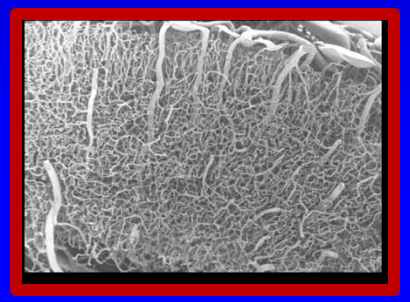
Taking It to the Streets

Why Are We Giving Plasma for TBI ?


Paul E. Pepe. MD, MPH, MCCM, FACEP, MACP, FAEMS, FRCP

Medical Director, EMS and Public Safety
County of Dallas, Texas, USA

Medical Director for Research and Special Ops
Palm Beach, Broward and Brevard County (Florida)

JUDITH WOODS
Why keeping hubby happy helps women to succeed

JAMES CORDEN
My joy at being part of the funniest play of the year

ESTHER RANTZEN
Old folk need to get with wine

The Daily Telegraph

Insert Headline Here

Why Would We Use Plasma for TBI *in the Prehospital Setting ?*

- **Future Potential for Use on Every EMS ALS Unit**
- **Will Be Cheaper (and More Available) than LTOWB**
- **Plasma Has Positive Effects on the BBB (Glycocalyx)**
- **It's Preservative --- and Restorative ! But …..**
- **The Earlier the Intervention, the Better the Results !**

Bottomline – We Are Already Doing This !!

During Last Year's Presentation ...

Some of My Conclusions Were That ....

… for Blood Products in the Field:

We Needed to Be More Inclusive with this Invaluable Resource!

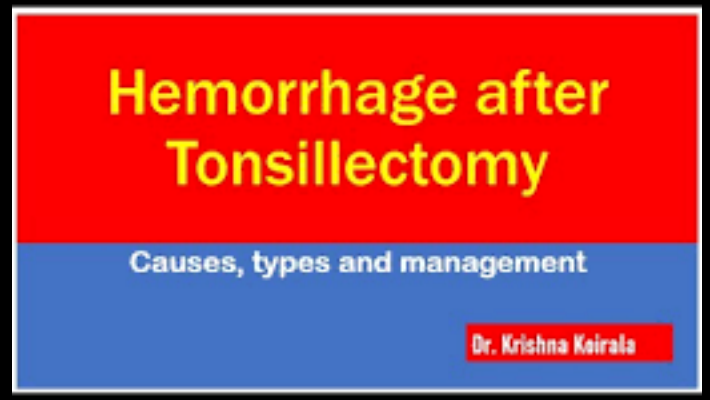
- **Current Criteria are Much Too Restrictive**
  - *e.g., BP <90 or Shock Index > 1.1*
- **Many with "Normal Vital Signs" Bleeding**
  - *POC Lactate can be > 4.0*
- **Shock Indices Have Limitations**

- An SI of .9 ==> BP = 80 mmHg, HR 72/min (Crashing/Beta Blocker)

Furthermore...

There Was a Re-Emphasis That Blood Products Are Not Just for Trauma ...

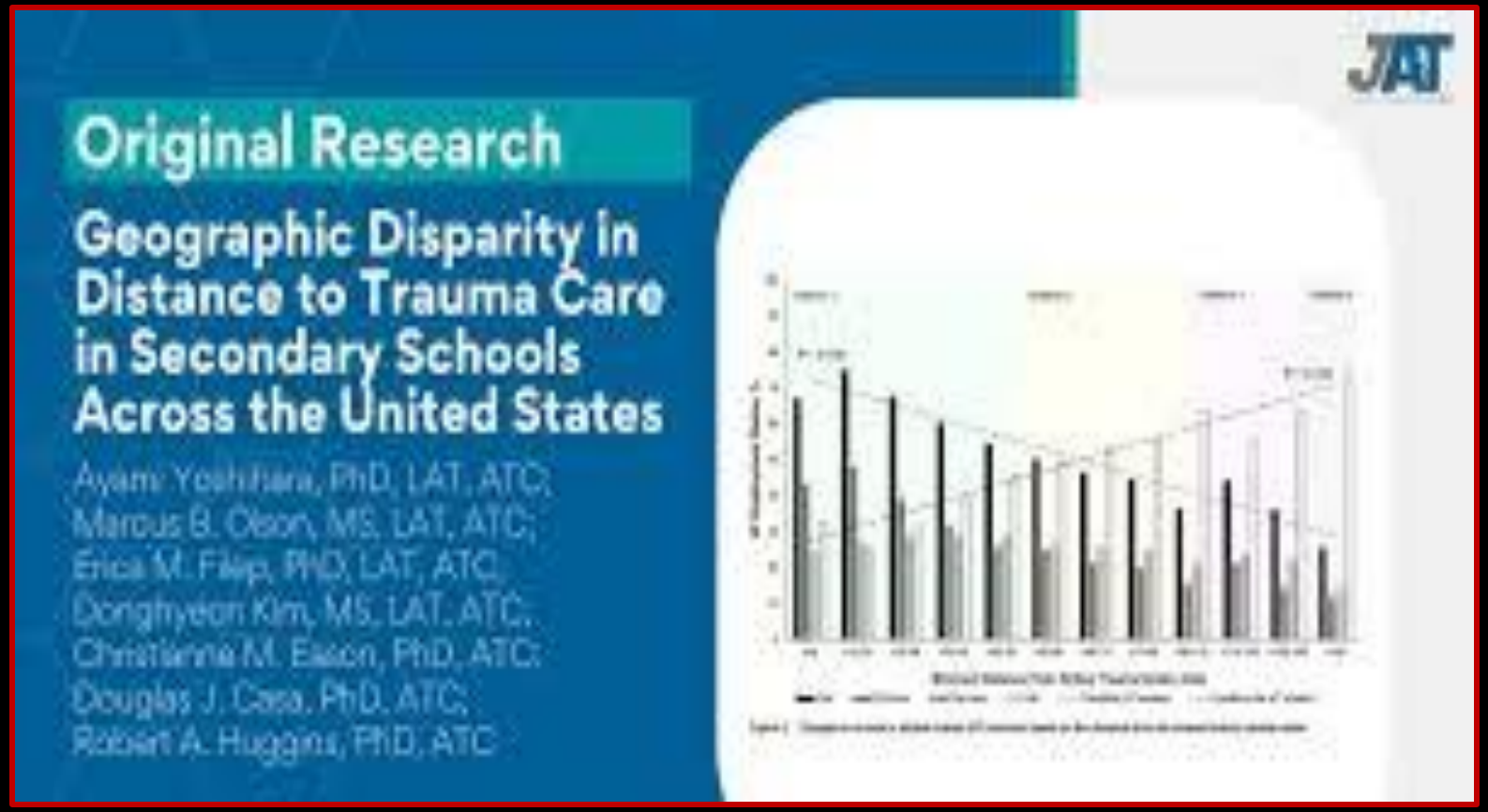
(So We Need Even More Supplies of Blood Products)



> 50% of Cases are Non-Traumatic in Some of the Early Adopter Systems Providing This Intervention …

But ....

There Are Also Disparities and Limitations …



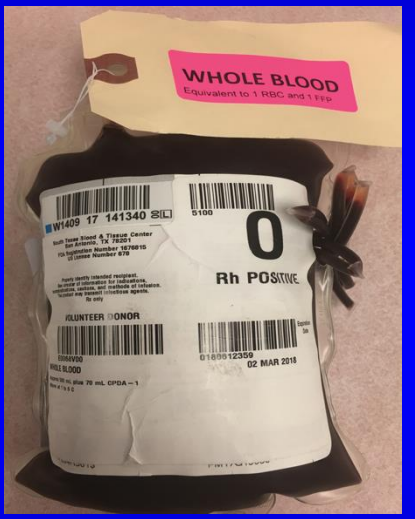
e.g., Distance to Trauma Centers…

And, More To The Point ....

Not Enough Whole Blood Supply for Every Ambulance …

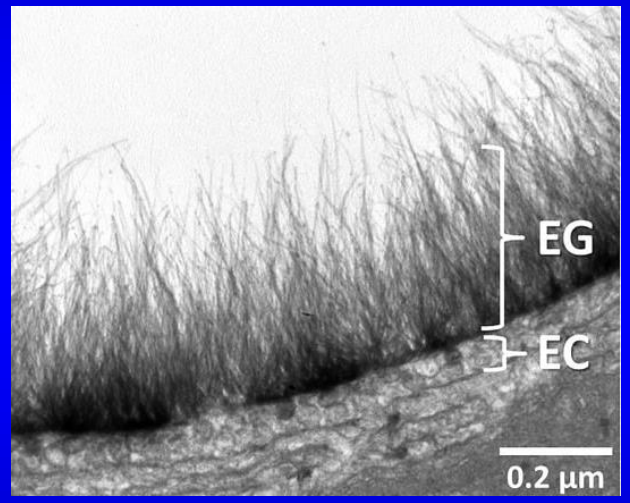
And Medics Usually Need to Wait for an Intercept from a Supervisor or Air Medical Team…

Does an Ambulance Always Have to Wait for Whole Blood or RBCs ?



Are There Other Earlier Viable Interventions?

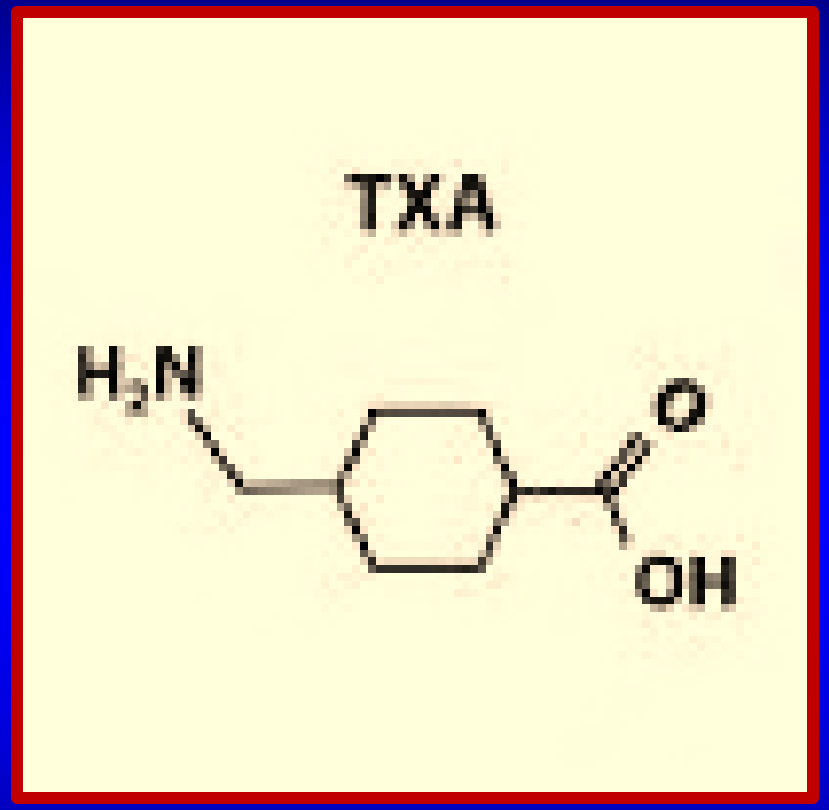
My Answer Then --- And Now :
We Can --- and Need to ---
Protect the Glycocalyx ASAP !



The Endothelial Glycocalyx (EG) Covering and "Caulking" the Endothelial Cells (EC)

(Which is Also Called the "Blood Brain Barrier" (BBB) in the Brain)

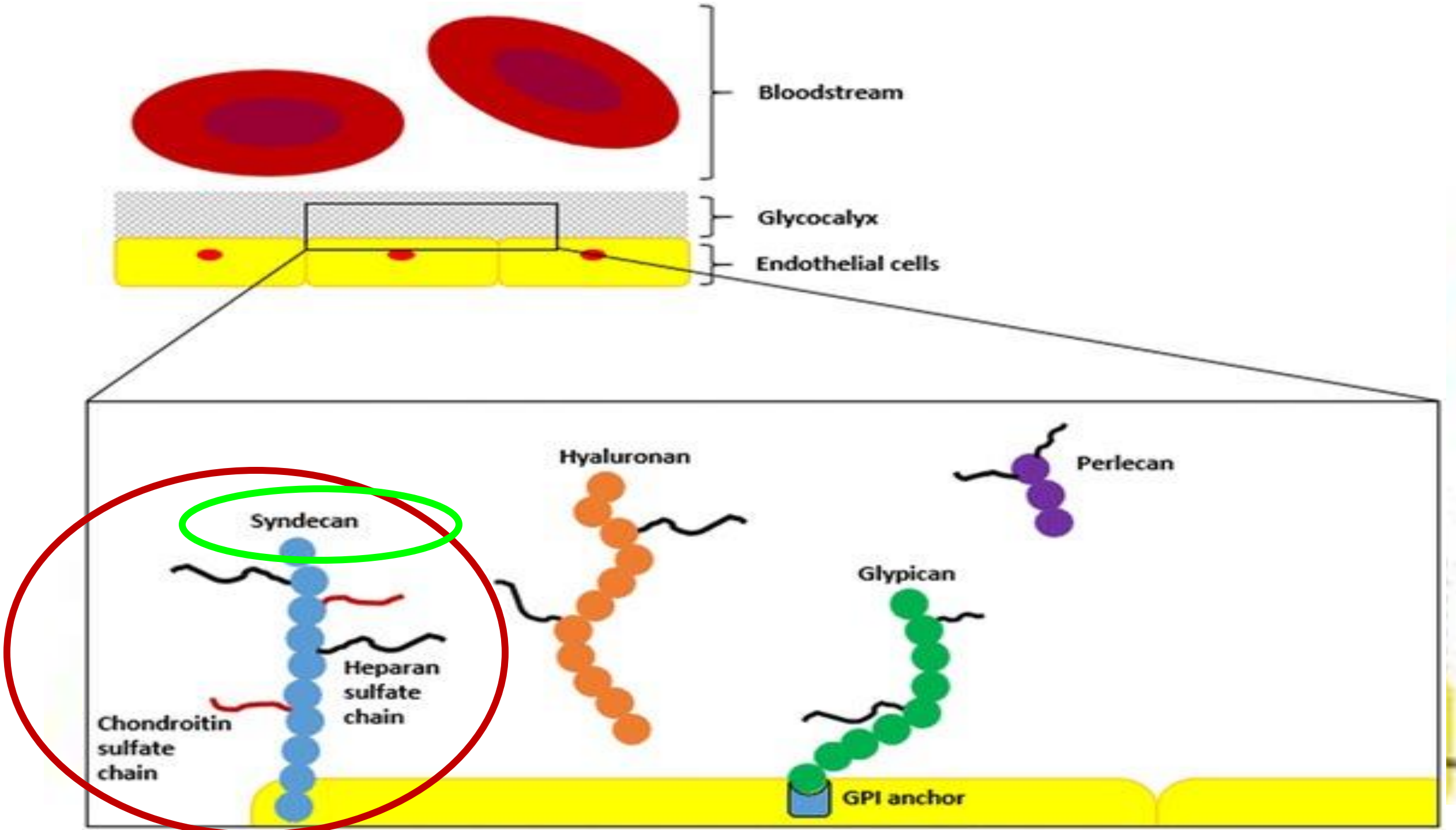
And We *Can* Protect It with TXA and Plasma



So What's a Glycocalyx ?

The Endothelial Glycocalyx

- Gel-like Layer of Glycoproteins that Covers the Luminal Surface of the Capillary Endothelium
- Thought to Maintain Organ & Vascular Homeostasis
- **Syndecan-1 (SDC-1)** is One of the Core Proteins
- It "Sheds" into Bloodstream in the Face of Various Systemic Inflammatory Conditions, Including Trauma
- Several Studies Have Shown Associations between **Serum SDC-1** Levels and **Mortality** in Trauma Patients


Bloodstream
Glycocalyx
Endothelial cells
Hyaluronan
Perlecan
Syndecan
Glypican
Heparan sulfate chain
Chondroitin sulfate chain
GPI anchor

Syndecan-I

(a.k.a. CD-138)

- When in Place, SDC1 is One of The Pivotal Elements that Maintains the Integrity of the Vascular Endothelium,
- It Helps to Seal a Tight Junction Between Endothelial Cells, Preventing Leakage into Surrounding Tissues Decreasing Edema
- Also Modulates Inflammatory Response ….

Scand J Trauma Resusc Emerg Med. 2016; 24: 48

Published online 2016 Apr 12. doi: 10.1186/s13049-016-0239-y
PMCID: PMC4828893
PMID: 27068016

The endothelial glycocalyx and its disruption, protection and regeneration: a narrative review

Ulf Schött, Cristina Solomon, Dietmar Fries, and Peter Bentzer

Such Studies Have Indicated That

1. Crystalloids and Other Clear IV Formulations Appear to Disrupt It (e.g., see more SDC-1 shedding)

2. Whole Blood and Plasma Protect It …. and Even Seem to Repair It

So That Explains a Lot for Me !

Early 1980s

Worse Outcomes with Preoperative IV Crystalloids ..

Journal of Medicine

Volume 331 OCTOBER 27, 1994 Number 17

IMMEDIATE VERSUS DELAYED FLUID RESUSCITATION FOR HYPOTENSIVE PATIENTS WITH PENETRATING TORSO INJURIES

WILLIAM H. BICKELL, M.D., MATTHEW J. WALL, JR., M.D., PAUL E. PEPE, M.D., R. RUSSELL MARTIN, M.D., VICTORIA F. GINGER, M.S.N., MARY K. ALLEN, B.A., AND KENNETH L. MATTOX, M.D.

Abstract *Background.* Fluid resuscitation may be detrimental when given before bleeding is controlled in patients with trauma. The purpose of this study was to determine the effects of delaying fluid resuscitation until the time of operative intervention in hypotensive patients with penetrating injuries to the torso.

Methods. We conducted a prospective trial comparing immediate and delayed fluid resuscitation in 598 adults with penetrating torso injuries who presented with a pre-

Results. Among the 289 patients who received delayed fluid resuscitation, 203 (70 percent) survived and were discharged from the hospital, as compared with 193 of the 309 patients (62 percent) who received immediate fluid resuscitation ($P = 0.04$). The mean estimated intraoperative blood loss was similar in the two groups. Among the 238 patients in the delayed-resuscitation group who survived to the postoperative period, 55 (23 percent) had one or more complications (adult respiratory distress syn-

Independent Prosecutor, Kenneth Starr

Pepe's Files

But, In the Lab, We Had Seen that IV Fluids …

Elevated Blood Pressure

During Uncontrolled Hemorrhage

- **Accelerating Hemorrhage**
- **Mechanically Disrupting Clots**
- **Diluting Clotting Factors**

(So… Our Simple Takeaway Was “Control Bleeding First”)

But ....

Apparently, There Was Also Something Else to Explain the Worse Patient Outcomes That We Found with IV Crystalloids!!

Rahbar et al. Journal of Translational Medicine (2015) 13:117
DOI 10.1186/s12967-015-0481-5

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Endothelial glycocalyx shedding and vascular permeability in severely injured trauma patients

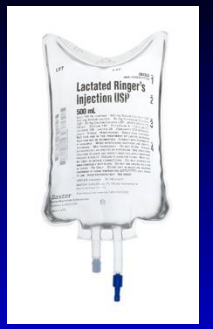
Elaheh Rahbar[1,2*], Jessica C Cardenas[1], Gyulnar Baimukanova[3], Benjamin Usadi[3], Roberta Bruhn[3], Shibani Pati[3,4], Sisse R Ostrowski[5], Pär I Johansson[5], John B Holcomb[1] and Charles E Wade[1]

Abstract

Background: The endothelial glycocalyx layer (EGL) is a key regulator of vascular permeability, cell adhesion, and inflammation. The EGL is primarily composed of syndecan-1, hyaluronic acid (HA), heparan sulfate (HS) and chondroitin sulfate (CS). While many studies have observed increased shedding of syndecan-1 during hemorrhagic shock, little is known about the shedding of other EGL components, and their effects on altered permeability and coagulation. We characterized shedding of all four primary components of the EGL, as well as the plasma's effect on permeability and thrombin generation in a cohort of trauma patients.

Methods: Plasma samples were collected from 5 healthy consented volunteers and 22 severely injured trauma patients upon admission to the emergency department. ELISA assays were performed to quantify shed HA, HS, CS and syndecan-1 in plasma. A colloid osmometer and Electric Cell-substrate Impedance Sensing (ECIS) system were

Evolving Thinking about the Endothelial Glycocalyx …



- Clear Fluids (e.g., Crystalloids) Disrupt It !
- Blood and Plasma Not Only Preserve It….
- They Seem to Heal It

- See Less SDC1 “Shedding” in Bloodstream & Less Inflammatory Cytokine Response !
- *Seeing Less ARDS? Less Sepsis Syndromes?*

In Essence, We Are Dealing with An Endotheliopathy

And One That Is Worsened by "Pasta Water"!

Fast Forward to 2025 …

So -- What Are this Year's Recommendations ?

We Know That Blood Seems to Work …

But ….

What About Plasma ?

Hematology Am Soc Hematol Educ Program. 2013;2013:656-9.
doi: 10.1182/asheducation-2013.1.656.

Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective.

Holcomb JB[1], Pati S.

Abstract

Over the past century, blood banking and transfusion practices have moved from whole blood therapy to components. In trauma patients, the shift to component therapy was achieved without clinically validating which patients needed which blood products. Over the past 4 decades, this lack of clinical validation has led to uncertainty on how to optimally use blood products and has likely resulted in both overuse and underuse in injured patients. However, recent data from both US military operations and civilian trauma centers have shown a survival advantage with a balanced transfusion ratio of RBCs, plasma, and platelets. This has been extended to include the prehospital arena

The NEW ENGLAND JOURNAL of MEDICINE

July 26, 2018

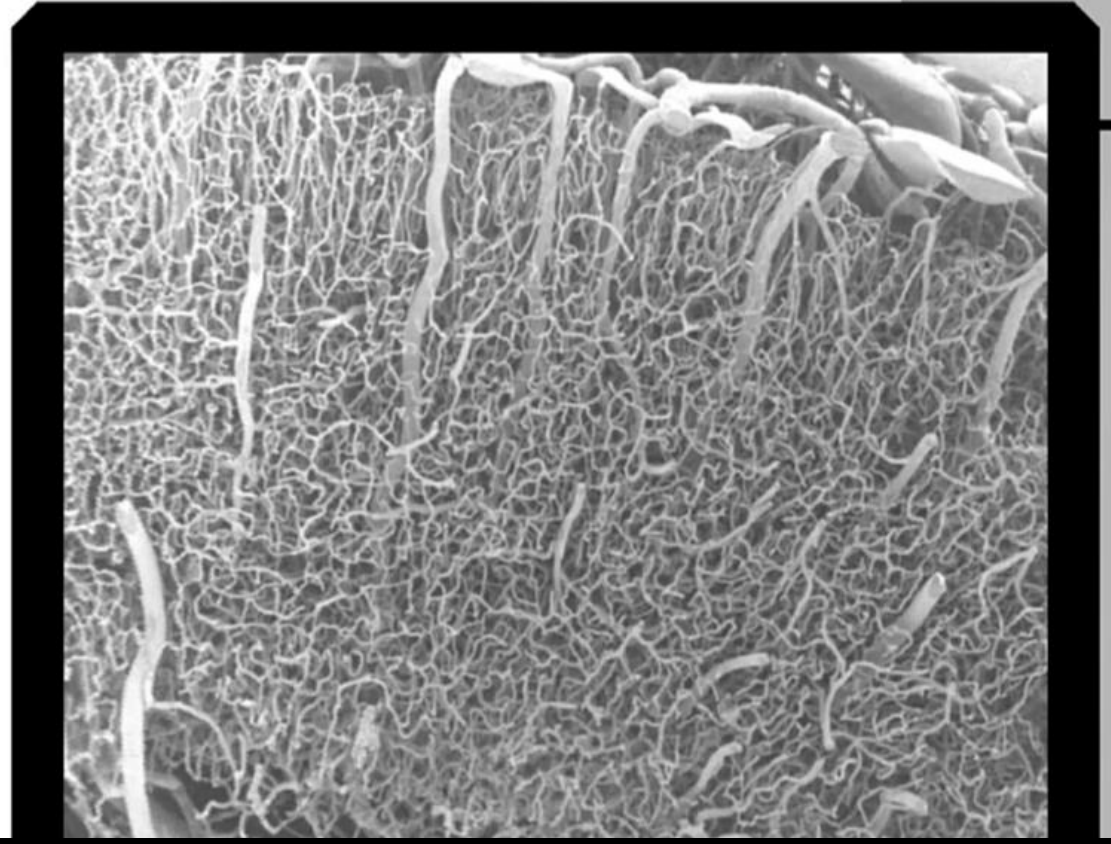
N Engl J Med 2018; 379:315-326

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock (PAMPer Study Group)

•Jason L. Sperry, M.D., M.P.H.,
•Francis X. Guyette, M.D., M.P.H.,
•Joshua B. Brown, M.D.,
•Mark H. Yazer, M.D.,
•Darrell J. Triulzi, M.D.,
•Barbara J. Early-Young, B.S.N.,
•Peter W. Adams, B.S.,
•Brian J. Daley, M.D.,
•Richard S. Miller, M.D.,
•Brian G. Harbrecht, M.D.,
•Jeffrey A. Claridge, M.D.,
•Herb A. Phelan, M.D., M.S.C.S.,
•et al., for the PAMPer Study Group*

Significant Survival Advantage Demonstrated !!

So Why Are We Asking About Plasma Use in TBI?

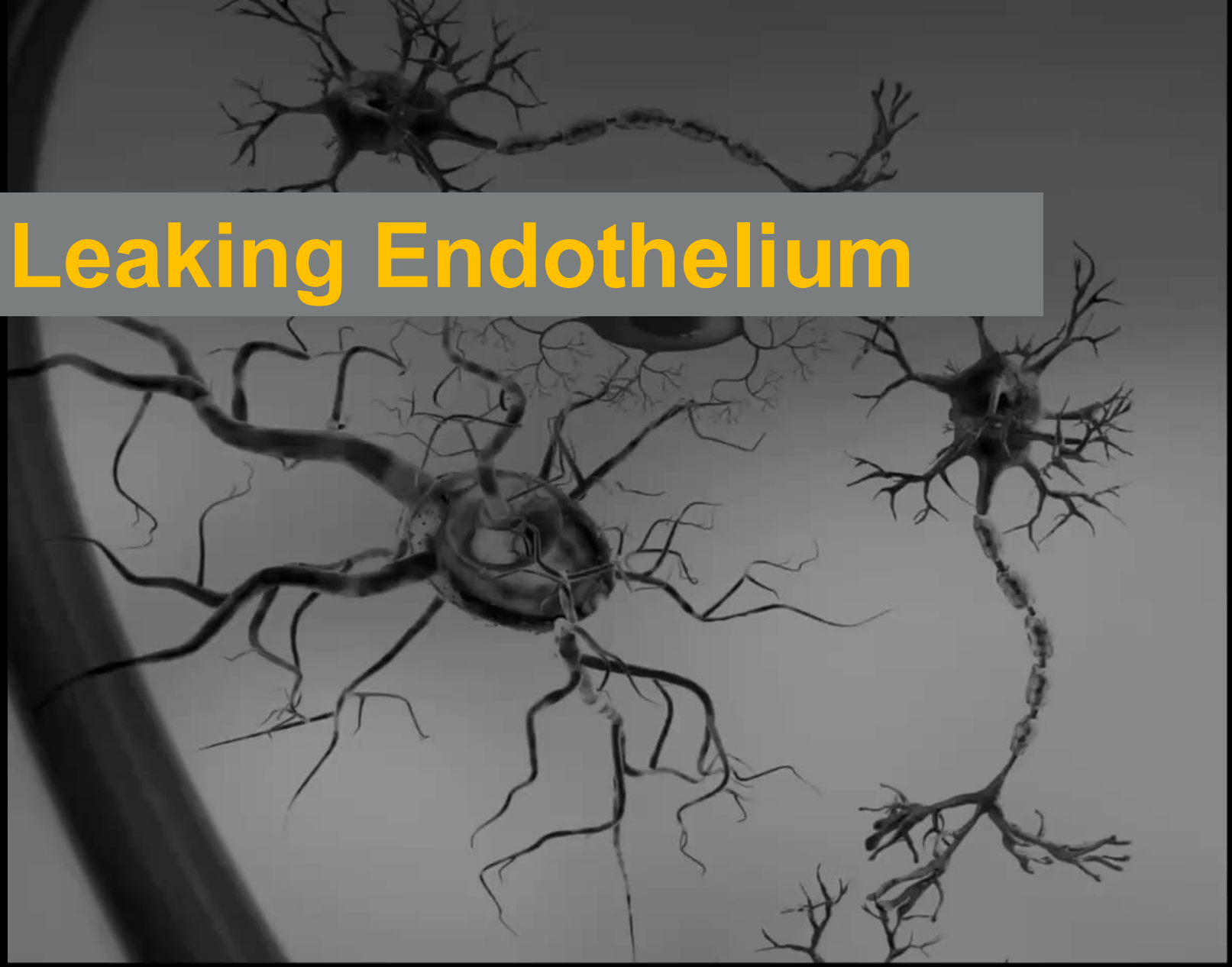


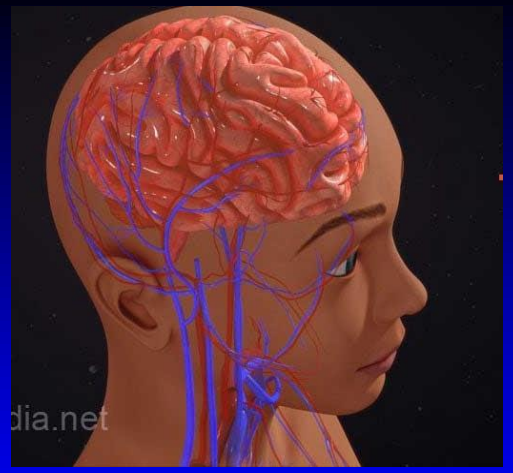
- Brain Not Just “Grey Matter”
- Actually Looks More Like Blood Vessels
- No Cell is >10 *u*m from a Capillary
- Every Neuron Has Its Own Capillary
- = 600 km of Capillary Network

So We Also Need to Protect the Glycocalyx Within the Cranium As Well !!

(aka -- the Blood Brain Barrier)

- Causes Edema
- Inflammation
- Neuronal Injury
- Mortality Seen Later than Bleeding Cases
- But Morbidity Early On
- = Dysfunctional Healing
- = Dysfunctional Neurons

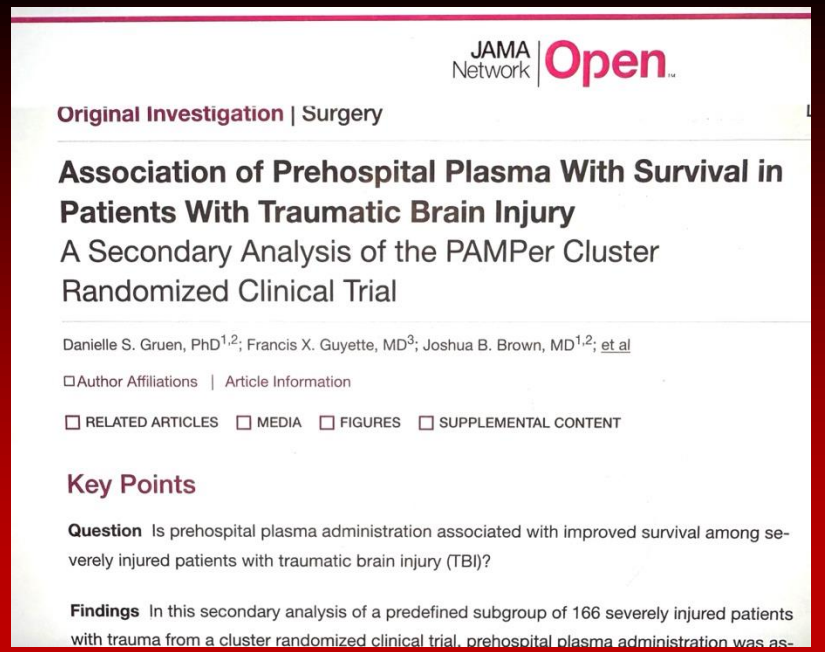




ANY Clinical Support for this Assertion ?

PAMPer Spin-Off Study

Sub-Analysis of TBI …



JAMA Network | Open

Original Investigation | Surgery

Association of Prehospital Plasma With Survival in Patients With Traumatic Brain Injury

A Secondary Analysis of the PAMPer Cluster Randomized Clinical Trial

Danielle S. Gruen, PhD[1,2]; Francis X. Guyette, MD[3]; Joshua B. Brown, MD[1,2]; et al

Author Affiliations | Article Information

RELATED ARTICLES MEDIA FIGURES SUPPLEMENTAL CONTENT

Key Points

Question Is prehospital plasma administration associated with improved survival among severely injured patients with traumatic brain injury (TBI)?

Findings In this secondary analysis of a predefined subgroup of 166 severely injured patients with trauma from a cluster randomized clinical trial, prehospital plasma administration was as-

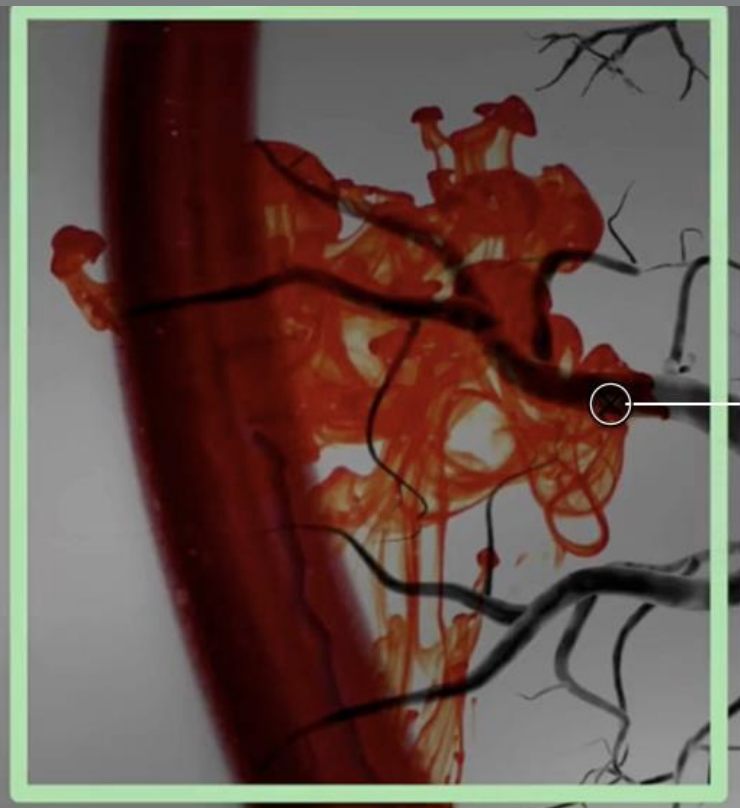
- ~ One-Third of Pts Had TBI
- 92 “Std. Care” Pts. vs. 74 Pts Who Got Plasma
- **OUTCOMES ALSO SIGNIFICANTLY BETTER !!**
- Including Analyses of those with Polytrauma, GCS < 8, etc

- **BUT NO DIFFERENCE IF GIVEN LATE !**

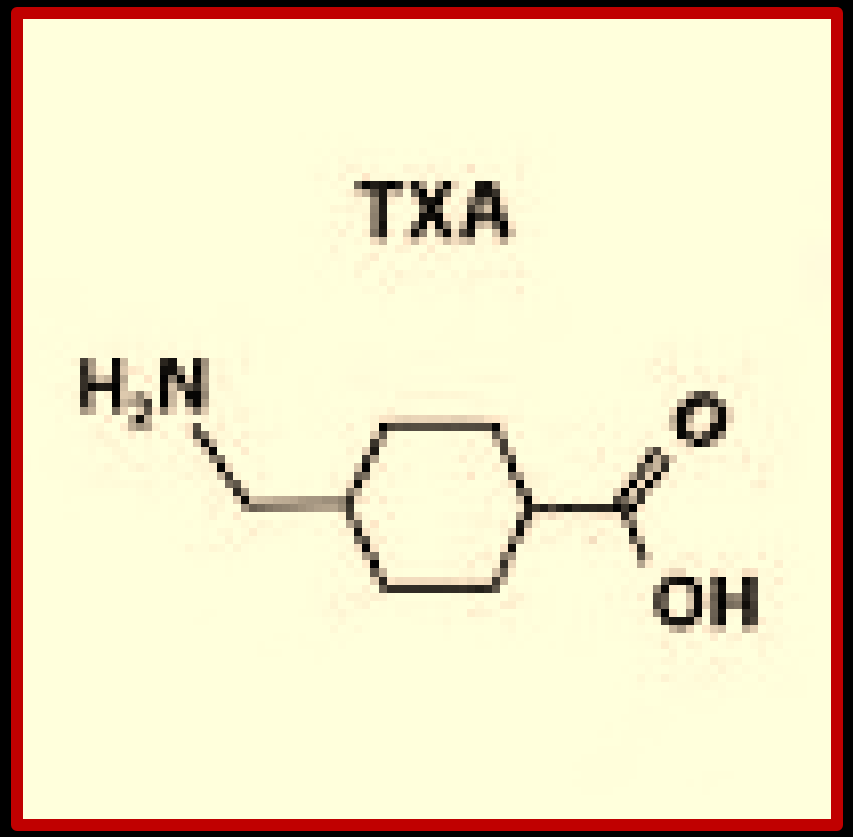
BUT –

DO IT EARLY ON !!!

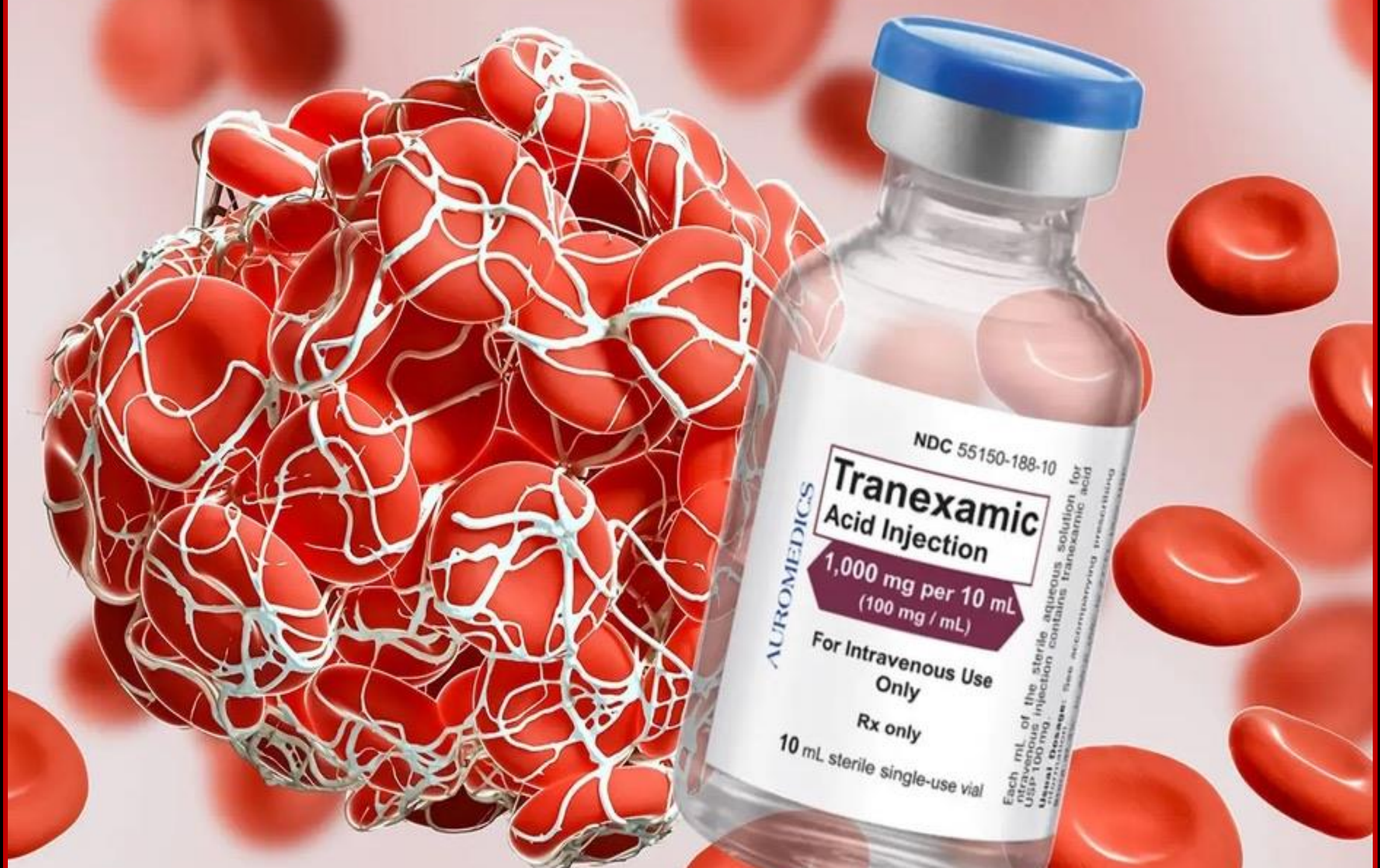
Bottomline:



NEED TO STOP THE LEAK



TXA and Plasma


NDC 55150-188-10
Tranexamic
Acid Injection
1,000 mg per 10 mL
(100 mg / mL)
For Intravenous Use
Only
Rx only
10 mL sterile single-use vial
AUROMEDICS

Journal of Clinical Medicine

MDPI

J Clin Med. 2021 Apr 1;10(7):1415. doi: 10.3390/jcm10071415

The Effect of Tranexamic Acid Administration on Early Endothelial Damage Following Posterior Lumbar Fusion Surgery

Hye Jin Kim [1], Bora Lee [1], Byung Ho Lee [2], So Yeon Kim [1], Byoung Jun Lim [1], Yong Seon Choi [1,*]

Editor: Bernard Allaouchiche

Author information Article notes Copyright and License information

PMCID: PMC8037070 PMID: 33915859

Abstract

Tranexamic acid (TXA) protects against endothelial glycocalyx injury in vitro. We aimed to evaluate whether TXA could protect against endothelial glycocalyx degradation in patients undergoing posterior lumbar fusion surgery.

"TXA Administration was associated with reduced Syndecan-1 "Shedding" in patients undergoing posterior lumbar fusion surgery."

TXA for TBI

ROC TXA for TBI JAMA

- Examining Those with CT-Confirmed Intracranial Hemorrhage – *the Target Group*…

16% mortality with 2 grams upfront

vs. 27% with 1g+1g infusion vs. 26% Placebo

- Median Time to Infusion was about 40 mins from the time of Injury

EMSWORLD PRINT ONLINE EXPO
EMS World November 2020; (49)11):14-17.

TXA IN TBI

Part 2: The earlier the intervention, the better the outcome

By Paul E. Pepe, MD, MPH, FAEMS, MCCM; Jonathan Jui, MD, MPH, FACEP, FAEMS; James P. Roach, DO, FACEP; and John B. Holcomb, MD, FACS

As discussed in last month's opening column about nonmechanical hemostasis in prehospital trauma care, the use of TXA had overall positive results when reported by the CRASH-2 investigators, who used it for presumed post-traumatic hemorrhage more than a decade ago.[1] Despite that apparent success and many other positive studies examined the use of TXA for those with mild to moderate head injury with the concern that if accompanying intracranial bleeding occurs, it can be life-threatening.[5]

The classic statement about patients with an epidural hematoma is that they are those who "first talked, then died." The relatively thin temporal bone is traversed by the middle meningeal artery (left or right), tion of TXA comes into play.

Like its predecessor trial in general trauma patients with bleeding, the number of patients enrolled in CRASH-3 was quite large, involving 175 hospitals in 29 countries. Published in November 2019, it was again a 1:1 trial of TXA for TBI vs. placebo. As in CRASH-2, the treatment protocol provided 1 gram over 10 minutes early on (within

For Me --- it's ...

First Hour -- *or Bust* !


And Same Applies
for Plasma !

A Multicenter RCT Has Begun

Received: 30 August 2023 | Revised: 8 January 2024 | Accepted: 16 February 2024

DOI: 10.1111/trf.17928

REVIEW ARTICLE

TRANSFUSION

Plasma therapy for traumatic brain injury: Rationale for a prospective randomized trial

Marjorie R. Liggett[1] | Sharnia Lashley[1] | Nathan P. Gill[2] | Denise M. Scholtens[2,3] | Zaiba Shafik Dawood[1] | Hasan B. Alam[1]

[1]Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[2]Department of Preventative Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[3]Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

But Therapy to Be Delayed Till First ER CT Scan

(to document baseline bleed and its size)

So It May Not Demonstrate The Most Optimal Effect (in My Opinion !)

So We Asked ....

What Are We Waiting For?

(Well, We're Not)

Palm Beach County Fire Rescue

Head Injuries *continued....*

HEAD INJURIES WITH NEW ONSET GCS ≤ 12

- GCS of ≤ 12 must be assessed prior to any sedation medication administration
- PLASMA TRANSFUSION:
  - Refer to the "Blood Product Transfusion" protocol (pp. 130-131) for PLASMA administration procedure
  - Adult:
    - 1 unit IV/IO, deliver over 5-10 minutes utilizing the LifeFlow device.
      - **Exception:** If SBP < 120 mmHg, deliver as rapid infusion
    - May repeat 1x prn, if SBP is < 120 mmhg after the first unit is delivered
      - Max total dose 2 units
  - Pediatric:
    - 10mL/kg IV/IO, deliver over 5-10 minutes utilizing the LifeFlow device.
      - **Exception:** If age appropriate hypotension is present, deliver as rapid infusion
    - Max total dose 1 unit

OTHER USES ?

Plasma:

- TBI
- Polytrauma
- Hemorrhage
- Burns
- ACE-inhibitor Angioedema
- Sepsis?

- Acne ? 😉

OTHER FORMULATIONS ?

Salsa Verde!

> Crit Care Med. 2010 Oct;38(10 Suppl):S620-9. doi: 10.1097/CCM.0b013e3181f243a9.

Rationale for routine and immediate administration of intravenous estrogen for all critically ill and injured patients

Jane G Wigginton [1], Paul E Pepe, Ahamed H Idris

Affiliations + expand

PMID: 21164406 DOI: 10.1097/CCM.0b013e3181f243a9

And Most Notably …

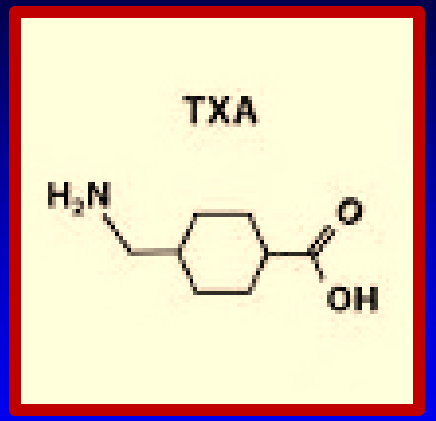
Spray Dried Plasma

Estimated Spring '26'

Multi-Year Shelf Life & No Refrigeration, etc

Plan/Budget Now for Use on Every ALS Response Unit ?

IN SUMMARY



- Mitigate Blood Brain Barrier Permeability
- Repair the Endotheliopathy
- Do It Early On !!
- Avoid Iatrogenic Injury

(such as crystalloids being given in later in-hospital)

Stay Tuned ….

Coming Soon to

PEPE / Jenkins TV

Sex, Drugs and R&R:

(Resuscitation & Recovery)



Sex Differences & the Evolving Role of Sex Hormones in Trauma and Burn Resuscitation

Paul E. Pepe, M.D., M.P.H.

Past Professor of Medicine, Surgery, Pediatrics, Public Health & Emergency Medicine;
Former Director, Out-of-Hospital Mobile Care Systems & Disaster/Event Preparedness
Office of Health System Affairs, University of Texas Southwestern Medical Ctr., Dallas

Current Medical Director, Dallas County Public Safety / Emergency Medical Services

On the Road to the 22nd Century...

I'm Paul Pepe…

… and I Approved this Message

Thank You !