RECOMMENDATIONS FOR REVIEWING RESEARCH ON ADVANCED FIRST-RESPONDER RESUSCITATION FLUIDS AND ADJUNCT THERAPIES

EXECUTIVE SUMMARY

July 2005

Editor:
Catherine J. Klein, Ph.D., R.D., C.N.S.D.

Sponsor:
The United States Army Medical Research and Materiel Command
and
The Office of Naval Research

This is a brief summary of the conclusions reached by LSRO and their Expert Panel. This is not an independent document and should be considered within the context of the full report, which can be obtained at WWW.LSRO.ORG.

Copies of this publication may be obtained from Life Sciences Research Office. Orders and inquiries may be directed to LSRO, 9650 Rockville Pike, Bethesda, MD 20814.
Phone: 301-634-7030. Fax: 301-634-7876. Website: www.LSRO.org.

ISBN: 0-9753167-5-3
Library of Congress Catalog Number: 2005929910

EXECUTIVE SUMMARY

The U.S. Army Medical Research and Materiel Command (USAMRMC) and the Office of Naval Research (ONR) are seeking novel treatments to resuscitate wounded combatants. Depending on terrain, weather, and military situation, U.S. soldiers and marines wounded in combat may have to endure a prolonged period of time before evacuation to surgical care. On the battlefield, combatants who are bleeding sufficiently to compromise perfusion of vital organs require immediate medical care by a medic or combat lifesaver. Resuscitation fluid to replace lost blood volume is carried in limited supply. Products are needed that are practical to transport and use on the battlefield and which are effective in increasing survival and decreasing adverse complications during and after prolonged evacuation.

The mission of the military medical services is to conserve and maintain the fighting power of the command by attending to wounded combatants so they can return to duty. This report may further help the military to learn more about potentially useful resuscitation products under development and help investigators learn more about the military conditions in which products might be used.

BACKGROUND

In warfare, bullets and penetrating fragments from exploding munitions frequently cause life-threatening hemorrhage. Exsanguinating hemorrhage was the mechanism of death for up to 50% of wounded soldiers who perished in past conflicts, and is considered to be the major cause of death in potentially salvageable battlefield casualties. Hemorrhage from wounded limbs alone has accounted for nearly one-tenth of all combat deaths, a portion of which were considered preventable had appropriate pre-hospital care been provided. To help address this issue, the military has improved the design and supply of tourniquets. Once bleeding is under control, and in the case of uncontrolled torso bleeding, life is sustained on the battlefield and in transit to surgical care units through the use of resuscitation fluids.

Prior to testing a new treatment in humans, medical products must undergo animal testing to address questions of safety and effectiveness. Developing new resuscitation fluid products is a considerable undertaking, requiring the commitment of considerable time and resources to secure approval by the U.S. Food and Drug Administration (FDA). Therefore, products that are relatively far along in development, that have preliminary data establishing safety and effectiveness for resuscitation, and have the potential to meet logistical considerations imposed by combat conditions would be of greatest interest to the military.

The amount of medical product used by the military fluctuates depending on whether the military is engaged in sustained combat. Therefore, it is advantageous for the military to develop resuscitation fluid products that have dual use in both the military and civilian markets so that product production can be increased as needed.

THE STUDY

The potentially preventable loss of life from exsanguinating hemorrhage has spurred the military to consider new, low-volume resuscitation therapies to try and reduce the rate of casualties killed-in-action. Collaborating in this effort are the ONR and the USAMRMC, which together retained the Life Sciences Research Office, Inc. (LSRO) to provide an independent review, and

are hereafter referred to as the sponsor. LSRO was asked to survey the types of novel resuscitation fluids and adjunct therapies under development and identify those candidates that may be worth an investment of military funding to advance research and product development.

LSRO conducted this study in two phases in conjunction with an independent, multidisciplinary expert panel of scientists:

- Phase I reviewed 59 preproposals for advanced first-responder resuscitation fluid (AFRRF) and evaluated their military relevance and scientific merit to identify and rank leading experimental therapies that were worthy of further review of a detailed full research proposal.

- Phase II examined processes and forms currently in use by the military and other federal programs for the review of scientific research. This was completed with an eye towards making recommendations for an effective program to further evaluate and prioritize current and future resuscitation technologies. The ultimate goal is to improve the quality of future proposals for the likelihood that such studies will advance development of resuscitation products for military use.

FINDINGS

Numerous products currently under development have the potential for use in civilian resuscitative care and several of these may meet the extraordinary demands for use under austere combat conditions to treat exsanguinating hemorrhage. LSRO identified 48 unique experimental products among the 59 preproposals under consideration. These products included coagulation effectors, products targeting cardiovascular responses and/or enhancing oxygen delivery, cytoprotectors supporting cell structure and metabolism, products purported to minimize inflammation and/or favorably modulate immune response, and products for blood volume expansion. LSRO prepared a critique of each preproposal for the sponsor using brief summaries prepared by two lead reviewers supplemented with comments of the expert panel.

Of the ten clinical preproposals submitted, the expert panel identified two leading candidates. Of the 49 preclinical preproposals submitted, the expert panel identified a group of five top-tier preproposals and a group of nine second-tier preproposals. The preclinical candidate with the top total score also ranked first in both military relevance and scientific merit. The five top preclinical preproposals had better scores for both military relevance and scientific merit than the two leading clinical preproposals.

Preproposals of anti-inflammatory treatments rated highly. One of the top two clinical proposals and seven of the top ten preclinical proposals included anti-inflammatory therapies.

To facilitate the future submission process for full proposals for resuscitation fluids and adjunct therapies, LSRO and the expert panel tailored proposal instructions and forms to comply with current USAMRMC requirements. Such materials and accompanying recommendations are intended to assist the sponsor in obtaining information and data useful for scientific peer review, evaluation of military relevance and assessment of commercial viability. For example, the expert panel created a standardized format for the inclusion in future proposals of detailed

information characterizing the proposed experimental product, which will assist reviewers in assessing military relevance and commercial viability.

CONCLUSIONS AND PRINCIPAL RECOMMENDATIONS

LSRO and the expert panel completed all tasks requested by the sponsor. A listing of principal recommendations is summarized in Table V-1 of this report.

The expert panel recognized that one or more pharmacologic agents may be needed in addition to a blood volume expander to improve survival rates of wounded combatants. The expert panel therefore recommended that the sponsor distinguish between two product categories, encouraging investigation of novel fluids for blood volume expansion as well as emphasizing the need for pharmacologic agents that can be used with or without various resuscitation fluids.

The expert panel acknowledged the value of using conscious animals in resuscitation research to avoid artifacts resulting from anesthesia, which can obscure hemodynamic responses to treatment. It also acknowledged that animal models can present similar physiological responses to the far-forward treatment interval in which the wounded combatant awaits evacuation to surgical care. To this end, the expert panel recommended that preclinical studies include non-anesthetized models to study hemorrhage alone and an anesthetized model to study uncontrolled hemorrhage plus trauma in two species of large animals with hypotensive resuscitation during prolonged periods. Preclinical studies should measure short-term survival during conditions that simulate delayed evacuation to surgical care, end organ damage, and long-term survival.

The number of patients and documentation required for FDA clinical efficacy testing preclude testing resuscitation products in combat situations. However, a situation that is relevant to combat inflicted hemorrhage is all too common in the United States. Blunt trauma, such as an extremity injury from a motor-vehicle accident, is the most frequent type of civilian traumatic injury in the United States. Thus, the expert panel considered the use of experimental resuscitation products by civilian emergency medical technicians to treat extensive blunt trauma as the best surrogate model for treatment of combat-inflicted hemorrhage. Important clinical measures include coagulation profile, neurological status, end organ failure, and survival to 28 and 60 days.

Having an obligatory research proposal format encourages offerors (applicants) to submit sufficient relevant information within reasonable page limits. This also serves to limit the burden of peer-review and set a consistent standard for all submissions. Of particular importance for assessing military relevance is the recommendation for the sponsor to define and prioritize the minimal and optimal product performance goals (*i.e.,* requirements) for the offeror, and for the offeror to characterize their product as recommended by this expert panel.

Competitive product development is strengthened by scheduled gate reviews in which decisions are made to advance or halt investigations. The expert panel recommended a maximum of two years funding for preclinical studies and a maximum of three years funding for clinical studies, with the potential for continuation of funds if the project is on track and successful.

NEXT STEPS

This report provides a framework for reviewing research on novel resuscitation products that can be implemented by the sponsor. (See Chapter IV.) Implementing and developing this framework could make substantial progress in assuring that the sponsor receives high quality research proposals of sufficient military relevance that lead to products with the potential to substantially improve resuscitative care in combat and save the lives of U.S. soldiers and marines.

***

Editor's Note:

For further information about this study, see "Resuscitation Fluids for Use in Combat" at: http://www.lsro.org