Overview of DoD Resuscitation Fluid Research

COL Jim Atkins, MD, PhD

Director, Division of Military Casualty Research
Walter Reed Army Institute of Research

Program Area Manager for Resuscitation Studies in the Army Combat Casualty Care Research Program

10 January 2005
Overview of DoD Resuscitation
Fluid Research

- Battlefield Resuscitation
- DoD and NIH Funded Research
- Prior Meetings and Collaborations
- Outcomes of This Panel
Battlefield Resuscitation: Non-Head Injured Casualties

Traditional constraints of battlefield resuscitation:
- Austere, dangerous environment
- Supply limitations
- Limited medical training

Potential future constraints include:
- Longer period of time before the medic can reach the casualty
- Increased difficulty in medical resupply
- Limited medical air evacuation
  - 12 hours in Somalia
  - 4-12 hours in Afghanistan (Transport times are relatively short in Iraq)

Issues with military specific fluids:
- Drugs/fluids must be FDA approved
  - Can’t conduct clinical trials in U.S. for exact military indication
- Military market not large enough to support unique product
Battlefield Resuscitation: Non-Head Injured Casualties

Panel selects hypotensive resuscitation to treat battlefield hemorrhage\(^1\)

- Combat Fluid Resuscitation Conference 2001, Bethesda, MD
- Resuscitate non-head injured combat casualties to:
  - Palpable radial pulse
  - Ability to mentate
  - Sustained systolic blood pressure of 85-90 mm Hg (if measure is available).
- Fluid of choice:
  - Forward (battlefield)-colloid (500 cc) or colloid and crystalloid
  - Aid station/forward surgical setting-isotonic crystalloid
Battlefield Resuscitation:
Non-Head Injured Casualties

Areas to Improve in the Cascade of Care
• Optimal battlefield resuscitation guidelines
  • Clinical evaluation of the casualty

  ? FDA approved fluid for trauma resuscitation (superior to LR)
  ? Risk balance of hypotensive period length vs. CASEVAC risk

• Identification of Markers of Resuscitation Failure
  ? Field device to test for biomarkers of impending failure (crashing)
  ? Method at CSH to test for biomarkers

• Treat/Prevent the Resuscitation Failure
  ? Field: small volume, shelf stable adjuvants
  ? CSH: adjuvants, blood products, coagulopathy repair, fluids; altered protocol for patients held hypotensive for longer periods.
DTO Title: MD. 28 Fluid Resuscitation and Prolonged Life Sustainment on the Battlefield

Objectives

• Develop life sustainment strategy for casualties that are expected to experience long delays before evacuation from the battlefield.
  – Determine the best composition and use of resuscitation fluids.
  – Develop adjunct therapy or drugs to improve outcomes.
  – Develop drugs or strategies that sustain life in the absence of fluid resuscitation.

Payoffs

• Decreased requirements for resuscitation fluids.
• Increased window of time in which the casualty may be evacuated.
• Decreased killed-in-action rate.
• Decreased blood requirements
• Decreased organ failure after successful resuscitation.
Major Accomplishments

- Animal studies predict that casualties may collapse without warning
- Full resuscitation (second resuscitation) may be complicated after prolonged hypotensive resuscitation.
- Late vascular decompensation in hemorrhagic shock is associated with a fall in blood levels of arginine-vasopressin. Administration of pharmacologic doses of AVP restores blood levels to those normal for shock and rescues the animals from imminent death.
- Hypertonic saline must be dose limited. Timing and rate of administration may be important.
- Studies indicated that L-lactated Ringers causes significantly less neutrophil activation and lung injury after hemorrhage/resuscitation than the racemic mixture of D- & L-lactated Ringers.
- HBOC alone may not be ideal for hypotensive resuscitation (under conditions where oxygen carrying capacity of blood is not critically low)
Research Tools at Hand

Animal models have been developed to examine hypotensive resuscitation with delayed evacuation. Three models were established in two species (rat and pig).

- Models mimic severely hemorrhaged but potentially salvageable casualties on the battlefield.
  - Some models without anesthesia.
  - Prolonged hypotensive periods.
  - Significant lactic acidosis.
  - Portion that become unresponsive to fluid resuscitation.

- Models mimic some aspects of patients from urban trauma centers
  - Complement activation.
Prior Meetings and Collaborations

**Combat Focus**
- Fluid Resuscitation Report
  Institute of Medicine, Nat'l Acad. Press, 1999
- Combat Fluid Resuscitation, Bethesda
- Fluid Resuscitation in Combat, Toronto
- Clinical Research Methodology in Combat Resuscitation and Casualty Care, Toronto

**General Resuscitation**
- PULSE Workshop, DC
  (Circulation, 2001; 103, 1182-4)
- PULSE Trauma WG I, NIH
  (SHOCK, 2002;17(3), 165-8)

**Clinical Trial Focus**
- Change in law (Title X, Sec. 980) allowing use of DoD funds for pre-hospital (community consent) clinical trials
- Formation of the Research Outcome Consortium
- Resuscitation Science Symposium
  2003 AHA Scientific Sessions, Orlando
- 12 NIH/DoD R01 Awards for Basic Research to Improve Outcomes after Trauma Resuscitation
- Resuscitation Science Symposium
  2004 AHA Scientific Sessions, New Orleans
- Future Workshop on NIH/DOD Teaming Approach to Accelerate the Transition to Clinical Trials

---

**Years**
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
Prior Meetings and Collaborations

Post-resuscitative and initial Utility in Life Saving Efforts (PULSE) Initiative – A “shotgun marriage” of researchers in CPR and trauma resuscitation.

– Initial workshop in 2000
– 12 NIH RO1 basic science grants awarded in 2002
– Trauma Working Group published recommendations in 2002 and 2004
– Created the Research Outcome Consortium for multi-center, international clinical trials in trauma
Outcomes of This Panel

• Applicants respond to Federal Funding Opportunity number W81XWY-BAA-AFRRF
• Panel reviews and ranks pre-proposals based on scientific merit and product maturity
• MRMC reviews regarding relevance to the combat situation
• Full proposals are requested from top 4-8 products and sent to AIBS for external review
• Awards of $100k-$1M/year through 2010, with the leading product receiving as much as $3M/year for clinical development
Outcomes of This Panel

• Short Term:
  – Select candidate products for developmental funding under AFRRF
  – Selection criteria for determining utility of future fluid resuscitation products in a combat scenario

• Longer Term:
  – FDA Approval of one or more products that will reduce the number of soldiers KIA and mitigate the post-resuscitation morbidity
  – Encourage development of the next generation of resuscitation fluids
Overview of DoD Resuscitation
Fluid Research
References

Cited

Uncited