Hypertonic Saline Resuscitation: The Way of The Future

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Surgical Grand Rounds
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Intravenous Saline

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 injury...
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 trauma
  - Enhances T-cell function
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**

<table>
<thead>
<tr>
<th>Epidemiologic Condition</th>
<th>HSD n</th>
<th>HSD %</th>
<th>STD n</th>
<th>STD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>153</td>
<td>73</td>
<td>151</td>
<td>72</td>
</tr>
<tr>
<td>Blunt</td>
<td>54</td>
<td>26</td>
<td>57</td>
<td>27</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51</td>
<td>28</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Black</td>
<td>71</td>
<td>39</td>
<td>77</td>
<td>44</td>
</tr>
<tr>
<td>Other</td>
<td>62</td>
<td>34</td>
<td>62</td>
<td>35</td>
</tr>
<tr>
<td>Males (% male)</td>
<td>184</td>
<td>83</td>
<td>175</td>
<td>85</td>
</tr>
</tbody>
</table>

- Age: 182, 34 ± 12
- Injury severity score: 184, 19 ± 13
- TRISS (Prob surv): 171, 0.84 ± 0.29
- Revised trauma score: Preinfusion, 172, 5.98 ± 1.61
- Emergency center, 149, 7.43 ± 0.97

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

![Graph showing survival rates over time](image.png)

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

<table>
<thead>
<tr>
<th>Complication</th>
<th>HSD</th>
<th>STD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specified in protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ARDS</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dead bowel</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
<td>24 (77%)</td>
<td>31</td>
</tr>
</tbody>
</table>

(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

Unadjusted HR, 0.75 (95% CI, 0.49-1.15)
Log rank: P = .16

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>ARDS</th>
<th>Death</th>
<th>28-d AFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSD</td>
<td>110</td>
<td>51</td>
<td>25</td>
<td>26</td>
<td>54</td>
</tr>
<tr>
<td>LRS</td>
<td>99</td>
<td>35</td>
<td>16</td>
<td>19</td>
<td>64</td>
</tr>
</tbody>
</table>
Subgroup: Massive Transfusion

Massive Transfusion

>10 U PRBCs
13% ARDS free

HDS group
0% ARDS free

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

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

<table>
<thead>
<tr>
<th>TABLE 3. Timing of Death by Transfusion Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HSD (N = 220)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>0 units PRBC in first 24 h, n (%)</td>
</tr>
<tr>
<td>Died in field, n (%)</td>
</tr>
<tr>
<td>Died in field or ED, n (%)</td>
</tr>
<tr>
<td>Died within 6 h of admission, n (%)</td>
</tr>
<tr>
<td>Died within 28 d, n (%)</td>
</tr>
</tbody>
</table>
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?

- 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 trauma
  - Enhances T-cell function
Multifactorial Cerebral Protection

Diagram:
- Improved Hemodynamics (plasma volume expansion)
- Vasoregulation (vascular endothelium)
- Decreased Cerebral Edema
- Cellular Modulation (immunologic & excitotoxic)
- Increased Cerebral Perfusion
- Decreased ICP
- Avoiding Secondary Injury

Connections:
- HTS

Flow direction:
- Improved Hemodynamics to HTS
- Vasoregulation to HTS
- Decreased Cerebral Edema to HTS
- Cellular Modulation to HTS
- Increased Cerebral Perfusion to HTS
- Decreased ICP to HTS
- Avoiding Secondary Injury to HTS
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 Glasgow 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
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 trauma
  - Enhances T-cell function
Immune Modulation with HS

Hypertonic saline resuscitation decreases susceptibility to sepsis after hemorrhagic shock.

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

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

Ciesla DJ, Moore EE, Musters RJ, Biffl WL, Silliman CA.

Hypertonic resuscitation modulates the inflammatory response in patients with hemorrhagic shock.

Brulger EM, Guschisch J, Warden K, Mager RV.

The immunomodulatory effects of hypertonic saline resuscitation in patients with traumatic hemorrhagic shock: a randomized, controlled, double-blinded study.

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

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

*Significantly different (p < 0.05)
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
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, Ph.D.

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

Abstract

Objective: Intestinal ischemia and reperfusion play a central role in acute lung injury (ALI) and subsequent multiple organ failure (MOF) resulting from hemorrhagic shock. Intravenous hypertonic saline (HTS) suppresses inflammation and can attenuate ALI/MOF; however, lung-protected HTS therapy may be less prone to systemic complications than systemic HTS therapy. We hypothesized that inhaled, aerosolized hypertonic saline therapy given at the onset of reperfusion will decrease acute lung injury following hemorrhagic shock.