Hypertonic Saline Resuscitation: The Way of The Future

Angela Gilliam, M.D.
University of Colorado
Surgical Grand Rounds
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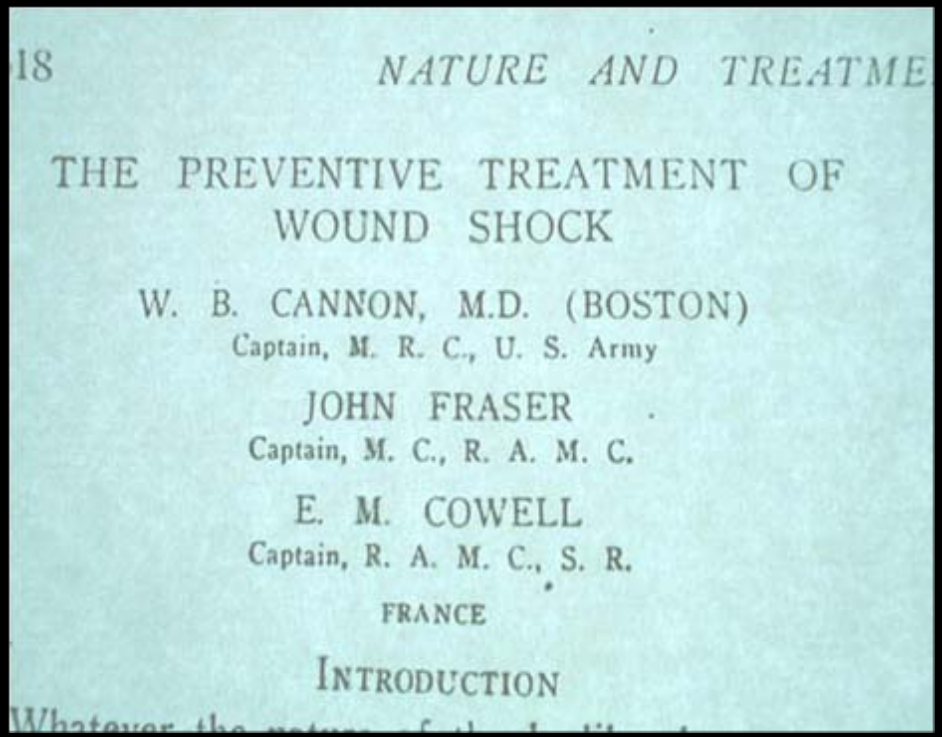
Intravenous Saline



18 NATURE AND TREATME

THE PREVENTIVE TREATMENT OF WOUND SHOCK

W. B. CANNON, M.D. (BOSTON)
Captain, M. R. C., U. S. Army

JOHN FRASER
Captain, M. C., R. A. M. C.

E. M. COWELL
Captain, R. A. M. C., S. R.

FRANCE

INTRODUCTION

Whatever the nature of the [illegible]

Why Hypertonic Saline?

- Hemodynamics
  - Redistributes fluid from interstitial space to intravascular space → Increasing preload
  - Causes vasodilation → Reducing afterload
- Traumatic Brain Injury
  - Decreases intracranial pressure
- Immune Modulation
  - Attenuates proinflammatory response to truama
  - Enhances T-cell function

Prehospital Hypertonic Saline/Dextran Infusion for Post-traumatic Hypotension

The U.S.A. Multicenter Trial

KENNETH L. MATTOX, M.D.,* PETER A. MANINGAS, M.D.,† ERNEST E. MOORE, M.D.,‡ JAMES R. MATEER, M.D.,§ JOHN A. MARX, M.D.,‡ CHARLES APRAHAMIAN, M.D.,‖ JON M. BURCH, M.D.,* and PAUL E. PEPE, M.D.*¶

Houston, Denver and Milwaukee

Randomized Controlled Trial

250cc 7.5%NaCl in 6% Dextran

vs.

250cc Standard Resuscitation fluid (NS,LR,Plasmalyte)

- 422 patients enrolled
- Inclusion
  - >16yo
  - Event within one hr
  - Initial SBP <90
- 359 in final analysis
  - 72% with penetrating injuries

TABLE 1. *Summary of Epidemiologic Data*

Epidemiologic Condition	HSD		STD	
	n	%	n	%
Etiology				
Penetrating	153	73	151	72
Blunt	54	26	57	27
Unknown	4	2	3	1
Race				
White	51	28	36	21
Black	71	39	77	44
Other	62	34	62	35
Males (% male)	184	83	175	85
	n	Mean ± SD	n	Mean ± SD
Age	182	34 ± 12	172	33 ± 12
Injury severity score	184	19 ± 13	175	19 ± 15
TRISS (Prob surv)	171	0.84 ± 0.29	164	0.83 + 0.32
Revised trauma score				
Preinfusion	172	5.98 ± 1.61	165	5.93 + 1.75
Emergency center	149	7.43 ± 0.97	139	7.25 + 1.16

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; TRISS, Trauma Index and Injury Severity Score; Prob surv, probability of survival; SD, standard deviation.

Survival

- Primary Endpoint
  - No statistical difference overall
- Pts requiring surgery
  - Significant benefit in the HSD arm (p 0.02)
  - 88% survival in HSD
  - 77% survival in STD

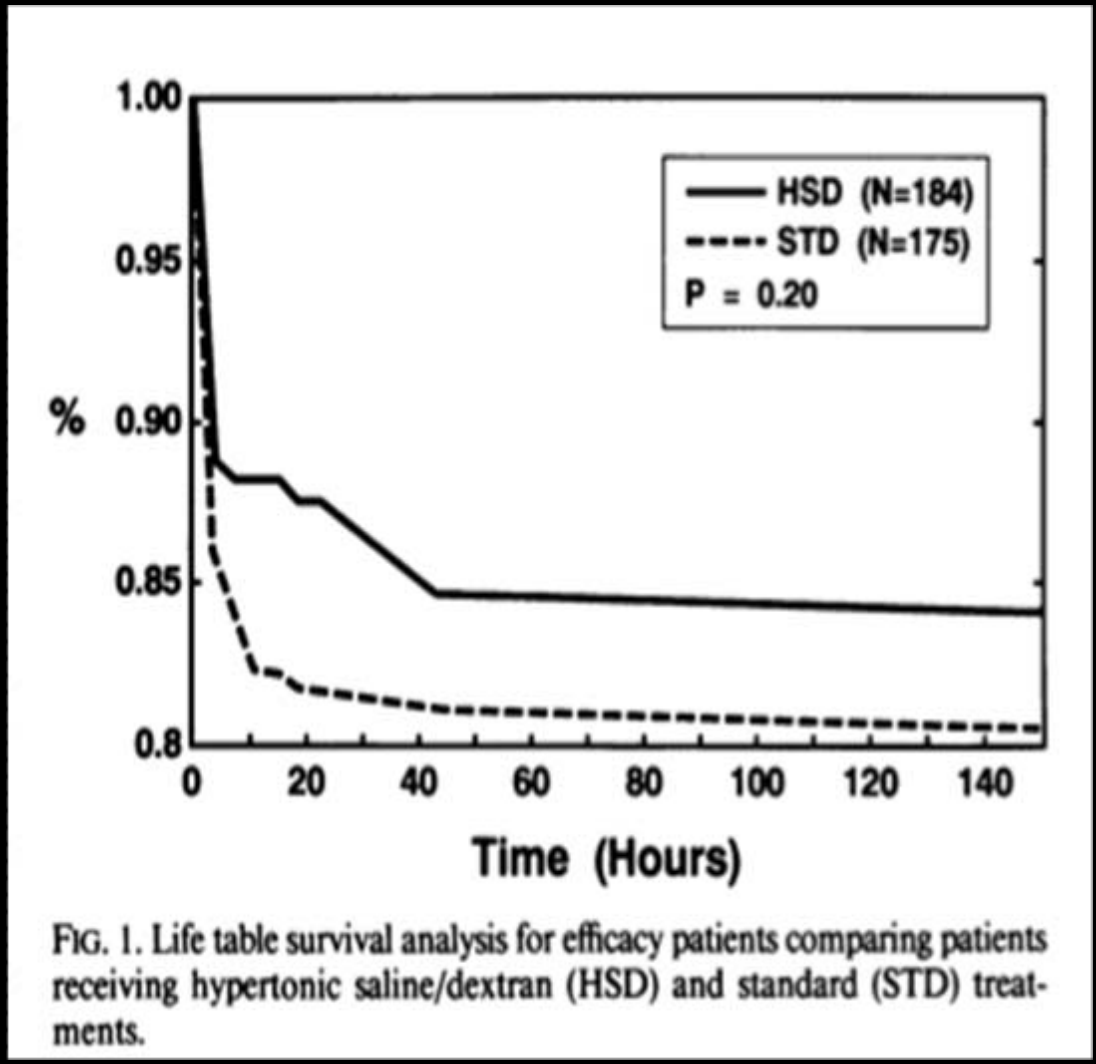


FIG. 1. Life table survival analysis for efficacy patients comparing patients receiving hypertonic saline/dextran (HSD) and standard (STD) treatments.

Complications

TABLE 5. *Summary of Postadmission Complications (Number of Occurrences, Not Patients)*

Complication	HSD	STD	Total
Specified in protocol			
Coagulopathy	2	8	10
Pneumonia	3	5	8
Sepsis	0	3	3
Abdominal abscess	1	1	2
Pulmonary embolism	0	2	2
ARDS	0	2	2
Acute renal failure	0	1	1
Heart failure	0	1	1
Dead bowel	0	1	1
Others			
Cardiac arrest	1	0	1
Total	7 (in 7 patients)	24 (77%) (in 13 patients)	31

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; ARDS, adult respiratory distress syndrome.

Outcomes

- Hypertonic resuscitation is safe.
- Hypertonic Resuscitation is at least equivalent to standard resuscitation.
- Within the study design, hypertonic saline demonstrated a potential benefit in the subgroup with penetrating injury and active hemorrhage.

Limitations

- No restriction on the amount of fluid given
- Underpowered
  - Patients used in analysis
    - 359
  - Projected number to achieve significant effect
    - 700
  - Given Injury severity in study population
    - 1200

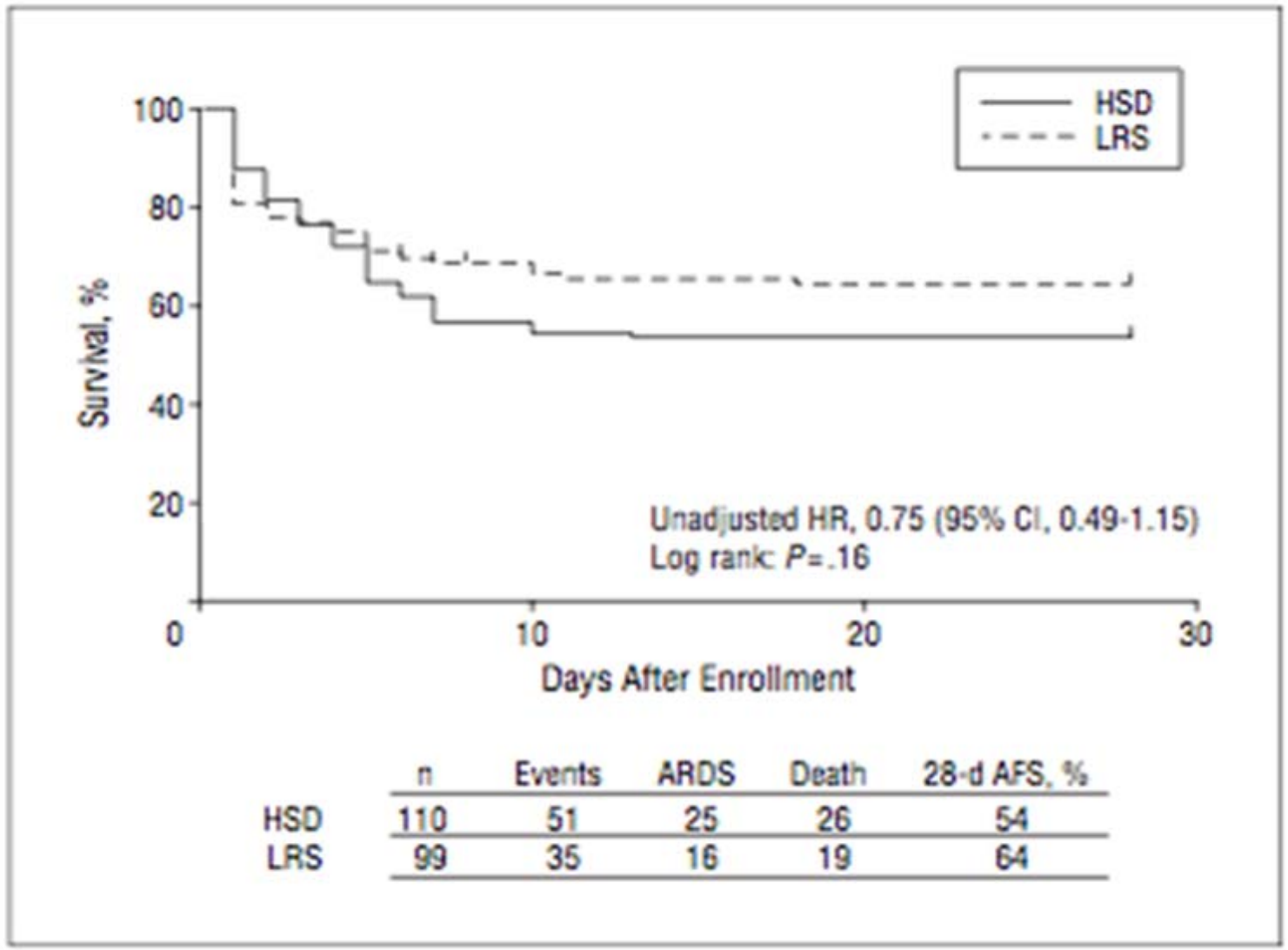
Hypertonic Resuscitation of Hypovolemic Shock After Blunt Trauma

A Randomized Controlled Trial

Eileen M. Bulger, MD; Gregory J. Jurkovich, MD; Avery B. Nathens, MD, PhD; Michael K. Copass, MD; Sandy Hanson, RN; Claudette Cooper, RN; Ping-Yu Liu, PhD; Margaret Neff, MD; Asaad B. Awan, PharmD; Keir Warner, BS; Ronald V. Maier, MD

- Single Center 2003-2005
- 250mL HSD vs 250mL LR
- 209 patients enrolled and analyzed

Primary Outcome



	n	Events	ARDS	Death	28-d AFS, %
HSD	110	51	25	26	54
LRS	99	35	16	19	64

Subgroup: Massive Transfusion

Massive Transfusion

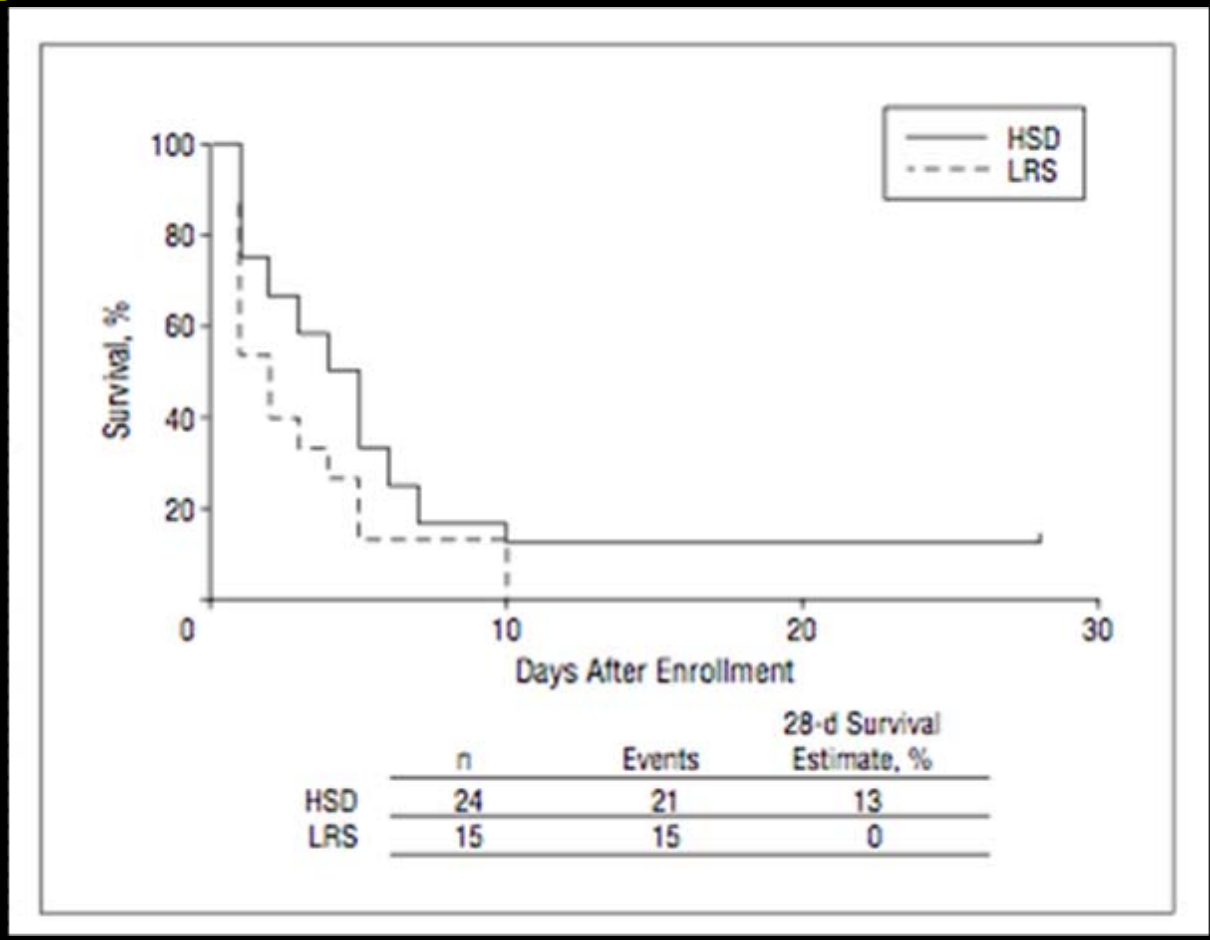
>10 U PRBCs

13% ARDS free

HDS group

0% ARDS free

LR group



	n	Events	28-d Survival Estimate, %
HSD	24	21	13
LRS	15	15	0

Outcomes and Limitations

- This study was closed secondary to futility
- The NNT for statistical significance was over 900
- Higher ISS in the HSD group
- Inclusion criteria of SBP<90 lead to enrollment of patients not at risk for ARDS

  45% of patients enrolled received no transfusions

Out-of-hospital Hypertonic Resuscitation After Traumatic Hypovolemic Shock

A Randomized, Placebo Controlled Trial

Eileen M. Bulger, MD, Susanne May, PhD*, Jeffery D. Kerby, MD, PhD†, Scott Emerson, MD, PhD*, Ian G. Stiell, MD‡, Martin A. Schreiber, MD§, Karen J. Brasel, MD, MPH‖, Samuel A. Tisherman, MD¶, Raul Coimbra, MD, PhD#, Sandro Rizoli, MD, PhD**, Joseph P. Minei, MD††, J. Steven Hata, MD‡‡, George Sopko, MD, MPH§§, David C. Evans, MD‖‖, and David B. Hoyt, MD¶¶ for the ROC investigators*

Double Blinded RCT

7.5% HS

vs.

7.5% HS plus 6% Dextran

vs.

0.9% NS

Inclusion: Prehospital SBP <70, or 71-90 with a HR >108.

Outcomes

- Primary: 28 day survival
- Secondary:
  - Fluid and Blood requirements
  - 28 day ARDS free survival
  - MOF
  - Infections

- 3726 patients needed to achieve significance
- 895 randomized

Outcomes

TABLE 2. Outcome Measures and Adverse Events

	HSD (N = 220)	HS N = 256	NS N = 376
28-d survival, n (%)	164 (74.5)	187 (73.0)	279 (74.4)
Survival at hospital discharge, n (%)	162 (74.0)	185 (72.3)	276(74.0)
ARDS-free survival to day 28, n (%)	147 (66.8)	169 (66.3)	246 (65.6)
Worst MODS score, mean (SD)§, median (1Q–3Q)	8.7 (9.8), 4 (0–24)	9.4 (9.7), 6 (0–24)	8.8 (9.7), 5 (0–24)
Ventilator-free days, mean (SD), median (1Q–3Q)	18.1 (12.3), 25 (0–29)	17.1 (12.2), 23 (0–28)	17.6 (12.4), 25 (0–29)
Days alive out of ICU to day 28, mean (SD), median (1Q–3Q)	16.3 (12.3), 22 (0–28)	15.7 (12.0), 21 (0–27)	16.0 (12.2), 21 (0–27)

Outcomes

Trial was terminated secondary to higher mortality in the HS and HSD groups that did not receive blood.

TABLE 3. Timing of Death by Transfusion Group

	HSD (N = 220)	HS (N = 256)	NS (N = 376)
0 units PRBC in first 24 h, n (%)	91 (41.6)	104 (40.8)	139 (37.1)
Died in field, n (%)	4 (1.8)	5 (2.0)	3 (0.8)
Died in field or ED, n (%)	14 (6.4)	23 (9.0)	13 (3.5)
Died within 6 h of admission, n (%)	15 (6.8)	23 (9.0)	14 (3.7)
Died within 28 d, n (%)	22 (10.0)	31 (12.2)	18 (4.8)

Limitations

- The study was stopped early secondary to safety concerns
  - ?earlier hemorrhage
  - ?late recognition of shock
- This study was underpowered
- There was no restrictions on fluids given
  - The hypertonic groups received the same amount of fluids as the control

Why Hypertonic Saline?

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  - Causes vasodilation → Reducing afterload
- Traumatic Brain Injury
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- Immune Modulation
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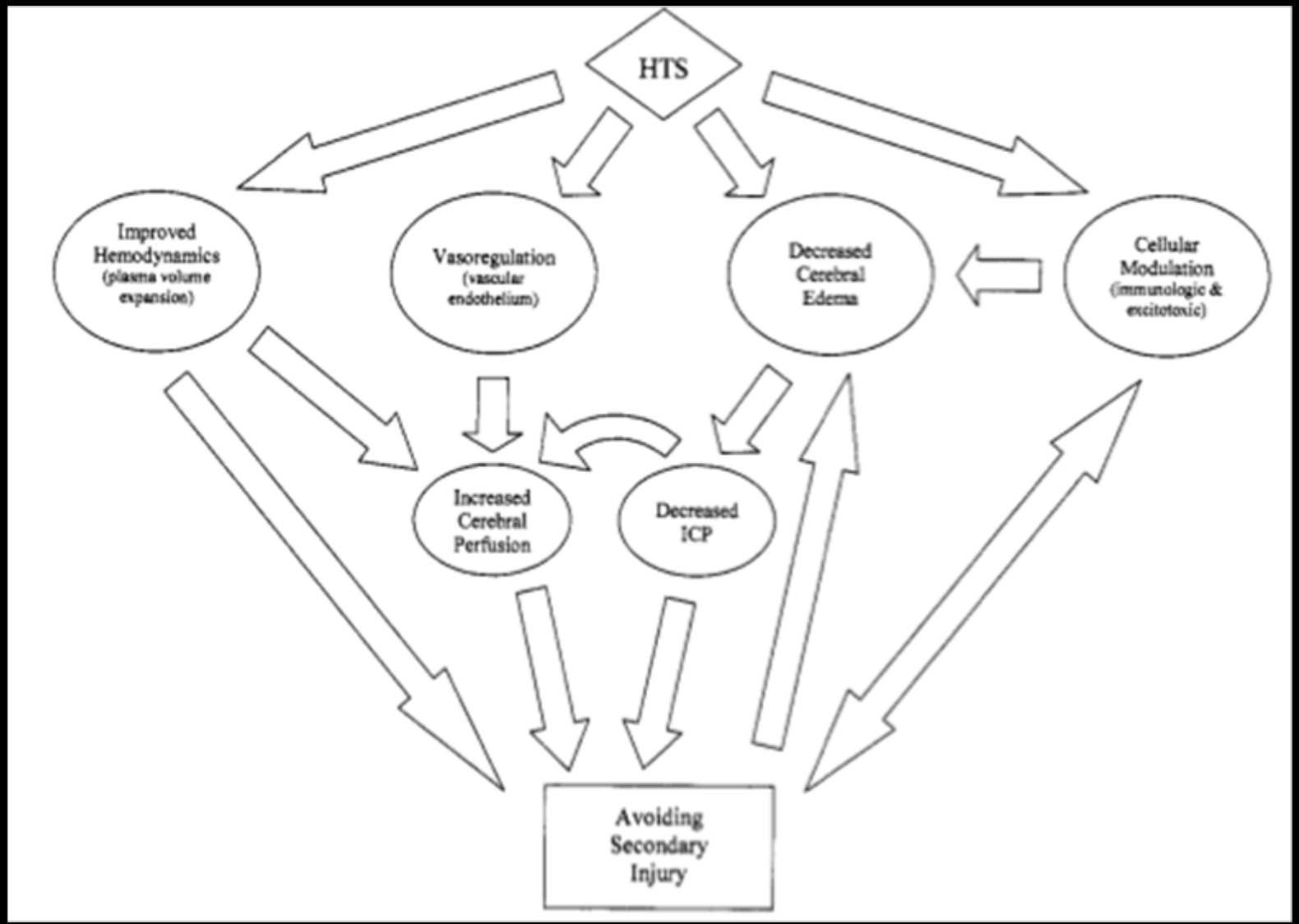
  - Enhances T-cell function

Multifactorial Cerebral Protection



Out-of-Hospital Hypertonic Resuscitation Following Severe Traumatic Brain Injury

A Randomized Controlled Trial

- RCT
- HSD vs. HS vs. NS
- Inclusion:
  - Blunt Mechanism
  - Age>15
  - GCS<8
  - Not in the hypotension arm of the study
- 1331 randomized, 1282 treated

Outcomes

- No difference in 6 month glascow outcome score
- No difference in ICU stay, 28d survival or organ dysfunction
- ICP monitors were placed in 28% of patients
  - No difference in ICPs between cohorts

Limitations

- There was no evidence of hypotension
- No standardized management for TBI
- ICPs were treated with additional HS or mannitol per surgeon preference
- Only 85% of patients were available for the 6 month analysis

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Immune Modulation with HS

J Trauma. 1997 Apr;42(4):602-6; discussion 606-7.

Hypertonic saline resuscitation decreases susceptibility to sepsis after hemorrhagic shock.

Coimbra R, Hoyt DB, Junger WG, Angle N, Wolf P, Loomis W, Evers MF.

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Gundersen Y, Ruud TEShock., Krohn CD, Sveen O, Lyngstadaas SP, Aasen AO.

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Hypertonic saline alteration of the PMN cytoskeleton: implications for signal transduction and the cytotoxic response.

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Ann Surg. 2007 Apr;245(4):635-41.

Hypertonic resuscitation modulates the inflammatory response in patients hemorrhagic shock.

J Trauma. 2007 Jan;62(1):104-11.

Bulger EM Cuschieri J Warner K Maier RV

Hypertonic saline and pentoxifylline reduce hemorrhagic shock resuscitation-induced pulmonary inflammation through attenuation of neutrophil degranulation and proinflammatory mediator synthesis.

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Ann Surg. 2006 Jan;243(1):47-57.

The immunomodulatory effects of hypertonic saline resuscitation in pati traumatic hemorrhagic shock: a randomized, controlled, double-blinded

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Rizoli SB Rhind SG Shek PN Inaba K Filips D Tien H Brenneman F Rotstein O

Hypertonic saline attenuates TNF-alpha-induced NF-kappaB activation in pulmonary epithelial cells.

Nydam TL Moore EE McIntyre RC Jr Wright FL Gamboni-Robertson F Eckels PC Banerjee A

Hypertonic Resuscitation Modulates the Inflammatory Response in Patients With Traumatic Hemorrhagic Shock

Eileen M. Bulger, MD, Joseph Cuschieri, MD, Keir Warner, BS, and Ronald V. Maier, MD

- Prehospital RCT of blunt abdominal trauma

7.5%HS/6%Dextran

vs.

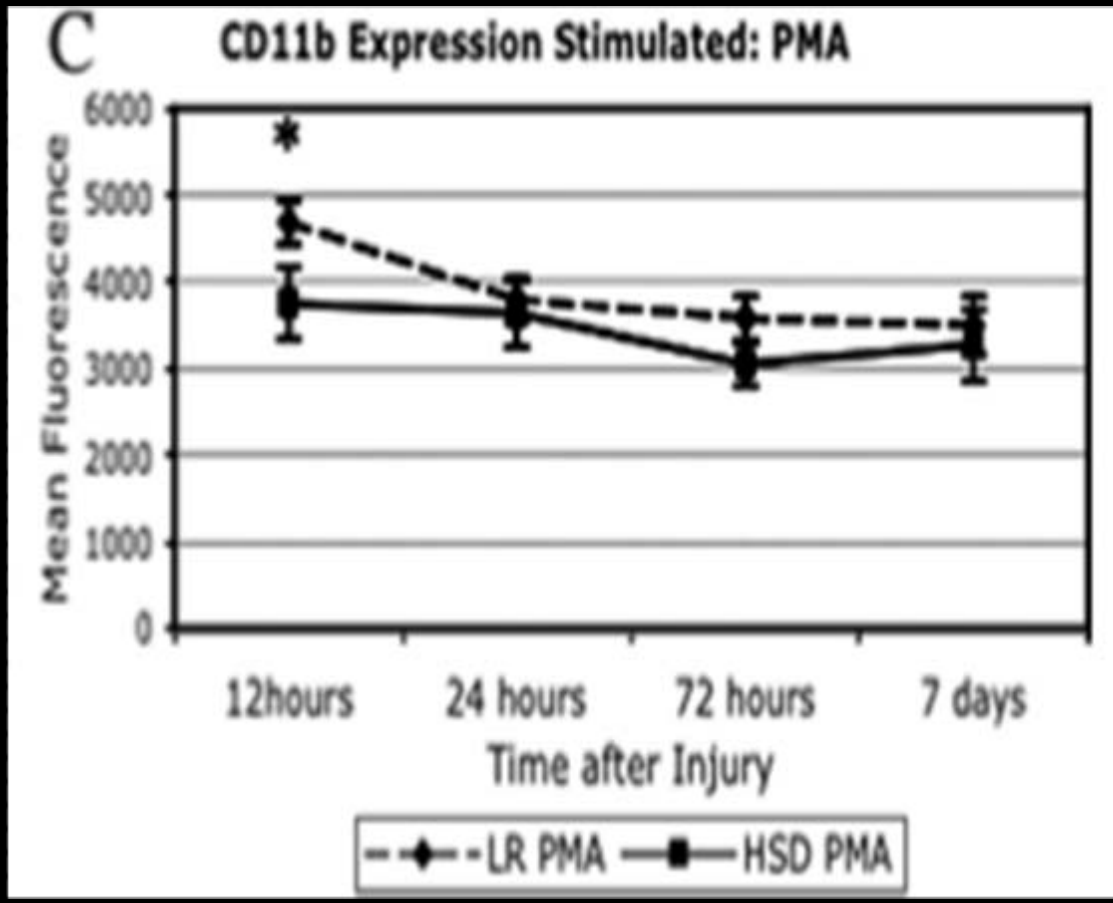
LR

- PMN Activation, CD 11b Surface expression, and Monocyte Activation studied

- Inclusion: blunt trauma, age>18, SBP<90

Outcomes

- No difference in PMN activation
- 1.5 fold increase in CD11b expression with LR
- CD11b with HSD was equal to healthy controls
- No sig difference in TNFα or IL-6



Outcomes

- All injured patients had a reduction in cytokine response
- Patients treated with HSD were less blunted than the std group

TABLE 3. Comparison of PBMC Cytokine Response to LPS Between Patients (12 Hours After Injury) and Normal Controls

	Normal; LPS (n = 20)	12-Hour HSD; LPS (% of NL) (n = 36)	12-Hour LR; LPS (% of NL) (n = 26)
TNF-α (pg/mL)	5542	4063 (73%)*	3195 (58%)*
IL-1β (pg/mL)	11619	7026 (60%)*	4103 (35%)*
IL-6 (pg/mL)	6234	5034 (81%)*	4752 (76%)*
IL-10 (pg/mL)	1115	476 (43%)*	334 (30%)*
IL-12 (pg/mL)	154	53 (34%)*	33 (21%)*

Conclusions

- Hypertonic resuscitation has been shown to have great potential for trauma resuscitation in vitro and animal models.
- Unfortunately, this has not been demonstrated in clinical trials for a variety of reasons.
- All the trials conducted to date, have utilized a single infusion of 250mL of HS/HSD with otherwise standard resuscitation

Future Directions

A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis

Mark R. Elkins, M.H.Sc., Michael Robinson, Ph.D., Barbara R. Rose, Ph.D., Colin Harbour, Ph.D., Carmel P. Moriarty, R.N., Guy B. Marks, Ph.D., Elena G. Belousova, M.Appl.Sc., Wei Xuan, Ph.D., and Peter T.P. Bye, Ph.D., for the National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group*

- Inhaled HS has been shown to decrease exacerbations in CF patients secondary to macrophage attenuation
- Possible translation into our trauma populations with inhaled HS in ARDS

Thank You

Aerosolized Hypertonic Saline Attenuates Lung Injury Following Hemorrhagic Shock.

Max Wohlauer, M.D., Ernest E. Moore, M.D., Miguel Fragoso, D.V.M.,
John Eun, M.D., Carlton C. Barnett, M.D. and Anirban Banerjee, PhD.

Rocky Mountain Regional Trauma Center at Denver Health Medical Center,
University of Colorado, Denver, CO.

ABSTRACT

jective: Intestinal ischemia and reperfusion play a central role in
te lung injury (ALI) and subsequent multiple organ failure (MOF)
wing hemorrhagic shock. Intravenous hypertonic saline (HTS)
ulates inflammation and can attenuate ALI/MOF, however, lung-
cted HTS therapy may be less prone to systemic complications
has not yet been investigated. We hypothesized that inhaled,
solized hypertonic saline therapy given at the onset of
scitation will decrease acute lung injury following hemorrhagic

RESULTS