Novel Fluids for Resuscitation of Hemorrhagic Shock on the Battlefield

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ABSTRACT

Objective: A survey was conducted to identify strategies under development for use as resuscitation fluid that potentially might reduce complications and improve chances for survival from hemorrhagic shock. Of particular interest were strategies that could be utilized by combat medics on the battlefield.
Methods: Information on novel resuscitation fluids was supplied by more than 50 researchers in response to a public call for information by the U.S. Army Medical Research and Materiel Command and in response to direct invitation by the Life Sciences Research Office. The survey was conducted in association with an expert panel assembled to review and prioritize proposed treatment regimens and develop a framework for future scientific reviews. Provisions were made to review but not reveal proprietary data by executing confidentiality agreements.
Results: Several parallel approaches are under consideration for resuscitation fluid that include one or more of the following strategies: improve oxygen delivery (*e.g.*, hemoglobin-based oxygen carriers); support metabolism (*e.g.*, ethyl pyruvate); favorably alter rheology and coagulation (*e.g.*, lyophilized platelets); promote cardiovascular stability; and modulate immune response (*e.g.*, human recombinant interleukin-6). More than 20 researchers proposed measuring markers of inflammation and immune function to assess effects of resuscitation fluid treatment.
Conclusion: Development of one or more of these novel strategies to treat hemorrhagic shock may lead to improved effectiveness of resuscitation fluids, earlier after the wounding event, reducing the number of military casualties who are killed-in-action.
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BACKGROUND

U.S. soldiers and marines continue to die of hemorrhagic shock in combat. Novel resuscitation fluids and adjunct therapies are needed for wounded combatants who await evacuation to surgical care.

To be relevant for combat care, resuscitation products must:

- Increase the probability of survival from exsanguinating shock
- Be durable, light-weight, and low-volume for transport and use in austere environments
- Be easy to prepare, administer, and monitor by minimally trained first-responders on a battlefield

In lieu of a military trial to test novel products, which would be difficult to conduct, a similar indication must be tested in a civilian population. A comparison of civilian clinical product trials is compared to use in combat in Table 1. Clinical studies are a high priority for U.S. Army Medical Research and Materiel Command (USAMRMC) funding. The civilian clinical data should be supplemented with other tests to justify approval for military use. Aspects of the military condition, such as prolonged evacuation, have been mimicked using animal models. As reviewed by Majde (J Trauma. 2003;54:S100-S105), conscious animal models that minimize anesthesia artifacts are being used to test resuscitation therapies.

OBJECTIVE

Identify 4 to 8 research preproposals of novel resuscitation products with sufficient military relevance and scientific merit for potential funding by the USAMRMC

SURVEY and REVIEW

Information on novel resuscitation fluids was supplied by more than 50 researchers in response to a public call for information by USAMRMC and in response to direct invitation by the Life Sciences Research Office (LSRO).

The survey was conducted in association with an expert panel that was assembled to review and prioritize proposed treatment regimens and develop a framework for future scientific reviews of advanced first-responder resuscitation fluids (AFRRF). Provisions were made to review but not reveal proprietary data by executing confidentiality agreements. The expert panel made recommendations to the sponsor for review criteria, then applied those criteria to score and rank the preproposals for military relevance and scientific merit. Moreover, the expert panel made recommendations to the sponsor for the submission and review of future full proposals.

Table 1. Comparison of controlled clinical trials of resuscitation products and their use and post-market surveillance in combat

Aspect	Clinical trial	Use and post-market surveillance in combat
Pre-hospital setting	Suburban and urban areas	Far-forward frontline of hostile combat
Population	Civilians (diverse age, medical history, physical fitness, use of illegal drugs and alcohol)	Soldiers and marines are less heterogeneous than civilians
Hemorrhagic injury	Multiple blunt trauma, some penetrating trauma, some with neurotrauma; injuries are well-diagnosed	Penetrating trauma from bullets or flying fragments, initially not completely diagnosed (*e.g.*, head injuries)
Personnel	Trained EMT and team; well stocked supplies and equipment; in communication with physician-directed center; back-up personnel available; Advanced Trauma Life Support® protocols	Minimally trained advanced-first responder and/or combat medic; limited supplies, equipment, communication, and back-up
Approval	Community consent and institutional review board approval are required for use of experimental products	Products must have U.S. FDA approval for similar indication and must be usable in austere environment. There are limited options for alternative treatment
Evacuation from scene to surgical care	Evacuation (minutes) by vehicle/aircraft on scene and waiting	Evacuation (hours) by any means necessary through successive echelons of care
Patient data from scene	Retained; paper trail	Data capture is a low priority; often not available
Outcome measures	Survival outcome, secondary biomarkers (*e.g.*, organ failure), surrogate measures (*e.g.*, days of ventilation, duration of hospital stay, cost of care)	Survival outcome and logistical advantages
Oversight from research team	Urban academic center located within minutes of accident scene and the delivery of patient critical care	Oversight location remote from combat scene and initial critical care

FINDINGS

Of the 59 preproposals reviewed, 35 had insufficient military relevance and/or scientific merit. The remaining 2 clinical and 22 preclinical preproposals were scored and ranked by the expert panel (Fig. 1). The expert panel classified these 24 ranked preproposals by the type of treatment (Fig. 2). Some proposed treatments included more than one component, which potentially had different modalities for treating hemorrhagic shock. The top 2 preclinical candidates were estimated to be, at best, within 4 years of clinical trials and the remaining 3 candidates in the top tier were estimated to be 5 or more years from clinical trials. Examples of study models derived from AFRRF preproposals are described in Table 2.

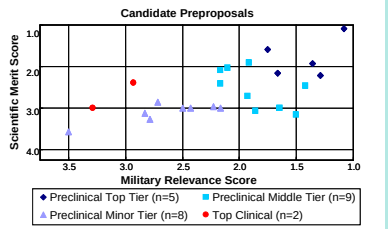

Figure 1. Scores assigned to AFRRF preproposals by the expert panel. The lower the score, the better the ranking. Not shown: scores for 35 preproposals eliminated for insufficient military relevance and/or scientific merit.

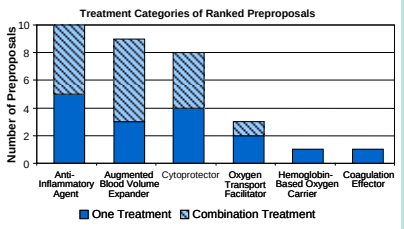

Figure 2. The 24 ranked preproposals are categorized by their proposed treatment. Some treatments spanned more than one category, represented here as combination treatment.

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Table 2. Some study models in AFRRF preproposals received that were proposed by principle investigators as relevant for investigating the treatment of hemorrhagic shock on the battlefield

Subject	Model			Variations
Small animal (mouse, rat, rabbit)	Hemorrhagic shock	Uncontrolled	Trauma	•Liver injury
			No trauma	•Lethal and small volume resuscitation •Bled via arteriotectomy punch
		Controlled	Trauma	•Crushed limb
			No trauma	•60% loss of blood volume •50% - 60% loss of blood volume via artery •Lethal via rapid loss of 40% blood volume over 10 minutes followed by a 3-hour period of shock (to simulate delayed transport) during which another 20% of blood volume is lost via slow pump •Nonheparinized animals under anesthesia •Bled via artery under anesthesia •Fixed pressure
		Control not specified	Trauma	•Traumatic brain injury via weight drop •Bled rapidly with trauma via laparotomy during inhalational anesthesia •Trauma, not described, in non-heparinized animal
	Other	•Blunt head trauma without hemorrhage •Renal ischemia (to produce hypovolemic anemia) under anesthesia •Shock induced intestinal ischemia via occluded superior mesenteric artery		
Large animal (pig, sheep, dog)	Hemorrhagic shock	Uncontrolled	Trauma	•Liver avulsion and blunt chest trauma via captive bolt gun under anesthesia •Liver crush injury and prolonged bleed •Cerebral injury and prolonged bleed •Femoral fracture and prolonged bleed
			No trauma	•Lethal bleed via aortic tear •Severe bleed via abdominal aorta in mechanically ventilated, anesthetized animals
		Controlled	Trauma	•Controlled via artery with traumatic brain injury
			No Trauma	•Controlled via jugular vein to simulate uncontrolled bleed with delayed (40 minutes) hypotensive resuscitation •Controlled via artery in sedated, anesthetized animals breathing spontaneously •Controlled, interrupted, in conscious animals
		Control not specified	No trauma	•Rapid bleed over 5 minutes followed by 2-minute cardiac arrest
	Other	•Thrombocytopenia		
Human studies	Hemorrhage	Uncontrolled	Trauma	•Active bleed, multi-trauma critically ill (excludes traumatic brain injury) •Penetrating torso wound •Isolated traumatic brain injury •Military combat
			No trauma	•Acute bleed via esophageal varices
		Controlled	No trauma	•Normal, healthy volunteers
	Other	•Burn injury •Elective surgery for abdominal aorta aneurysm		

FURTHER RESEARCH

Modest amounts of resuscitation solutions will be administered on the battlefield to restore some level of perfusion short of complete restoration of blood pressure. The optimal blood pressure to achieve during resuscitation of the wounded combatant has yet to be ascertained.

Blood volume expansion:
- What is adequate and optimal blood volume expansion?
- What is an appropriate endpoint for volume expansion measures?

Tissue oxygenation:
- What is adequate and optimal tissue oxygenation?
- What is the best noninvasive measure of tissue oxygenation?
- What is an appropriate endpoint for tissue oxygenation measures?

Patient selection and monitoring:
- Can current practices to discern the need for resuscitation fluid and adjunct therapies be further improved?
- What secondary clinical endpoints are predictive of efficacy and survival?

CONCLUSION

Development of one or more of these novel strategies to treat hemorrhagic shock may lead to improved effectiveness of resuscitation fluids and adjunct therapies, reducing the number of military casualties who are killed-in-action or who die of late complications.

USAMRMC will invite full proposals for leading resuscitation fluids and adjunct therapies. It is likely that in the near future, USAMRMC will adopt new criteria for submission and review of AFRRF preproposals.

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