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TERLIPRESSIN WITH LIMITED FLUID RESUSCITATION IN A SWINE MODEL OF HEMORRHAGE

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□ **Abstract—Background: Principles of damage control resuscitation include minimizing intravenous fluid (IVF) administration while correcting perfusion pressure as quickly as possible. Recent studies have identified a potential advantage of vasopressin over catecholamines in traumatic shock. Terlipressin (TP) is a vasopressin analogue used to reverse certain shock etiologies in some European countries. Study Objective: We evaluated three dosages of TP when combined with a limited colloid resuscitation strategy on mean arterial pressure (MAP) and lactatemia in a swine model of isolated hemorrhage. Methods: Sixty anesthetized swine underwent intubation and severe hemorrhage. Subjects were randomized to one of four resuscitation groups: 4 mL/kg Hextend® (Hospira Inc, Lake Forest, IL) only, 3.75 μg/kg TP + Hextend, 7.5 μg/kg TP + Hextend, or 15 μg/kg TP + Hextend. MAP and heart rate were recorded every 5 min. Baseline and serial lactate values at 30-min intervals were recorded and compared. Results: Subjects receiving 7.5 μg/kg TP had significantly higher MAPs at times t_{15} ($p = 0.012$), t_{20} ($p = 0.004$), t_{25} ($p = 0.018$), t_{30} ($p = 0.032$), t_{35} ($p = 0.030$), and t_{40} ($p = 0.021$). No statistically significant differences in lactate values between TP groups and controls were observed. Conclusion: Subjects receiving 7.5 μg/kg of TP demonstrated improved MAP within 10 min of administration. When combined with minimal IVF resuscitation, TP doses between 3.75 and 15 μg/kg do not elevate lactate levels in hemorrhaged swine. Published by Elsevier Inc.**

□ **Keywords—terlipressin; hemorrhage; military; shock; resuscitation; damage control**

INTRODUCTION

During hemorrhagic shock, data strongly suggest that perfusion pressure should be restored as soon as possible and that delays in correcting hypotension in the field worsen outcomes (1,2). Conventional practice reserves vasopressor use for patients who fail to respond to intravascular repletion with intravenous fluids (IVF), either crystalloid or colloid. The practice reflects concern that if cardiac filling pressures are not optimized before vasopressor administration, excessive vasoconstriction ensues, leading to a paradoxical decrease in vital organ blood flow and elevated lactate levels. For this reason, IVF resuscitation has been the mainstay of field shock reversal during the last century.

Civilian and military medical communities have now embraced limited fluid resuscitation as the ideal strategy

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in uncontrolled hemorrhage (3). To minimize the deleterious effects of IVF resuscitation during hemorrhagic shock, some providers will administer vasoactive medications early, before complete intravascular repletion. Recent animal studies support this practice (4–6). Although the ideal vasopressor choice in trauma patients is debatable, emerging preclinical evidence and case reports suggest that arginine-vasopressin (AVP) and its analogues offer better resuscitation characteristics when compared to catecholamine vasopressors (7–11).

Because AVP requires a continuous infusion due to its extremely short half-life, it is unsuitable for the battlefield environment. Additionally, its use must be guided by meticulous blood pressure monitoring equipment that cannot be maintained in the field. However, terlipressin (TP; N3-triglycyl-8-lysine vasopressin, ProSpec, East Brunswick, NJ), a vasopressin analogue, has an effective half-life of 4–6 h and can be administered in a bolus dose (12). Further, TP has more V1a-receptor agonist activity, making it a more potent vasoconstrictor (13). TP is not available in the United States, but has been used successfully in Europe to reverse hypotension associated with anesthesia overdose, anaphylactic shock, septic shock, and hemorrhage from variceal bleeding (14–19). However, TP's role in traumatic hemorrhagic shock has not been evaluated. The first step in this evaluation is determining the ideal dose of TP in concert with limited IVF resuscitation in a model of isolated hemorrhage.

MATERIALS AND METHODS

This randomized, prospective, controlled trial was approved by the Institutional Animal Care and Use Committee as NMCP Protocol 09-0057, "A randomized controlled trial of terlipressin dosing during small volume resuscitation in a swine model of controlled severe hemorrhage." All research was conducted in compliance with the Animal Welfare Act, and adhered to the principles stated in the *Guide for the Care and Use of Laboratory Animals: Eighth Edition* (20). All animals were maintained in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. A total of 66 farm-raised Yorkshire/Landrace swine (*Sus scrofa*), weighing 29–47 kg, participated in the study. Animals were fed a standard swine diet and observed for a minimum of 5 days to ensure good health. Food was withdrawn the night before the procedures, although water was provided ad libitum.

Animal subjects were pre-medicated with butorphanol (0.1–0.3 mg/kg intramuscularly [i.m.]) and ketamine (20 mg/kg i.m.) in their pens before transport to the operating theater. General anesthesia was induced via facemask with isoflurane (5%) and oxygen flowing at a rate of 2 L/min from an MDS Matrix VMC Small Animal Anesthesia Machine (Matrix Medical, Orchard Park, NY). Once an acceptable level of sedation was achieved, animals were intubated and placed in a supine position on the operating table. Isoflurane was set at 2% or as necessary to maintain a surgical plane of anesthesia, and the subjects were allowed to breathe spontaneously for the duration of the protocol. Continuous vital parameters, including heart rate (HR), oxygen saturation, respiratory rate, and core body temperature were monitored via a Philips MP50 IntelliVue monitoring system (Philips Medical Systems, Böblingen, Germany).

After exposure via cut-down technique, the right carotid artery was cannulated with a 20-gauge catheter for continuous arterial blood pressure monitoring via the Philips MP50 IntelliVue monitor. The external jugular vein was cannulated with a 9-French central venous catheter for blood collection purposes, initial hemorrhage, and infusion of resuscitative fluid. Animals were allowed at least a 15-min stabilization period after placement of catheters, in which vital signs were recorded. Blood was collected from the external jugular catheter to obtain a baseline lactate (iSTAT, Abbott Point of Care Inc., Princeton, NJ) and then monitored every 30 min to assess shock severity. A baseline lactate level < 2 mmol/L was required to enter the protocol. Anesthesia was decreased to 1.5% 5 min before hemorrhage.

Hemorrhage was achieved via blood collection with 60-mL syringes from the external jugular venous catheter. Subjects were hemorrhaged to a mean arterial pressure (MAP) < 25 and a HR increase of 10% over baseline (established by the mean HR over the 5 min before initiation of the bleed). The 60-mL aliquots of blood were dispensed into a pre-weighed suction canister. Subjects were not resuscitated for 10 min after hemorrhage initiation to simulate the time required for hemorrhage control and starting an intravenous line on the battlefield. After this 10-min period, subjects were randomized into one of the four following resuscitative treatment groups consisting of TP (ProSpec, East Brunswick, NJ) and Hextend® (Hospira Inc, Lake Forest, IL), the military's recommended colloidal resuscitation fluid, bolused into the external jugular catheter:

A. No TP bolus + 4 mL/kg of Hextend
B. TP 3.75 μg/kg i.v. bolus + 4 mL/kg of Hextend
C. TP 7.5 μg/kg i.v. bolus + 4 mL/kg of Hextend
D. TP 15 μg/kg i.v. bolus + 4 mL/kg of Hextend

Vital signs were continuously recorded at 5-min intervals throughout the procedure. At 60 min post-hemorrhage, subjects were further resuscitated to their pre-injury MAP by infusion of normal saline to gravity. The volume of normal saline required to maintain the subjects' baseline MAP was recorded. Subjects that survived through 120 min after hemorrhage time were