“Hypertonic Saline for Resuscitation: Lost in Translation.”

Max Wohlauer
PGY-4
3/7/2011
Lesson learned in war: large volume resuscitation (3:1) with crystalloid.

Administering plasma in a foxhole on the invasion beach at Iwo Jima.

Crystalloid use during Vietnam War led to dramatic decrease in mortality.
Aggressive Resuscitation: ARDS and ACS - the “New” Syndromes.

Acute Respiratory Distress Syndrome

Abdominal Compartment Syndrome
HTS: Lost in Translation.

1. In-Vitro / Animal Studies
   - Immunomodulation
   - Improved hemodynamics

2. Phase II Clinical Trials
   - Underpowered

3. Phase III Clinical Trials
   - No mortality difference
Phase II Trial
Primary Outcome: Survival 30 days after injury or at discharge.
Results: Increased blood pressure in HSD group (p<0.005).
Limitations: Small sample size (20 patients), control group more severely injured.
Mattox et. al. 1991.

Phase III RCT
Primary Outcome: 24 hr and 30 day survival.
Results: HSD: no statistically significant survival difference compared to LR ( HSD 83.4% vs. LR 80.1%, P=0.94)
Limitation: Terminated for futility.
Vassar et. al. 1993.

Primary Outcome: Survival

Conflicting Results:
- HTS increased survival compared to NS, HSD decreased survival.

Meta-analysis of 13 studies, 8 DBRCTs (N=615 HSD, N=618 LR / NS).

Results: Found no increased survival with HTS or HSD (p=0.14).

Limitations: Meta-analysis of small trials involving both out of hospital and ED fluid administration.
Bulger et. al. 2008.

Phase III RCT
Primary Outcome: 28-day ARDS-free survival.
Results: No difference in ARDS-free survival, increased mortality for patients receiving HSD who did not receive blood transfusion.
Limitation: No difference in primary end point, closed for futility.
The Resuscitation Outcomes Consortium (ROC) Trial 2011

Phase III RCT
Primary Outcome: 28-day survival
Results: No difference in overall mortality (p=0.91); increased mortality for patients receiving HTS or HSD who did not receive blood transfusion.
Limitation: Trial terminated by data and safety monitoring board.
The ROC Trial: Increased Early Mortality in HTS and HSD groups.

TABLE 3. Timing of Death by Transfusion Group

<table>
<thead>
<tr>
<th></th>
<th>HSD (N = 220)</th>
<th>HS (N = 256)</th>
<th>NS (N = 376)</th>
<th>P*</th>
<th>HSD-NS† (95% CI)</th>
<th>HS-NS† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 units PRBC in first 24 h, n (%)</td>
<td>91 (41.6)</td>
<td>104 (40.8)</td>
<td>139 (37.1)</td>
<td>0.48</td>
<td>4.5 (−4.0 to 13.0)</td>
<td>3.7 (−4.4 to 11.8)</td>
</tr>
<tr>
<td>Died in field, n (%)</td>
<td>4 (1.8)</td>
<td>5 (2.0)</td>
<td>3 (0.8)</td>
<td>−‡</td>
<td>1.0‡</td>
<td>1.2‡</td>
</tr>
<tr>
<td>Died in field or ED, n (%)</td>
<td>14 (6.4)</td>
<td>23 (9.0)</td>
<td>13 (3.5)</td>
<td>0.01</td>
<td>2.9 (−1.2 to 7.0)</td>
<td>5.6 (1.2 to 9.9)</td>
</tr>
<tr>
<td>Died within 6 h of admission, n (%)</td>
<td>15 (6.8)</td>
<td>23 (9.0)</td>
<td>14 (3.7)</td>
<td>0.02</td>
<td>3.1 (−1.1 to 7.3)</td>
<td>5.3 (1.0 to 9.6)</td>
</tr>
<tr>
<td>Died within 28 d, n (%)</td>
<td><strong>22 (10.0)</strong></td>
<td><strong>31 (12.2)</strong></td>
<td><strong>18 (4.8)</strong></td>
<td>&lt;0.01</td>
<td>5.2 (0.4 to 10.1)</td>
<td>7.4 (2.5 to 12.2)</td>
</tr>
</tbody>
</table>
HTS: Problems with the Clinical Trials.

1. Study Design
2. Patient Population
3. Potency of Intervention
   - Timing is everything
   - Duration of hypertonicity
Increased mortality due to:
• Higher rate of early hemorrhage.
• Early resuscitation leading to delayed diagnosis and management of shock.
Increased bleeding?

- HTS impairs enzymatic clotting function when it replaces 7.5-10% of blood volume.
- A 4 cc / kg bolus of HTS equates to at least 6% blood volume replacement (higher bleeding patients), many of whom may already be coagulopathic on arrival to ED.

Conclusion

Based on existing data, HTS cannot be recommended for resuscitating trauma patients.
Thank You.
Recipe for success:

1. The right patient: Inclusion criteria paramount.
2. The right place: Ambulance, ED, or SICU.
3. The right time: HTS may be harmful if given too early or too late.
4. The right dose. Benefit of a single dose early or sustained hypertonicity of repeated dosing regimen?