- Hemoptysis
- Gastrointestinal Hemorrhage
- Post-partum Hemorrhage
ROADMAP

- Trauma
- Traumatic Brain Injury
- Epistaxis
- Hemoptysis
- Gastrointestinal Hemorrhage
- Post-partum Hemorrhage
POST PARTUM HEMORRHAGE: BACKGROUND

- Post partum hemorrhage is the most common cause of maternal mortality worldwide.
- Commonly defined as greater than 500 mL of blood loss within 24 hours of delivery.
- Initial management includes administration of uterotonics and resuscitation with fluids and blood products.
POST PARTUM HEMORRHAGE: BACKGROUND

- Why consider TXA?
- Similar to trauma, early activation of fibrinolysis is recorded after childbirth
- Within 1 hour, the serum concentration of tissue plasminogen activator can double
- Mechanistically, TXA can work to attenuate this process and reduce bleeding

WOMAN TRIAL COLLABORATORS.. LANCET. 2017
Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

WOMAN Trial Collaborators*
WOMAN TRIAL

Study Design

• International, randomized, double-blind placebo-controlled trial of women aged 16 years and older with a clinical diagnosis of post-partum hemorrhage after a vaginal birth or caesarean section

Methods

• Patients received either tranexamic 1 gm IV injection (n=10,036) or placebo (n=9,985) along with usual care
• Patients could receive a second dose of study drug if bleeding continued after 30 min or restarted after 24 hours

Outcomes

• Primary outcome: composite of death from all causes or hysterectomy within 42 days
• Secondary outcomes: death due to bleeding, thromboembolic events, surgical interventions, complications, adverse events
### Inclusion

- 16 years or older with clinical diagnosis of post-partum hemorrhage defined below:
  - >500 mL blood loss after vaginal delivery
  - >1000 mL after cesarean section
  - Any blood loss leading to hemodynamic compromise

### Exclusion

- Clinician certainty that tranexamic indicated in the given patient
# WOMAN TRIAL: RESULTS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TXA group</th>
<th>Placebo group</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all causes or hysterectomy</td>
<td>534 (5.3%)</td>
<td>546 (5.6%)</td>
<td>0.97 (0.87 – 1.09)</td>
<td>0.65</td>
</tr>
<tr>
<td>Death due to bleeding: Adjusted for baseline risk</td>
<td>155 (1.5%)</td>
<td>191 (1.9%)</td>
<td>0.81 (0.65 – 1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>TXA given within 3 hours</td>
<td>89 (1.2%)</td>
<td>127 (1.7%)</td>
<td>0.78 (0.62 – 0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.69 (0.52 – 0.91)</td>
<td>0.008</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>30 (0.3%)</td>
<td>34 (0.3%)</td>
<td>0.88 (0.54 – 1.43)</td>
<td>0.603</td>
</tr>
</tbody>
</table>
WOMAN TRIAL: CONCLUSIONS

- TXA reduced risk of death due to bleeding from post partum hemorrhage if given within 3 hours of birth
- No increased risk of thromboembolic or other adverse events
- Administration recommended by ACOG when initial therapies fail
- Dose: 1 gm over 10-20 minutes
  - May re-dose in 30 minutes if bleeding not controlled
OVERALL CONCLUSIONS

- TXA is one of the few pharmacologic agents available to combat acute hemorrhage.
- For certain types of life-threatening hemorrhage, several trials have shown a modest mortality benefit without a corresponding increase in adverse events.
- For other types of bleeding, small trials have demonstrated improvements in time to bleeding cessation and length of stay.
- Several trials that are currently in progress may help better inform clinical practice in the future.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence for TXA use?</th>
<th>Who benefits the most?</th>
<th>Administration route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma associated hemorrhage</td>
<td>+</td>
<td>≤ 3 hours of injury</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Massive transfusion</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>+/-</td>
<td>≤ 3 hours injury</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild to moderate TBI</td>
<td></td>
</tr>
<tr>
<td>TPA associated hemorrhage</td>
<td>-</td>
<td>Unknown</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>+</td>
<td>Unknown</td>
<td>Topical/Intranasal (atomized)</td>
</tr>
<tr>
<td>Non-massive hemoptysis</td>
<td>+/-</td>
<td>Excludes patients with massive hemoptysis</td>
<td>Inhaled (nebulized)</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>-</td>
<td>No benefit</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Post-partum hemorrhage</td>
<td>+</td>
<td>≤ 3 hours of delivery</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>
## UPCOMING TRIALS

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HALT-IT</td>
<td>Upper GI hemorrhage</td>
</tr>
<tr>
<td>EXARHOSE</td>
<td>Cirrhosis and upper GI hemorrhage</td>
</tr>
<tr>
<td>NO-PAC</td>
<td>Anterior epistaxis</td>
</tr>
</tbody>
</table>
POST TEST ASSESSMENT QUESTION #1

For acute traumatic hemorrhage, tranexamic has shown to reduce death due to bleeding if given within what time frame?

A. Greater than 8 hours after injury
B. Between 3 and 4.5 hours of injury
C. Within 3 hours of injury
D. 24 to 48 hours after injury
For acute traumatic hemorrhage, tranexamic has shown to reduce death due to bleeding if given within what time frame?

A. Greater than 8 hours after injury
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D. 24 to 48 hours after injury
Tranexamic use in the setting of symptomatic intracerebral hemorrhage after tissue plasminogen activator is based on what type of published evidence?

A. Case reports
B. Retrospective studies
C. Randomized controlled trials
D. Meta-analyses
Tranexamic use in the setting of symptomatic intracerebral hemorrhage after tissue plasminogen activator is based on what type of published evidence?

A. Case reports  
B. Retrospective studies  
C. Randomized controlled trials  
D. Meta-analyses
Which modes of administration of tranexamic acid have been studied in the setting of epistaxis?

A. Nasal atomization
B. Topical solution
C. Sublingual
D. Both A & B
POST TEST ASSESSMENT QUESTION #3

Which modes of administration of tranexamic acid have been studied in the setting of epistaxis?

A. Nasal atomization
B. Topical solution
C. Sublingual
D. Both A & B
ACKNOWLEDGEMENTS

- Diana Park, PharmD, BCCCP
- Christine Lee, PharmD
REFERENCES


QUESTIONS