Acknowledgment

• Thank you to ICEMA for sharing training materials
Goals & Objectives

At the end of this presentation, participants will be able to:

• Discuss basic clotting physiology
• Tranexamic Acid (TXA), Evidence-based medicine
• State the indications for the TXA administration.
• State the contraindications to TXA administration
• State the EMS ePCR documentation requirements
Coagulopathy that is frequently encountered in hemorrhagic shock has been shown to be an independent risk factor for death after trauma.

Platelets In Fibrin Mesh
Three steps to achieve Hemostasis

• Vascular Spasm
• Formation of the Platelet Plug
• Coagulation – Our Focus
Primary hemostasis: Vasoconstriction & Plug Formation

1. Exposed collagen binds and activates platelets.
2. Release of platelet factors
3. Attracts more platelets
4. Aggregate into platelet plug
1. Injury to lining of blood vessel exposes connective tissue; platelets adhere

2. Platelet plug forms

3. Fibrin clot with trapped cells

Collagen fibers

Platelet releases chemicals that make nearby platelets sticky

Platelet plug

Fibrin

Clotting factors from:
- Platelets
- Damaged cells
- Plasma (factors include calcium, vitamin K)

Prothrombin ➔ Thrombin

Fibrinogen ➔ Fibrin
Coagulation

• The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall.

• The result is the production of a gelatinous but robust clot made up of a mesh of Fibrin—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped.
Clotting Factors Involved in Coagulation

In the coagulation cascade, chemicals called *clotting factors* prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

- **The extrinsic pathway**, which normally is triggered by trauma.
- **The intrinsic pathway**, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.
- Both of these merge into a third pathway, referred to as the **common pathway**
Extrinsic pathway

Factor VIIa
Tissue factor
Phospholipids
Ca^{2+}

Intrinsic pathway

Factor IXa
Factor VIIIa
Phospholipids
Ca^{2+}

Factor IX → Factor IXa

Factor X

Indirect Factor Xa inhibitors
- Fondaparinux
- Idraparinux

Prothrombinase complex

Factor Xa

Phospholipids
Factor Va–Factor Xa
Ca^{2+}

Direct Factor Xa inhibitors
- DX-9065a
- Otamixaban
- Rivaroxaban
- Apixaban
- LY-517717
- YM150
- DU-176b

Prothrombin

Thrombin

Fibrinogen → Fibrin

Direct thrombin inhibitors
- Hirudin
- Argatroban
- Bivalirudin
- Dabigatran
Trauma-Associated Hyperfibrinolysis

- Depletion of coagulation factors secondary to blood loss, and consumption
- Dilution due to fluid infusion, >1000ml
- Dysfunction of the remaining coagulation factors due to hypothermia and acidosis
- Severe shock and major tissue trauma are the main drivers of this HF.
- According to visco-elastic testing of trauma patients upon emergency room admission, HF is present in approximately 2.5-7% of all trauma patients.
- Visco-elastic tests provide information on severe forms of HF only.
Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration.

**Tissue & Endothelial injury**

- T-PA (tissue plasminogen activator)
- PAI-1 (plasminogen activator inhibitor)

**Antifibrinolytics**

- Fibrinogen conc.
- Cryoprecipitate

**In Initial Phase t-PA > PAI-1**

**Hyperfibrinolysis and Hemorrhagic Shock**
Antifibrinolytics

- These agents enhance hemostasis when fibrinolysis contributes to bleeding
- Lysine analogs
  * EACA (e-AminoCaproic acid)
  * TXA (Tranexamic acid)
  * Aprotinin (No marking since 2007)
Mechanism of Action

• A synthetic derivative of lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen
• Inhibits both Plasminogen activation and Plasmin activity thus preventing clot breakdown.
• 10x more potent than Aminocaproic acid in vitro.
Prothrombin $\rightarrow$ Fibrinogen $\rightarrow$ Thrombin $\rightarrow$ Fibrin monomers $\rightarrow$ Fibrin polymers $\rightarrow$ Factor XIIIa $\rightarrow$ Cross-linked Fibrin (Stable Clot) $\rightarrow$ Plasminogen

Plasminogen $\rightarrow$ Plasmin $\rightarrow$ Fibrin degradation products
TXA

- Is useful in a wide range of hemorrhagic conditions.
- In large, randomized controlled trials, significantly reduced perioperative blood loss compared with placebo in a variety of surgical procedures, including cardiac surgery with or without cardiopulmonary bypass, total hip and knee replacement and prostatectomy, gynecological procedures.
FIBRINOLYSIS

Intact fibrin clot

Fibrin clot exposed to plasmin
Dosing/Storage

- TXA (Cyklokapron) – 1gm in 100cc/NSS given over 10 minutes (loading dose)
  - Followed by 1gm in 100cc/NSS over 8 hrs
- Can be mixed with just about any available solution
- Not to be administered in the same line as blood or blood products or in a line used for rFVIIa or Penicillin
- Should be stored between 15-30C or 56-86F
Side Effects

- **Acute gastrointestinal disturbances** (nausea, vomiting and diarrhea; generally dose-related).
- **Visual disturbances** (blurry vision and changes in color perception, especially with prolonged use).
- **Thromboembolic events** (deep venous thrombosis, pulmonary embolism).
- Dizziness, fatigue, headache, and hypersensitivity reaction.
- Seizure
Contraindications

- Acquired defective color vision
- SAH
- Active intravascular clotting
- Hypersensitivity to TXA
Jehovahs Witnesses – approved

- Desmopressin (DDAVP)
- e-aminocaproic acid (Amicar)
- **Tranexamic acid (Cyklokapron)**
- Vasopressin (Pitressin)
- Aprotinin (Trasylol)
- Vincristine (Oncovin)
- Conjugated estrogens
- Vitamin K (Phylonadione)
- Recombinant Factor VIIa (NiaStase)
- Recombinant Factor IX (BeneFIX)
Alameda County TXA Trial Study

Introduction

Alameda County EMS will be involved in a trial study in preparation for county wide implementation of prehospital TXA administration.
Trauma and Trauma Care

- Trauma is one of the leading causes of death amongst people 16–35.
- Roughly 1/3 of all trauma related deaths are caused by bleeding

- Until now our treatment for trauma patients has been limited.
  - Tourniquets
  - Patient positioning
  - Direct pressure
  - Two IV’s with boluses of LR or NS.
Ineffectiveness in trauma care:

- All trauma patients get two large bore IV’s and fluid resuscitation!!!
  - Why?
  - Too much fluid can dilute coagulation factors.
  - It increases mean arterial pressure which can dislodge clots and cause hypothermia.
  - Fluid resuscitation is inefficient and dangerous for the patient.
- And what about those patients with internal hemorrhage?
  - We don’t carry a tourniquet for that.
What is the next step in Trauma care?

- Tranexamic Acid or TXA
- TXA is a medication introduced in the 1970’s which promotes vascular clotting.
- Studies show that early administration of TXA increases the patients survivability rate by reducing blood loss along with decreasing the amount of transfused blood products in trauma patients.
TXA Trial Study

**Study Drug:**
- Tranexamic acid
Tranexamic Acid or TXA is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. Plasmin is a molecule responsible for the degradation of fibrin, the protein that forms the framework of blood clots. TXA is a synthetic medication void of any blood products. i.e. should have no religious objections to use.
Hospital Settings to minimize blood loss.
Dental Offices to control oral bleeding
Treatment via oral tablet for heavy menstrual periods.
Surgeries with high risk of blood loss such as cardiac, liver, vascular and large orthopedic procedures.
New Studies
CRASH2 and MATTERS

- CRASH2: Clinical Randomization of Antifibrinolytic in Significant Hemorrhage-2
  - CRASH2 is a study introduced in 40 countries and 274 hospitals around the world
  - It involved 20,000 randomized trauma patients considered hemodynamically unstable
  - Determined by GCS, Systolic BP below 90 and type of injury
• Half of the 20,000 were treated with TXA
• The TXA patients showed a 32% decrease in mortality Rate due to death by bleeding when given under 1 hour from time of trauma
• TXA showed a 21% decrease in mortality when given to patients in under 3 hours
• Adversely, there is a 30% increase in mortality when the medication is given after the 3 hour mark
MATTERS: Military Application of Tranexamic Acid in Trauma Emergency Resuscitation

- Matters was a military study done on 1,000 patients injured in combat.
  - Just as in the CRASH2 half the patients were administered TXA at random.
  - The results were roughly the same. The TXA patients showed a 30% decrease in mortality rate.
  - In patients who received a large volume blood transfusion (10 units or more,) the mortality rate decreased by 50%.
• The military currently uses TXA to treat combat patients
• The military considers TXA a class 1a drug and uses it prior to fluids.

Final Conclusion?
• Both studies showed the **EARLIER** you give TXA the greater the survivability rate becomes.

**TXA SAVES LIVES!**
Alameda County and the State of California have approved a trial study for TXA in the anticipation of likely county-wide implementation.

We will be administering TXA in the pre-hospital setting to trauma patients meeting a specific criteria.

Other counties are also implementing new trauma protocols that include TXA.
What do we hope to accomplish?

• The prevention of hemorrhagic shock
• Prevention of coagulopathy
• Reduction of critical patients in the operating room leading to less surgical intervention
• Reduction of length of stay at the hospital
• Prevention of DEATH due to blood loss
What is the criteria for administering TXA?

- Adults, age ≥ 18 years old
- < 3 hours from time of injury
- TXA should be considered for any trauma patient exhibiting signs and symptoms of hemorrhagic shock:
  - Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock including systolic blood pressure less than 90mmHG.
  - Estimated blood loss of 500 milliliters in the field.
  - Bleeding not controlled by direct pressure or tourniquet.
  - Major amputation of any extremity, proximal to wrist or ankle.
Paramedic considerations:

- TXA does require a specific set of parameters for use but don’t forget to look for early/other signs and symptoms of shock:
  - Poor skin signs
  - Altered level of consciousness
  - Sustained tachycardia
- Patients displaying these symptoms could fall into the TXA parameters rather quickly.
What would exclude patients from receiving TXA?

- Any Patient under 18 years of age.
- Any patient with an active thromboembolic event (within the last 24 hours) – i.e. active stroke, myocardial infarction or pulmonary embolism.
- Any patient with a hypersensitivity anaphylactic reaction to TXA
- Any patient more than three hours post injury
TXA Procedure

- TXA administration and route
  - TXA is typically given twice – once as a loading dose and then as a sustained infusion.
  - Our focus is the first, loading dose, which will be given by the pre–hospital providers.
  - The first dose by the EMS (1gm in 100cc’s of NS)
  - The first dose should be given as soon as possible but no later than three hours after injury!
  - The second dose will be given by the trauma surgeons at either Highland or Eden hospitals.
TXA Procedure

- TXA administration continued
  - TXA is supplied in 1000mg ampoules in 10mL of normal saline.
  - TXA will be administered via IV or IO.
  - The first dose: 1gm mixed in a 100mL bag of NS and administered as a drip over 10 minutes.
  - Any patient with a GCS of 15 requires verbal consent, all patients with GCS of ≤14 shall fall under implied consent.
TXA Procedure

- TXA administration continued
  - It should not be administered through same line as blood products.
  - DO NOT administer as IV push, this could cause hypotension.
  - The drug must be stored at 59–86 degrees Fahrenheit
  - All TXA patients must be transported to a designated trauma center.
  - It MUST be reported to the receiving TRAUMA SURGEON OR ER ATTENDING that the patient received TXA in the field.
Data Collection:

- Each patient who receives TXA will need to have a trailing document completed in addition to our normal PCR’s.
- The document will be a form of data collection and must contain some baseline characteristics:
  - Time of Injury
  - Time of first (EMS) and second (Highland, Eden) dose of TXA
  - Demographics: age, gender, race
  - Vital signs: five sets (pre-hospital, during first dose, post drip, during second dose, post second dose.)
    - Heart rate, respiratory rate, body temperature, blood pressure, cap refill
Data Collection Continued:

- Baseline characteristics continued:
  - Glasgow coma scale (pre treatment, 24 hours, 48 hours)
    - $\leq 8, 9-12, 13-15$
  - Mechanism of injury
  - Area of Injury
  - Estimated blood loss
    - This will be a combination of EMS and Hospital tallied blood loss
TXA Procedure

- Data collection continued:
  - 12 lead EKG prior and post first infusion. (Do not delay transport or infusion due to 12 lead)
  - Number of transfused blood products
  - Length of stay at hospital, use of ventilator?
  - Adverse side effects i.e. deep vein thrombosis, pulmonary embolisms, seizures
Statistical Analysis:
• Once implemented in Oakland and Alameda City, we expect to administer TXA 7–8 times per month, with the number increasing significantly with county wide roll out.
• We will gauge the mortality rate at 24hrs, 48hrs and 28 days of TXA trauma patients verses all other trauma patients.
• We will also be measuring total amount of blood products transfused and total blood loss in TXA patients verses all other trauma patients.
• Analysis will also include the number of adverse events occurred. i.e. pulmonary embolisms, deep vein thrombosis.
Quality Improvement:

- 100% completion of documentation is necessary for this study to be effective.
- Our QI team will follow up with every patient involved in the TXA study and review every document submitted.
- We must maintain 100% compliance to garner the best and most true results.
- ePCR data will be linked with the trauma registry to monitor outcome data.
REQUIRED DATA ELEMENTS TO BE ENTERED IN THE FIELD
Data Collection

- The success of this trial study depends on the accuracy of pre-hospital and hospital data collection. The following are REQUIRED data elements that are necessary for outcome tracking.
Pre-Hospital Data Collection

- Date and Time of Incident
- Incident Number
- Primary Impression
- Mechanism of Injury
- Patient Age
- Weight
- Gender
Pre–Hospital Data Collection

- Time of Injury
- Dose and Time of TXA administration
- Pre and Post TXA vital signs
- Narrative Details