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Hextend–perfluorocarbon cocktail inhibits mean arterial pressure response in a rabbit shock model

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ABSTRACT

Background: Hextend (HEX) is standard of care resuscitation fluid for combat-related traumatic hemorrhage. Because HEX has limited oxygen-carrying capacity, combination therapy with oxygen therapeutics could improve oxygen delivery after hemodynamic shock. We hypothesized that addition of perfluorocarbon (PFC) to HEX would improve hemodynamics and oxygen delivery marker response in a rabbit model of hemorrhagic shock.

Methods: Anesthetized New Zealand rabbits ($n = 23$) were randomly allocated to resuscitation with fresh whole blood (FWB), HEX, or HEX plus PFC (HEX + PFC) after 60 min of hemorrhagic hypotension. Mean arterial pressure (MAP) was sampled every 2–3 min for 120 min postinfusion; MAP profiles were modeled by a one-compartment pharmacokinetic model to determine peak MAP (P_{max}), time to peak MAP (t_{max}), and postinfusion MAP persistence. Arterial blood was sampled every 15 min to examine pH, blood gases PO_2 and pCO_2, metabolites lactate and glucose, methemoglobin (metHb), and electrolytes.

Results: Compared with FWB and HEX, HEX + PFC administration resulted in delayed peak MAP and less persistent ($P < 0.0001$) MAP elevation; metHb was significantly elevated ($P < 0.0001$) compared with FWB and HEX. There were no significant differences in PO_2, pCO_2, or pH. Glucose, hematocrit, and hemoglobin of both HEX and HEX + PFC were significantly lower relative to FWB. Lactate clearance was modest and transient for all treatments; base deficit was significantly more negative for HEX + PFC.

Conclusions: Addition of PFC to HEX did not improve hemodynamics or acidosis. Further dose- and volume-range studies are required to test efficacy of PFC in combination with HEX for hemorrhagic shock.

1. Introduction

Hextend (HEX) is the current combat casualty care field standard for fluid resuscitation after hypovolemic hemorrhagic shock. Current military and/or Tactical Field Care guidelines recommend a 500-mL bolus of HEX to restore or maintain field vital signs (palpable radial pulse, improved mentation) until definitive care; the bolus is repeated once if no improvement is noted in 30 min [1]. This represents a fluid load of roughly 12–14 mL/kg over 30 min for a 75- to 80-kg patient. However, although HEX is an excellent volume expander, it has limited oxygen-carrying capacity. These low volumes may result in patient under-resuscitation if they are not sufficient to correct any persistent oxygen delivery and/or demand mismatch (and resulting oxygen debt) after hemorrhage.

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Combinational therapy consisting of a reduced-volume therapeutic such as HEX with additional agents targeted toward improved tissue oxygen delivery could result in increased efficacy; in addition, a therapeutic that could be administered as a single bolus would have considerable logistic advantages in the far-forward environment [3]. Perfluorocarbon (PFC) emulsions are intravascular oxygen therapeutics that temporarily enhance tissue oxygenation because of increased solubility of physiological gases relative to plasma [4,5]. Increased tissue O_2 delivery is expected to minimize the potential for ischemic tissue damage [5], and therefore, the risk of multiple organ failure. Stand-alone PFC emulsions cannot be used as large-volume replacement fluids as they have no oncotic potential [6]; administration volumes have been limited to a maximum of 6 mL/kg in prior human testing. However, when PFCs are combined with standard plasma expanders animal data suggest that both systemic O_2 delivery and extraction are increased, and in far greater proportions to those expected from the actual volume of PFC infused [7]. Addition of PFC to resuscitation fluids, together with supplementary oxygen, has been demonstrated to result in modest improvements in both regional and/or tissue oxygen delivery [6,8] and systemic oxygenation [6] in animal models of hemorrhagic shock.

To be a useful adjunct, ideally PFC should act synergistically with HEX to compensate for the poor oxygen delivery capacity of HEX and improve hemodynamic support. However, effects of PFC on hemodynamics are rarely evaluated directly, although improvements in systemic hemodynamics have been reported incidental to the primary outcomes of tissue oxygenation [9–11].

In this study, we used a rabbit model of hemorrhagic shock to directly determine effects of combination therapy with PFC on hemodynamics, acidosis, and lactate clearance, a surrogate measure of oxygen debt. We hypothesized that animals treated with a combination of PFC and HEX should show increased benefit (in terms of improved mean arterial pressure [MAP] response, reduced acidosis, and increased speed of lactate clearance) compared with HEX alone. We defined clinical effectiveness in terms of immediacy of effect (increase in MAP support to >60 mm Hg within 20–30 min of infusion), persistence of effect (hemodynamic support maintained for at least 2-h postresuscitation), and clinically relevant outcomes (life support for 2 h and resolution of clinical markers of tissue hypoperfusion by 2-h postinfusion).

2. Materials and methods

2.1. *Animals and animal husbandry*

This study was approved in advance by the Institutional Care and Use Committee of Virginia Commonwealth University (VCU protocol number AD20285) and conforms to the Public Health Service Policy on Humane Care and Use of Laboratory Animals (2002). Twenty-four male SPF New Zealand white rabbits (Robinson Services Inc, Mocksville, NC) were housed individually in standard raised-flooring cages. Toys and grass hay were provided for enrichment. Animals were maintained at approximately 25°C and 12-h light and/or 12-h dark for a minimum of 1 wk in the animal colony before experimentation. Animals were fed commercial pelleted rabbit chow supplemented with grass hay and water *ad lib*.

2.2. *Surgical methods*

Rabbit body weight averaged 3.24 kg (standard deviation [SD], 0.29) on the day of experiment. Animals were not fasted before surgery. Animals were premedicated with ketamine and xylazine (35 and 3–4 mg/kg, respectively) for surgical preparation. Heart rate and pulse oximetry (sPO_2, %) were monitored by a portable veterinary oximeter with the sensor placed on the tongue (PulseSense; NONIN Medical Inc, Plymouth, MN). Airway support was provided with a veterinary supraglottic airway (Rabbit V-gel R3; Docsinnovent, London, United Kingdom). Animals were preoxygenated with 100% O_2 until respiratory quality was adequate and sPO_2 >96%. Anesthetic plane was subsequently maintained by isoflurane (1–3%, balance 100% O_2), with positive end-expiratory pressure of 5–8 cm H_2O, and flow rate 0.5–0.6 L/min; anesthetic plane was assessed every 3–5 min by vital signs and reflex response (corneal reflex, toe pinch, and limb retraction).

Arterial and venous catheters were implanted by surgical isolation and cannulation of the left carotid artery, jugular vein, femoral artery, and femoral vein. Catheters were polyethylene PE-90 tubing and flushed with sterile heparinized normal saline (3 U heparin/mL NS) as needed in volumes sufficient to clear the dead space (<100 μL) to minimize clotting in the lines while avoiding systemic heparinization. The carotid artery and jugular vein were used to monitor MAP and central venous pressure, respectively. During surgery, core temperature was monitored continuously with a rectal probe and maintained at 36.5°C–38°C with a thermostatically controlled feedback heating blanket (Harvard Apparatus, Holliston, MA). Surgical plane of anesthesia was assessed at least every 5 min by vital signs and reflex response (corneal reflex, toe pinch, and limb retraction). Two or three blood samples (100 μL) were obtained during surgery to determine arterial pO_2 and pCO_2 for assessment of oxygenation and ventilation adequacy. Animals were allowed to stabilize for approximately 1 h (median, 61 min; interquartile range, 56–70 min) past the end of surgery; physiological stabilization was defined as MAP >50 mm Hg, lactate <2 mmol/L, pO_2 >400 mm Hg, and pCO_2 of 40–55 mm Hg.

2.3. *Hemorrhage protocol*

Animals were hemorrhaged from the femoral artery. We performed a controlled stepwise hemorrhage by withdrawing blood with a programmable syringe pump (PHD 22/2000 Series; Harvard Apparatus), at 3 mL/kg/min until MAP declined to 40 mm Hg, then continued at 1 mL/kg/min to maintain hypotension (MAP, 35–40 mm Hg) for 60 min. Hemorrhage was paused if MAP remained between 35–40 mm Hg. If MAP <30 mm Hg, autologous shed blood was returned immediately at 3 mL/kg, hemorrhage was resumed when MAP >40 mm Hg.