Feasibility and Safety of Changing Tranexamic Acid Administration Route from IV to IM

Agenda

Introduction

Research Questions

Therapeutic Concentration Achievement

Study on Healthy Volunteers

Second Study on Healthy Volunteers

Absorption in States of Shock

- Impact of Hypovolemic Shock
- Human Studies on Shock Patients
- Swine-Model Studies 1&2

Discussion

- Absence of Adequate Data
- Comparison of IM and IV Routes
- Advantages of IM Route

Introduction

Purpose of Discussion

Explore changing TXA administration from IV to IM

Mortality Benefits of TXA

Established in CRASH-2 and MATTERs studies

Current Dosing Regimen

1g IV over 10 minutes, followed by 1g IV over 8 hours

Timing and Survival Benefits

TXA reduces hemorrhage deaths by one-third if given within an hour of bleeding onset

Survival benefits decrease by 10% for every 15 minutes of delay until 3 hours

Research Questions

Therapeutic Concentration Levels

- Does the IM route achieve necessary levels for maximum inhibition of fibrinolysis?

Compensatory Mechanisms During Hemorrhage

- Do these mechanisms reduce blood flow?
- Does reduced blood flow lead to less absorption of the IM depot?

Therapeutic Concentration Achievement

Therapeutic Concentrations of TXA

Required range: 10 to 15 mg/mL

Routes of Administration

IM and IV routes achieve therapeutic concentration

IM Route Characteristics

- Reaches therapeutic concentration at 3.5 minutes
- Median peak serum concentration lower than IV
- Stays above therapeutic requirement 30 minutes longer than IV

Study on Healthy Volunteers

Study Participants

- 15 adult healthy volunteers
- 11 nonpregnant women and 4 men
- Aged between 22 and 44 years

TXA Administration Methods

- 1 g TXA IV
- 1 g TXA IM (two x 5 ml intramuscular injections)
- 2 g TXA oral solution

Injection Sites for IM

- Deltoid (9 volunteers)
- Vastus lateralis (6 volunteers)

Time to Reach 10 mg/L

- 1 min→IV
- 3.5 min→IM
- 66 min→oral

Second Study on Healthy Volunteers

Study Overview

- Blood samples from 15 volunteers
- Routes: IV, IM, and oral
- Doses: 1g IV and IM, 2g orally

Time to Reach 10 mg/L Concentration

- IM route: 3.5 minutes

Median Peak Concentrations

- IV: 57.5 mg/L
- IM: 34.4 mg/L
- Oral: 12.8 mg/L

Duration Above 10 mg/L Threshold

- IV route: 2.9 hours
- IM route: 3.4 hours

Impact of Hypovolemic Shock

Hemorrhage and Hypovolemic Shock

- Leads to hypovolemic shock
- Compensatory mechanisms increase vasoconstriction
- Preserves blood supply to vital organs like heart and brain

Decreased Blood Flow to IM Depot Site

- Severity of shock affects blood flow
- Potentially decreases blood flow to TXA depot site

Studies on Absorption in Shock States

- One human study
- Two swine-model studies

Swine-Model Study 1

Study Design

- 18 Norwegian landrace pigs (40-50 kg)
- Subjects exposed to abdominal and thoracic trauma

Serum TXA Levels

- Collected in trauma IV, IM, and control groups

Maximum Concentrations

- IM route: 20.9 mcg/ml at 15 minutes post administration
- IV route: 48 mcg/ml at 5 minutes post administration
- Control group-non-injured (IM): 36.9 mcg/ml at 15 minutes post administration

Therapeutic Threshold

- Serum concentrations above 10 mcg/ml for both IV and IM routes in traumatized pigs after 5 minutes

Swine-Model Study 2

Study Design

- 12 Yorkshire cross swine used
- 35% controlled hemorrhage induced
- Animals diagnosed with class III shock

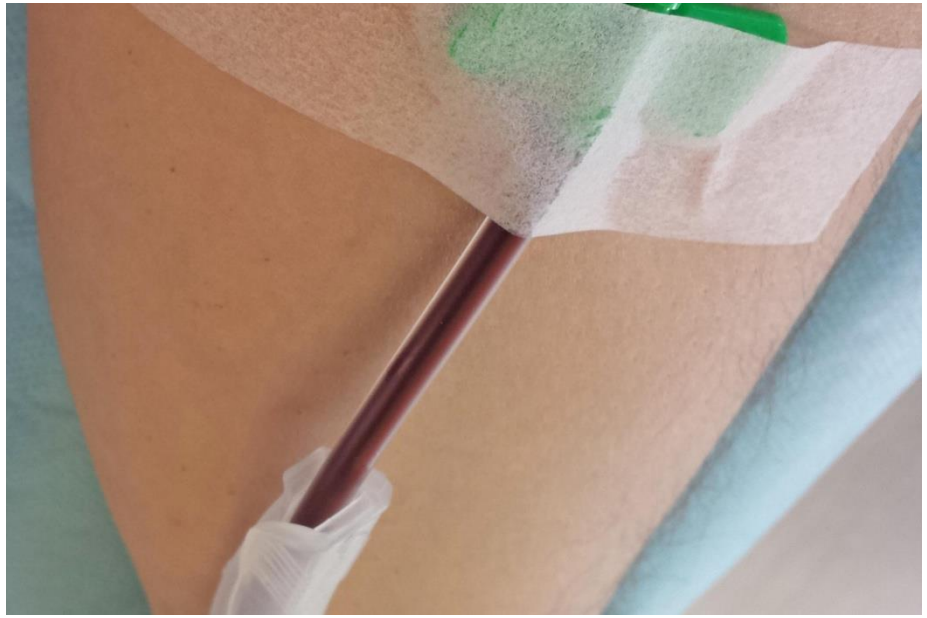
Treatment Groups

- 1 g IV TXA infusion over 10 min
- 1 g IM TXA in two 5mL injections
- 10mL normal saline IM injection as placebo

Results

- Time to maximum concentration not significantly different between IV and IM routes
- IV: 5 [5–10] min, IM: 10 [10–15] min, P 0.12
- IRQ of maximum concentration above therapeutic range

Human Study on Shock Patients



Patient Demographics

- 30 patients involved
- Blunt or penetrating trauma
- 18 patients with clinical signs of shock

Blood Product Administration

- 23 patients received blood products
- Average of 2 units per patient

TXA Dosage and Concentration

- 1 g IM TXA administered
- Concentration of 5mg/L reached in 4 minutes
- Concentration of 10mg/L reached in 11 minutes
- Concentration remained above 10mg/L for 5.6 hours

Prehospital Administration of Tranexamic Acid (TXA) in Trauma Patients

Study Highlights

Survival Benefit

- Prehospital TXA linked to lower 28-day mortality

Reduced Transfusions

- TXA recipients required fewer red blood cell transfusions

Safety Profile

- No increase in adverse events like VTE, seizures, or strokes

Dose-Response Effect

- Higher doses of TXA correlated with better outcomes

Broad Application

- Effective across diverse trauma populations

Dosing Importance

- Demonstrated dose-response relationship
- Need for protocols that optimize TXA administration
- Potential for enhancing patient outcomes

Future Research Directions

- Promising results of current studies
- Exploration of TXA's role in various trauma contexts
- Potential for innovative treatments and guidelines

CRASH-4

Study Design

- Randomized, double-blind, placebo-controlled
- Focus on intramuscular tranexamic acid (TXA)

Target Population

- Older adults aged 50 and above
- Approximately 10,000 participants

Primary Objectives

- Evaluate effectiveness of TXA in treating mild TBI
- Measure emergency department discharge within 24 hours

Secondary Objectives

- Assess rates of intracranial bleeding

Significance

Key Insights

Rising Incidence of TBI in Aging Population

- Increasing cases of traumatic brain injury (TBI) among older adults

Promise of Tranexamic Acid (TXA)

- TXA shows potential in reducing head injury-related mortality
- Effectiveness increases with early administration

Trial Design and Adaptation

- Includes a pilot phase to test procedures
- Adaptations made for challenges posed by COVID-19

Focus on Older Adults

- Older adults have worse outcomes from mild TBIs

Primary Outcome: Timely Discharge

- Emphasis on efficacy and patient safety

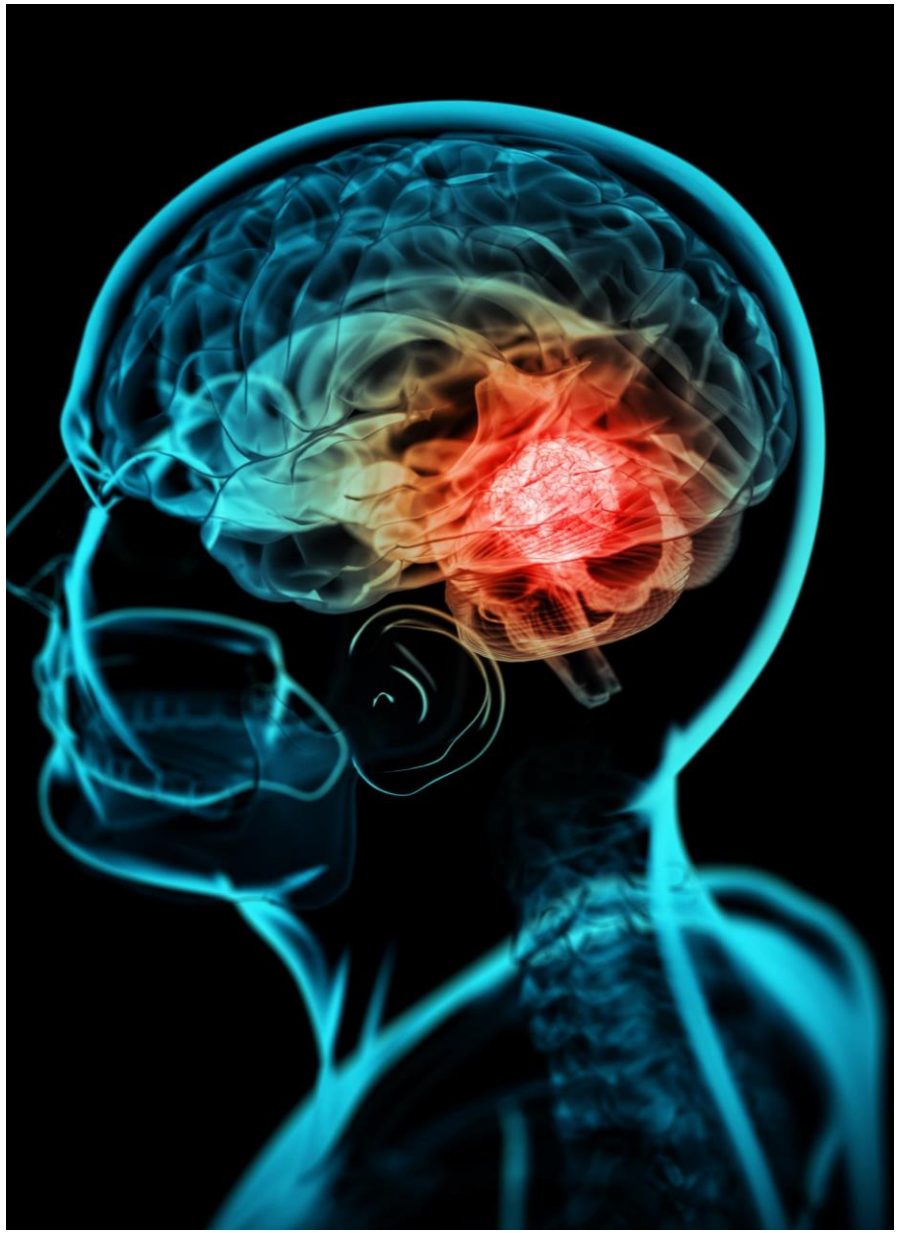
Primary Goal of the CRASH-4 Trial

Objective of the CRASH-4 Trial

- Evaluate the effectiveness of tranexamic acid
- Assess the safety of early intramuscular administration

Target Population

- Older adults
- Individuals with mild traumatic brain injury



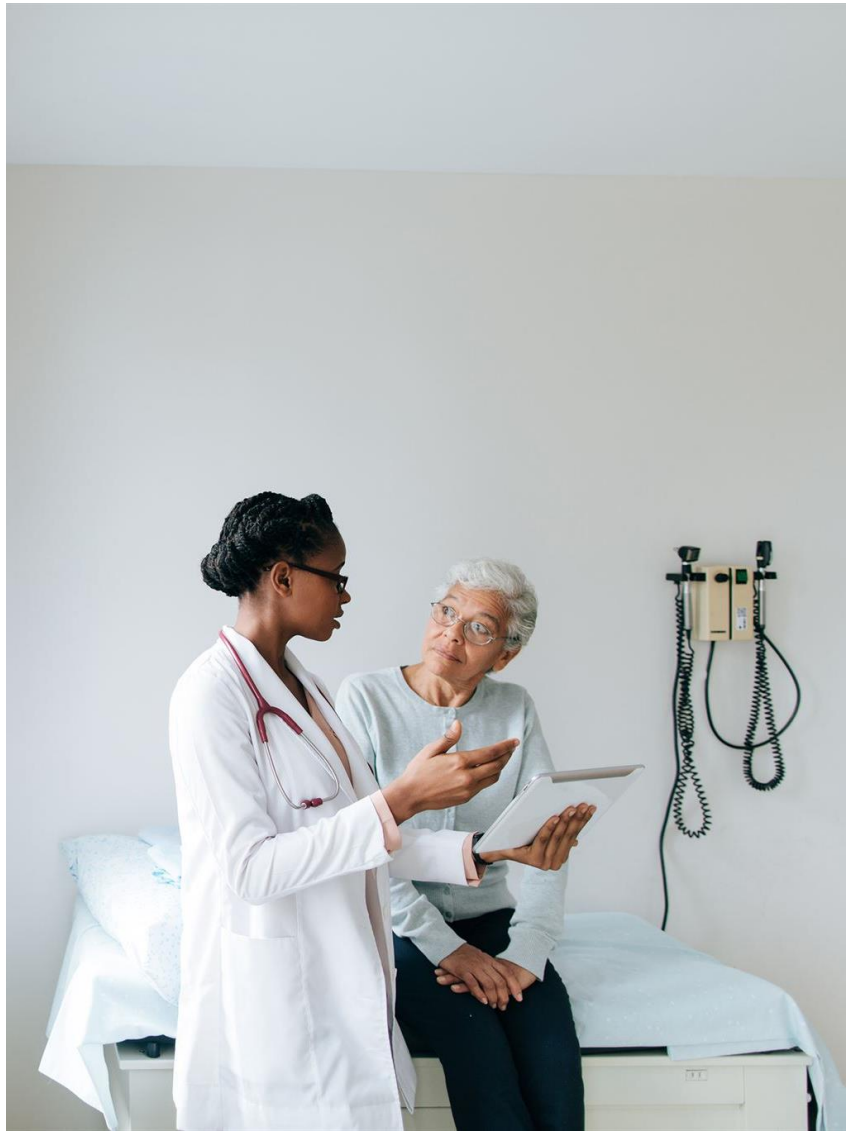
Measured Outcomes

Primary Outcomes

- Emergency department discharge within 24 hours

Secondary Outcomes

- Rates of intracranial bleeding
- Death rates
- Disability rates
- Risk of dementia over a year



Impact on Clinical Practice

Potential Changes in Treatment Protocols

- Focus on older adults with mild TBI
- Implementation of new guidelines based on trial results

Improvement in Patient Outcomes

- Reduction in long-term complications
- Enhanced recovery rates

Discussion

Pharmacokinetic Data on IM TXA

- Absence of adequately powered data
- Consistency in results showing therapeutic levels of 10 to 15 mg/L

Comparison of IM and IV Routes

- IM route slightly slower by 5 to 10 minutes
- IV route requires time to prep and find a vein

Advantages of IM Route

- No need to choose between resuscitation and TXA infusion
- Provides a depot with longer time above therapeutic concentration

Practical Benefits

- Saves time in medication delivery

Recommendation

Comparison of IM and IV Routes

Time to Therapeutic Concentration

- IM route is slightly slower than IV by 5-10 minutes
- IV route requires time for IV-bag prep, vein access, and 10-minute infusion

IM Route Advantages

- No need to choose between resuscitation with blood products and TXA infusion
- Provides a depot with slower time to maximum concentration
- Longer time above therapeutic concentration level

Theoretical Benefits for Bleeding Patients

- Longer absorption and distribution phase
- Less medication lost to hemorrhage due to torniquets and compressions

Recommendation

1. Administer first dose (1gm) of TXA as IM injection
2. If IO/IV access cannot be established quickly, administer follow on dose as IM TXA 1gm
    a. Consider IM TXA if multiple resuscitations with limited medical staff is occurring.
3. Encourage and support further experimentation and research to examine IM TXA in traumatic patients

Way Forward

- RXBandz ®
  - Multi drug autoinjector delivery platform
  - Includes IM TXA as an agent
- Navy Medicine Research Command
  - IM TXA autoinjector program
- Revisit with CoTCCC
  - In 2025/2026 after CRASH 4 study data release?