

# Use of Whole Blood and Tranexamic Acid in the Pediatric Patient

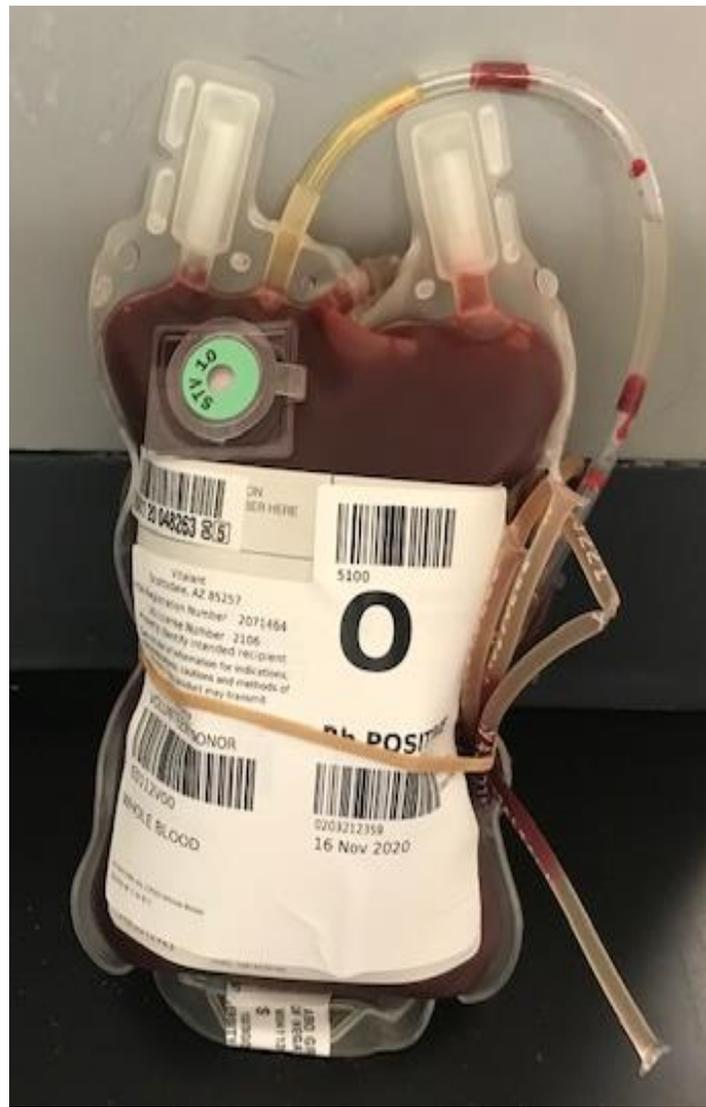
Bradford Ray, LP, PBMT, RABT  
Director, Patient Blood Management & Research  
University Medical Center, El Paso

Rio Grande Trauma Conference  
December 03, 2020

# Disclosures

- No disclosures for the past year

# Whole Blood



“Fatboy” is whole blood  
Each unit contains RBC’s – Plasma –Cryo - Platelets

# Whole Blood in Adults

## Convincing Evidence it Works

“Low titer group O whole blood for prehospital hemorrhagic shock:  
*It's an offer we cannot refuse*”

Transfusion Volume 59 July 2019 p. 2177

### Rationale for Cold Storage LTOWB\*

\*(Low Titer Group O Whole Blood)

1. LTOWB is more concentrated than components with less dilutional effects of additive solutions (500mL bag of Whole Blood has 70mL of CP2D - red cells 100mL of additive solution AS-1 or AS-3) (Important to check Calcium when using components)
2. Cold- stored platelets support hemostasis better than room temperature – stored platelets
3. Logistical benefits of transporting and transfusing ONE product instead of three components
4. Fewer donor exposures

# Whole Blood in Adults

- This is a Big Change in Transfusion Medicine

*Slowly moving away from components*

*Slow moving due to blood banking being a multi billion business*

- Many Pre-Hospitals Systems are moving away from Crystalloids to resuscitate severely bleeding patients with Whole Blood.
- Based on recent data collected from battle fields, several are now stocking Whole Blood on Helicopters. (Military as well as Civilian)



# Adult Whole Blood

“Use of low titer group O whole for resuscitation of civilian trauma patients”  
Survey Questions (16 responded)

How many units of Whole Blood can a patient receive? 5 (Ave 4-8)

What type of patient qualifies for Whole Blood (Trauma 11) (Mass Trans 5)

D type of Whole Blood supplied to MALES (D+ 6 D- 3 D+ & D- 7)

D type of Whole Blood supplied to FEMALES (D+ regardless of age 2)  
(D- regardless of age 2 //D- if not of reproductive age 5//D+ Not of reproductive age 5)

Is the Whole Blood Luekoreduced? (Yes 9 No 7)

Maximum storage days for Whole Blood (10 days- 2) (14 days- 5) (21 days – 7)  
*Vitalant uses CP2D 21 day storage*

Do you use Whole Blood for Pediatrics? (Trauma & MHG) **YES 2 No 14**

*Transfusion Vol 58 November 2018 p. 2744*

**TABLE 2. Names of the participants in this survey**

Brooke Army Medical Center, San Antonio, TX  
Cincinnati University, Cincinnati, OH  
Cooper University, Camden, NJ  
Emory University, Atlanta, GA  
Haukeland University Hospital, Bergen, Norway  
Intermountain Medical Center, Salt Lake City, UT  
Johns Hopkins University, Baltimore, MD  
Mayo Clinic, Rochester, MN  
Penn Presbyterian Medical Center, Philadelphia, PA  
University California at Los Angeles, Los Angeles, CA  
University of Oregon, Portland, OR  
University of Pittsburgh Medical Center, Pittsburgh, PA  
University of Texas, Houston, TX  
University of Texas, San Antonio, TX  
University of Washington in St Louis, St Louis, MO  
Wake Forest University, Winston-Salem, NC

# Is use of Whole Blood Convincing for Pediatric Trauma?

*2 Pioneering Hospitals using Whole Blood in Pediatrics are:*

**University of Pittsburgh and University of Texas at San Antonio**

U of Pittsburgh uses WB starting at 2 years of age

U of Texas at San Antonio starts at age 5

## Positive Outcomes?

**Outcomes so far are encouraging**

Studies point to decreased mortality when compared to crystalloid or blood components. Can lead to less blood transfused – thus fewer donor exposures

Mayoclinic.org Resuscitation scheme changing for pediatric patients

For Pediatric patients, most of the publications say;  
Whole Blood May Be Viable Treatment Option for Pediatric Trauma

Recently published data from the Department of Defense;  
January 2007 and January 2016

543 pediatric patients included in this analysis  
23 received Whole Blood  
18 met definition of Massive Transfusion

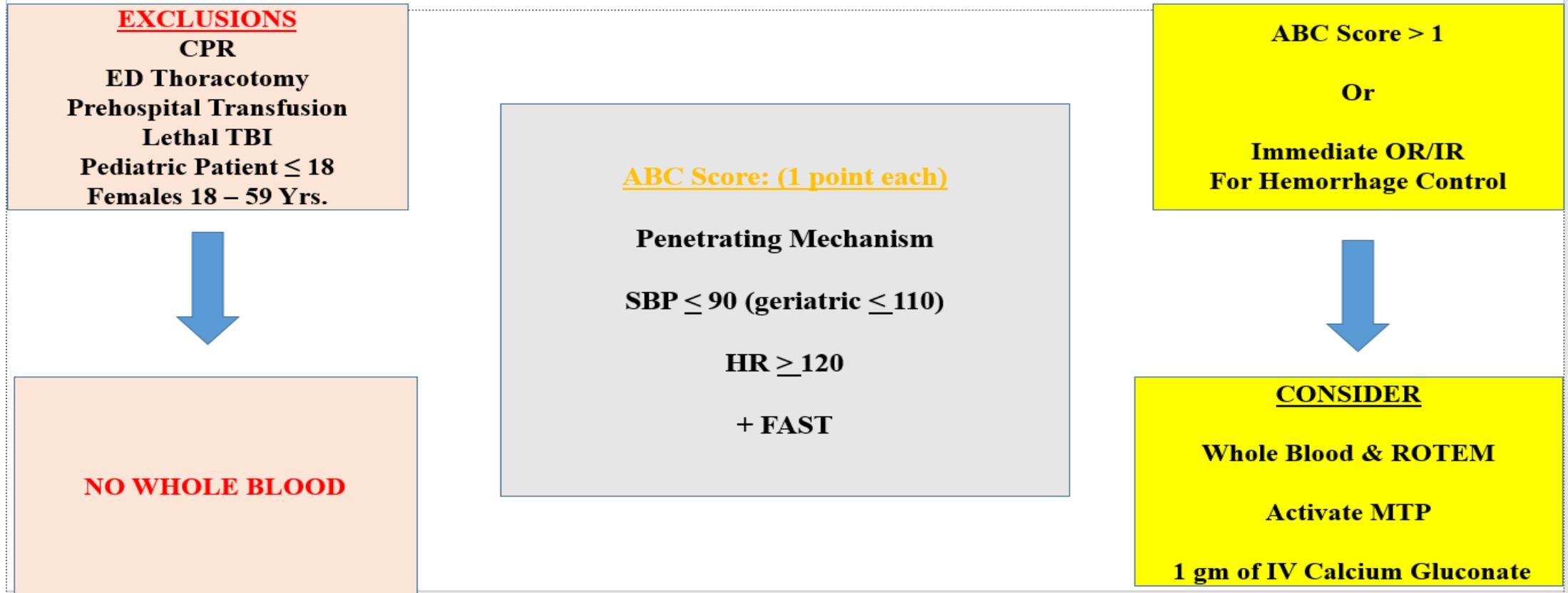
Results:

“Survival is no worse when using Whole Blood”

When adjusted for additional factors “Whole Blood was associated with higher survival rates”

# Whole Blood at UMC

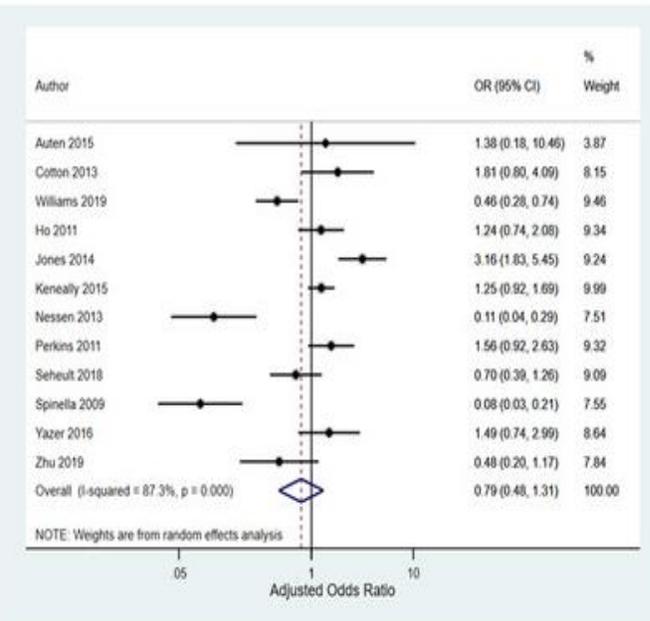
## WHOLE BLOOD RESUSCITATION FOR TRAUMATIC INJURY



Guideline from U of New Mexico, Albuquerque  
Not currently using Whole Blood in Pediatrics

# Whole Blood in Pediatrics

## Where do the clinical studies stand now?

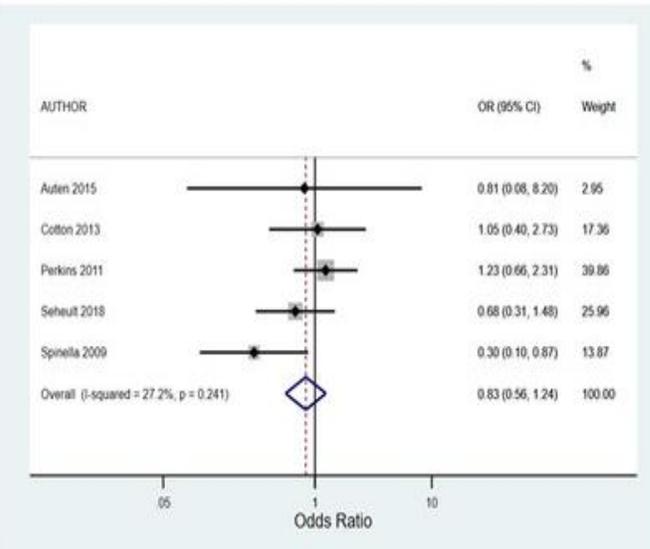


### The Bottom Line

The use of whole blood instead of balanced component therapy during massive transfusion following trauma has been increasing. This meta-analysis of current studies demonstrates no difference in outcomes when whole blood is used, but it is limited by the small number of existing studies and significant heterogeneity of those studies.

Our systematic review and meta-analysis of 12 studies of whole blood resuscitation in trauma revealed wide heterogeneity in study design, methods, setting, population, interventions, and outcomes

If the objective is to evaluate whole blood in civilian trauma, then the trial should take place in trauma systems currently using whole blood, the selection of patients should **include both blunt and penetrating trauma patients as well as females of child-bearing age**. Studies must identify whole blood transfusion practices, including the types of whole blood used, the application of leukoreduction and methods of storage. The **minimum quantity of whole blood transfused that constitutes the whole blood group should be agreed upon**, including the type and number of components allowed before receiving whole blood. Study endpoints might include not just hospital mortality but also early mortality or physiologic measures such thromboelastmetry.



12 studies mentioned above – all in Adult patients  
For Pediatric trauma patients **“We Are Not There Yet”**

# Tranexamic Acid In Pediatric Trauma

## What is the current evidence?

Military leading the way on use of TXA in pediatric trauma.

From 2008 – 2012, 766 pediatric patients were injured/treated. 66 receiving TXA. Pediatric patients had severe abdominal or extremity trauma and metabolic acidosis.

No adverse safety or medication related complications identified.

*RESULTS: TXA administration was independently associated with a decrease of 27% in mortality*

J Trauma & Acute Care Surgery Dec. 2014 p. 852-858

# Tranexamic Acid use in US Children's Hospitals

Objective: Describe use of TXA in US hospitals in general and specifically for trauma.

Time frame: 2009 – 2013

Setting & Population: 36 Pediatric Hospitals included // 21 Level 1 & 5 Level II trauma centers

Results: 35,478 pediatric encounters with TXA. Only 110 trauma encounters.

Common conditions where TXA was considered or infused:



Journal of Emergency Medicine Vol 50, No 6 p 868-874, 2016

**Table 2. Five Most Frequent ICD-9 Principal Diagnoses and Procedures in the Trauma Category**

Diagnosis or Procedure	n
<b>ICD-9 principal diagnosis</b>	
Open wound of tongue and floor of mouth, without mention of complication	11
Injury of face and neck	7
Head injury, unspecified	6
Ankle sprain	5
Secondary and recurrent hemorrhage	4
Open wound of tooth (broken) (fractured) (due to trauma), without mention of complication	4
<b>ICD-9 principal procedure</b>	
Transfusion of platelets	3
Extraction of other tooth	2
Other repair and plastic operations on bronchus	2
Esophagogastroduodenoscopy with closed biopsy	2
Closed reduction of fracture without internal fixation, radius and ulna	2
Open reduction of fracture with internal fixation, radius and ulna	2
Open reduction of fracture with internal fixation, femur	2
Closure of skin and subcutaneous tissue of other sites	2

ICD-9 = *International Classification of Diseases, Ninth Revision.*

# Results with TXA usage in Pediatric Trauma

Critical Care 02 July 2014 Suzanne Beno, MD

Based on results of adult trials & observational pediatric studies, several advocated for TXA usage in injured children with potential hemorrhagic injuries.



One strong advocate is Susanne Beno, MD from “The Hospital for Sick Children”

Trauma is a leading cause of mortality in the pediatric population. In 2008, the *American Academy of Pediatrics* trauma accounts for more deaths than all other causes combined. Bleeding remains the most preventable cause of death after trauma.

*Pediatrics*. 2008, 121: 849-854.

MATTERS Trial proved TXA reduces mortality and Blood Loss

(MATTERS) study. *Arch Surg*. 2012, 147: 113-119.

There is no scientific or biological reason to suggest that a similar mortality benefit will not be seen in pediatric trauma. We feel the incorporation of TXA into pediatric trauma management has the potential to also significantly reduce mortality in children and youths, without increasing adverse events.

The basis for using TXA in children would appear to be nearly identical to that for adults, if not more intuitive.

In adolescents, the role of TXA should be adopted immediately.

The Royal College of Paediatrics and Child Health in the United Kingdom issued an Evidence statement in November 2012 entitled:

“Major trauma and the use of TXA in children’ that proposes the use of TXA for all children”

# Use of tranexamic acid in pediatric hemorrhagic trauma

TXA significantly decreases mortality in bleeding trauma patients 16 years of age and older without significantly increasing prothrombotic complications if administered within 3 hours of injury.

evidence specifically for TXA in pediatric trauma is not yet available, TXA should be considered for use in adolescent trauma patients in the same dosing regimen and indications as used in adults.

we feel that young children with hemodynamic instability and ongoing risk for hemorrhage would also benefit from TXA

Denying injured children TXA due to the lack of pediatric trauma trial evidence in this indication is likely shortsighted and unnecessary given the ample clinical evidence in other pediatric settings,

## Table 1 Criteria for the use of tranexamic acid in pediatric trauma

From: [Tranexamic acid in pediatric trauma: why not?](#)

Immediate need for transfusion, with any one of the following indicating severe shock <sup>a</sup>	
•	Systolic blood pressure low (<80 mmHg <5 years and <90 mmHg ≥5 years)
•	Poor blood pressure response to crystalloid 20–40 ml/kg
•	Obvious significant bleeding

## Table 2 Tranexamic acid dosing in pediatric trauma

From: [Tranexamic acid in pediatric trauma: why not?](#)

Age	Loading dose (administer within 3 hours)	Subsequent dose
≥12 years::adult protocol	1 g intravenously over 10 minutes	1 g intravenous infusion over 8 hours
<12 years	15 mg/kg intravenously over 10 minutes (maximum dose 1 g)	2 mg/kg/hr intravenous infusion over 8 hours or until bleeding stops

# Tranexamic Use in Pediatric Trauma

Potential side effects : The adverse effects of TXA in pediatrics are very rare but include gastrointestinal effects, hypotension with rapid intravenous injection, dizziness, headache, muscle pain and spasms, and postoperative convulsions in children receiving (high doses)\*\* during cardiac surgery.

\*\* Studies in TXA have not shown increased rates of thromboembolic events.

For Children under 12 years of age

The **Royal College of Pediatrics and Health Health committee** recommend a pragmatic dosage schedule – **15mg / kg Tranexamic Loading dose (max 1g)** infused over 10 minutes followed by **2mg / kg per hour** over 8 hours.

For Children over 12 years Adult Doses are recommended

Evidence Statement – Major trauma and use of Tranexamic Acid in children Nov 2012

# TXA in Pediatric Trauma Used in US Pediatric Hospitals



Spectrum Health Grand Rapids

## Clinical Guideline

**Subject:** Use of Tranexamic Acid (TXA) for pediatric trauma patients with uncontrolled hemorrhage

Last Reviewed / Revised Date: May 16, 2013

**Purpose:** To provide guidelines for the use of TXA for pediatric trauma patients with uncontrolled hemorrhage.

**Background:** No evidenced based guidelines are available for the use of TXA in pediatric trauma patients. Evidence is available in pediatric operative literature and adult trauma literature. Bleeding trauma patients are at high risk for mortality (35% of deaths were attributed to bleeding in the CRASH-2 study with a 5% mortality overall). Children in general have healthier vasculature than adults, so there is no clear reason for a lower age limit.

### Guidelines

- a. Give 20 mg/kg bolus over 10 minutes (maximum of 1000 mg) followed by the same dose (20mg/kg, maximum of 1000 mg) infused over 8 hours. May continue if significant ongoing bleeding is observed beyond eight hours but not to exceed 24 hours.
- b. The first dose optimally should be given within three hours of injury.
- c. If a dedicated intravenous access for an infusion is not available, a repeat of the 20 mg/kg (maximum 1000 mg) bolus dose could be given after 3 hours instead of the 8 hour

# TXA use in pediatric surgery –Current Evidence?

## Abstract

**Purpose of review:** Perioperative bleeding and blood product transfusion are associated with significant morbidity and mortality. Prevention and optimal management of bleeding decreases risk and lowers costs. Tranexamic acid (TXA) is an antifibrinolytic agent that reduces bleeding and transfusion in a broad number of adult and pediatric surgeries, as well as in trauma and obstetrics. This review highlights the current pediatric indications and contraindications of TXA. The efficacy and safety profile, given current and evolving research, will be covered.

**Recent findings:** Based on the published evidence, prophylactic or therapeutic TXA administration is a well-tolerated and effective strategy to reduce bleeding, decrease allogeneic blood product transfusion, and improve pediatric patients' outcomes. TXA is now recommended in recent guidelines as an important part of pediatric blood management protocols.

**Summary:** Based on TXA pharmacokinetics, the authors recommend a dosing regimen of between 10 to 30 mg/kg loading dose followed by 5 to 10 mg/kg/h maintenance infusion rate for pediatric trauma and surgery. Maximal efficacy and minimal side-effects with this dosage regime will have to be determined in larger prospective trials including high-risk groups. Furthermore, future research should focus on determining the ideal TXA plasma therapeutic concentration for maximum efficacy and minimal side-effects.

Anesthesia Dept of Research, Harvard U

# TXA use in pediatric surgery –Current Evidence?

## Abstract

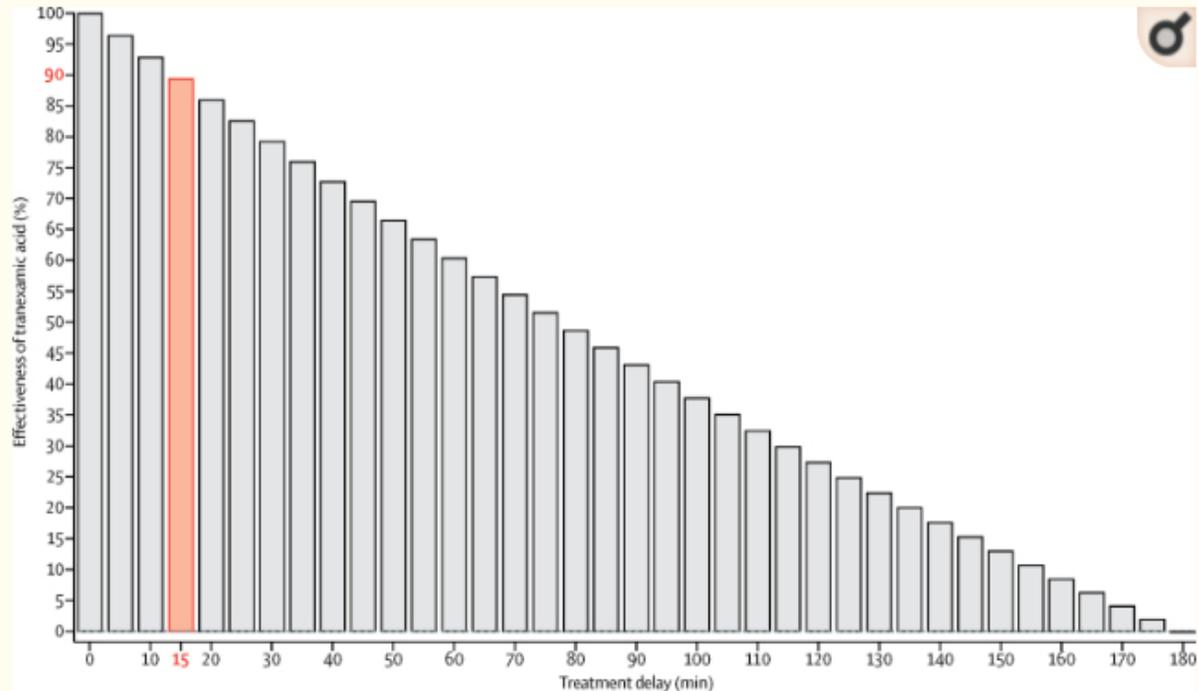
**Background:** Our objective was to quantify blood loss and transfusion requirements for high-dose and low-dose tranexamic acid (TXA) dosing regimens in pediatric patients undergoing spinal fusion for correction of idiopathic scoliosis. Previous investigators have established the efficacy of TXA in pediatric scoliosis surgery; however, the dosing regimens vary widely and the optimal dose has not been established.

**Methods:** We retrospectively analyzed electronic medical records for 116 patients who underwent spinal fusion surgery for idiopathic scoliosis by a single surgeon and were treated with TXA. In total, 72 patients received a 10 mg/kg loading dose with a 1 mg/kg/h maintenance dose (low-dose) and 44 patients received 50 mg/kg loading dose with a 5 mg/kg/h maintenance dose (high-dose). Estimated blood loss and transfusion requirements were compared between dosing groups.

**Results:** Patient characteristics were nearly identical between the 2 groups. Compared with the low-dose TXA group, the high-dose TXA group had decreased estimated blood loss (695 vs. 968 mL, P=0.01), and a decrease in both intraoperative (0.3 vs. 0.9 units, P=0.01) and whole hospitalization (0.4 vs. 1.0 units, P=0.04) red blood cell transfusion requirements. The higher-dose TXA was associated with decreased intraoperative (P=0.01), and whole hospital transfusion (P=0.01) requirements, even after risk-adjustment for potential confounding variables.

**Conclusions:** High-dose TXA is more effective than low-dose TXA in reducing blood loss and transfusion requirements in pediatric idiopathic scoliosis patients undergoing surgery.

# TXA infusions, When? Why?



**Figure 4**

Reduction in effectiveness of tranexamic acid with increasing treatment delay

The bars represent the estimated treatment effectiveness (y-axis, estimated by  $[(OR \text{ at time } t - 1)/(OR \text{ at } t = 0 - 1) \times 100]$  in %) at 5-min intervals of treatment delay. The bar highlighted in red shows the estimated treatment effectiveness (90%) with a treatment delay of 15 min.

TXA is most effective when given immediately, with increased bleeding & survival decreasing 10% for every 15 minute delay in administration. No benefit after 3 hours (180 minutes)

Findings based on 40,138 bleeding patients

Effect of treatment 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 Jan 13; 391(10116): 125–132

# TXA administration in Pediatric Trauma

40. Tranexamic acid should be administered as soon as intravenous or intraosseous access is achieved but within 3 hours from time of injury or within 3 hours from MHP activation in all other patients.

Tranexamic acid reduces mortality in the setting of trauma<sup>93</sup> and postpartum hemorrhage.<sup>94</sup> It is most effective when given immediately, with the survival benefit decreasing by 10% for every 15-minute delay in administration and with no benefit after 3 hours from injury/onset of bleeding.<sup>95</sup> There is no increased risk of venous or arterial thromboembolic complications.<sup>96</sup> Dosages and infusion rates vary depending on the study protocol (1-g bolus plus 1-g infusion over 8 h,<sup>93</sup> 1-g bolus and 1-g bolus repeated at 1 h,<sup>97</sup> 1-g bolus and repeated if ongoing bleeding at  $\geq 30$  min<sup>94</sup> and 2-g bolus at the scene of the injury (Clinicaltrials.gov; [NCT01990768](#); trial completed). The dosage and infusion rate should be determined by the local institution. Simplification may be needed in more resource challenged locations, and a single 2-g bolus may be preferred. Evidence of the efficacy of tranexamic acid in pediatric trauma is currently limited, but its use in pediatric patients with trauma requiring transfusion is accepted practice, within the same time parameters as for adults. For pediatric patients, the initial bolus of tranexamic acid can be dosed at 15 mg/kg up to a maximum of 1 g, with additional doses/infusion based on local policy.<sup>98,99</sup> The role of tranexamic acid in gastrointestinal bleeding has not been confirmed; a large multicentre trial (Haemorrhage Alleviation With Tranexamic Acid – Intestinal System [HALT-IT]) is under way to determine whether tranexamic acid assists with hemostasis and reduces transfusion or mortality rates.<sup>100</sup> Tranexamic acid should be readily available in clinical areas where massive hemorrhage is common to prevent delays in administration.

Evidence of the efficacy of TXA in pediatric trauma is currently limited, but its use in pediatric patients with trauma requiring transfusion is accepted practice within the same parameters as for adults. Initial dose – 15mg/kg up to a maximum of 1gm.

Flight helicopters serving El Paso all carry TXA on board. Working on getting land ambulances to carry TXA.

# Inventor of TXA & Ian Roberts, MD



Inventor was a Japanese medical doctor “Utako” She is 91 in this photo

Her goal was to improve Post-Partum Hemorrhage.

She has previously discovered Amicar

Ian Roberts, MD is responsible for the majority of the landmark studies on Tranexamic Acid

# TXA in GI Bleeding - Does it Work?

## Halt – It trial

**Background:** Tranexamic acid reduces surgical bleeding and reduces death due to bleeding in patients with trauma. Meta-analyses of small trials show that tranexamic acid might decrease deaths from gastrointestinal bleeding. We aimed to assess the effects of tranexamic acid in patients with gastrointestinal bleeding.

**Methods:** We did an international, multicentre, randomised, placebo-controlled trial in 164 hospitals in 15 countries. Patients were enrolled if the responsible clinician was uncertain whether to use tranexamic acid, were aged above the minimum age considered an adult in their country (either aged 16 years and older or aged 18 years and older), and had significant (defined as at risk of bleeding to death) upper or lower gastrointestinal bleeding. Patients were randomly assigned by selection of a

**Findings:** Between July 4, 2013, and June 21, 2019, we randomly allocated 12 009 patients to receive tranexamic acid (5994, 49.9%) or matching placebo (6015, 50.1%), of whom 11 952 (99.5%) received the first dose of the allocated treatment. Death due to bleeding within 5 days of randomisation

**Interpretation:** We found that tranexamic acid did not reduce death from gastrointestinal bleeding. On the basis of our results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

# Take home points

## WHOLE BLOOD

“Survival is no worse when using Whole Blood”

UMC is currently not using Whole Blood in Pediatrics

For pediatrics patients and the use of Whole Blood- *“We are not there yet”*

Ongoing research U of Pittsburgh and U of Texas, San Antonio



## TRANEXAMIC ACID

27% reduction in mortality and significant reduction in intra-op and post-op bleeding

No scientific or biologic reason TXA would not work for children as it does in adults

Many Children’s hospitals have published guidelines on TXA use in trauma

Current Guidelines Recommend TXA for Pediatric Patient Blood Management

Infuse immediately before surgery or as soon as patients presents. 10% reduction in benefit for every 15 minutes delayed.

Thank you

