A Trauma Surgeon’s Journey Through the World of Basic Research

Hasan B Alam, MD

Norman Thompson Professor of Surgery
Chief of General Surgery. University of Michigan Health Care System
Disclaimers

- Personal stories
- Biased opinions
Academic Surgery
Washington, DC in the 90’s

Crack
The Drug that Consumed the Nation’s Capital

MARION BARRY
"Outside of the killings, Washington has one of the lowest crime rates in the country."

BUSTED
FBI’s bait was an ex-lover
Scandal called tragedy for city

Barry vows to fight charges, run city
Getting hooked on trauma

Murder Capital

<table>
<thead>
<tr>
<th>Comparison of the District with 11 other cities</th>
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<tr>
<td>Homicide rates per 100,000 people</td>
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<tr>
<td>Baltimore</td>
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<td>Los Angeles</td>
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<td>New York City</td>
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Washington Hospital Center
Trauma Surgeons Ruled
Early mentor

- Scientific inquiry
- Writing clearly
- Being a good mentor
- Importance of funding

John Kirkpatrick, MD
Area of Investigation

Early Trauma Care
The Trimodal Distribution Of Trauma Deaths

The group that matters
The Trimodal Distribution of Trauma Deaths

- Within the first 6 hours: 75% of penetrating deaths
  
  Velmahos, J Trauma, 2004

- Within the first 3 hours: 54% of blunt trauma deaths
  
  Marson, J Trauma, 2001

Velmahos et al, J Trauma 2004
Today: trauma deaths

- RCT- 274 hospital, 40 countries, >20K patients
- Most died on the day of randomization
- Deaths due to MOF <2.5%

CRASH-2 trial
Lancet 2010
Stop the bleeding!

Percentage of Total Combat Deaths
Time from Wounding

Bellamy Anes & Periop Care of Combat Cas
Goals of early trauma care

- Keep alive
- Minimize organ injury
- Decrease bleeding

- Keep alive
- Preserve key organs
- ABC’s

- Fix injuries
- Resuscitate
- Support organs
Hemorrhage Control

First you must stop the bleeding....
Success = talent + hard work + opportunity

June 1999: “Why don’t you work with me?” - Peter Rhee
First job
A year of sharing an office with Peter

- Challenge the dogma
- Innovative solutions for common problems
- Share credit
- Promote team members
- Military funding system

Alam HB and Rhee P = 40 manuscripts + 3 grants + 1 patent
Big decisions- Early 2001

• Married
• Smaller salary- more discretionary time
• Develop a research focus
• Grant writing:
  – Forward Treatment of Hemorrhagic Shock- ONR. $1,728,488.00
  – Induced Hypothemric Arrest in Traumatic Shock . RO1 HL71698- $1,482,000.00
Sept 2001

- “Can you find a new hemostatic dressing”
- “Need it now”
Comparative Analysis of Hemostatic Agents in a Swine Model of Lethal Groin Injury

Hasan B. Alam, MD, Gemma B. Uy, MD, Dana Miller, MD, Elena Koustova, PhD, Timothy Hancock, BS, Ryan Inocencio, BS, Daniel Anderson, BS, Orlando Llorente, MD, and Peter Rhee, MD, MPH

QuikClot improved survival to 100%. Wound temp 44 C
Hemorrhage Control in the Battlefield: Role of New Hemostatic Agents

Guarantor: Hasan B. Alam, MD FACS
Contributors: Hasan B. Alam, MD*; COL David Burris, MC USA*; LCDR Joseph A. DaCorta, MHA MSC USN (Ret.)*; CDR Peter Rhee, MC USN*
A NATION AT WAR: Tending the Wounded

The New York Times
SUNDAY, MARCH 30, 2003

Armed With New Tools and Tactics, Doctors Head to the Battlefield

By GINA KOLATA

From redesigned first-aid kits to a radically new kind of surgery on the front lines, battlefield medicine has changed markedly and, as a result, doctors in the war in Iraq hope to significantly reduce the death rate from battlefield wounds — a rate that has peaked for 150 years.

Since the Civil War, experts in military medicine say, one of five wounded soldiers has died, half from profuse bleeding. Pentagon doctors hope to change that, and have mobilized an army of innovations.

Some, like putting pressure bandages in first-aid kits, are drugstore cheap. Others, like a new anticoagulant drug for internal bleeding, are high-tech expensive, about $7,000 per dose. And some, like sending radically redesigned medical teams to operate at the front lines, involve tactics and equipment that simply were not available in the last Gulf war. These special surgery units were tested in Afghanistan, where they reduced the 42-died-wounds rate, the death rate for those who survived long enough for a surgeon to operate, to a fraction of a percent. For the past half-century, it has hovered around 2 percent.

Doctors said it was hard to overestimate the difference.

There was little change from Vietnam to the first Gulf war in doctors’ instruments, drugs, techniques or tactics. Except for some in the Army, which put surgeons in the front lines in Desert Storm, wounded soldiers received first aid from medical but no surgical care until they were evacuated to a larger hospital.

Now, all the services have small mobile surgical teams scattered throughout the battlefield, where they operate on the most severely wounded as close to the front as possible. They do the minimum care.

Medical Evacuation

The system used by America’s military to evacuate wounded service members is a well-established procedure. But the substance was tested for battlefield use by Dr. Hasan Alam, a trauma surgeon at the Uniformed Services University of the Health Sciences in Bethesda, Md. Dr. Alam said he was haunted by troops who bled to death in Somalia before surgeons could help them.

For Dr. Alam, it meant that “your buddy has to stop the bleeding, not the medic, not the surgeon.”

So he turned to QuikClot, a product made of the mineral zeolite and sold over the counter by Z-Medica. It looks like cat litter but, sprinkled on a wound, it absorbs water from blood, concentrating the body’s own clotting factors and speeding up the formation of a clot.

Z-Medica has supplied $50,000 doses to the military.

Dr. Alam and his colleagues tested the substance on 36 Yorkshire swine, which are close to a person’s size. The results have not been published, but Dr. Alam said QuikClot converted wounds that were 100 percent fatal into wounds that were 100 percent nonfatal — clots formed and none of the animals died.

Although the Marine Corps plans to use it, other branches of the military are not yet convinced. The question is whether to use it, and at what dose. One concern is that heat is generated when QuikClot is poured on a wound, and the fear is that it might burn tissue. “We don’t have a huge amount of data,” Dr. Alam said. “We’ve done two studies.”

Also, the troops must be trained in how to use it and surgeons must be
Clotting substance hailed as lifesaver

By S Europ

Hemostatic hero

Lifesaving product of the war

Bandages that stop bleeding instantly may have saved the lives of soldiers wounded in Iraq. Now they’re making thei

chest.

By Melissa Healy
Times Staff Writer

June 23, 2003

The Wounded Come Home

WAR IN IRAQ
Battlefield Medical Advances May Save Wounded Soldiers

By DAVID P. HAMILTON
Staff Reporter of THE WALL STREET JOURNAL

March 20, 2003

did, and now—10 years and three patents later—the erstwhile inventor is commercializing QuikClot. When sprinkled into a wound, the
QUICKCLOT EVALUATION SHEET
(Please print and answer all questions possible. Answers will not be released to the public without written specific authorization.)

Name: Jerom Taylor, MD  Title: Battalion Surgeon/2nd Marine Division
Company/Organization: Currently: Lightweight Armored Reconnaissance/Promoted: 2nd Battalion 5th Marines
Address: Camp Lejeune, NC
City, State, Zip: 28540  Country: USA
Phone: 910-451-5987  Fax: 910-451-5987  Email: taylorjoe2.marinemc.mil

PLEASE DESCRIBE YOUR USE OF QUICKCLOT: (attach additional sheets if necessary)
Date: 10/29/03  Location: Operation Iraqi Freedom

Description: I was the battalion surgeon for a Marine Infantry battalion during the start of OIF. While on the battlefield I treated ten casualties with QuickClot and without a doubt it prevented massive hemorrhage as well as loss of limbs. I recommend wide usage of this product.

Evaluation: Outstanding.

Any additional comments:

I agree that different sizes should be made available or some sort of re-sealable package.

Signature: Jerom Taylor  Date: 10/29/03

PLEASE RETURN TO ADDRESS BELOW, ATTENTION: JESSICA PERKINS

Z-MEDICA, LLC, 35 Badney Road, Newington, CT 06111  Phone: 860.662.2201  Fax: 860.662.2222  Web: www.z-medica.com  Email: info@z-medica.com
QUIKCLOT EVALUATION SHEET

(Please print and answer all questions possible. Answers will not be released to the public without written specific authorization.)

Name: Breunert David J. Title: SGT

Company/Organization: U.S. Army

Address: 15354 Murphy St Apt A

City, State, Zip: Ft Polk LA 71449 Country: USA

Phone: 337-538-8057 Fax:

Email: david.breunert.6@us.army.mil

PLEASE DESCRIBE YOUR USE OF QUIKCLOT: (attach additional sheets if necessary)

Date: 24 May 03 Location: Baghdad Iraq

Description: Treat a gunshot wound (GSW) to right thigh. Patient was bleeding profusely. Applied Quikclot. The bleeding stopped in 10.5 minutes. Saved the soldier's leg and life.

Evaluation: I think this product is great. I am recommending to superiors to keep product on hand.

Any additional comments:

Signature: [Signature] Date: 09.04.03

PLEASE RETURN TO ADDRESS BELOW, ATTENTION: JESSICA PERKINS

The greatest privilege is to make a difference.
Application of a Zeolite Hemostatic Agent Achieves 100% Survival in a Lethal Model of Complex Groin Injury in Swine

Hasan B. Alam, MD, Zheng Chen, MD, PhD, Amin Jaskille, MD, Racel Ireneo Luis C. Querol, MD, Elena Kousta, PhD, Ryan Inocencio, BS, Richard Conran, MD, Adam Seufert, HS, Nanna Ariaban, BS, Kevin Toruno, BS, and Peter Rhee, MD, MPH

Testing of Modified Zeolite Hemostatic Dressings in a Large Animal Model of Lethal Groin Injury

Naresh Ahuja, MD, Todd A. Ostomel, PhD, Peter Rhee, MD, Galen D. Stucky, PhD, Richard Conran, MD, Zheng Chen, MD, PhD, Ghada A. Al-Mubarak, MD, George Velmahos, MD, Marc deMoya, MD, and Hasan B. Alam, MD
QuikClot Use in Trauma for Hemorrhage Control: Case Series of 103 Documented Uses

Peter Rhee, MD, MPH, Carlos Brown, MD, Matthew Martin, MD, Ali Salim, MD, Dave Plurad, MD, Donald Green, MD, Lowell Chambers, MD, Demetrios Demetriades, MD, PhD, George Velmahos, MD, and Hassan Alam, MD

J Trauma 2008
You stay with me, man— you hear me?

Medic! We’re gon-na get you outa here! Everything’s gonna be cool, man!

Hey!

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Hey!
QuikClot Combat Gauze now recommended as first line of treatment
Lessons learned

- Take risks
- Think big
- WRITE

Biggest predictor of academic success = Ability to write Clearly, on Schedule, and Consistently
A word about intellectual property

A Portable Handpump Is Effective in the Evacuation of Hemothorax in a Swine Model of Penetrating Chest Injury

Amin Jaskille, MD, Peter Rhee, MD, MPH, Elena Koustova, PhD, Timothy Hancock, BS, Ryan Inocencio, BS, Troy A. Lewis, BS, Adam Seufert, HS, and Hasan B. Alam, MD


WTA 2003- Earl Young Paper
Abstract
A manually operable pump for the effective removal of fluids to include blood, blood slugs, fluid, and air from a body cavity of a subject is provided. The manually operable pump is adapted to be connect to a range of fluid conduits and is equipped with one-way valves that effectively permit flow of fluid through the pump in only one direction. The sensitivity of the one-way valves is such that when properly positioned, fluid can flow through the valves and out of the pump without manual compression of the pump and with the aid of gravity power alone.
Compassionate Treatment for Malignant Pleural Effusion Patients

The Aspira* Pleural Drainage Catheter is a tunneled, long-term catheter used to drain accumulated fluid from the pleural cavity to relieve symptoms associated with malignant pleural effusion and other recurrent pleural effusions. The Aspira* Pleural Drainage Catheter is easy to insert and the
Resuscitation
Aggressive fluid resuscitation for bleeding trauma patient: Good or bad?

Institute of Medicine 1999
Impact of Resuscitation fluids on Cellular Functions
Effect of different resuscitation strategies on neutrophil activation in a swine model of hemorrhagic shock

Hasan B. Alam\textsuperscript{a,b,*}, Kathleen Stanton\textsuperscript{a}, Elena Koustova\textsuperscript{a}, David Burris\textsuperscript{a}, Norman Rich\textsuperscript{a}, Peter Rhee\textsuperscript{a,c}
NEUTROPHIL ACTIVATION

FLUIDS

Human Polymorphonuclear Cell Death after Exposure to Resuscitation Fluids In Vitro: Apoptosis versus Necrosis

Kathleen Stanton, MS, Hasan B. Alam, MD, Peter Rhee, MD, MPH, Orlando Llorente, MD, John Kirkpatrick, MD, and Elena Koustova, PhD
Effects of Lactated Ringer’s Solutions on Human Leukocytes

Elena Koustova, PhD, Kathleen Stanton, MS, Vadim Gushchin, MD, Hasan B. Alam, MD, Svetlana Stegalkina, MS, and Peter M. Rhee, MD, MPH
Cytokine Expression Profiling in Human Leukocytes after Exposure to Hypertonic and Isotonic Fluids

Vadim Gushchin, MD, Svetlana Stegalkina, MS, Hasan B. Alam, MD, John R. Kirkpatrick, MD, Peter M. Rhee, MD, MPH, and Elena Koustova, PhD

Resuscitation-Induced Pulmonary Apoptosis and Intracellular Adhesion Molecule-1 Expression in Rats Are Attenuated by the Use of Ketone Ringer’s Solution

Hasan B Alam, MD, Brenda Austin, BS, Elena Koustova, PhD, Peter Khee, MD, MPH, FACS
Elimination of D-lactate decreases apoptotic cell death
MGH and Harvard Med School
1820s
Harvard Medical School today
Making survivors out of non-survivors

Surviving Blood Loss (SBL) Program
Identification of Expression Patterns Associated with Hemorrhage and Resuscitation: Integrated Approach to Data Analysis

Huazhen Chen, MD, Hasan B. Alam, MD, Racel Ireneo Luis C. Querol, MD, Peter Rhee, MD, Yongqing Li, MD, PhD, and Elena Koustova, PhD
Epigenetic regulation
Acetylation

• Controlled by two enzyme systems:

  Histone acetyltransferase (HAT) - ↑ transcription
  Histone deacetylase (HDAC) - ↓ transcription

• Histone Deacetylase Inhibitors (HDACI- ↑ acetylation
  – Nuclear histones= ↑ transcription
  – Cytoplasmic proteins= altered function
Surviving Blood Loss Without Fluid Resuscitation

Christian Shults, MD, Elizabeth A. Sailhamer, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Malek Tabbara, MD, Muhammad Umar Butt, MD, Fahad Shuja, MD, Marc deM, George Velmahos, MD, and Hasan B. Alam, MD

Acetylation: a novel method for modulation of the immune response following trauma/hemorrhage and inflammatory second hit in animals and humans

Elizabeth A. Sailhamer, MD, Yongqing Li, MD, PhD, Eleanor J. Smith, Fahad Shuja, MD, Christian Shults, MD, Baoling Liu, MD, Chad Soupir, MD, Marc deMoya, MD, George Velmahos, MD, and Hasan B. Alam, MD, Boston, Mass and Washington, DC
HDACI improve survival in intestinal ischemia-reperfusion

Resuscitation August 2011
.. and decreased distant organ injury (ALI)
Histone deacetylase inhibitors enhance endothelial cell sprouting angiogenesis in vitro

Guang Jin, MD, PhD, a Dirk Bausch, MD, a,b,c Knightly Thomas, BS, a Zhengcai Liu, MD, a Yongqing Li, MD, PhD, a Baoling Liu, MD, a Jennifer Lu, BS, a Wei Chong, MD, PhD, a George Velmahos, MD, PhD, a and Hasan B. Alam, MD, a

Cambridge, Massachusetts, and Freiburg, Germany

Surgery Sep 2011
Histone deacetylase inhibitor suberoylanilide hydroxamic acid attenuates Toll-like receptor 4 signaling in lipopolysaccharide-stimulated mouse macrophages

Wei Chong, MD, PhD, Yongqing Li, MD, PhD, Baoling Liu, MD, Ting Zhao, MD, Eugene Y. Fukudome, MD, Zhengcai Liu, MD, PhD, William M. Smith, George C. Velmahos, MD, PhD, Marc A. deMoya, MD, and Hasan B. Alam, MD

Department of Surgery, Division of Trauma, Emergency Surgery and Surgical Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
Emergency Department, the First Hospital, China Medical University, Shenyang, China
Department of Hepatobiliary Surgery, Xijing Hospital, the Fourth Military Medical University, Xi’an, China

J Surg Res 2012
Anti-inflammatory properties of histone deacetylase inhibitors: A mechanistic study

Wei Chong, MD, PhD, Yongqing Li, MD, PhD, Baoling Liu, MD, Zhengcai Liu, MD, PhD, Ting Zhao, MD, Diane R. Wonsey, PhD, Changmin Chen, PhD, George C. Velmahos, MD, PhD, Marc A. deMoya, MD, David R. King, MD, Andrew L. Kung, MD, PhD, and Hasan B. Alam, MD, Boston, Massachusetts
Modulation of Acetylation: Creating a Pro-survival and Anti-Inflammatory Phenotype in Lethal Hemorrhagic and Septic Shock

Yongqing Li and Hasan B. Alam
Hemorrhagic shock

HDACI
Loss of claudin-3, and so forth
Gut barrier loss

Gut
Bacteria endotoxin inflammatory cytokines

Liver
Endotoxin inflammatory cytokines

Lungs
Inflammatory cytokines
Neutrophils infiltration, inflammation

ERK, JNK, p38
Systemic circulation

Bacteria endotoxin inflammatory cytokines

Lymphatics
Surviving blood loss without blood transfusion in a swine poly-trauma model

Hasan B. Alam, MD,* Fahad Shuja, MD,* Muhammad U. Butt, MD, Michael Duggan, DVM, Yongqing Li, MD, PhD, Nikolaos Zacharias, MD, Eugene Y. Fukudome, MD, Baoling Liu, MD, Marc deMoya, MD, and George C. Velmahos, MD, Boston, Massachusetts
3-D CT image of femur fracture

Image provided by: Jill Sondeen, PhD (USAISR)
Holcomb JB, et al. Model developed at the US Army ISR, Fort Sam Houston, TX
Base excess

* = p<0.05 compared to VPA
# = p<0.05 compared to Control

- Control
- FWB
- VPA
Survival

End of Hemorrhage

% Survival

* Fresh whole blood-100% (n=6)

* Valproic acid-85.7% (n=7)

Control-25% (n=8)

* = Log-Rank (Mantel-Cox test), p<0.05 compared to control

Alam et al. Surgery 2009
Hemostatic and Pharmacologic Resuscitation: Results of a Long-Term Survival Study in a Swine PolyTrauma Model

Hasan B. Alam, MD, Kristopher B. Hamwi, MD, Michael Duggan, DVM, Karim Fikry, MD, Jennifer Lu, BS, Eugene Y. Fukudome, MD, Wei Chong, MD, PhD, Athanasios Bramos, MD, Kyuseok Kim, MD, PhD, and George Velmahos, MD, PhD
Survival

Survival Analysis

* = p<0.05 compared to Hex

Survival (percent)

Injury

Time After Injury (minutes)

FWB*

VPA + Hextend

Hextend

SDP*
PROTECTIVE EFFECT OF SUBEROYLANILIDE HYDROXAMIC ACID AGAINST LPS-INDUCED SEPTIC SHOCK IN RODENTS

Yongqing Li,* Baoling Liu,* Hang Zhao,† Eugene Y. Fukudome,* Xiaobo Zhang,‡ Tareq Kheirbek,* Robert Finkelstein,* George Velmahos,* Marc deMoya,* Charles A. Hales,† and Hasan B. Alam*
Surviving lethal septic shock without fluid resuscitation in a rodent model

Yongqing Li, MD, PhD, Baoling Liu, MD, Eugene Y. Fukudome, MD, Ashley R. Kochanek, BS, Robert A. Finkelstein, MD, CM, Wei Chong, MD, PhD, Guang Jin, MD, PhD, Jennifer Lu, BS, Marc A. deMoya, MD, George C. Velmahos, MD, PhD, and Hasan B. Alam, MD, FACS, Boston, MA

Post-treatment equally effective

*Surgery 2010;148:246-54*
Creating a “pro-survival” phenotype through epigenetic modulation

Yongqing Li, MD, PhD, a Baoling Liu, MD, a Xuesong Gu, PhD, b Ashley R. Kochanek, MD, a Eugene Y. Fukudome, MD, a Zhengcai Liu, MD, PhD, a,c Ting Zhao, MD, a Wei Chong, MD, PhD, a,d Yili Zhao, a Dainan Zhang, PhD, e Tovia A. Libermann, PhD, b and Hasan B. Alam, MD, FACS, a Boston, MA, and Xi’an, Shenyang, and Xinxiang, China Surgery 2012; 152: 455-64.

A
Sham

LPS

SAHA + LPS

B

MPO (ng/ml)

0
1000
2000
3000
4000
5000
6000
Sham

LPS

SAHA + LPS

Groups

TLR2

IRAK1

MYD88

TNFR2

TRAF6

TNFR1

C1QC

C1QA

C1QB

PTX3

C1Q
g

CCL3

HSPA1A

HSPA1L

RCN2

UBE2B

UBE2E

UBE2G1

UBE2J1

UBE2S

SCA12

IL18

RAF1

PAK3

PSMD13

MAP

TRAF7

RPS27A

EZH1

AKT2

NAIP1

C1QA

C1QB

C1QC

CCL3

TNFR1

TNFR2

TLR2

IRAK1

MYD88

TRAF6

C1QA

C1QB

C1QC

CCL3
Novel pharmacologic treatment attenuates septic shock and improves long-term survival

Ting Zhao, MD, a Yongqing Li, MD, PhD, a Baoling Liu, MD, a,b Zhengcai Liu, MD, PhD, a,c Wei Chong, MD, PhD, a,d Xiuzhen Duan, MD, PhD, e Danielle K. Deperalta, MD, a George C. Velmahos, MD, PhD, a and Hasan B. Alam, MD, a,b Boston, MA, Ann Arbor, MI, Xi’an and Shenyang, China, and Maywood, IL
Trauma patients

Acetylation: a novel method for modulation of the immune response following trauma/hemorrhage and inflammatory second hit in animals and humans

Elizabeth A. Sailhamer, MD, Yongqing Li, MD, PhD, Eleanor J. Smith, Fahad Shuja, MD, Christian Shults, MD, Baoling Liu, MD, Chad Soupir, MD, Marc deMoya, MD, George Velmahos, MD, and Hasan B. Alam, MD, Boston, Mass and Washington, DC

Surgery 2008

Hypoxic “second hit” in leukocytes from trauma patients: Modulation of the immune response by histone deacetylase inhibition

Elizabeth A. Sailhamer, Yongqing Li, Eleanor J. Smith, Baoling Liu, Fahad Shuja, Chad P., Marc A., George C., and Hasan B. Alam

Cytokine 2010 [Epub ahead of print]
Histone deacetylase Inhibitors

• In models of lethal shock HDACI treatment:
  • Improves survival
  • Prevents apoptosis
  • Reduces organ dysfunction
  • Activates survival pathways
  • Modulates inflammatory response

• Human in-vitro data

• “Resuscitation in a syringe”

• ~$10 Million new funding- NIH, DoD

FDA approval for clinical trial 2012
A Study to Evaluate the Safety and Tolerability of Valproic Acid in Healthy Volunteers or Trauma Patients

This study is currently recruiting participants.
Verified September 2013 by University of Michigan

Sponsor:
Dr. Hasan Alam

Information provided by (Responsible Party):
Dr. Hasan Alam, University of Michigan

ClinicalTrials.gov identifier:
NCT01951560
First received: September 23, 2013
Last updated: NA
Last verified: September 2013
History: No changes posted

Purpose

The purpose of the first part of this study is to determine the safety and tolerability of ascending doses of valproic acid (also known as Depacon) administered as intravenous infusion from 45 to 360 milligrams per hour in healthy patients.
“Damage Control” Resuscitation

- Permissive hypotension
- Limited crystalloids
- Early blood products
- Prevention of coagulopathy
MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: Optimal Resuscitation of Severely Injured Soldiers

1. Combat resuscitation data analyzed by the US Army Institute of Surgical Research (USAISR) demonstrate that casualties who receive more than 10 units of packed red blood cells (PRBCs) in a 24 hour period (massive transfusion) have a profound survival benefit when the plasma (FFP) to PRBC transfusion ratio is 1:1. Casualties who receive less FFP (1 unit FFP to 4 units PRBCs, or less) have an overall mortality of 65%, while those who receive a 1:1 ratio have an overall mortality of 20% (p< 0.001).

2. Severely injured casualties should have the 1:1 ratio initiated as early after injury as possible. Transfusions must be accomplished according to guidelines established by the CENTCOM Blood Program Manager. The current approved CENTCOM Clinical Practice Guideline for Damage Control Resuscitation and Transfusion is posted on the Joint Patient Tracking Application (JPTA) website:

3. No new equipment is required to implement this change in clinical resuscitation practice. Training is currently incorporated into the Joint Combat Trauma Management Course (US Army Medical Department Center & School (AMEDDC&S)) and posted on the AMEDDC&S website.

4. POC for this memorandum is COL John Holcomb, Trauma Consultant to The Surgeon General and Commander, USAISR, Ft. Sam Houston, TX, at (210) 916-2720, DSN 429-2720, or e-mail john.holcomb@amedd.army.mil.

REDO C. KILEY, M.D.
Lieutenant General
The Surgeon General
Plasma and red cells are good but...
New approach

• Freeze dried plasma and platelets
• Combined with hemoglobin based solution, +/- recombinant factors +/- preserved platelets
• Low volume, hypertonic, hyperoncotic
Development and Testing of Freeze-Dried Plasma for the Treatment of Trauma-Associated Coagulopathy

Fahad Shuja, MD, Christian Shults, MD, Michael Duggan, DVM, Malek Tabbara, MD, Muhammad U. Butt, MD, Thomas H. Fischer, PhD, Martin A. Schreiber, MD, Brandon Tieu, MD, John B. Holcomb, MD, Jill L. Sondeen, PhD, Marc deMoya, MD, George C. and Hasan B. Alam, MD

J Trauma. 2008;65:000–000.

WTA Squaw Valley 2008
Spray dried
1/3rd volume
Just as good as FFP
Easy to reconstitute
Traumatic Brain Injury
Model development

Dynamic mechanical response of brain tissue in indentation in vivo, in situ and in vitro

Thibault P. Prevost\textsuperscript{a}, Guang Jin\textsuperscript{b}, Marc A. DeMoya\textsuperscript{b}, Hasan B. Alam\textsuperscript{b}, Subra Suresh\textsuperscript{a}, Simona Socrate\textsuperscript{c,*}

2011
Surgery and physiological monitoring
Controlled cortical impact device

Impactor mounted on an Adjustable frame

Impactor in position before firing

Impactor Piston \( \Phi = 15 \text{ mm} \)
Creating the CCI
Brain coronal sections

Brain post-CCI

Brain swelling = \[
\frac{\text{ipsilateral hemisphere's volume}}{\text{contralateral hemisphere's volume}} - 1\] \times 100 (Takano et al. Stroke 28:1255-62).


Brain slicer, 5 mm thickness
FFP decreases lesion size and brain swelling

Jin et al. SHOCK 2012
Valproic acid is even more effective

Combination is the best

Imam et al. Surgery 2013
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

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

WTA 2013 PLENARY PAPER

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

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

Platelet activation and dysfunction in a large-animal model of traumatic brain injury and hemorrhage

Martin Sillesen, MD, Pär I. Johansson, MD, DMsc, Lars S. Rasmussen, MD, PhD, DMsc, Guang Jin, MD, PhD, Cecilie H. Jepsen, MD, Ayesha M. Imam, MD, John Hwabejire, MD, MPH, Jennifer Lu, BS, Michael Duggan, DVM, George Velmahos, MD, PhD, Marc deMoya, MD, and Hasan B. Alam, MD, Ann Arbor, Michigan
Massive blood loss and no pulse

Emergency Department
Thoracotomy
The ultimate resuscitation strategy
Putting Life On Hold—For How Long? Profound Hypothermic Cardiopulmonary Bypass in a Swine Model of Complex Vascular Injuries

Hasan B. Alam, MD, Michael Duggan, DVM, Yongqing Li, MD, PhD, Konstantinos Spaniolas, MD, Baoling Liu, MD, Malek Tabbara, MD, Marc deMoya, MD, Elizabeth A. Sallhau and George C. Velmahos, MD


Profound hypothermia is superior to ultraprofound hypothermia in improving survival in a swine model of lethal injuries

Hasan B. Alam, MD, Zheng Chen, MD, PhD, Yongqing Li, MD, PhD, George Velmahos, MD, Marc DeMoya, MD, Christopher E. Keller, DVM, MPH, Kevin Toruno, BS, Tina Mehrani, BS, Peter Rhee, MD, MPH, and Konstantinos Spaniolas, MD Bethesda, Md, Boston, Mass, and Los Angeles, Calif
Profound Hypothermia Protects Neurons and Astrocytes, and Preserves Cognitive Functions in a Swine Model of Lethal Hemorrhage

Hasan B. Alam, M.D., Naresh Ahuja, M.D., M.P.H., Huazhen Chen, M.D.," Richard Conran, M.D., Eduardo C. Ayuste, M.D., Kevin Toruno, B.S., Nanna Ariaban, B.S., Peter Rhee, M.D., Amal Nadel, M.S., and Elena Koustova, Ph.D.

Profound Hypothermic Cardiopulmonary Bypass Facilitates Survival Without a High Complication Rate in a Swine Model of Complex Vascular, Splenic, and Colon Injuries

Elizabeth A. Sailhamer, MD, Zheng Chen, MD, PhD, Naresh Ahuja, MD, George C Velmahos, MD, FACS, Marc de Moya, MD, Peter Rhee, MD, FACS, Christian Shultis, MD, Hasan B Alam, MD, FACS

Role of hypothermia in hemorrhagic shock

Journal of Organ Dysfunction, 2008; 4: 151–160

FAHAD SHUJA, JOSÉ PEDRO ALMEIDA and HASAN B. ALAM
Cognitive function testing

- Operant conditioning
- Recognize and open color coded box
- Number of sessions, time to finish task, performance score
Emergency Preservation and Resuscitation

• Rate of induction – Fast (2°C/minute)
  Alam et al. J Trauma 2004

• Optimal Depth – Profound (10°C)
  Alam et al. Surgery 2006

• Rate of re-warming – (0.5°C/minute)
  Alam et al. J Trauma 2006

• Duration – short (60 minutes)
  Alam et al. J Trauma 2008

• Poly-trauma – feasible without complications
  Sailhamer et al. JACS 2007
Profound Hypothermia Decreases Cardiac Apoptosis Through Akt Survival Pathway

Fahad Shuja, MD, Malek Tabbara, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Muhammad Umar Butt, MD, George C Velmahos, MD, FACS, Marc deMoya, MD, FACS, Hasan B Alam, MD, FACS


Alterations in Gene Expression After Induction of Profound Hypothermia for the Treatment of Lethal Hemorrhage

Hasan B. Alam, MD, Sahar Hashmi, MD, Robert A. Frankelstein, MD, Fahad Shuja, MD, Eugene Y. Fukudome, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Marc deMoya, MD, and George C. Velmahos, MD, PhD

The Journal of TRAUMA® Injury, Infection, and Critical Care • Volume 68, Number 5, May 2010
Hypothermia and hemostasis in severe trauma: A new crossroads workshop report

Hasan B. Alam, MD, Anthony E. Pusateri, PhD, Andrei Kindzelski, MD, PhD, Debra Egan, MPH, Keith Hoots, MD, PhD, Matthew T. Andrews, PhD, Peter Rhee, MD, MPH, Samuel Tisherman, MD, Kenneth Mann, PhD, Jaroslav Vostal, MD, PhD, Patrick M. Kochanek, MD, Thomas Scalea, MD, Virgil Deal, MD, Forest Sheppard, MD, George Sopko, MD, MPH,

and on behalf of the HYPOSTAT workshop participants, Boston, Massachussets

October 2012

Sponsored by the NIH and the DoD

Guidelines for future research
**Emergency Preservation and Resuscitation (EPR) for Cardiac Arrest From Trauma (EPR-CAT)**

<table>
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<tr>
<th><strong>This study is not yet open for participant recruitment.</strong></th>
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<tr>
<td>Verified August 2011 by University of Pittsburgh</td>
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**Sponsor:**
University of Pittsburgh

**Collaborators:**
University of Maryland
University of Pennsylvania
Massachusetts General Hospital
University of Arizona
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**Information provided by:**
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**ClinicalTrials.gov Identifier:**
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First received: January 4, 2010
Last updated: August 2, 2011
Last verified: August 2011

**History of Changes**
Goals of early trauma care

- Keep alive
- Minimize organ injury
- Decrease bleeding

- Keep alive
- Preserve key organs
- ABC’s

- Fix injuries
- Resuscitate
- Support organs

Pre-hospital

Pro-survival drugs

Freeze dried plasma

ED

OR/SICU

EPR
The difficulty lies, not in the new ideas, but in escaping from the old ones..

John Maynard Keynes (1883-1946)
Key points

- Identify need - area of investigation
- Think big
- Mentors
- Collaborators
- Mentees
- Scheduled writing
- Marry the right person
Funding acknowledgement:
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