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6. AUTHOR(S) Kenneth G. Proctor				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Miami School of Medicine, Daughtry Department of Surgery, Divisions of Trauma & Surgical Critical Care, Ryder Trauma Center, 1611 NW 12th Avenue, Suite 215, Miami, FL 33136				B. PERFORMING ORGANIZATION REPORT NUMBER FINAL	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of Naval Research Ballston Centre Tower One 800 North Quincy Street Arlington, VA 22217-5660				10. SPONSOR/MONITOR'S ACRONYM(S)	
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14. ABSTRACT To develop clinically-relevant experimental models of 1A° and 2A° injuries after civilian or military trauma; to determine mechanisms/therapeutic targets in those models; to develop/evaluate novel resuscitation strategies based on those mechanisms/therapeutic targets; to translate those findings to patients. 20090327442					
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Project Title: Fluid Resuscitation from Traumatic Shock
ONR Award No: N000140210339
Reporting Period: June 1, 2005 - May 31, 2006
Award Period: March 1, 2002 - February 28, 2006

Scientific and Technical Objectives

OVERALL OBJECTIVE: To develop clinically-relevant experimental models of 1st and 2nd injuries after civilian or military trauma; to determine mechanisms/therapeutic targets in those models; to develop/evaluate novel resuscitation strategies based on those mechanisms/therapeutic targets; to translate those findings to patients.

Approach

Approach

Anesthetized, instrumented swine receive a traumatic injury to the head, chest, abdomen, or extremity. After a 10-60 min shock period, the animal receives initial resuscitation with crystalloid, colloid, or novel test fluid, supplemented with various pharmacologic agents to mimic pre-hospital care. This is followed by definitive resuscitation with standard of care cardiopulmonary support. After a 2-72 hr post trauma observation period, the outcome is graded on the basis of mortality, physiologic changes, neurologic function, biochemical/metabolic changes, and/or histologic changes.

Concise Accomplishments

1. A novel non-invasive strategy correlated with radiological findings in traumatic brain injury patients
2. Three different fluid restriction resuscitation strategies were superior to a standard of care in a new clinically-relevant model of polytrauma.
3. A mass casualty situational training exercise was developed for US Army forward surgical teams
4. Beneficial actions of arginine vasopressin during fluid resuscitation were demonstrated in 3 different animal models of trauma + hemorrhage
5. We provided data from two different models to the Naval Medical Research Center to support the use of a novel hemoglobin-based oxygen carrying compound for pre-hospital resuscitation of trauma patients.
6. We demonstrated coagulation changes caused by pulmonary artery catheters in animals and then in patients
7. We demonstrated that ubiquitin, a small, normally intracellular peptide

- a. is released into cerebrospinal fluid after traumatic brain injury in animals and humans
- b. reduces fluid shifts across the blood brain barrier after traumatic brain injury in animals
- c. is released during storage of human red blood cells and may explain some immunological changes during blood transfusion

Expanded Accomplishments

1. We showed that several factors reduce heart rate variability (HRV) in patients. When HRV is indexed for some of these confounding factors, the specificity and efficiency were improved for predicting positive head CT scans in trauma patients. The basic statistical approach can incorporate other demographic or physiologic variables to refine and improve the diagnostic and/or prognostic ability of HRV as a non-invasive screening and/or monitoring tool.
2. Trauma patients frequently suffer multiple severe injuries and hemorrhagic shock is less common, but most animal models include the opposite pattern. We developed a new clinically-relevant polytrauma model and showed that cerebrovascular function is improved with IVF restriction.
3. Civilian and military mass casualty incidents (MCI) are an unfortunate reality in the 21st century, but there are few situational training exercises (STX) to prepare for them. To fill this gap, we developed an MCI STX for U.S. Army Forward Surgical Teams (FST). From 2003-2005, sixteen FSTs completed the STX. The data showed that an MCI can overwhelm even combat-experienced FSTs; Adherence to basic principles of emergency trauma care by all FST members is essential to effectively and efficiently respond to this MCI. By prospectively identifying deficiencies, future military or civilian performance during an actual MCI may be improved. This MCI STX could provide a template for similar programs to develop, train, and evaluate civilian surgical disaster response teams.
4. Supplemental vasopressin improved multiple outcome parameters during fluid resuscitation from profound hemorrhagic shock after severe head, chest, or liver trauma.
5. During fluid resuscitation from traumatic brain injury in simulated pre-hospital conditions, the safety of Oxyglobin or Hemopure equalled or exceeded standard of care fluids. Furthermore, multiple outcome parameters were improved with Oxyglobin or Hemopure vs standard of care fluids.
6. Placement of pulmonary artery catheters caused a 50% reduction in clotting time in pigs. Similar hypercoagulable effects were seen even in patients receiving prophylactic heparin.
7. Ubiquitin, is a 76 amino acid peptide with an essential intracellular role in protein catabolism. We demonstrated that ubiquitin
 - a. is released into cerebrospinal fluid after traumatic brain injury in animals and humans
 - b. reduces fluid shifts across the blood brain barrier after traumatic brain injury in animals
 - c. is released during storage of human red blood cells and may explain some immunological changes during blood transfusion

Work Plan

Determine the risk/benefit profile of vasopressin relative to phenylephrine during management of cerebral perfusion pressure after polytrauma.

Determine heart rate variability changes in trauma patients

Determine whether ubiquitin alters leukocyte-endothelial interactions during reperfusion injury.

Problems/Issues

No problems

Peer-Reviewed Journal Articles

Status	Text
In Press	Patel MB, Feinstein AJ, Saenz AD, Majetschak M, Proctor KG: Pre-hospital HBOC-201 After Traumatic Brain Injury and Hemorrhagic Shock in Swine. J Trauma
In Press	Patel MB, Proctor KG, Majetschak M: Extracellular ubiquitin increases in packed red blood cell units during storage J Surgical Research
In Press	King DR, Patel MB, Feinstein AJ, Earle, SA, Topp RF, Proctor KG: Simulation training for a mass casualty event: A two year experience at the Army Trauma Training Center. J Trauma
Published	Crookes BA, Cohn SM, Bloch S, Amortegui J, Manning R, Li P, Proctor MS, Hallal A, Blackbourne LH, Benjamin R, Soffer D, Habib F, Schulman CI, Duncan R, Proctor KG: Can Near Infrared Spectroscopy identify the severity of shock in trauma patients? J Trauma. 2005 Apr;58(4):806-816
Published	Majetschak M, King DR, Krehmeier U, Busby L, Thome L, Muench E, Proctor KG: Ubiquitin immunoreactivity in cerebrospinal fluid after traumatic brain injury: Clinical and experimental findings Crit Care Med. 2005 Jul;33(7):1589-1594
Published	King DR, Cohn SM, Proctor KG: Resuscitation with a hemoglobin-based oxygen carrier after traumatic brain injury. J Trauma 2005 Sep;59(3):553-62
Published	Earle SA, Proctor KG, Patel MB, Majetschak M: Ubiquitin reduces fluid shifts after traumatic brain injury Surgery 2005 Sep; 138(3):431-8
Published	Feinstein AJ, Patel MB, Sanui M, Cohn SM, Majetschak M, Proctor KG. Resuscitation with pressors after traumatic brain injury. J Am Coll Surg. 2005 Oct;201(4):536-45.
Published	King DR, Cohn SM, Feinstein AJ, Proctor KG: Systemic coagulation changes caused by pulmonary artery catheters: laboratory findings and clinical correlation. J Trauma 2005 Oct;59(4):853-9
Published	Feinstein AJ, Cohn SM, Sanui M, King DR, Proctor KG: Early vasopressin improves short term survival after pulmonary contusion. J Trauma 2005 Oct;59(4):876-83.
Published	Sanui M, King DR, Feinstein AJ, Varon AJ, Cohn SM, Proctor KG: Effects of arginine vasopressin during resuscitation from hemorrhagic hypotension after traumatic brain injury. Crit Care Med 2006 Feb;34(2):433-8.

Books or Book Chapters

No book or book chapters reported.

Technical Reports (Non-refereed Publications)

No technical reports reported.

Abstracts/Presentations/Posters/Conference Proceedings

Abstract: Zaky A, Pretto EA, Earle SA, Piraccini E, Zuccarelli JE, Proctor KG: Hepatosplanchnic and systemic hemodynamic effects of dopamine and norepinephrine in brain dead organ donor "a swine model.

a. Presented at Gulf Atlantic Anesthesia Resident Research Conf., Tampa, FL Apr 2006

b. Accepted for presentation at Amer. Society of Anesthesiology 2006 annual meeting in Chicago, IL Oct 2006

Abstract: Earle SA, DeMoya MA, Zuccarelli JE, Proctor KG: Fluid restriction in novel clinically-relevant model of polytrauma.

a. Accepted for presentation at the Surgical Forum program of the American College of Surgeons' 92nd Annual Clinical Congress Meeting, Chicago, IL Oct 2006

b. Presented at 17th Annual Fellow, Resident, and Medical Student Surgical Research Forum South Florida Chapter of the American College of Surgeons in Miami FL Apr 2006

Abstract: Patel MB, Proctor KG, Veltman Y, Nguyen M, Sinclair SB, Majetschak M. Extracellular ubiquitin increases in human packed red blood cell units during storage.

a. J Surgical Res 2006 Feb; 130(2):226. Presented at 1st Annual Academic Surgical Congress (Association for Academic Surgery) in San Diego, CA Feb 2006.

b. Presented at 17th Annual Fellow, Resident, and Medical Student Surgical Research Forum South Florida Chapter of the American College of Surgeons Miami FL Apr 2006 (* First place Research Award)

Abstract: Patel MB, Feinstein AJ, Majetschak M, Norenberg MD, Proctor KG: Hemoglobin-based oxygen carrier (HBOC) use in neurotrauma care. J Trauma 2005 Dec; 59(6):1539. Presented at 19th Annual Meeting of the Eastern Assoc. for the Surgery of Trauma, Orlando, FL Jan 2006 (* Alexander Research Award)

Abstract: Patel MB, Busby L, Proctor KG, Majetschak M: Assessment of 26S proteasome activity in skeletal muscle after trauma. J Am Coll Surg. 2005; 201 (3S): S32-S33. Presented at 91st Annual Clinical Congress and 60th Annual Surgical Forum, American College of Surgeons, San Francisco, CA Oct 2005

Abstract: Feinstein AJ, Patel MB, Earle SA, Majetschak M, Proctor KG: Resuscitation with pressors after traumatic brain injury.

a. Presented at American College of Surgeons Florida Committee on Trauma Resident Paper Competition, Miami Beach, FL Nov 2004 (* First place Research Award)

b. Presented at American College of Surgeons Region IV Committee on Trauma Resident Paper Competition, Lexington, KY Nov 2004 (* First place Research Award)

c. Presented at American College of Surgeons National Committee on Trauma Resident Paper Competition Washington DC Mar 2005

(DUPLICATE) Abstract: Earle SA, Proctor KG, Patel MB, Majetschak M: Ubiquitin reduces fluid shifts after traumatic brain injury.

a. Presented at American College of Surgeons Florida Committee on Trauma Resident Paper Competition, Miami Beach, FL Nov 2004

b. Presented at The Society of University Surgeons 66th Annual Meeting, Resident Paper Competition Nashville, TN Feb 2005

(DUPLICATE) Abstract: Feinstein AJ, Cohn SM, Sanui M, King DR, Proctor KG: Vasopressin prevents cardiopulmonary collapse after severe chest trauma.

a. J Trauma 2004 Dec; 57(6):1377. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005.

b. Presented at ATACCC2004, Advanced Technology Applications to Combat Casualty Care, St. Pete Beach, FL Aug. 2004.

Abstract: Atapattu S, Cohn SM, Feinstein AJ, Ferrada M, Manning R, Cook K, Proctor KG Novel method for quantifying heart rate variability in patients with traumatic brain injury. J Trauma 2004 Dec; 57(6):1388. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005.

(DUPLICATE) Abstract: King DR, Cohn SM, Lopez PP, deMoya MA, O'Keefe T, Feinstein AJ, Majetschak M, Proctor KG: Systemic coagulation changes caused by pulmonary artery catheters: laboratory findings and clinical correlation. J Trauma 2004 Dec; 57(6):1379. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005 (* Alexander Research Award)

Abstract: Ricci M, Lombardi P, Galindo A, Coscarella E, Vasquez A Proctor KG, Rosenkranz E: Single Ventricle Physiology Reduces Cerebral Oxygen Delivery in a Piglet Model Presented at the 41st Annual Meeting of The Society of Thoracic Surgeons, Tampa, FL, Jan 2005

Awards/Honors/Invention Disclosure

Heart rate variability index to predict severity in patients with traumatic brain injury; KG Proctor and RC Duncan; filed Feb 2006 by Univ of Miami; <http://www.miami.edu/techtransfer>

Mayur B Patel won the first place research award at the 17th Annual Fellow, Resident, and Medical Student Surgical Research Forum South Florida Chapter of the American College of Surgeons Miami FL Apr 2006

Mayur B. Patel won the Alexander Research Award at 19th Annual Meeting of the Eastern Assoc. for the Surgery of Trauma, Orlando, FL Jan 2006

Patents Submitted

Heart rate variability index to predict severity in patients with traumatic brain injury; KG Proctor and RC Duncan; filed Feb 2006 by Univ of Miami; <http://www.miami.edu/techtransfer>

Patents Issued

No patents issued reported.

Technology Transfer

Data were submitted to the Naval Medical Research Center to support the pre-hospital trauma trial with a hemoglobin-based oxygen carrying compound (Principle investigator = CDR DE Freilich)

Confidentiality agreement was signed by Univ of Miami and GE medical systems regarding new method for measuring and interpreting heart rate variability in trauma patients

During the past several years of ONR funding, we have evaluated several compounds that were being developed by bio-pharmaceutical companies for possible use in combat casualty care or civilian trauma. Many of these products are, or have been, used by other DOD-funded investigators, including:

polynitroxylated dextran & hemoglobin from Synzyme Technologies, LLC, Irvine, CA.

6% hetastarch in balanced electrolyte solution from BioTime Inc, Berkely, CA

HBOCs from Baxter Hemoglobin Therapeutics, Boulder, CO and Biopure Corp, Cambridge, MA

ATL-146e from Adenosine Therapeutics, Charlottesville, VA

RDH bandage from Marine Polymer Technologies, Cambridge MA

In addition, we have evaluated several different monitoring devices that have potential usefulness in emergency or field situations:

bispectral EEG analysis from Aspect Medical Systems, Inc., Newton, MA

non-invasive cardiac output monitoring from Novamatrix NICO, Wallingford, CT

heart rate variability from Medical Automation Systems, Charlottesville, VA

Near infrared (NIR) spectroscopy by Hutchinson Technologies (Hutchinson, MN)

thromboelastograph from Haemoscope, Inc Niles, IL

sub-lingual CO2 sensor, Nellcor, Ballwin, MO

portable, automatic ventilator, Impact Instrumentation, West Caldwell, NJ

ONR Database Statistics

Use of Human Subjects	Yes
DoD Personnel Used	
Use of Animals	Yes
Animals Used	Other
Use of Recombinant DNA	No
Degree(s) Granted	0

PI/CoPI Information				
0 PI/CoPI Minority Women **	Minority Non-Minority Total			
0 PI/CoPI Non-Minority Women	Women	0	0	0
0 PI/CoPI Minority Men **	Men	0	0	0
0 PI/CoPI Non-Minority Men	Total	0	0	0

Post Doctoral Information				
1 Post Doctoral Minority Women **	Minority Non-Minority Total			
0 Post Doctoral Non-Minority Women	Women	1	0	1
0 Post Doctoral Minority Men **	Men	0	3	3
3 Post Doctoral Non-Minority Men	Total	1	3	4

Grad Students Information				
0 Grad Students Minority Women **	Minority Non-Minority Total			
0 Grad Students Non-Minority Women	Women	0	0	0
0 Grad Students Minority Men **	Men	0	0	0
0 Grad Students Non-Minority Men	Total	0	0	0

Undergrad Students Information				
0 Undergrad Students Minority Women **	Minority Non-Minority Total			
0 Undergrad Students Non-Minority Women	Women	0	0	0
0 Undergrad Students Minority Men **	Men	0	0	0
0 Undergrad Students Non-Minority Men	Total	0	0	0

Publication Totals	
Total Number of Peer-Reviewed Journal Articles:	11
Total Number of Books or Chapters:	0
Total Number of Technical Reports:	0
Total Number of Patents Issued:	0
Total Number of Patents Pending:	1

*** Under-represented or minority groups include Blacks, Hispanics, and Native Americans. Asians are not considered an under-represented or minority group in science and engineering.*

**** Supported at least 25% this year on contract/grant.*

Other Sponsored Work

No sponsored work reported.

Foreign Collaborations

No foreign collaborations reported.

Uploads

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