UPDATES ON HYPERTONIC SALINE IN TRAUMA RESUSCITATION

Dr. Wan Nasrudin bin Wan Ismail
Consultant Intensivist
Hosp.Raja Perempuan Zainab II, KB
Traumatic injury

- Traumatic injury - leading cause of death between the ages of 1 and 40
- An estimated five million people die per year worldwide from traumatic injuries
- The biggest cause of preventable death is early hemorrhage within the first 6 hours of injury
- 10 to 20% of these deaths are potentially preventable.

TRAFFIC FATALITY CAUSES AND TRENDS IN MALAYSIA

by Akmal Abdelfatah
Civil Engineering Department, American University of Sharjah
LECTURE OUTLINE
Lecture outline

- Introduction to hypertonic saline (HS)
- Trauma resuscitation – Role of fluid
- Benefit of Hypertonic saline (HS) in trauma resuscitation
  - Small volume resuscitation
  - Reduction of tissue oedema
  - immunomodulation
- Current evidence
- Take home message
HYPERTONIC SALINE

3% Sodium Chloride Injection USP
500mL

Each 190 mL contains 3 g Sodium Chloride USP.
PH may have been adjusted with hydrochloric acid.
PH 5.0 (4.5 to 7.0) mEq/L. Sodium 513, Chloride 531.
Osmolarity 1027 mOsm/kg, (calc). Hypertonic May cause
Adohtes may be incompatible. Consult with pharmacist if
available. When introducing additives use aseptic technique
as directed by a physician. See directions. Cautions:
Squeeze and inspect inner bag which maintains product sterility.
Discard if leaks are found. Must not be used in series
connections. Do not use unless solution is clear. Rx Only.
Store unit in moisture barrier overwrap at room
temperature (25°C/77°F) until ready to use. Avoid
excessive heat. See insert.

Baxter Healthcare Corporation
Deerfield, IL 60015 USA
MADE IN USA

281353
NDC 0338-6205-83

ASMIC 2017
<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity (mOsmol.l(^{-1}))</th>
<th>Sodium concentration (mmol.l(^{-1}))</th>
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<tr>
<td>0.9% normal saline</td>
<td>308</td>
<td>154</td>
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<tr>
<td>Ringer’s lactate</td>
<td>275</td>
<td>130</td>
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<tr>
<td>1.7% saline</td>
<td>291</td>
<td>582</td>
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<tr>
<td>3% saline</td>
<td>1026</td>
<td>513</td>
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<tr>
<td>7.2% saline/6% Haes (200/0.6)</td>
<td>2464</td>
<td>1232</td>
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<tr>
<td>7.5% saline</td>
<td>2566</td>
<td>1283</td>
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<tr>
<td>7.5% saline/6% dextran 70</td>
<td>2568</td>
<td>1283</td>
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<tr>
<td>10% saline</td>
<td>3424</td>
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<td>4004</td>
</tr>
<tr>
<td>30% saline</td>
<td>10 000</td>
<td>5000</td>
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</table>
OBSERVATIONS ON THE INHIBITORY INFLUENCE EXERTED BY HYPERTONIC SALINE SOLUTIONS AND CALCIUM CHLORIDE SOLUTIONS ON THE ACTION OF SPECIFIC HAEMOLYSINS, WITH SUGGESTIONS AS TO THE THERAPY OF BLACKWATER FEVER

By Major W. D. SUTHERLAND, M.D., I.M.S., on special duty at the Medical College, Calcutta, and Captain D. McCAY, M.B., I.M.S., Professor of Physiology, Medical College, Calcutta.

From the Physiological Laboratories, Medical College, Calcutta

(Received October 23rd, 1909)
EXPERIMENTAL ALTERATION OF BRAIN BULK

LEWIS H. WEED, Capt., Med. Corps

AND

PAUL S. MCKIBBEN, 1st Lt., San. Corps

From The Army Neuro-Surgical Laboratory, Johns Hopkins Medical School, Baltimore, Maryland

Received for publication March 22, 1919
TRAUMA RESUSCITATION
Fluid resuscitation in trauma and burn

- First line: isotonic or near isotonic crystalloid such as 0.9% saline or ringer’s lactate (ATLS and American Burn Association)

- Goals: to provide intravascular volume expansion and restore organ perfusion
- Damage control resuscitation
- Permissive hypotension

J Trauma. 2006; 60(suppl)
J Trauma. 2008; 64:1638-50
POTENTIAL ROLES OF HYPERTONIC SALINE IN TRAUMA RESUSCITATION
Potential benefit of HS in resuscitation

- Rapid expansion of intravascular volume
- Reduction of endothelial and tissue edema that improves microcirculation
- Improvement of blood viscosity caused by hemodilution
- Increased myocardial contractility
- Reduce organ failure
- Ability to modulate immune response
Proposed mech of Hypertonic saline

HTS

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

Avoiding Secondary Injury
DOES INTRAVENOUS HYPERTONIC SALINE INCREASE BLOOD PRESSURE AND SURVIVAL IN HYPOTENSIVE STATES?
Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure*

G. F. Strandvik

Specialist Registrar in Anaesthesia and Intensive Care Medicine, South Eastern School of Anaesthesia, London, UK

- HS in critical care
- Blood pressure restoration and outcome benefit in both haemorrhagic and non-haemorrhagic shock, and the management of raised intracranial pressure.
- Issues of clinical improvement and outcome benefit are addressed

Anaesthesia, 2009, 64, pages 990–1003
# REVIEW ARTICLE

Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure*

G. F. Strandvik

*Specialist Registrar in Anaesthesia and Intensive Care Medicine, South Eastern School of Anaesthesia, London, UK

<table>
<thead>
<tr>
<th>Study</th>
<th>Type and quality</th>
<th>Clinical scenario (patient numbers in parentheses)</th>
<th>Interventions</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNamara [38]</td>
<td>Cohort (2–)</td>
<td>Trauma (60)</td>
<td>3% HS vs 50% glucose vs mannitol vs NS</td>
<td>Blood pressure**</td>
</tr>
<tr>
<td>Holcroft [96]</td>
<td>RCT (1++)</td>
<td>Trauma (32)</td>
<td>7.5% HSD vs RL</td>
<td>Mortality, fluid balance, blood pressure</td>
</tr>
<tr>
<td>Maringas [93]</td>
<td>Cohort (2–) pilot study</td>
<td>Trauma (pre-hospital) (48)</td>
<td>7.5% HSD vs Plasmalyte B</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Mattos [63]</td>
<td>RCT (1+)</td>
<td>Trauma (pre-hospital) (422)</td>
<td>7.5% HSD vs NS</td>
<td>Mortality, fluid balance, blood pressure</td>
</tr>
<tr>
<td>Vassar [39]</td>
<td>RCT (1++)</td>
<td>Trauma (pre-hospital) (166)</td>
<td>7.5% HSD vs RL</td>
<td>Mortality, fluid balance, blood pressure**</td>
</tr>
<tr>
<td>Younes [40]</td>
<td>RCT (1–)</td>
<td>Trauma (105)</td>
<td>7.5% HS vs HSD vs NS</td>
<td>Mortality, fluid balance, blood pressure**</td>
</tr>
<tr>
<td>Vassar [41]</td>
<td>RCT (1+)</td>
<td>Trauma (258)</td>
<td>7.5% HS vs 7.5% HSD vs NS</td>
<td>Mortality†, fluid balance, blood pressure**</td>
</tr>
<tr>
<td>Vassar [44]</td>
<td>RCT (1+)</td>
<td>Trauma (pre-hospital) (194)</td>
<td>7.5% HSD vs 7.5% HSD vs 7.5% HSD (12%) vs RL</td>
<td>Mortality†, blood pressure**</td>
</tr>
<tr>
<td>Younes [42]</td>
<td>RCT (1+)</td>
<td>Trauma (212)</td>
<td>7.5% HSD vs NS</td>
<td>Mortality†, fluid balance, blood pressure**</td>
</tr>
<tr>
<td>Alpar [43]</td>
<td>RCT (1–)</td>
<td>Trauma (180)</td>
<td>7.5% HSD vs RL</td>
<td>Mortality, fluid balance, blood pressure**</td>
</tr>
<tr>
<td>Bulger [65]</td>
<td>RCT (1–)</td>
<td>Trauma (209)</td>
<td>7.5% HSD vs RL</td>
<td>Mortality, ARDS-free survival</td>
</tr>
<tr>
<td>Wade [60]</td>
<td>Meta-analysis</td>
<td>Trauma (604)</td>
<td>7.5% HSD vs RL</td>
<td>Mortality†</td>
</tr>
<tr>
<td>Perel [62]</td>
<td>Meta-analysis</td>
<td>Trauma (1283)</td>
<td>7.5% HSD vs NS</td>
<td>Mortality</td>
</tr>
<tr>
<td>Wade [45]</td>
<td>Meta-analysis</td>
<td>Trauma (penetrating) (230)</td>
<td>7.5% HSD vs NS</td>
<td>Mortality, blood pressure**</td>
</tr>
<tr>
<td>Bunn [61]</td>
<td>Meta-analysis</td>
<td>Trauma, burns and general surgery (including head injury) (956)</td>
<td>HS vs NS or RL</td>
<td>Mortality, neurological outcome</td>
</tr>
</tbody>
</table>
Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure*

G. F. Strandvik

Specialist Registrar in Anaesthesia and Intensive Care Medicine, South Eastern School of Anaesthesia, London, UK

Current evidence confirms that hypertonic saline is effective in raising blood pressure in hypovolaemic shock (Grade A), and is probably of benefit in non-obstructive cardiogenic shock (Grade C).

No survival benefit for HS in shock state.
11 RCT’s (4 ED’s and 7 Prehosp setting)
- trauma patients with hypotension were included
- Randomised to hypertonic saline solutions (7.5% HS (HS7.5%) and dextran 70 (HSD) or isotonic crystalloid solutions
- Study endpoint: Patient’s survival and organ failure
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Resuscitation fluid</th>
<th>End point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[32]</td>
<td>20 pre-hospital trauma patients with SBP ≤ 100 mmHg</td>
<td>HSD or LR</td>
<td>Survival to hospital discharge and hemodynamic variables</td>
<td>Improved SBP and overall survival rate.</td>
</tr>
<tr>
<td>[33]</td>
<td>32 trauma patients with a SBP &lt; 80 mm Hg admitted to ED</td>
<td>HSD or LR</td>
<td>Survival to hospital discharge and hemodynamic variables</td>
<td>There were no differences in survival rate.</td>
</tr>
<tr>
<td></td>
<td><strong>Prog Clin Biol Res. 1989;299:331–8</strong></td>
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<tr>
<td>[34]</td>
<td>106 trauma patients with SBP &lt;80 mm Hg for 6 % HSD or &lt; 90 mmHg for H5 and</td>
<td>H5 or HSD or</td>
<td>Survival to hospital discharge and hemodynamic variables</td>
<td>There were no differences in overall survival between any of the groups.</td>
</tr>
<tr>
<td></td>
<td>were 18 years or older admitted to ED</td>
<td>LR</td>
<td></td>
<td></td>
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<tr>
<td>[35]</td>
<td>422 pre-hospital trauma patients ≥ 16 years with SBP ≤ 90 mmHg</td>
<td>HSD or LR</td>
<td>Primary end points included: survival at 24 h and 30 days (if possible).</td>
<td>In the HSD 6 % group which requiring surgery: there was a significant</td>
</tr>
<tr>
<td></td>
<td>72 % of participants had sustained penetrating trauma</td>
<td></td>
<td>Secondary end points included: complications and safety of HSD</td>
<td>treatment effect in favor of HSD 6 % (p = 0.02). This effect was</td>
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<tr>
<td></td>
<td><strong>Ann Surg. 1991;213(5):482–91</strong></td>
<td></td>
<td></td>
<td>significant in those patients sustaining penetrating trauma (p = 0.01),</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>but not in those with blunt trauma.</td>
</tr>
<tr>
<td>[36]</td>
<td>166 pre-hospital trauma patients with SBP ≤ 90 mmHg</td>
<td>HSD or LR</td>
<td>Survival to hospital discharge and hemodynamic variables</td>
<td>There was no difference in overall survival and there is a trend to</td>
</tr>
<tr>
<td></td>
<td><strong>Arch Surg. 1991;126(9):1065–72</strong></td>
<td></td>
<td></td>
<td>improve survival in patients with severe head injuries.</td>
</tr>
<tr>
<td>[37]</td>
<td>105 trauma patients ≥ 18 years with SBP &lt; 80 mm Hg admitted to ED</td>
<td>HSD or HS or NS</td>
<td>Survival to hospital discharge, hemodynamic variables</td>
<td>There were no significant differences in overall complication and</td>
</tr>
<tr>
<td></td>
<td><strong>Surgery. 1992;111(4):380–5</strong></td>
<td></td>
<td></td>
<td>mortality rates in the three groups.</td>
</tr>
<tr>
<td>[38]</td>
<td>194 pre-hospital trauma patients with SBP &lt; 90 mm</td>
<td>HSD or HS or LR</td>
<td>Survival to hospital discharge, hemodynamics variables, MTOS and</td>
<td>Overall survival in the four treatment groups was not statistically</td>
</tr>
<tr>
<td></td>
<td><strong>Arch Surg. 1993;128(9):1003–11</strong></td>
<td></td>
<td>neurological outcome scores</td>
<td>significant. Survival in the hypertonic group, however, was</td>
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<td>significantly higher than that predicted by the MTOS norms. The survival</td>
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<td></td>
<td>rate in the H5 group was higher than that in the LR group for the</td>
</tr>
</tbody>
</table>

Glasgow Coma Scale scores of 8 or less (P < .05 by logistic regression and P < .01)
[39] 258 pre-hospital trauma patients with SBP < 90 mm Hg.

J Trauma. 1993;34(5):622–32

HSD or HS or NS
Survival to hospital discharge, hemodynamics variables, MTOS and neurological outcome scores

[40] 212 hypovolemic shock patients admitted to ED


HSD or NS
Survival at 24 h and 30 days and complications

[41] 209 pre-hospital blunt trauma patients with SBP ≤90 mm Hg

"The study was stopped for futility after the second interim analyses."


HSD or LR
Primary outcome was 28 day ARDS-free survival. Secondary outcome; nosocomial infection, multiple organ failure syndrome

[42] 853 pre-hospital hypovolemic shock patients with SBP ≤ 70 mm Hg or center SBP = 71–90 mm Hg with HR equal or higher than 108 beats per minute. (62 % of patients were with blunt trauma.)

"The study was stopped early (23 % of proposed sample size) for futility and potential safety concern."


HSD or HS or NS
Primary outcome was 28 day survival. Secondary outcomes included: fluid and blood requirements in the first 24 h, physiologic parameters of organ dysfunction, 28 day ARDS-free survival, multiple organ dysfunction score and nosocomial infections

There were no differences in overall survival. Improved survival vs. predicted MTOS in high-risk HS & HSD 6 % patients, HS patient with GCS 8 or less and HSD 6 % patients with unobtainable BP at the time of randomization.

The 24 h survival rate was significantly higher in HSD 6 % (87 %) compared with NS (72 %) (P < .007). HSD 6 % improved long term survival rate significantly only in the patients with MAP < 70 mmHg (p < .01).

There was no significant difference in ARDS-free survival. There was an improved in ARDS-free survival in the patients (19 % of the population) requiring 10 U or more of packed RBC in the first 24 h. (HR, 2.18; 95 % CI, 1.09–4.36).

There was no significant difference in 28 day survival between treatment groups. There was a higher mortality for the post-randomization subgroup of patients who did not receive blood transfusions in the first 24 h, who received hypertonic fluids compared to NS (P < .001).

There were no differences between groups in organ failure or nosocomial infections.
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Description</th>
<th>Outcome</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>[40]</td>
<td>212 hypovolemic shock patients admitted to ED</td>
<td>HSD or NS</td>
<td>Survival at 24 h and 30 days and complications. The 24 h survival rate was significantly higher in HSD 6% (87%) compared with NS (72%) (P &lt; .007). HSD 6% improved long term survival rate significantly only in the patients with MAP &lt; 70 mmHg (P &lt; .01).</td>
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<td>[41]</td>
<td>209 pre-hospital blunt trauma patients with SBP ≤ 90 mm Hg. “The study was stopped for futility after the second interim analyses.”</td>
<td>HSD or LR</td>
<td>Primary outcome was 28 day ARDS-free survival. Secondary outcome; nosocomial infection, multiple organ failure syndrome. There was no significant difference in ARDS-free survival. There was an improved in ARDS-free survival in the patients (19% of the population) requiring 10 U or more of packed RBC in the first 24 h. (HR, 2.18; 95% CI, 1.09–4.36).</td>
</tr>
<tr>
<td>[42]</td>
<td>853 pre-hospital RCT, hypovolemic shock patients multi center SBP 71–90 mm Hg with HR equal or higher than 108 beats per minute. (62% of patients were with blunt trauma. “The study was stopped early (23% of proposed sample size) for futility and potential safety concern.”</td>
<td>HSD or HS or NS</td>
<td>Primary outcome was 28 day survival. Secondary outcomes included: fluid and blood requirements in the first 24 h, physiologic parameters of organ dysfunction, 28 day ARDS-free survival, multiple organ dysfunction score and nosocomial infections. There was no significant difference in 28 day survival between treatment groups. There was a higher mortality for the post-randomization subgroup of patients who did not receive blood transfusions in the first 24 h, who received hypertonic fluids compared to NS (P &lt; .01). There were no differences between groups in organ failure or nosocomial infections.</td>
</tr>
</tbody>
</table>

HSD dextran 70 in HS. HS hypertonic saline 7.5%. NS 0.9% saline. LR ringer's lactate. SBP systolic blood pressure. MAP mean arterial pressure. MTOS major trauma outcome study. BP blood pressure. RTS revised trauma score. ARDS acute respiratory distress syndrome. CI confidence interval. HR hazard ratio. RBC red blood cells. HR heart rate. RCT randomized clinical study. ED emergency department.
PROGNOSTIC FACTORS TO PREDICT OUTCOME FOLLOWING THE ADMINISTRATION OF HYPERTONIC/HYPERONCOTIC SOLUTION IN HYPOVOLEMIC PATIENTS

Riad N. Younes, Frederico Aun, Chan T. Ching, Dov C. Goldenberg, Márcia H. Franco, Flávio K. Miura, Sigrid S. Santos, Iara M.M. Sequeiros, Maurício Rocha e Silva, Ikurou Fujimura, and Dario Birolini

Trauma Service, Department of Surgery, University of São Paulo School of Medicine; and Department of Thoracic Surgery, Hospital A.C. Camargo, São Paulo, Brazil

Received 8/2/96; accepted in the final form 10/15/96.

ABSTRACT—Hypertonic solutions effectively improve hemodynamic parameters in patients admitted to the emergency room. However, no significant differences in outcome were observed compared with standard isotonic treatment in most previously published studies. This study evaluates pretreatment prognostic factors that predict a beneficial effect of hypertonic solution in patients admitted to the emergency room with hemorrhagic hypovolemia in a prospective double-blind fashion. The patients \( n = 212 \) were randomized upon admission to receive 250 mL intravenous (i.v.) bolus of hypertonic 7.5% NaCl + 6% dextran (HSD, \( n = 101 \)), or isotonic 0.9% NaCl solutions (IS, \( n = 111 \)) as the first treatment, followed by standard resuscitation. Pretreatment factors assessed were sex, age, cause of hypovolemia, revised trauma score (RTS), Glasgow index, and mean arterial pressure (MAP) on admission. Both groups were compared for survival at 24 h and 30 days postadmission. Infused volumes were registered. HSD administration significantly increased MAP and reduced i.v. crystalloid infusions to maintain hemodynamic parameters, compared with IS. There was no difference between groups in the number of blood transfusions administered. Overall complication rates in both groups were similar (24%). There was a significant difference \( (p < .03) \) in overall (30 days) survival rate between HSD (73%) and IS (64%) groups. The 24 h survival rate was significantly lower in IS (72%) compared with HSD (87%); \( p < .01 \). Multivariate analyses showed that RTS and MAP were identified as independent predictors for 24 h survival in the group that received HSD. When evaluated for overall survival rate, hypertonic infusion benefited significantly only patients with MAP <70 mmHg \( (p < .01) \).
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ABSTRACT—Hypertonic solutions effectively improve hemodynamic parameters in patients admitted to the emergency room. However, no significant differences in outcome were observed compared with solutions administered. Overall complication rates in both groups were similar (24%). There was a significant difference ($p < .03$) in overall (30 days) survival rate between HSD (73%) and IS (64%) groups. The 24 h survival rate was significantly lower in IS (72%) compared with HSD (87%); $p < .01$. Multivariate analyses showed that RTS and MAP were identified as independent predictors for 24 h survival in the group that received HSD. When evaluated for overall survival rate, hypertonic infusion benefited significantly only patients with MAP $< 70$ mmHg ($p < .01$).
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

Objective—to determine whether out-of-hospital administration of hypertonic fluids would improve survival after severe injury with hemorrhagic shock.

Background—Hypertonic fluids have potential benefit in the resuscitation of severely injured patients because of rapid restoration of tissue perfusion, with a smaller volume, and modulation of the inflammatory response, to reduce subsequent organ injury.

Methods—Multicenter, randomized, blinded clinical trial, May 2006 to August 2008, 114 emergency medical services agencies in North America within the Resuscitation Outcomes Consortium. Inclusion criteria: injured patients, age ≥15 years with hypovolemic shock (systolic blood pressure ≤70 mm Hg or systolic blood pressure 71–90 mm Hg with heart rate ≥108 beats per minute). Initial resuscitation fluid, 250 mL of either 7.5% saline per 6% dextran 70 (hypertonic saline/dextran, HSD), 7.5% saline (hypertonic saline, HS), or 0.9% saline (normal saline, NS) administered by out-of-hospital providers. Primary outcome was 28-day survival. On the recommendation of the data and safety monitoring board, the study was stopped early (23% of proposed sample size) for futility and potential safety concern.

Results—a total of 853 treated patients were enrolled, among whom 62% were with blunt trauma, 38% with penetrating. There was no difference in 28-day survival—HSD: 74.5% (0.1; 95% confidence interval [CI], −7.5 to 7.8); HS: 73.0% (−1.4; 95% CI, −8.7–6.0); and NS: 74.4%, P = 0.91. There was a higher mortality for the postrandomization subgroup of patients who did not
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

Objective—To determine whether out-of-hospital administration of hypertonic fluids would improve survival after severe injury with hemorrhagic shock.

RCT, multi-center 853 pre-hospital hypovolemic shock patients with SBP ≤ 70 mm Hg or SBP ≈ 71–90 mm Hg with HR equal or higher than 108 beats per minute. (62% of patients were with blunt trauma.)

“The study was stopped early (23% of proposed sample size) for futility and potential safety concern.”

HSD or HS or NS Primary outcome was 28 day survival. Secondary outcomes included: fluid and blood requirements in the first 24 h, physiologic parameters of organ dysfunction, 28 day ARDS–free survival, multiple organ dysfunction score and nosocomial infections

recommendation of the data and safety monitoring board, the study was stopped early (23% of proposed sample size) for futility and potential safety concern.

Results—A total of 853 treated patients were enrolled, among whom 62% were with blunt trauma, 38% with penetrating. There was no difference in 28-day survival—HSD: 74.5% (0.1; 95% confidence interval [CI], −7.5 to 7.8); HS: 73.0% (−1.4; 95% CI, −8.7–6.0); and NS: 74.4%, P = 0.91. There was a higher mortality for the postrandomization subgroup of patients who did not
Objective—To determine whether out-of-hospital administration of hypertonic fluids would improve survival after severe injury with hemorrhagic shock.

Background—Hypertonic fluids have potential benefit in the resuscitation of severely injured patients, and could help improve outcomes of hemorrhagic shock, with a smaller volume, and modulation of the inflammatory response, to reduce subsequent organ injury.

Methods—Multicenter, randomized, blinded clinical trial, May 2006 to August 2008, 114 emergency centers from 42 countries in North America within the Resuscitation Outcomes Consortium. Inclusion criteria: injured patients, age ≥ 15 years with hypovolemic shock (systolic blood pressure ≤ 90 mmHg or systolic blood pressure < 70 mmHg with heart rate ≥ 108 beats per minute), Initial resuscitation fluid, 250 mL of either 7.5% saline per 6% dextran 70 (hypertonic saline/dextran, HSD), 7.5% saline (hypertonic saline, HS), or 0.9% saline (normal saline, NS) administered over 1 hour, was compared to NS in 28-day survival. On the recommendation of the data and safety monitoring board, the study was stopped early (23% of proposed) because of the potential safety concern.

Results—A total of 853 treated patients were enrolled, among whom 62% were with blunt trauma, 38% with penetrating. There was no difference in 28-day survival—HSD: 74.5% (0.1; 95% confidence interval [CI], −7.5 to 7.8); HS: 73.0% (−1.4; 95% CI, −8.7–6.0); and NS: 74.4%, P = 0.91. There was a higher mortality for the postrandomization subgroup of patients who did not

No difference in 28-day survival—HSD: 74.5%; HS: 73.0%; P = 0.91.

Higher mortality
- did not receive blood transfusions in the first 24 hours,
- who received hypertonic fluids compared to NS, P < 0.01].
Potential benefit of HS in resuscitation

- Rapid expansion of intravascular volume
- Reduction of endothelial and tissue edema that improves microcirculation
- Improvement of blood viscosity caused by hemodilution
- Increased myocardial contractility
- Reduce organ failure
- Ability to modulate immune response

Clinics. 2005;60(2):159–72
Anaesthesia. 2009;64(9):990–1003.
Chasing 100%: The use of hypertonic saline to improve early, primary fascial closure after damage control laparotomy

John A. Harvin, MD, Mark M. Mims, BS, Juan C. Duchesne, MD, Charles S. Cox, Jr., MD, Charles E. Wade, PhD, John B. Holcomb, MD, and Bryan A. Cotton, MD, MPH, Houston, Texas

BACKGROUND: Failure to achieve fascial closure after damage control laparotomy (DCL) is associated with increased morbidity and long-term disability. In addition, early closure is associated with reduces infectious, wound, and pulmonary complications. We hypothesized that hypertonic saline (HTS), which attenuates resuscitation-induced intestinal edema in animals, would improve early primary fascial closure (EPFC) rates.

METHODS: This is a retrospective study of trauma patients undergoing DCL, from January 2010 to July 2011. Patients in the HTS group had 30 mL/h of 3% sodium chloride as maintenance fluids while the fascia was open. Patients in the cohort group had isotonic fluids (125 mL/h). The primary outcome, EPFC, was defined as primary fascial closure by postinjury day 7.

RESULTS: Seventy-seven patients underwent DCL (23 received HTS and 54 received isotonic fluids). There were no differences in demographics, injury severity, or pre-intensive care unit vitals, laboratories, fluids, or transfusions. Median fluids in the first 24 hours were lower in the HTS group (3.9 vs. 7.8 L, p < 0.001). Times to fascial closure were shorter in those receiving HTS (34 vs. 49 hours, p < 0.001), as were the rates of closure at first take back (78% vs. 53%, p = 0.036). The primary outcome of EPFC was higher in the HTS group compared with standard fluids (100% vs. 76%, p = 0.010). At discharge, the HTS group had a 96% primary fascial closure rate compared with 80% with standard fluids.

CONCLUSION: The use of 3% HTS as maintenance fluids after DCL was associated with 100% EPFC. HTS may be used as an adjunct to facilitate fascial closure in patients undergoing DCL. (J Trauma Acute Care Surg. 2013;74: 426–432. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic study, level III.

KEY WORDS: Hypertonic saline; open abdomen; damage control laparotomy; fascial closure.
The use of 3% HTS as maintenance fluids after DCL was associated with 100% EPFC. HTS may be used as an adjunct to facilitate fascial closure in patients undergoing DCL.

<table>
<thead>
<tr>
<th></th>
<th>STD (n = 54)</th>
<th>HTS (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPFC, %</td>
<td>76</td>
<td>100</td>
<td>0.010</td>
</tr>
<tr>
<td>Median time to fascial closure, hour</td>
<td>50 (35–127)</td>
<td>33 (21–48)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median ICU-free days</td>
<td>15 (6–23)</td>
<td>23 (7–26)</td>
<td>0.163</td>
</tr>
<tr>
<td>Median ventilator-free days</td>
<td>22 (14–27)</td>
<td>26 (12–28)</td>
<td>0.138</td>
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<tr>
<td>24-hour mortality, %</td>
<td>4.7</td>
<td>0.0</td>
<td>0.290</td>
</tr>
<tr>
<td>30-day mortality, %</td>
<td>9.4</td>
<td>8.7</td>
<td>0.923</td>
</tr>
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</table>

All continuous values are presented as median (25th–75th IQR). HTS, hypertonic saline fluids; ICU, intensive care unit; STD, standard fluids.
HS AND IMMUNOMODULATION
Secondary injury related to severe trauma
Pathways leading to tissue and organ damage after trauma
Activation of the immune system after trauma and tissue damage

- Penetrating trauma
- Thermal injury
- Blunt trauma
- Tissue Damage
- Infection

DAMPs:
- mtDNA
- Formyl Peptides
- HMGB1
- CIRP
- F-actin

PAMPs:
- Endotoxin
- Flagellin
- dsRNA
- Peptidoglycan

Cells and cytokines:
- Neutrophils
- Monocytes
- γδ T cells
- PDCs
- DCs
- Complement
- TNF-α
- IL-8
- IL-1β
- IL-6
- MCP-1
- G-CSF
- IFN-α/β
- IL-10
- IL-1ra
- TGF-β
- IL-12p40

Pro and anti-inflammatory cytokines

Tissue damage
- Endothelial & organ damage
- Immune paresis
- Sepsis
SMALL-VOLUME FLUID RESUSCITATION WITH HYPERTONIC SALINE PREVENTS INFLAMMATION BUT NOT MORTALITY IN A RAT MODEL OF HEMORRHAGIC SHOCK

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ABSTRACT—Hemorrhage remains a primary cause of death in civilian and military trauma. Permissive hypotensive resuscitation is a possible approach to reduce bleeding in patients until they can be stabilized in an appropriate hospital setting. Small-volume resuscitation with hypertonic saline (HS) is of particular interest because it allows one to modulate the inflammatory response to hemorrhage and trauma. Here, we tested the utility of permissive hypotensive resuscitation with hypertonic fluids in a rat model of hemorrhagic shock. Animals were subjected to massive hemorrhage [mean arterial pressure (MAP) = 30 – 35 mmHg for 2 h until decompensation] and partially resuscitated with a bolus dose of 4 mL/kg of 7.5% NaCl (HS), hypertonic hydroxyl ethyl starch (HHES; hydroxyl ethyl starch + 7.5% NaCl), or normal saline (NS) followed by additional infusion of Ringer solution to maintain MAP at 40 to 45 mmHg for 40 min (hypotensive state). Finally, animals were fully resuscitated with Ringer solution and the heparinized shed blood. Hypotensive resuscitation with NS caused a significant increase in plasma interleukin (IL)-1β, IL-6, IL-2, interferon γ (IFNγ), IL-10, and granulocyte-macrophage colony stimulating factor (GM-CSF). This increase was blocked by treatment with HS. HHES treatment significantly reduced the increase of IL-1β and IL-2 but not that of the other cytokines studied. Despite the strong effects of HS and HHES on cytokine production, both treatments had little effect on plasma lactate, base excess (BE), white blood cell (WBC) count, myeloperoxidase (MPO) content, and the wet/dry weight ratio of the lungs. Moreover, on day 7 after shock, the survival rate in rats treated with HS was markedly, but not significantly, lower than that of NS-treated animals (47% vs. 63%, respectively). In summary, hypotensive resuscitation with hypertonic fluids reduces the inflammatory response but not lung tissue damage or mortality after severe hemorrhagic shock.
SMALL-VOLUME FLUID RESUSCITATION WITH HYPERTONIC SALINE PREVENTS INFLAMMATION BUT NOT MORTALITY IN A RAT MODEL OF HEMORRHAGIC SHOCK

![Graph showing the effects of small-volume fluid resuscitation with hypertonic saline on arterial pressure during hemorrhagic shock.](image-url)

- Laparotomy after 20 min
- Hemorrhage causing a drop in mean arterial pressure to 30–35 mmHg
- Bolus of 4 mL/kg HHES, HS, or NS
- Permissive hypotensive resuscitation (40–45 mmHg) over 40 min
- Complete resuscitation with Ringer's solution
- Observation period of 3 hrs

Base line to end of permissive hypotensive resuscitation (low flow phase) to end of observation.
- Increase in plasma interleukin (IL)-1", IL-6, IL-2, interferon + (IFN+), IL-10, and GM-CSF in NS resusc.
- Effect blocked with HS
- HHES – Significant reduction in IL-1 and IL-2
- No different in lung injury and mortality

<table>
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<tr>
<th>Cytokine</th>
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<th>NS</th>
<th>HS</th>
<th>HHES</th>
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<tr>
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<td>Baseline</td>
<td>0</td>
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<td></td>
<td>End of flow</td>
<td>43 ± 17</td>
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<td></td>
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<td>107 ± 21*</td>
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<td>22 ± 9†</td>
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<td>End of resuscitation</td>
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<td>IL-2</td>
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<td>3 ± 1</td>
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<td>198 ± 49</td>
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<td>914 ± 299*†</td>
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<td>2368 ± 591*</td>
<td>302 ± 74†</td>
<td>756 ± 244</td>
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<td>11 ± 10</td>
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<tr>
<td></td>
<td>End of resuscitation</td>
<td>0</td>
<td>0</td>
<td>1 ± 1</td>
</tr>
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</table>
SMALL-VOLUME FLUID RESUSCITATION WITH HYPERTONIC SALINE PREVENTS INFLAMMATION BUT NOT MORTALITY IN A RAT MODEL OF HEMORRHAGIC SHOCK

[Graph showing MPO (mU/g wet weight) and lung (wet/dry weight ratio) for different conditions: cont, HHES, HS, NS.]

[Graph showing survival (%) over time (days) for HS and NS conditions.]
Resuscitation of traumatic hemorrhagic shock patients with hypertonic saline - without dextran - inhibits neutrophil and endothelial cell activation

Wolfgang G. Junger¹,², Shawn G. Rhind², Sandro B. Rizoli³, Joseph Cuschieri³, Maria Y. Shiu³, Andrew J. Baker³, Linglin Li¹, Pang N. Shek², David B. Hoyt³, and Eileen M. Bulger

Background—Post-traumatic inflammation and excessive neutrophil activation cause multiple organ dysfunction syndrome (MODS), a major cause of death among hemorrhagic shock patients. Traditional resuscitation strategies may exacerbate inflammation and thus novel fluid treatments are needed to reduce these post-traumatic complications. Hypertonic resuscitation fluids inhibit inflammation and reduce MODS in animal models. Here we studied the anti-inflammatory efficacy of hypertonic fluids in a controlled clinical trial.

Methods—Trauma patients in hypovolemic shock were resuscitated in a pre-hospital setting with 250 ml of either 7.5% hypertonic saline (HS; n=9), 7.5% hypertonic saline + 6% dextran-70 (HSD; n=8), or 0.9% normal saline (NS; n=17). Blood samples were collected on hospital admission and 12 and 24 h post-resuscitation. Multi-color flow cytometry was used to quantify neutrophil expression of cell-surface activation/adhesion (CD11b, CD62L, CD64) and degranulation (CD63, CD66b, CD35) markers as well as oxidative burst activity. Circulating concentrations of soluble intercellular adhesion molecule (sICAM)-1, vascular cell adhesion molecule (sVCAM)-1, P-, E-selectins, myeloperoxidase (MPO), and matrix metalloproteinase (MMP)-9 were assessed with immunoassays.

Results—MODS, leukocytosis, and mortality were lower in the HS and HSD groups than in the NS group. However, these differences were not statistically significant. HS prevented priming and activation and neutrophil oxidative burst and CD11b and CD66b expression. HS also reduced circulating markers of neutrophil degranulation (MPO and MMP-9) and endothelial cell activation (sICAM-1, cVCAM-1, sE-selectin, and sP-selectin). HSD was less capable than HS of suppressing the upregulation of most of these activation markers.
MODS, leukocytosis, and mortality were lower in the HS and HSD group.

HS also reduced circulating markers of neutrophil degranulation (MPO and MMP-9) and endothelial cell activation (sICAM-1, cVCAM-1, sE-selectin, and sP-selectin).

HSD was less capable than HS of suppressing the upregulation of most of these activation markers.
DO WE HAVE ENOUGH EVIDENCE TO CHANGE OUR PRACTICE?
For Release
March 26, 2009

Contact: NHLBI Communications Office
Phone: 301-496-4236
E-mail: nhlbi_news@nhlbi.nih.gov

The NHLBI Halts Study of Concentrated Saline for Patients with Shock Due to Lack of Survival Benefit

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has halted the United States trial of concentrated saline solutions for treating shock (injury-related shock or blood loss due to trauma at initial arrival) to trauma patients. The study was stopped because patients who received concentrated saline solutions were no more likely to survive than those who received a normal saline solution.

Typically, in the crucial early minutes before blood transfusions can be safely administered in the hospital, trauma patients receive normal saline solution intravenously.
Hypertonic saline solution no better than normal saline

NHLBI Stops Enrollment in Study of Concentrated Saline for Patients with Traumatic Brain Injury

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped enrollment into a clinical trial testing the effects of highly concentrated (hypertonic) saline solutions on patients with severe traumatic brain injury (TBI) when given as soon as possible after the injury – that is, before the patient arrives at the hospital or emergency room. After reviewing data on more than 1,000 patients, NHLBI determined that the hypertonic saline solution was no better than normal saline and that it is unlikely that continuing the study would provide useful information. Therefore, NHLBI completed their six month follow-up visit and data collection, and the study was stopped.

The TBI study is the largest randomized clinical trial ever conducted in this severely injured patient population. It is one of two clinical trials on the use of hypertonic saline for trauma being conducted by a network of clinical research sites in the United States and Canada called the Resuscitation Outcomes Consortium (ROC). In March, the NHLBI stopped a parallel study of hypertonic saline in trauma patients who went into shock due to severe bleeding because the highly concentrated saline solutions did not improve survival compared to standard saline solution.
Take home message

- HS is effective in raising blood pressure in hypovolaemic shock
- HS has modulatory effects on various functions of immune cells such as degranulation, adhesion molecules and cytokines expression, as well as reactive oxygen species production
- HS resuscitation showed no improvement in survival, organ failure or reduction in nosocomial infection in spite of promising results in animal.