Early Resuscitation with Fresh Frozen Plasma for Traumatic Brain Injury Combined with Hemorrhagic Shock Improves Neurologic Recovery

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BACKGROUND: We have shown that early administration of fresh frozen plasma (FFP) reduces the size of brain lesions 6 hours after injury in a large animal model of traumatic brain injury (TBI) and hemorrhagic shock (HS). To examine long-term outcomes, we hypothesized that early treatment with FFP would result in faster neurologic recovery and better long-term outcomes in a combined TBI and HS model.

STUDY DESIGN: Anesthetized Yorkshire swine underwent combined TBI and volume-controlled hemorrhage (40% blood volume). After 2 hours of shock, animals were randomized (n = 5/group) to normal saline (3× shed blood) or FFP (1× shed blood) treatment. A neurologic severity score was assessed for 30 days. Magnetic resonance imaging of the brain was performed at days 3, 10, and 24. Cognitive function was tested by training animals to retrieve food from color-coded boxes.

RESULTS: Neurologic impairment was lower and speed of recovery was considerably faster in the FFP-treated animals. There was a trend toward a smaller lesion size in FFP-treated animal at days 3 and 10, but this did not reach statistical significance. Both groups reached baseline performance on the cognitive testing; however, FFP-treated animals were able to participate, on average, 8 days earlier due to quicker recovery.

CONCLUSIONS: This is the first study to demonstrate the beneficial effects of FFP treatment in a long-term survival model of combined TBI and HS. Our data show that early treatment with FFP substantially attenuates the degree of neurologic impairment, improves the rate of recovery, and preserves the cognitive functions. (J Am Coll Surg 2015;220:809−819. © 2015 by the American College of Surgeons)

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Traumatic injuries are the leading cause of mortality in patients younger than age 46 years in the United States, and account for >5.8 million deaths worldwide.[1-3] Traumatic brain injury (TBI) occurs in 1.7 million people each year in the United States.[4] It is also considered the "signature injury" of the current military conflicts, and was reported in 30,703 military members serving in the combat zone in 2010.[5] Hypotension and hypoxemia are independently associated with substantial increases in morbidity and mortality after TBI.[6] The combination of TBI and hemorrhagic shock (HS) is common and especially lethal, with studies showing that HS can double TBI-associated morbidity and mortality.[7,8] Tissue hypoxia after TBI is an important component of secondary brain injury leading to increased cerebral edema and ICP, and ultimately cell death. The presence of disrupted cerebral autoregulation after TBI exacerbates the ischemic insult that results from HS.[9]

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Abbreviations and Acronyms

FFP = fresh frozen plasma
HS = hemorrhagic shock
MAP = mean arterial pressure
NSS = Neurologic Severity Score
POD = postoperative day
TBI = traumatic brain injury

The ideal resuscitation strategy should replace the lost blood and minimize the secondary brain injury. There have been limited advances in resuscitation strategies for TBI and HS, with isotonic crystalloids serving as the standard resuscitation fluid, without good supporting evidence. We have previously shown that early administration of fresh frozen plasma (FFP) decreases the size of the brain lesion and associated swelling (compared with normal saline) 6 hours after injury in a clinically relevant large animal model of combined TBI and HS. The current study was performed to test whether this early improvement would translate into better long-term outcomes. We hypothesized that treatment with FFP would result in faster neurologic recovery and better long-term outcomes in a combined insult model.

METHODS

All research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals. The study adhered to the principles stated in the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research (2011) and was approved by the appropriate institutional animal care and use committees. Strict aseptic technique was used for all surgical procedures.

Animal selection and preparation

Ten female Yorkshire swine (40 to 45 kg; Michigan State University) were fed a standard diet and observed for at least 1 week to ensure a good state of health. Food was withheld the night before the experiment, but access to water was allowed. Anesthesia was induced with intramuscular injection of ketamine hydrochloride (10 mg/kg) and inhaled isoflurane (4% to 5%). After endotracheal intubation, isoflurane was adjusted between 1% and 3% to maintain inhaled anesthesia for the duration of the procedure. Mechanical ventilation (Narkomed-M; North American Drager) settings included a tidal volume of 10 mL/kg body weight, peak pressure of 20 cm H_2O, and a respiratory rate of 10 breaths/min to maintain an end-tidal PCO_2 of 40 mmHg. A fentanyl patch (75 μg/h) was applied to the skin before incision and continued for 72 hours. One gram of cefazolin was administered preoperatively and re-dosed every 6 hours intraoperatively.

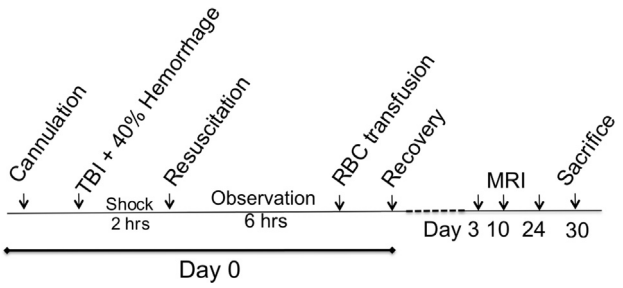

Figure 1. Timeline of hemorrhagic shock and traumatic brain injury (TBI) model.

Instrumentation and monitoring

A timeline of the model is shown in Figure 1. Instrumentation and monitoring are described in detail in previous models.[10-12] Briefly, the bilateral femoral arteries, left femoral vein, and left external jugular vein were cannulated using cut-down technique. A cystostomy tube was placed through a mini-laparotomy for urine output monitoring. Blood pressure, heart rate, pulse oximetry, end-tidal CO_2, cardiac output, venous oxygen saturation, and core body temperature were recorded every 5 minutes.

Laboratory monitoring

Arterial blood gases were withdrawn through the femoral arterial catheter at the following time points: baseline, post shock, post resuscitation, and post observation. Blood gas analysis was performed using the Critical Care Xpress Blood Gas Analyzer (Nova Biochemical). Blood samples were obtained at these time points plus 24 and 72 hours post injury, and plasma was separated and frozen at −80°C. Samples were analyzed for the following: alkaline phosphatase, alanine aminotransferase, aspartate transaminase, creatine kinase, BUN, and creatinine (Quality Veterinary Laboratory). All blood samples were included in the total blood loss calculations.

Controlled cortical impact

A computer-controlled cortical impact device developed by the University of Michigan Medical Innovation Center was used for these experiments based on a previously published model.[13] The impactor device assembly consisted of a voice coil linear actuator with a built-in Linear Variable Differential Transformer displacement