“Hypertonic Saline for Resuscitation: Lost in Translation.”

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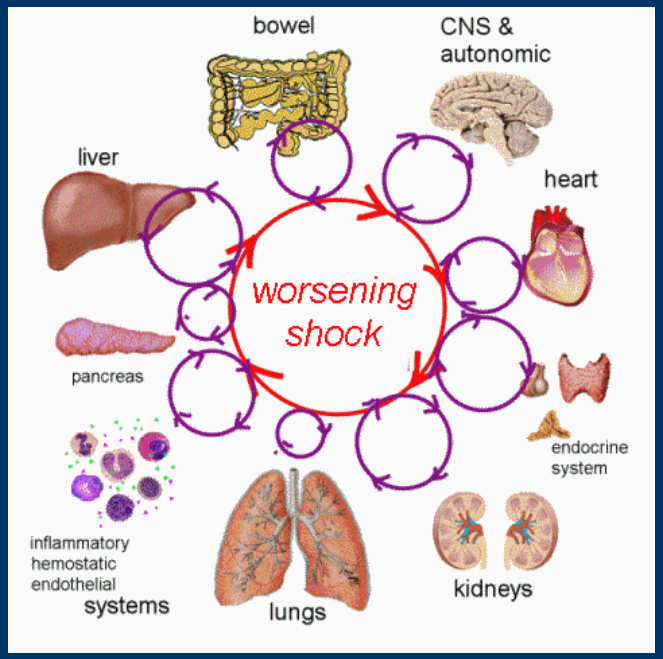
Lesson learned in war: large volume resuscitation (3:1) with crystalloid.

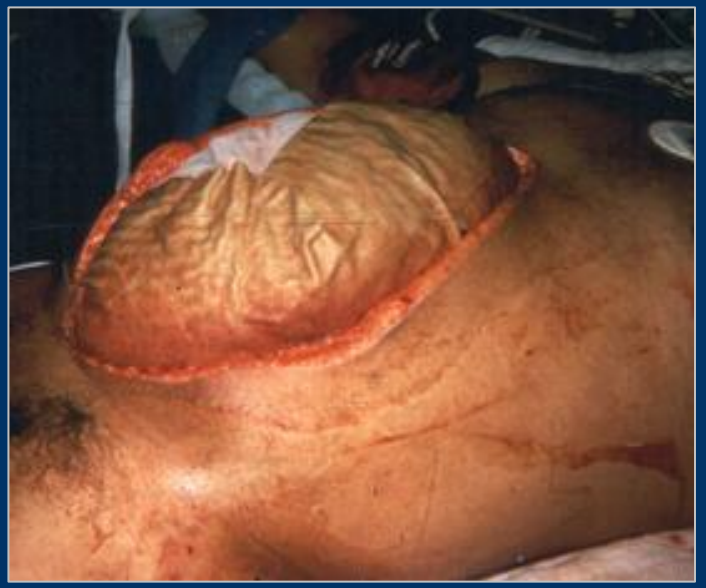
Administering plasma in a foxhole on the invasion beach at Iwo Jima.

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

Holcroft et. al. 1987.

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.

Trauma.org

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.

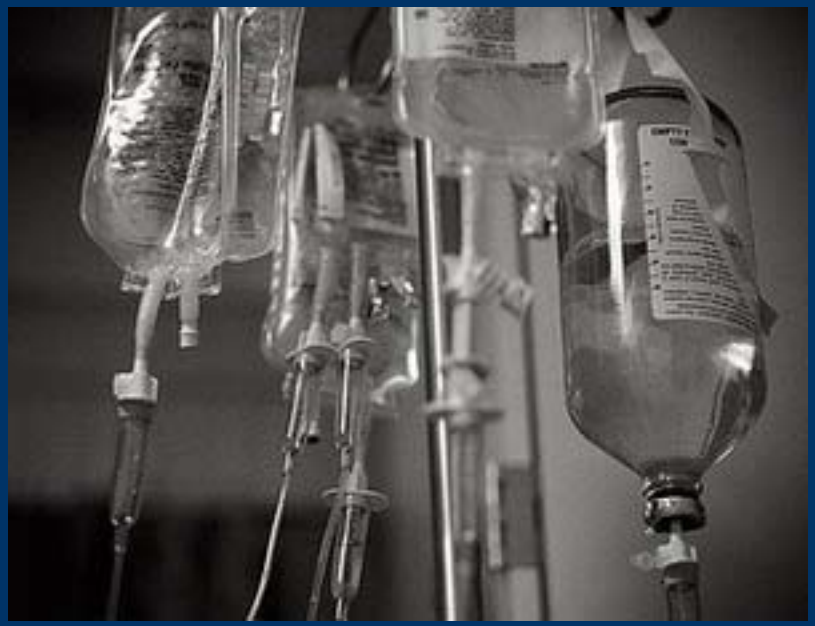
Vassar et. al. 1993.

Primary Outcome: Survival

Conflicting Results:

- HTS increased survival compared to NS, HSD decreased survival.

Wade et. al. 1997.



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- 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

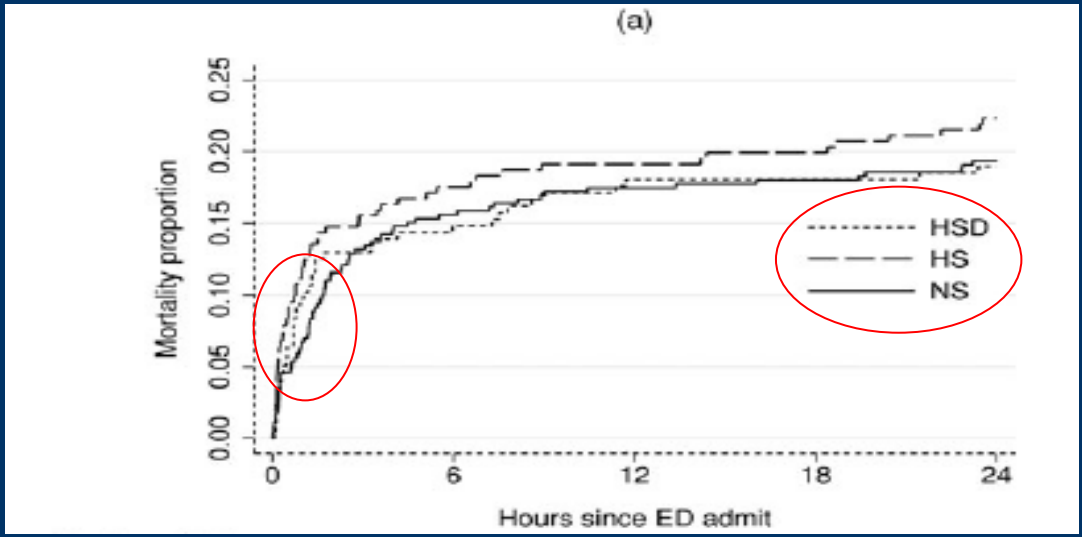
Results: No difference in overall mortality (p=0.91); increased mortality for patients receiving HTS or HSD who did not receive blood transfusion.

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

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



HTS: Problems with the Clinical Trials.

1. Study Design
2. Patient Population
3. Potency of Intervention
   - Timing is everything
   - Duration of hypertonicity

ROC Trial: HTS and HSD: Lower Hemoglobin on Arrival.

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.

Reed RL II J Trauma 1991. Tan TS Anesthesia 2002.

Moore et. al. JACS 2009. Brohi et. al. Ann Surg 2007.

Conclusion

1. In-Vitro
2. In-Vivo
3. Phase II/III trials

Based on existing data, HTS can not 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 ?