Plasma and Traumatic Brain Injury

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COL(ret), US Army
Chief, Emergency General Surgery
LA General + USC Medical Center

Keck Medicine of USC

Los Angeles General Medical Center

"A great war leaves the country with three armies - an army of cripples, an army of mourners, and an army of thieves." ~German Proverb

“The only winner in any war is medicine”

Every talk/paper on trauma or DCR…

- “hemorrhage remains the most common cause of death on the battlefield”
- “…remains the most common POTENTIALLY PREVENTABLE cause…”
- TBI?

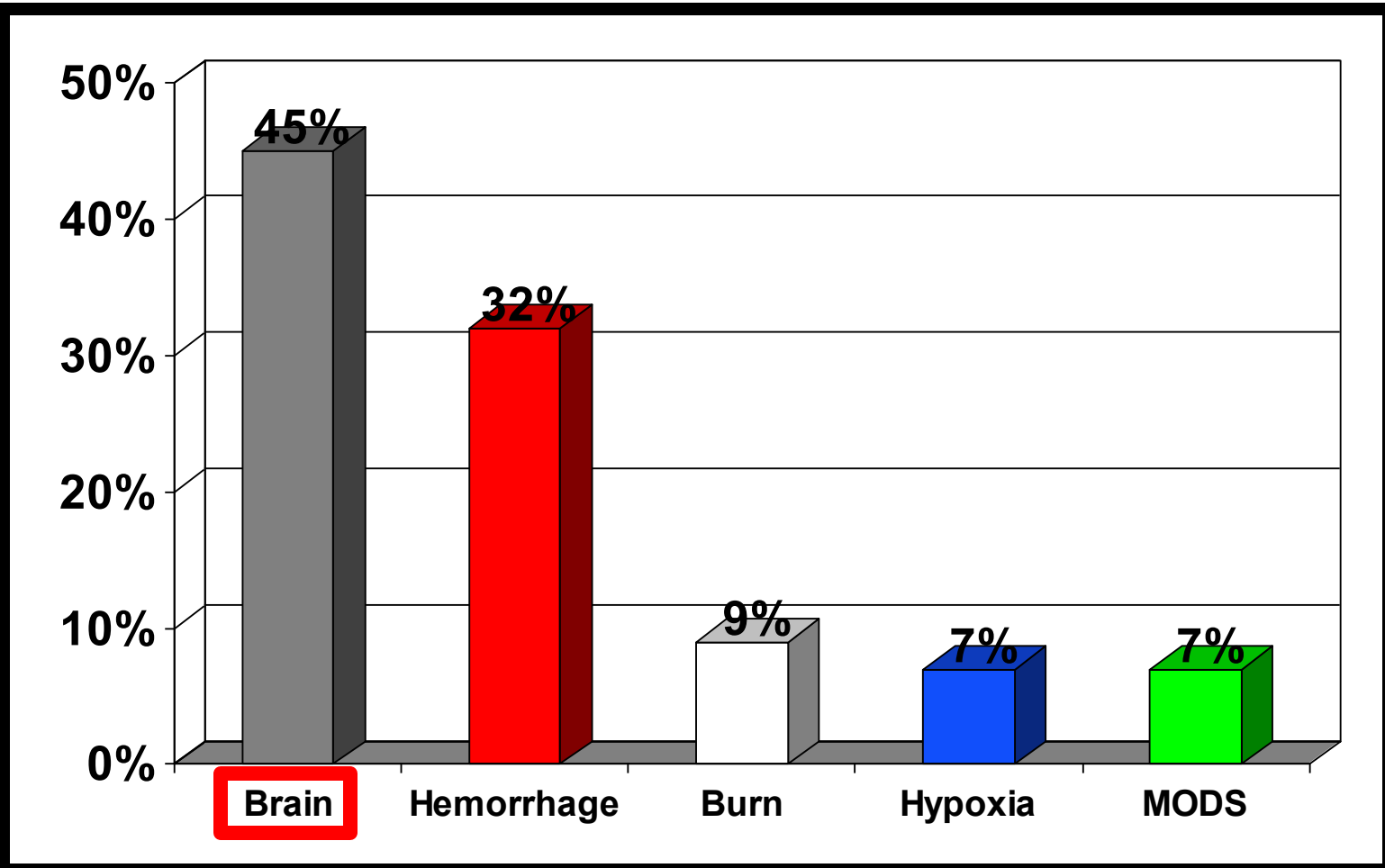
MILITARY DATA

- Review of US deaths in Vietnam (n=210)
- Causes of death
  - head injury in 50%
  - bleeding in 22%
- 4 surgeon panel review
  - 25% possibly preventable “today”

Blood et al., J Trauma 2002

An Analysis of In-Hospital Deaths at a Modern Combat Support Hospital

LTC Matthew Martin, MD, MAJ John Oh, MD, MAJ Heather Currier, MD, LTC Nigel Tai, FRCS, LTC Alec Beekley, MD, CPT Matthew Eckert, MD, and COL John Holcomb, MD



J Trauma. 2009;66:S51–S61.

Original Investigation | PACIFIC COAST SURGICAL ASSOCIATION

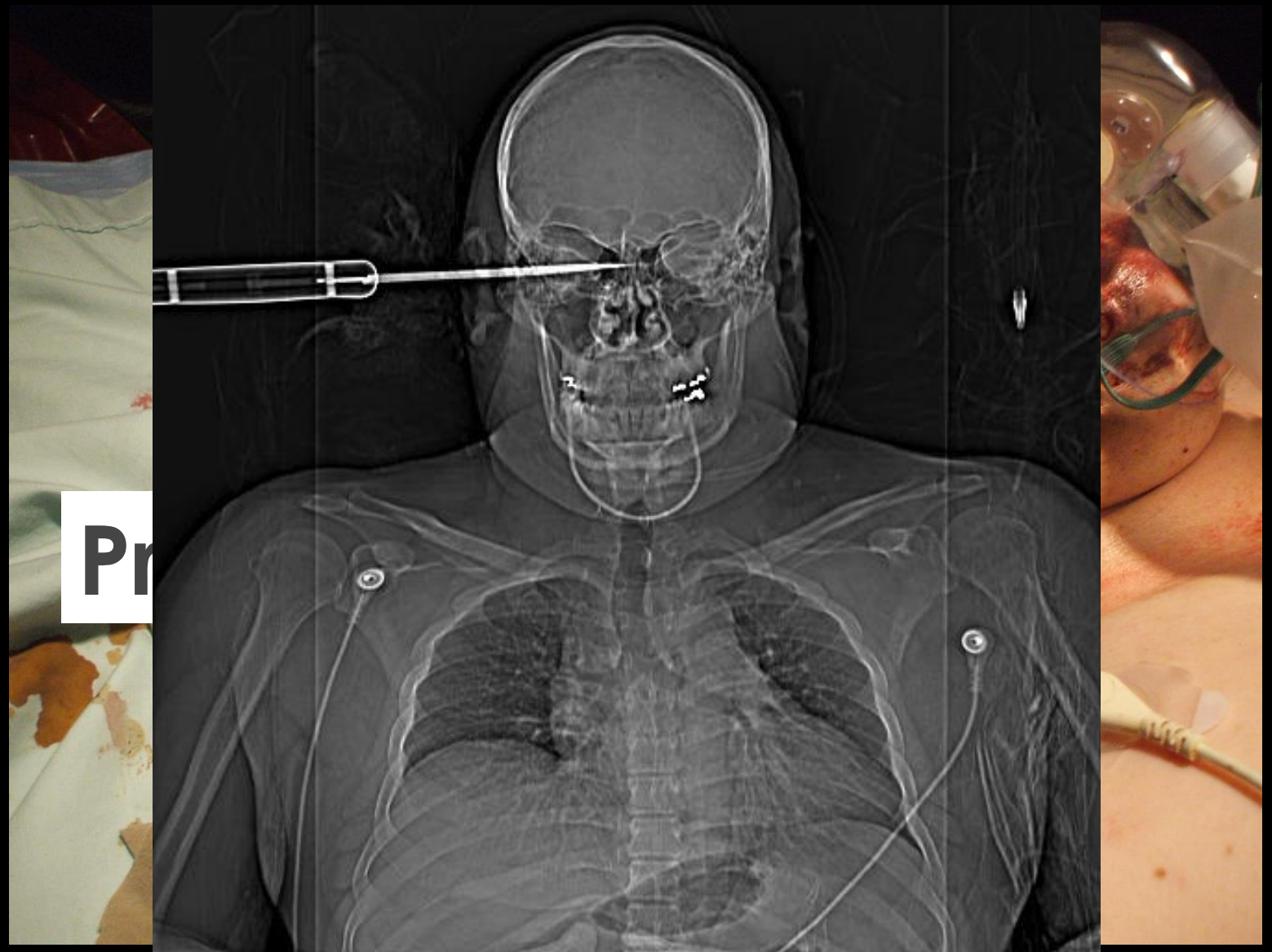
Changing Patterns of In-Hospital Deaths Following Implementation of Damage Control Resuscitation Practices in US Forward Military Treatment Facilities

Nicholas R. Langan, MD; Matthew Eckert, MD; Matthew J. Martin, MD

JAMA Surg. 2014;149(9):904-912.

Severe injury (AIS score >3), No.	
Any	1670
Head	908
Chest	251
Abdomen	225
Extremities	161

Wide Variety of Mechanisms




101-00-3578

Long-term outcomes of combat casualties sustaining penetrating traumatic brain injury

J Trauma Acute Care Surg
Volume 73, Number 6

Allison B. Weisbrod, MD, Carlos Rodriguez, DO, Randy Bell, MD, Christopher Neal, MD, Rocco Armonda, MD, Warren Dorlac, MD, Martin Schreiber, MD, *and* **James R. Dunne, MD,** *Bethesda, Maryland*

- Mortality only 6%
- 80% underwent craniectomy
- Looked at 2-year outcomes

- GCS 3-5 = 32% functional independence
- GCS 6-8 = 63%
- GCS 9-11 = 74%

REALITIES OF ENVI

SENSITIVITY > SP

- Capture all severe TBI but with C
- Interventions must be effective
- Benign and wide safety margin

Overview

- Rationale
  - Preclinical data
  - Clinical data
- Study design
- Approach
- Discussion

Traumatic Brain Injury

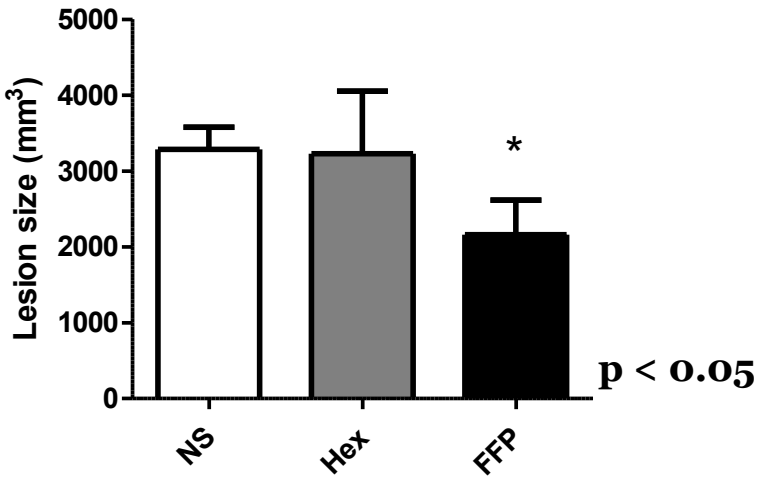
Preclinical data

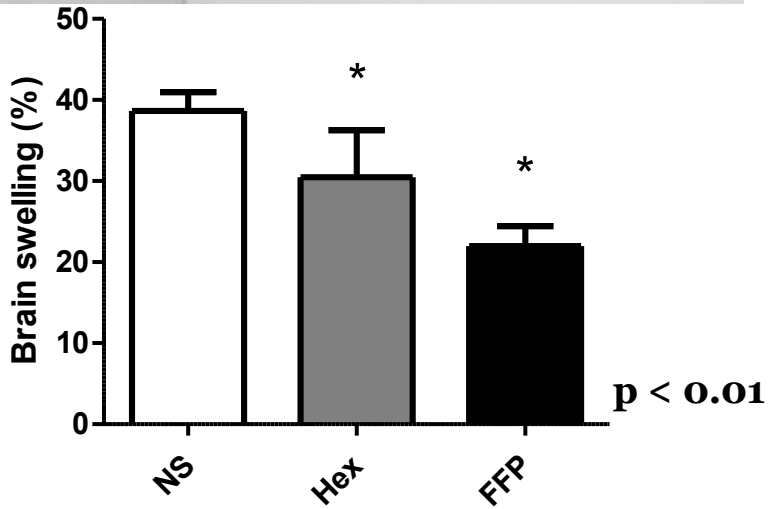
SHOCK, Vol. 38, No. 1, pp. 49–56, 2012

TRAUMATIC BRAIN INJURY AND HEMORRHAGIC SHOCK: EVALUATION OF DIFFERENT RESUSCITATION STRATEGIES IN A LARGE ANIMAL MODEL OF COMBINED INSULTS

Guang Jin,* Marc A. deMoya,* Michael Duggan,* Thomas Knightly,* Ali Y. Mejaddam,* John Hwabejire,* Jennifer Lu,* William Michael Smith,* Georgios Kasotakis,* George C. Velmahos,* Simona Socrate,† and Hasan B. Alam*

FFP decreased lesion size & swelling within 6-8 hrs



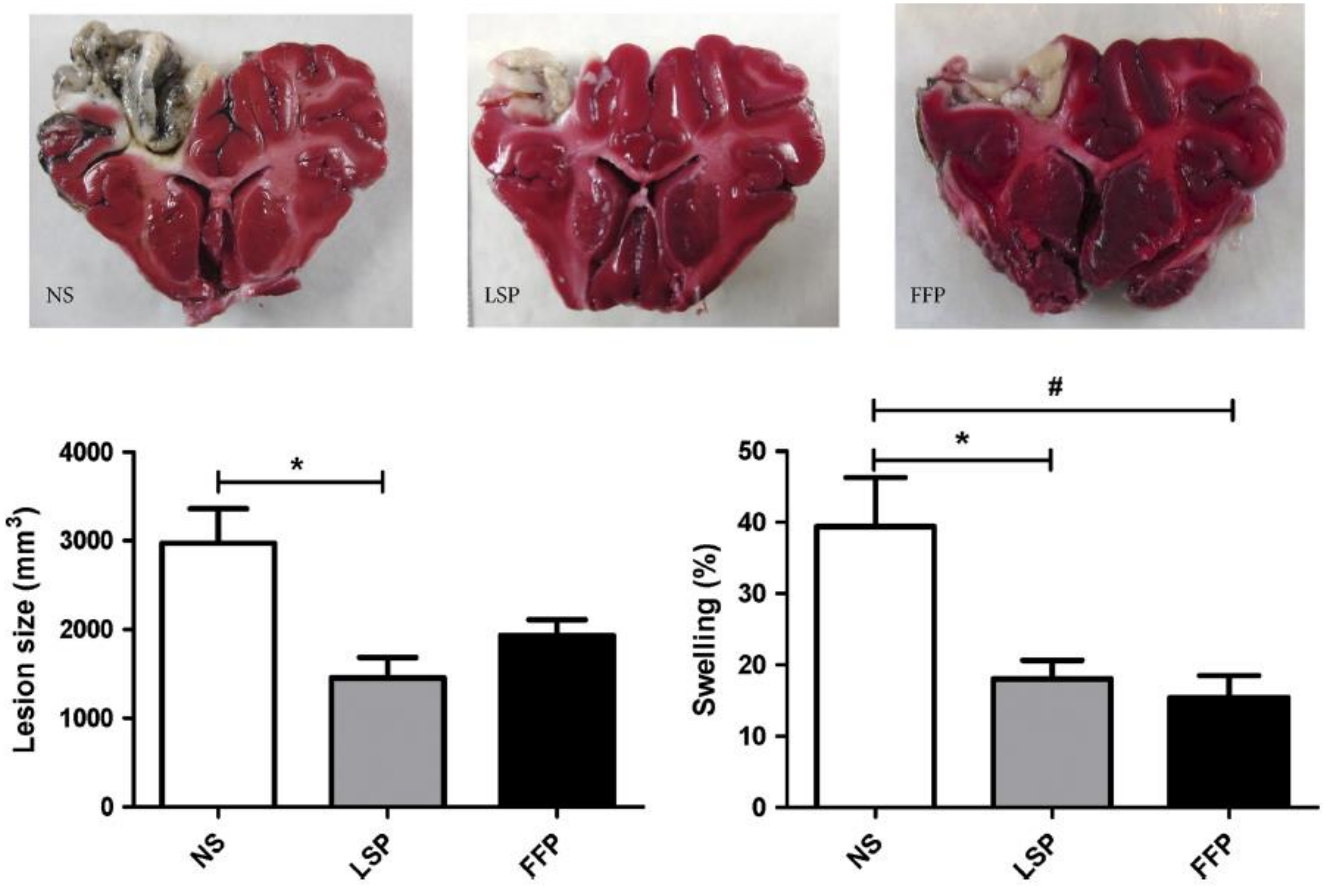


Early treatment with lyophilized plasma protects the brain in a large animal model of combined traumatic brain injury and hemorrhagic shock

J Trauma Acute Care Surg. 2013;75: 976–983

Ayesha M. Imam, MD, Guang Jin, MD, PhD, Martin Sillesen, MD, Michael Duggan, DVM, Cecilie H. Jepsen, MD, John O. Hwabejire, MD, MPH, Jennifer Lu, BS, Baoling Liu, MD, Marc A. DeMoya, MD, George C. Velmahos, MD, PhD, *and* **Hasan B. Alam, MD,** *Ann Arbor, Michigan*

Lyophilized plasma was equally effective

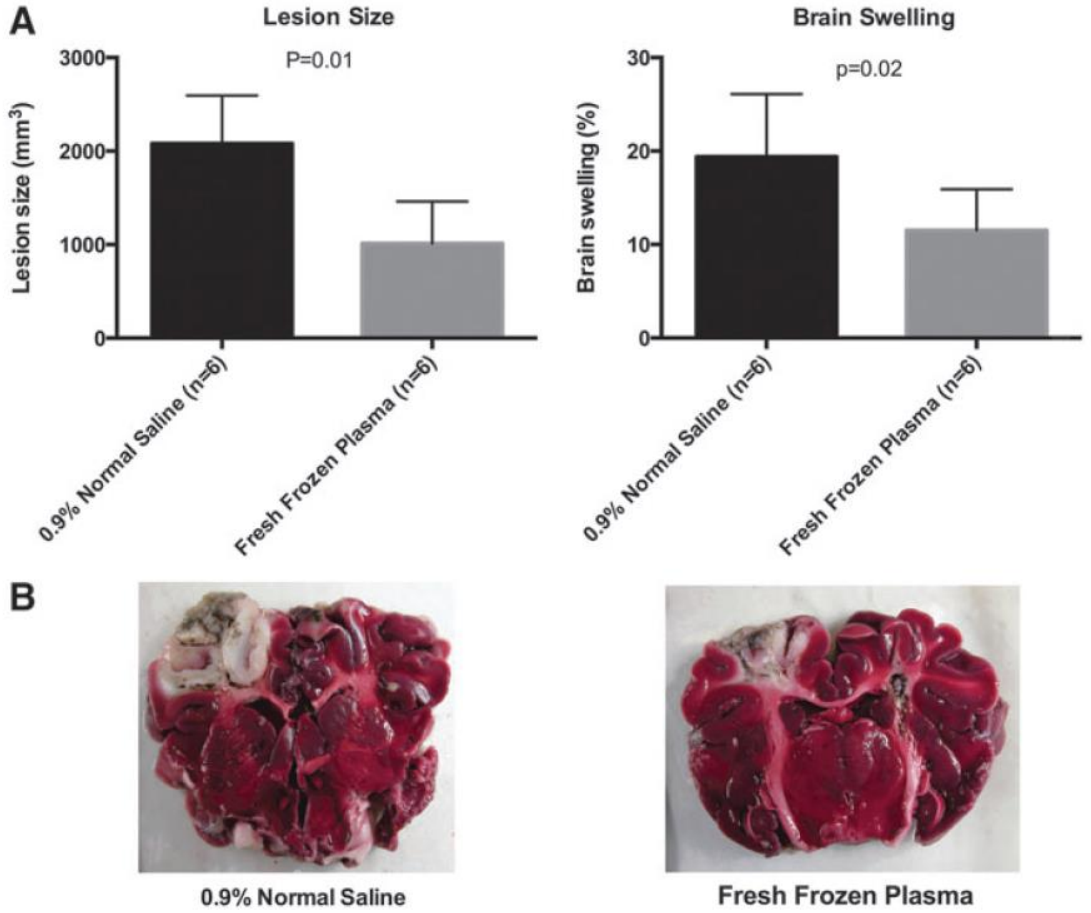


Fresh Frozen Plasma Resuscitation Provides Neuroprotection Compared to Normal Saline in a Large Animal Model of Traumatic Brain Injury and Polytrauma

JOURNAL OF NEUROTRAUMA 32:307–313 (March 1, 2015)

Ayesha Imam,[1] Guang Jin,[2] Martin Sillesen,[1,3] Simone E. Dekker,[2,4] Ted Bambakidis,[2] John O. Hwabejire,[1] Cecilie H. Jepsen,[1] Ihab Halaweish,[2] and Hasan B. Alam[2]

Equally effective in a polytrauma model

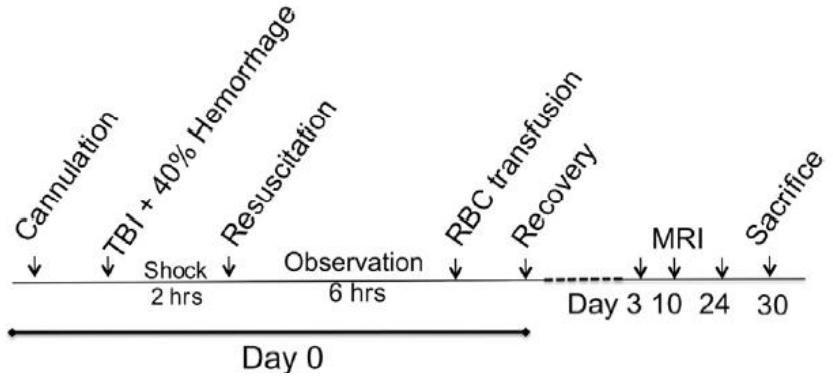


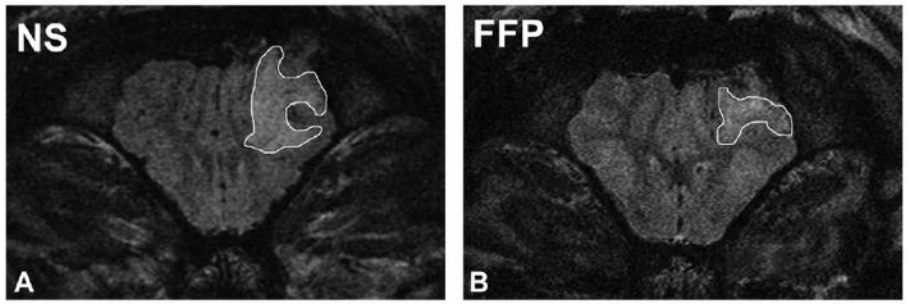
Early Resuscitation with Fresh Frozen Plasma for Traumatic Brain Injury Combined with Hemorrhagic Shock Improves Neurologic Recovery

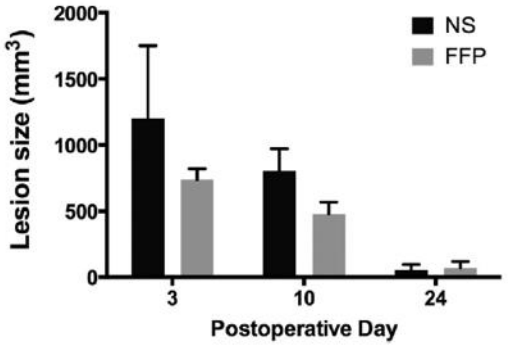
Ihab Halaweish, MD, Ted Bambakidis, MS, Wei He, MD, Durk Linzel, MD, Zhigang Chang, MD, Ashok Srinivasan, MD, Simone E Dekker, BSc, Baoling Liu, MD, Yongqing Li, MD, PhD, Hasan B Alam, MD, FACS

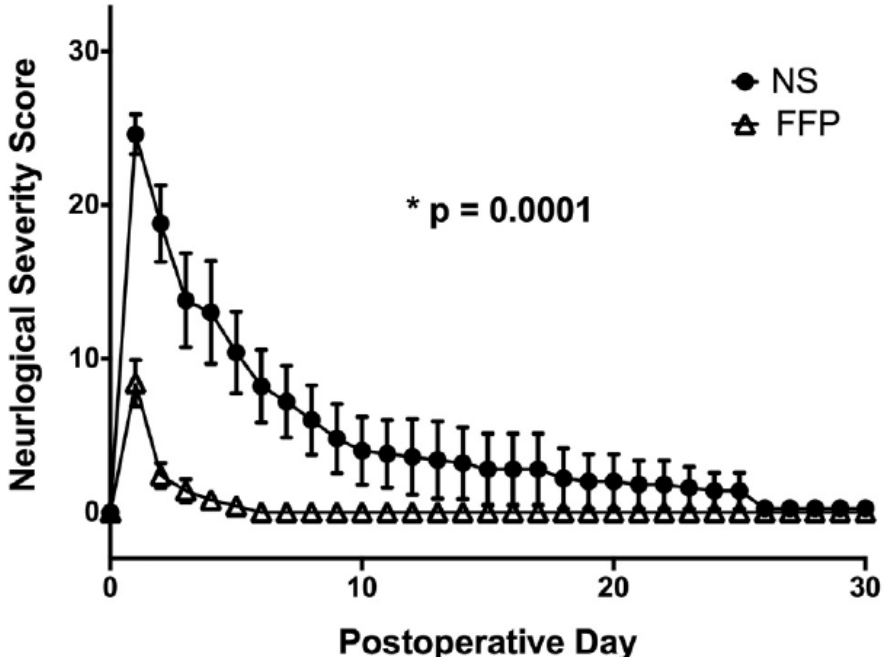
J Am Coll Surg 2015;220:809–819.

Improved functional recovery and lesion size on MRI









Plasma treatment is associated with decreased brain lesion and resuscitation requirements after traumatic brain injury in a swine model of prolonged damage-control resuscitation

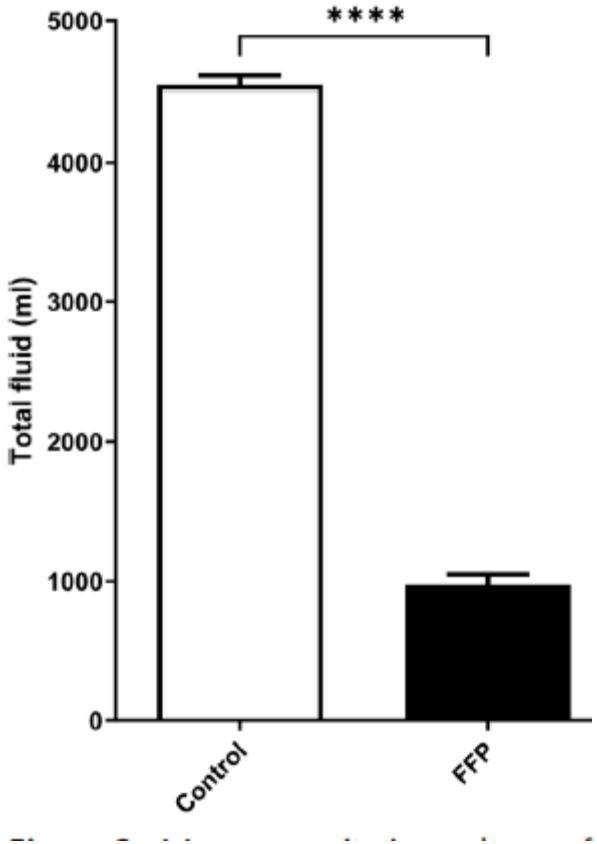
J Trauma Acute Care Surg
Volume 97, Number 6

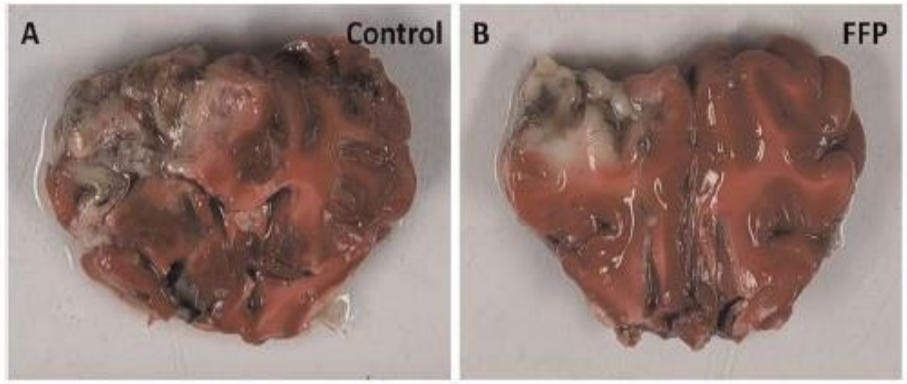
Guang Jin, MD, PhD, Marjorie R. Liggett, MD, Jessie W. Ho, MD, Zaiba Shafik Dawood, MD, Kiril Chtraklin, DVM, Dariel Diaz, MD. *and* Hasan B. Alam. MD. FACS. *Chicago. Illinois*

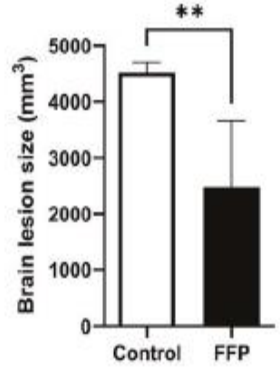
PFC Scenario:

Decreased lesion size

Decreased fluids







Fresh Frozen Plasma Modulates Brain Gene Expression in a Swine Model of Traumatic Brain Injury and Shock: A Network Analysis

Martin Sillesen, MD, PhD, Ted Bambakidis, MSc, Simone E Dekker, MD, Yongqing Li, MD, PhD, Hasan B Alam, MD, FACS

J Am Coll Surg
2017;224:49–58.

Downregulation of inflammatory pathway genes and expression of gene clusters mapping to increased metabolic and platelet signaling

Table 2. Top 10 Genes with the Highest Association with Fresh Frozen Plasma Resuscitation (Gene Significance) Clusters A and B Membership (Module Membership)

Gene	Title	Human gene function summary
Cluster A		
GBA2	Beta glucosidase	Carbohydrate transport and metabolism
LOC100516875	Neurabin-2 like	Scaffold protein in multiple signaling pathways
SGSM2	Small G protein signaling modulator 2	Unknown
LOC100153714	Run domain Beclin-1 interacting and cysteine-rich containing protein	Negative regulator of autophagy and endocytic trafficking
LOC100155348	BRI3-binding protein-like	Stabilization of p53/TP53
ZDHHC8	Zinc finger, DHHC-type containing 8	Member of zinc finger DHHC domain-containing protein family. Might function as palmitoyltransferase.
INPP5A	Inositol polyphosphatase-5-phosphatase	Mobilizes intracellular calcium, second messenger to various stimulation
PRR14L	Proline rich 14-like	Protein coding
STX16	Syntaxin 16	Docking and fusion of synaptic vesicles
CPT1C	Carnitine palmitoyltransferase	Beta oxidation and transport of long-chain fatty acids into mitochondria
Cluster B		
TTBK2	Tau tubulin kinase 2	Phosphorylation of tau and tubulin proteins
SRSF12	Serine/arginine splicing factor 2	Protein coding
SIX4	SIX homeobox 4	Transcription factor with potential role in differentiation or maturation of neuronal cells
LOC100739045	Glycine dehydrogenase, mitochondrial like	Degradation of glycine
GBA2	Beta glucosidase	Carbohydrate transport and metabolism
NR6A1	Nuclear receptor subfamily 6, group A, member 1	Nuclear hormone receptor family. Might be involved in neurogenesis
SMYD3	SET and MYND Domain containing 3	Histone methyltransferase, functions in RNA polymerase II
LOC100512626	ORM1-like protein 3-like	Negative regulator of sphingolipid synthesis
LOC100522896	Tectin3-like	Filament-forming protein
SLC26A6	Solute carrier family 26, member 6	Transport of chloride, oxalate, sulfate, and bicarbonate

Better platelet, coagulation, endothelial, and mitochondrial functions

Fresh frozen plasma resuscitation attenuates platelet dysfunction compared with normal saline in a large animal model of multisystem trauma

J Trauma Acute Care Surg. 2014;76: 998–1007.

Martin Sillesen, MD, Pär I. Johansson, MD, DMsc, MPA, Lars S. Rasmussen, MD, PhD, DMsc, Guang Jin, MD, PhD, Cecilie H. Jepsen, MD, Ayesha Imam, MD, John O. Hwabejire, MD, MPH, Danielle Deperalta, MD, Michael Duggan, DVM, Marc deMoya, MD, George C. Velmahos, MD, PhD, *and* **Hasan B. Alam, MD,** *Ann Arbor, Michigan*

Normal saline influences coagulation and endothelial function after traumatic brain injury and hemorrhagic shock in pigs

Surgery 2014;156:556-63.

Simone E. Dekker, BSc,[a,b] Martin Sillesen, MD,[c,d] Ted Bambakidis, MSc,[a] Guang Jin, MD, PhD,[a] Baoling Liu, MD,[a] Christa Boer, PhD,[b] Pär I. Johansson, MD, DMSc, MPA,[e,f] Ihab Halaweish, MD,[a] Jake Maxwell,[a] *and* **Hasan B. Alam, MD,[a]** *Ann Arbor, MI, Amsterdam, The Netherlands, Boston, MA, Hillerød and Copenhagen, Denmark, and Houston, TX*

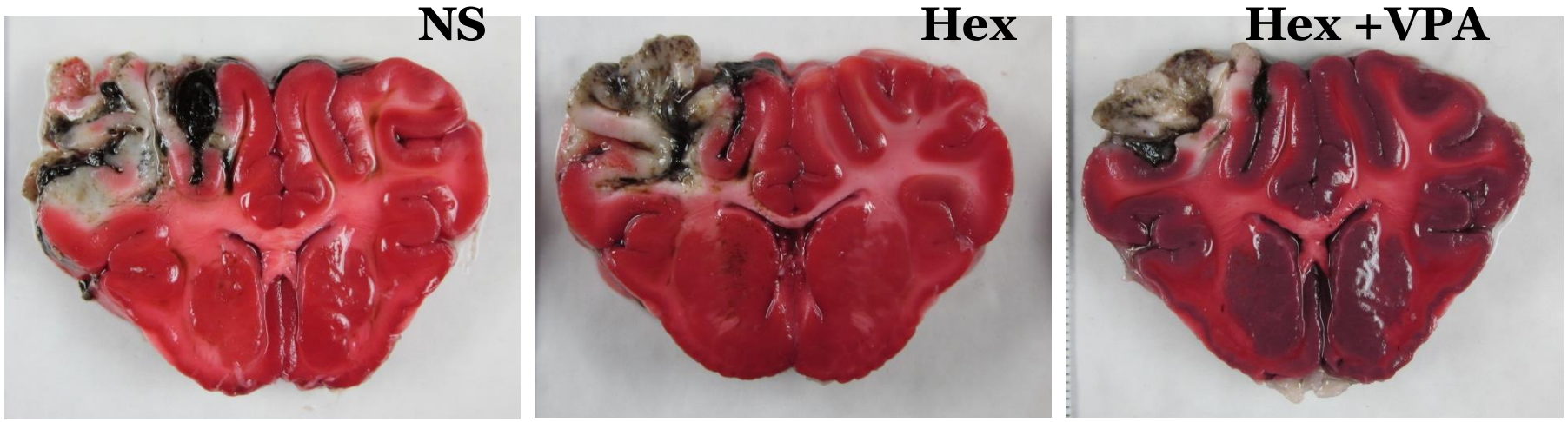
Differential effects of fresh frozen plasma and normal saline on secondary brain damage in a large animal model of polytrauma, hemorrhage and traumatic brain injury

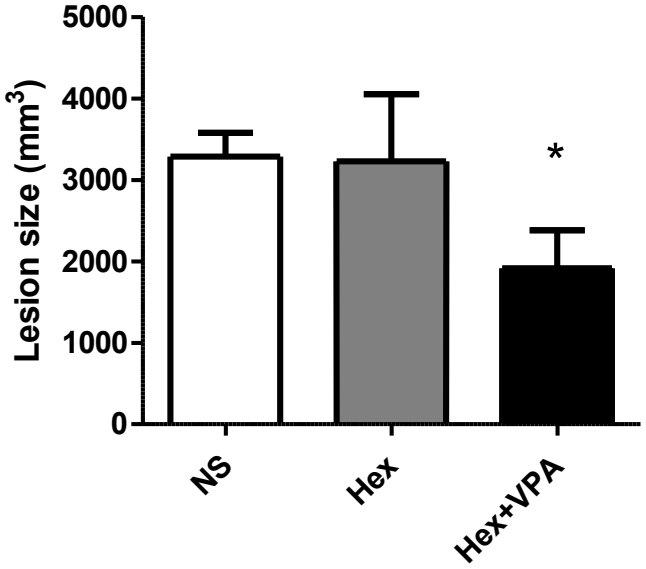
J Trauma Acute Care Surg 2013;75: 968–975.

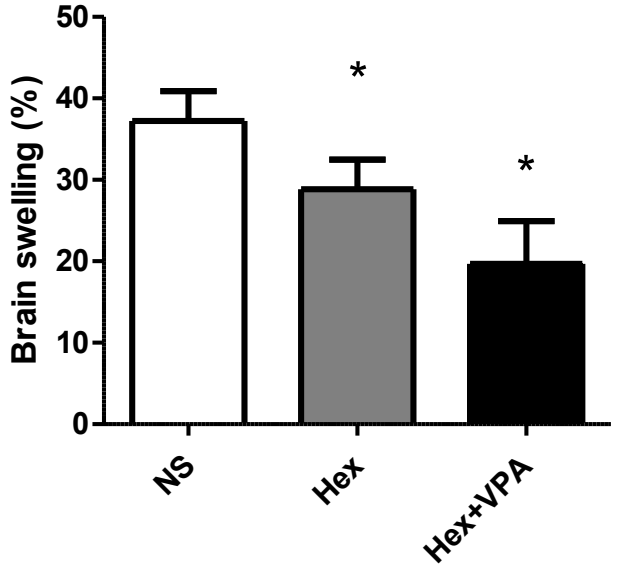
John O. Hwabejire, MD, MPH, Ayesha M. Imam, MD, Guang Jin, MD, PhD, Baoling Liu, MD, Yongqing Li, MD, PhD, Martin Sillesen, MD, Cecilie H. Jepsen, MD, Jennifer Lu, BS, Marc A. deMoya, MD, *and* **Hasan B. Alam, MD,** *Ann Arbor, Michigan*

Valproic Acid for TBI

Decrease in Brain Lesion Size and Edema
Within 6 hrs- High dose VPA (300 mg/kg)





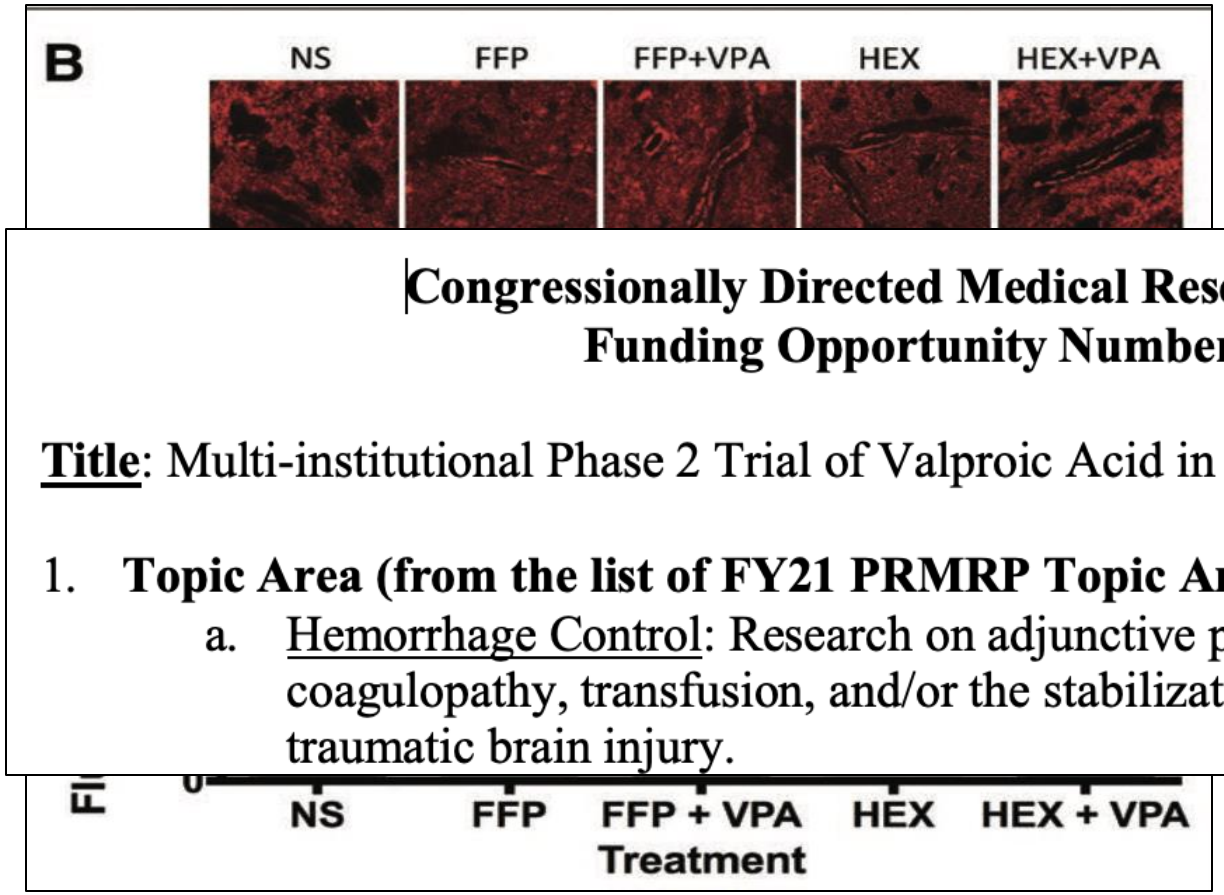


Jin et al. J Trauma 2012

Neurological Impairment & Recovery – POD 1

Improvement of Blood-Brain Barrier Integrity in Traumatic Brain Injury and Hemorrhagic Shock Following Treatment With Valproic Acid and Fresh Frozen Plasma

Vahagn C. Nikolian, MD[1]; Simone E. Dekker, MD[1]; Ted Bambakidis, MS[1];
Gerald A. Higgins, MD, PhD[2]; Isabel S. Dennahy, MD[1]; Patrick E. Georgoff, MD[1];
Aaron M. Williams, MD[1]; Anuska V. Andjelkovic, MD, PhD[3]; Hasan B. Alam, MD, FACS[1]



Congressionally Directed Medical Research Programs (Clinical Trial Award)
Funding Opportunity Number: W81XWH-21-PRMRP-CTA

Title: Multi-institutional Phase 2 Trial of Valproic Acid in Patients with Moderate to Severe Traumatic Brain Injury

1. **Topic Area (from the list of FY21 PRMRP Topic Areas):**
   a. Hemorrhage Control: Research on adjunctive pharmacological solutions for hemorrhage, shock, coagulopathy, transfusion, and/or the stabilization of polytrauma, with attention to the impact on potential traumatic brain injury.

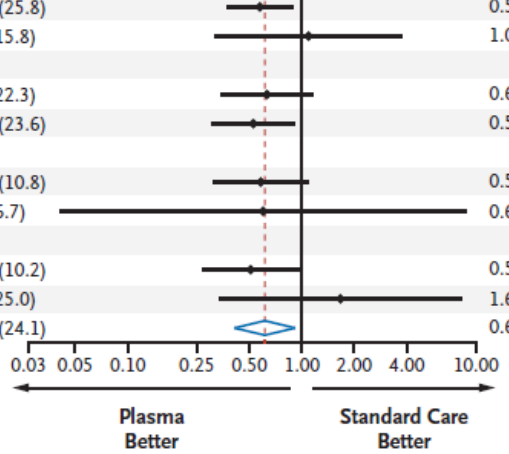
Clinical data

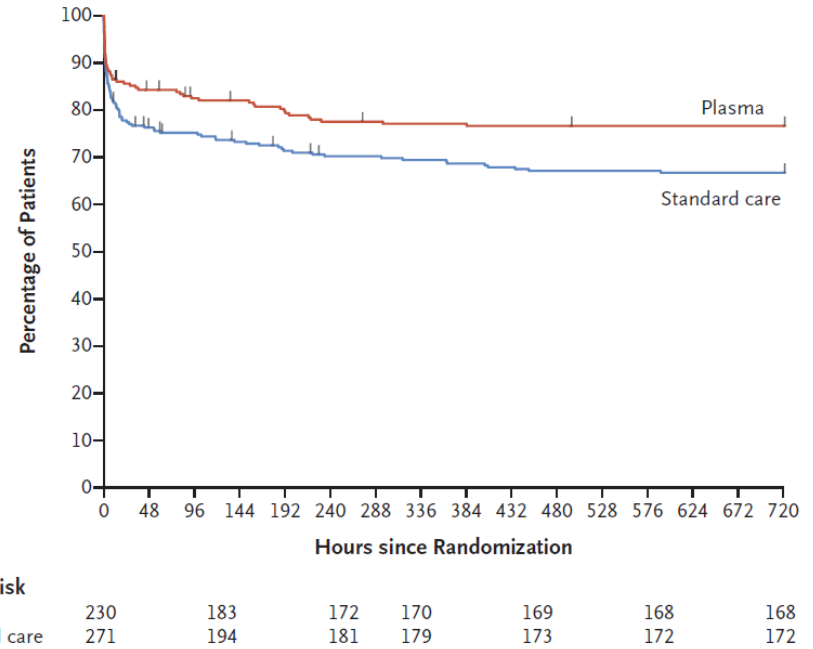
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

B 30-Day Mortality in Prespecified Subgroups

Subgroup	No. of Patients	Standard Care	Plasma	Odds Ratio (95% CI)	Adjusted P Value for Interaction
		no. of events/total no. (%)			
≥10 units packed red cells in 24 hr					>0.99
No	377	63/198 (31.8)	35/179 (19.6)	0.52 (0.32–0.84)	
Yes	104	26/63 (41.3)	18/41 (43.9)	1.11 (0.50–2.47)	
≥4 units packed red cells in 24 hr					>0.99
No	243	32/124 (25.8)	20/119 (16.8)	0.58 (0.31–1.09)	
Yes	238	57/137 (41.6)	33/101 (32.7)	0.68 (0.40–1.17)	
Prehospital packed red cells					>0.99
No	309	50/148 (33.8)	36/161 (22.4)	0.56 (0.34–0.93)	
Yes	172	39/113 (34.5)	17/59 (28.8)	0.77 (0.39–1.52)	
Traumatic brain injury					>0.99
No	295	36/165 (21.8)	22/130 (16.9)	0.73 (0.41–1.32)	
Yes	181	51/94 (54.3)	29/87 (33.3)	0.42 (0.23–0.77)	
Enrollment location					>0.99
Scene	373	76/203 (37.4)	40/170 (23.5)	0.51 (0.33–0.81)	
Referral emergency department	105	11/56 (19.6)	13/49 (26.5)	1.48 (0.59–3.69)	
Mechanism of injury					>0.99
Blunt	402	83/220 (37.7)	47/182 (25.8)	0.57 (0.37–0.88)	
Penetrating	79	6/41 (14.6)	6/38 (15.8)	1.09 (0.32–3.74)	
Prehospital transport time					>0.99
Short	225	41/131 (31.3)	21/94 (22.3)	0.63 (0.34–1.16)	
Prolonged	253	48/130 (36.9)	29/123 (23.6)	0.53 (0.30–0.91)	
Vitamin K antagonist					>0.99
No	353	32/186 (17.2)	18/167 (10.8)	0.58 (0.31–1.08)	
Yes	14	2/8 (25.0)	1/6 (16.7)	0.60 (0.04–8.73)	
Antiplatelet medication					>0.99
No	338	33/181 (18.2)	16/157 (10.2)	0.51 (0.27–0.97)	
Yes	38	3/18 (16.7)	5/20 (25.0)	1.67 (0.34–8.26)	
Overall	481	89/261 (34.1)	53/220 (24.1)	0.61 (0.41–0.92)	





. at Risk

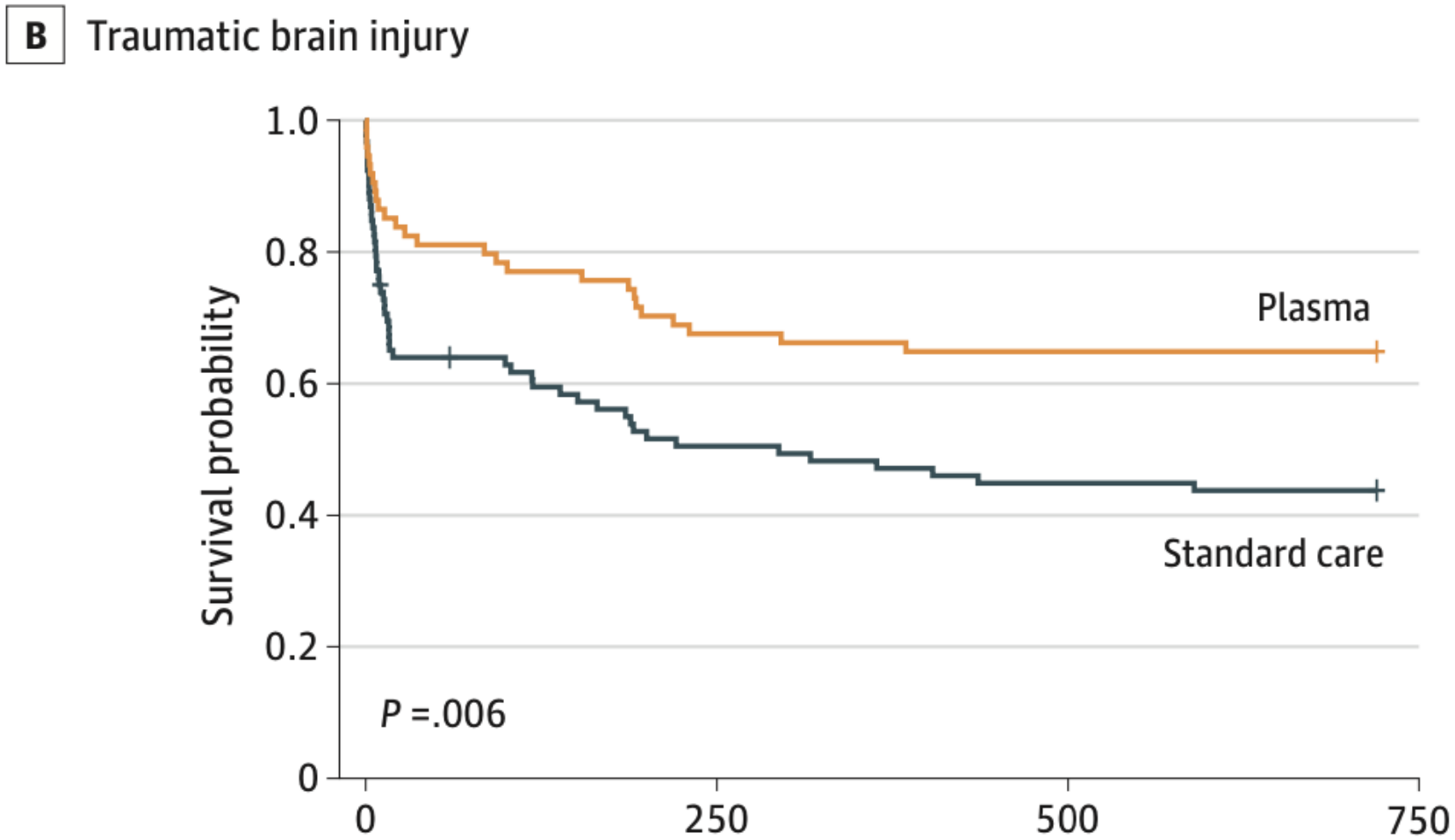
sma	230	183	172	170	169	168	168
ndard care	271	194	181	179	173	172	172

Better survival in TBI subgroup

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; Francis X. Guyette, MD; Joshua B. Brown, MD; David O. Okonkwo, MD; Ava M. Puccio, PhD; Insiyah K. Campwala, BS; Matthew T. Tessmer, BS; Brian J. Daley, MD; Richard S. Miller, MD; Brian G. Harbrecht, MD; Jeffrey A. Claridge, MD; Herb A. Phelan, MD; Matthew D. Neal, MD; Brian S. Zuckerbraun, MD; Mark H. Yazer, MD; Timothy R. Billiar, MD; Jason L. Sperry, MD



JAMA Network Open. 2020;3(10):e2016869. doi:10.1001/jamanetworkopen.2020.16869

JAMA Network Open

JAMA Network Open. 2020;3(10):e2016869.

Original Investigation | Surgery

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

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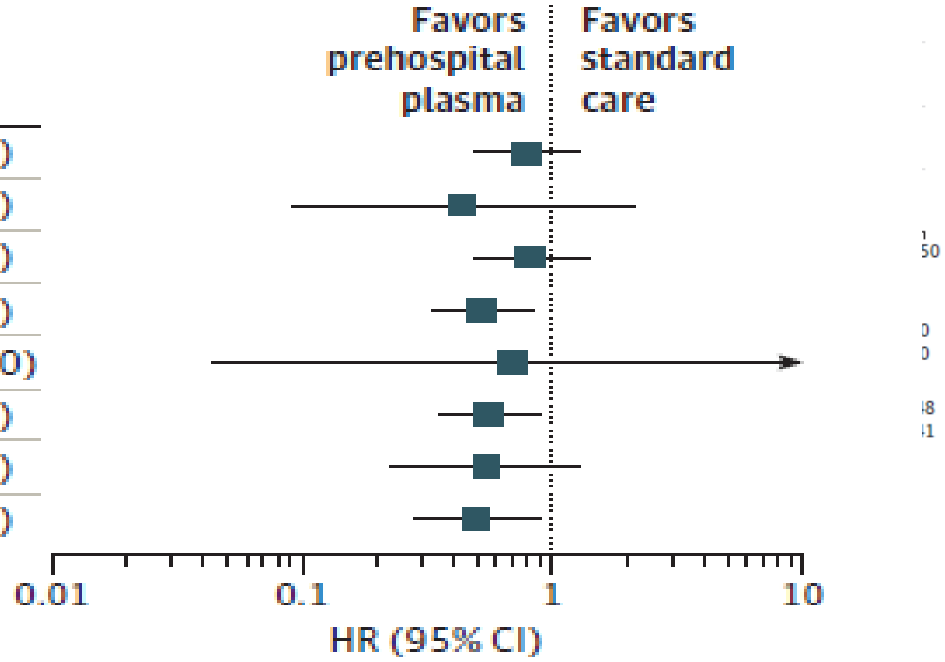
Danielle S. Gruen, PhD; Francis X. Guyette, MD; Joshua B. Brown, MD; David O. Okonkwo, MD; Ava M. Puccio, PhD; Insiyah K. Campwala, BS; Matthew T. Tessmer, BS; Brian J. Daley, MD; Richard S. Miller, MD; Brian G. Harbrecht, MD; Jeffrey A. Claridge, MD; Herb A. Phelan, MD; Matthew D. Neal, MD; Brian S. Zuckerbraun, MD; Mark H. Yazer, MD; Timothy R. Billiar, MD; Jason L. Sperry, MD

Figure 3. Hazard Ratios (HRs) for Each Subgroup Derived From a Cox Proportional Hazard Model

Source	No. of patients: Standard care	No. of patients: Prehospital plasma	HR (95% CI)
No TBI	179	156	0.80 (0.49-1.30)
Nonhead AIS <3	54	33	0.44 (0.09-2.10)
Nonhead AIS ≥3	123	120	0.82 (0.48-1.40)
TBI	92	74	0.52 (0.33-0.84)
GCS ≥8	17	22	0.70 (0.04-11.00)
GCS <8	72	52	0.56 (0.35-0.91)
Nonhead AIS <3	28	18	0.55 (0.23-1.30)
Nonhead AIS ≥3	63	53	0.50 (0.28-0.89)



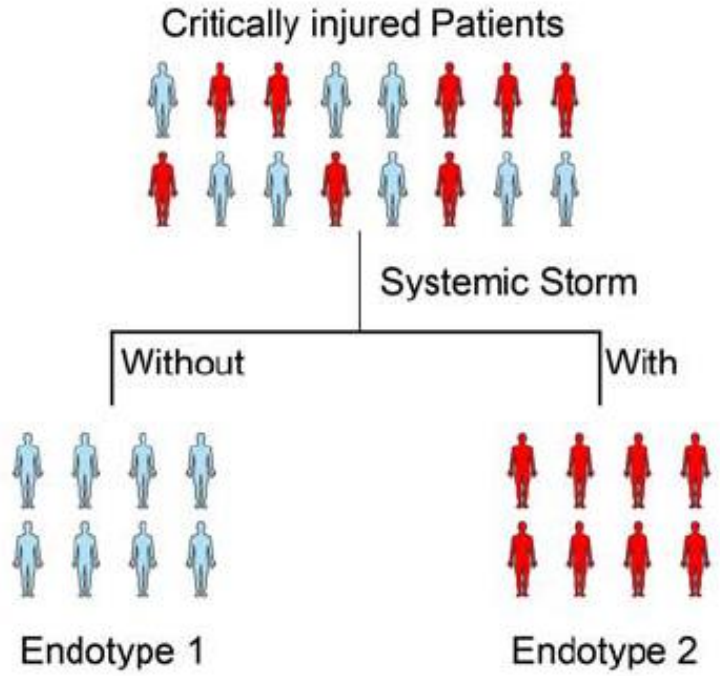
High Dimensional Multiomics Reveals Unique Characteristics of Early Plasma Administration in Polytrauma Patients With TBI

Junru Wu, MD,†‡ Hamed Moheimani, MD, MPH,†‡ Shimena Li, MD, MSc,†‡ Upendra K. Kar, PhD, MBA,†‡ Jillian Bonaroti, MD,†‡ Richard S. Miller, MD,§ Brian J. Daley, MD,‖ Brian G. Harbrecht, MD,¶ Jeffrey A. Claridge, MD,# Danielle S. Gruen, PhD,†‡ Herbert A. Phelan, MD,** Francis X. Guyette, MD, MPH,†† Matthew D. Neal, MD,†‡ Jishnu Das, PhD,‡‡✉ Jason L. Sperry, MD, MPH,†‡✉ and Timothy R. Billiar, MD†‡✉*

Annals of Surgery • Volume 276, Number 4, October 2022

Different endotypes

TBI patients process plasma differently



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
820 CHANDLER STREET
FORT DETRICK MD 21702-5014

REPLY TO ATTENTION OF

January 6, 2022

Grants Division

RE: PR212312 - "Multi-Institutional Phase 2/3 Trial of Fresh Frozen Plasma (FFP) in Patients with Moderate to Severe Traumatic Brain Injury (TBI)"

STATUS: RECOMMENDED FOR FUNDING

Hasan Alam
Northwestern University
Department of Trauma Critical Care
676 North St. Clair Street, Suite 650
Chicago, IL 60611-4579
hasan.alam@nm.org

Dear Hasan Alam:

Congratulations! On behalf of the Department of Defense office of the

Participants: Eight Level 1 centers

Clinical Sites:

- **Northwestern Memorial Hospital, Northwestern University (NMH)**
- **Vanderbilt University Medical Center (VUMC)**
- **Los Angeles County, University of Southern California Medical Center (USC)**
- **Oregon Health & Science University Hospital (OHSU)**
- **Froedtert Hospital, Medical College of Wisconsin (MCW)**
- **Parkland Memorial Hospital, UT Southwestern (PMH)**
- **University of Alabama at Birmingham (UAB)**
- **University of California Davis Medical Center (UCD)**

Regulatory: Broom Street Associates, Wilmington, DE

Single IRB: Vanderbilt University

EFIC: University of Alabama at Birmingham

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TRANSFUSION

REVIEW ARTICLE

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

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Objectives: Our long-term objective is to develop effective, safe, and easily administered life-saving treatments for the combat casualty environment.¶

Hypothesis: Treatment with fresh frozen plasma (FFP) is neuroprotective and safe in patients with moderate to severe TBI.¶

Specific Aims: Determine whether administration of 2 units of FFP in patients with moderate to severe TBI improves functional outcome as measured by Extended Glasgow Outcome Score (GOS-E) three months after injury.¶

Sub Aim 1: Document the safety (as measured by Treatment Emergent Adverse Events) of FFP administration in TBI patients, who do not require FFP for resuscitation.¶

Sub Aim 2: Determine whether FFP treatment has an impact on attenuation of hemorrhagic and/or ischemic progression of brain lesions during early (24 hours) post-injury, 24-hour, 3-month, and 6-month Disability Rating Score (DRS), 24-hour Glasgow Coma Scale (GCS), 6-month Extended Glasgow Outcome Score (GOS-E), intensive-care-free days, mortality, and hospital neurologic and functional discharge status of the patients.¶

Sub Aim 3: Establish peripheral blood biomarkers, and radiographic features on the initial cross-sectional imaging, that could identify the optimal target population and predict the response to treatment.¶

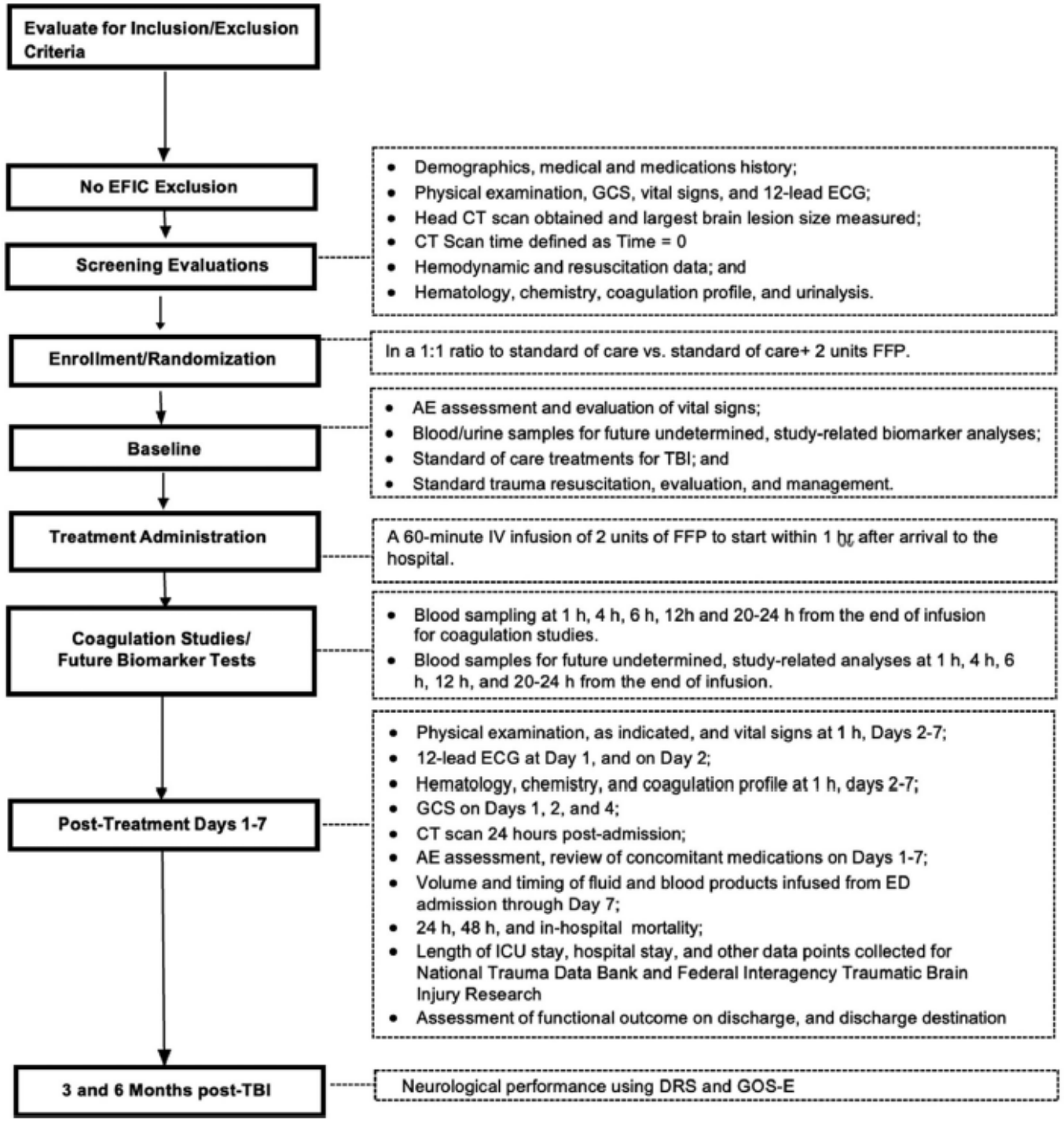
6.2 Inclusion and Exclusion Criteria

In order to be eligible for participation in this trial, each subject must meet the following criteria:

1. Male or female between the ages of 18 and 65 years
2. Moderate to severe TBI: GCS 3-12
3. Cerebral contusion confirmed on the initial CT scan with Brain Injury Guidelines (BIG) = 3 (corresponding to lesion ≥ 8 mm)[42]

Subjects who meet any of the following criteria will be excluded from the study:

1. Persons with a known history of adverse reaction to plasma products.
2. Persons with a known history of congestive heart failure, renal failure, liver failure, or severe respiratory dysfunction requiring home use of supplemental oxygen.
3. Persons who are currently incarcerated.
4. Persons with inadequate venous access.
5. Treatment cannot start within 1 hour of arrival at the hospital.
6. The time of injury is unknown.
7. Non-survivable injuries in the estimation of the attending trauma and/or neurosurgeon.
8. Interfacility transfers
9. Class 3 hemorrhagic shock
10. Persons with known “do not resuscitate” orders prior to randomization
11. Persons who refuse the administration of blood products
12. Persons with a research “opt out” bracelet
13. Persons who require FFP for any other indication (e.g., reversal of coagulopathy)



- **Key points:**
  - **early head CT (time=0)**
  - **randomization**
  - **2U plasma within 1 hr***
  - **CT at 24 hrs**
  - **Clinical parameters**
  - **3 & 6 month functional outcomes**

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Exception from Informed Consent

Link to UAB EFIC Video, click here.

Acute care research is sometimes conducted under Exception from Informed Consent regulations. In many life-threatening illnesses, patients are unconscious or too sick to provide written or verbal informed consent. The federal EFIC rules were developed in 1996 to allow for the waiver of obtaining and documenting informed consent for a strictly limited class of research.

FFP In Traumatic **BRA**in **IN**jury (**FIT-BRAIN**) Trial

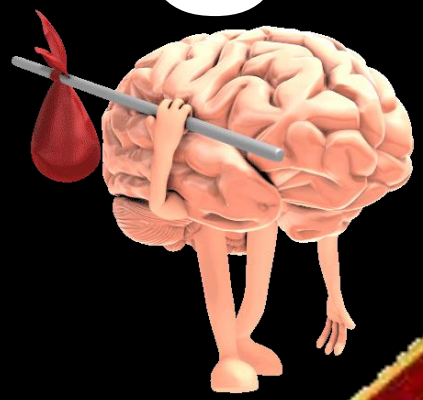
Supported by Congressionally Directed Medical Research Program Contract # W81XWH-09-1-0520

Congressionally Directed Medical Research Programs (Clinical Trial Award)
Funding Opportunity Number: W81XWH-21-PRMRP-CTA

Title: Multi-institutional Phase 2 Trial of Valproic Acid in Patients with Moderate to Severe Traumatic Brain Injury

1. **Topic Area (from the list of FY21 PRMRP Topic Areas):**
    a. Hemorrhage Control: Research on adjunctive pharmacological solutions for hemorrhage, shock, coagulopathy, transfusion, and/or the stabilization of polytrauma, with attention to the impact on potential traumatic brain injury.

Right Care - TBI



The Long Tail of TBI