Slow Intravenous Infusion of a Novel Damage Control Cocktail Decreases Blood Loss in a Pig Polytrauma Model

Nathan J. White, MD, MS[1]; Chloe Asato, BS[2]; Andrew Wenthe, BS, MS, SOCM[3]; Xu Wang, MD[4]; Kristyn Ringgold, PhD[5]; Alexander St. John, MD, MS[6]; Chang Yeop Han, PhD[7]; Jennifer C. Bennett, DVM, MS[8]; Susan A. Stern, MD[9]*

ABSTRACT

Background: Our objective was to optimize a novel damage control resuscitation (DCR) cocktail composed of hydroxyethyl starch, vasopressin, and fibrinogen concentrate for the polytraumatized casualty. We hypothesized that slow intravenous infusion of the DCR cocktail in a pig polytrauma model would decrease internal hemorrhage and improve survival compared with bolus administration. **Methods:** We induced polytrauma, including traumatic brain injury (TBI), femoral fracture, hemorrhagic shock, and free bleeding from aortic tear injury, in 18 farm pigs. The DCR cocktail consisted of 6% hydroxyethyl starch in Ringer's lactate solution (14mL/kg), vasopressin (0.8U/kg), and fibrinogen concentrate (100mg/kg) in a total fluid volume of 20mL/kg that was either divided in half and given as two boluses separated by 30 minutes as control or given as a continuous slow infusion over 60 minutes. Nine animals were studied per group and monitored for up to 3 hours. Outcomes included internal blood loss, survival, hemodynamics, lactate concentration, and organ blood flow obtained by colored microsphere injection. **Results:** Mean internal blood loss was significantly decreased by 11.1mL/kg with infusion compared with the bolus group ($p = .038$). Survival to 3 hours was 80% with infusion and 40% with bolus, which was not statistically different (Kaplan Meier log-rank test, $p = .17$). Overall blood pressure was increased ($p < .001$), and blood lactate concentration was decreased ($p < .001$) with infusion compared with bolus. There were no differences in organ blood flow ($p > .09$). **Conclusion:** Controlled infusion of a novel DCR cocktail decreased hemorrhage and improved resuscitation in this polytrauma model compared with bolus. The rate of infusion of intravenous fluids should be considered as an important aspect of DCR.

KEYWORDS: *hemorrhage; resuscitation; hemorrhagic shock, traumatic brain injury; fibrinogen; vasopressin; combat casualty care*

Introduction

Hemorrhage is the leading cause of preventable death from battlefield injuries, and more than 90% of these deaths take place in the prehospital environment.[1] In the Special Forces community, hemorrhage from explosions and gunshot wounds has consistently been the leading cause of potentially survivable death for the past 20 years, including, crucially, death from noncompressible torso hemorrhage (NCTH).[2,3] Importantly, polytrauma that includes both TBI and hemorrhagic shock often coincide.[4–6] This is critical because even brief episodes of hypotension induced by hemorrhage can exacerbate TBI mortality.[7–9]

The concept of advanced resuscitative care was introduced by the Committee on Tactical Combat Casualty Care (TCCC) to meet the need for better treatment of battlefield hemorrhage, including NCTH.[10] Advanced resuscitative care interventions include frontline whole blood transfusion, tranexamic acid, and zone 1 (i.e., above the celiac artery) resuscitative endovascular balloon occlusion of the aorta (REBOA). However, operationalizing whole blood transfusions and REBOA on the battlefield is difficult because of the lack of immediate supply and logistics.

Combat medics are tasked to sustain a casualty for up to 72 hours prior to turning over to a higher echelon of care. The quality of care and likelihood of survival, however, are highly contingent on the resources available to the medic on scene. Typically, a 30-person element will have up to four medics, with the average closer to three. In an ideal situation, two will carry their own med bags while the other two carry Golden Minute Containers (Bloodstone, Tampa, FL) that include blood coolers to facilitate whole blood transfusion. It is likely, however, that at least one will carry a casualty litter instead of a med bag or blood cooler. In some cases, when vehicles are employed as a mode of transportation, medics are afforded space for a truck bag in a designated "med vic" to store extra supplies; however, this is not always the case and cannot be relied upon. Within each med bag, medics will typically carry two to four extremity tourniquets, a junctional tourniquet, a pelvic binder, endotracheal tubes, a bag valve mask, a manual suction pump, intravenous/intraosseous access supplies, drugs, blood draw/administration supplies, saline (to reconstitute drugs), hypertonic saline, a pulse oximeter, and sometimes a

*Correspondence to whiten4@uw.edu

[1]**Dr Nathan J. White** is affiliated with the University of Washington School of Medicine, Department of Emergency Medicine, Seattle, WA, and the University of Washington Resuscitation Engineering Science Unit (RESCU), Seattle. [2]**Chloe Asato** is affiliated with the John A. Burns School of Medicine, University of Hawaii, Honolulu, HI. [3]**Andrew Wenthe** is affiliated with the U.S. Navy, Active Duty, Special Operations Combat Medic–SOCM, Fort Bragg, NC. [4]**Dr Xu Wang,** [5]**Dr Kristyn Ringgold**, [6]**Dr Alexander St. John**, and [7]**Dr Chang Yeop Han** are affiliated with the University of Washington School of Medicine, Department of Emergency Medicine, Seattle, and the University of Washington Resuscitation Engineering Science Unit (RESCU), Seattle. [8]**Dr Jennifer C. Bennett** is affiliated with the University of Washington School of Medicine, Department of Emergency Medicine, Seattle, the University of Washington Resuscitation Engineering Science Unit (RESCU), Seattle, and the University of Washington Department of Comparative Medicine, Seattle. [9]**Dr Susan A. Stern** is affiliated with the University of Washington School of Medicine, Department of Emergency Medicine, Seattle, and the University of Washington Resuscitation Engineering Science Unit (RESCU), Seattle.

portable ultrasound machine. Therefore, medics today lack logistical options for providing whole blood transfusions to multiple casualties and for sustaining polytrauma patients over prolonged periods.

To meet the need for a deployable far-forward resuscitation fluid capable of extending survivability of polytrauma casualties when whole blood is unavailable, we developed a multifunctional DCR cocktail. The DCR cocktail was built upon a base of 6% hydroxyethyl starch solution (Hextend; Pfizer, Kalamazoo, MI) to expand intravascular volume. In previous published work,[11] we found that Hextend alone was insufficient to raise blood pressure during resuscitation of polytrauma because of TBI-induced systemic vasoplegia. In response, we added vasopressin to support neurovascular tone and finally fibrinogen concentrate to support hemostasis. Vasopressin and Hextend recovered impaired systemic blood pressure responses after combined TBI with hemorrhage, but also increased internal blood loss resulting from NCTH. Therefore, fibrinogen concentrate was added to the cocktail as a hemostatic agent, resulting in decreased internal blood loss, improved blood pressure, and improved vital organ blood flow when given as discrete boluses, according to TCCC doctrine.[11,12] However, with the bolus method of delivery of the cocktail, we observed that blood pressure tended to spike, likely contributing to increased internal blood loss from NCTH.

The objective of this study was to further optimize the DCR cocktail as a potential solution for immediate resuscitation of the polytraumatized casualty by determining its most appropriate intravenous delivery method. We hypothesized that the cocktail would decrease internal hemorrhage and increase 3-hour survival when infused slowly compared with rapid bolus administration by avoiding early spikes in systemic blood pressure that may exacerbate bleeding. To test this hypothesis, we tested equal total volumes of the DCR cocktail administered as two separate boluses versus a single slow infusion using a preclinical swine model simulating battlefield polytrauma with NCTH.

Methods

We used a previously published porcine model of polytrauma with hemorrhagic shock with TBI and NCTH to compare bolus versus slow infusion of the DCR cocktail.[11] This protocol was approved by the University of Washington Office of Animal Welfare and the U.S. Army Animal Care and Use Review Office. Briefly, female Yorkshire swine (*Sus scrofa domestica*; Progressive Swine Farms, Woodinville, WA) weighing 20kg to 30kg were used for this study. The animals were sedated using intramuscular ketamine (30mg/kg) (Bioniche Pharma, Galway, Ireland), intubated, and provided general anesthesia using inhaled isoflurane (1%–4%) (VetOne, Boise, ID) for the remainder of the experiment. Animals were ventilated (Anesco SAV 2000 and 2500 ventilators, Anesco, Georgetown, KY), and fraction of inspired oxygen (FiO_2) was titrated to an arterial O_2 saturation >95%, while end-tidal CO_2 (Capnomac Ultima, Datex, Madison, WI) was maintained at 35mmHg to 40mmHg. For additional analgesia, intramuscular buprenorphine (0.01mg/kg) (Ben Venue Laboratories, Bedford, OH) was given as a single injection. A warming blanket was used to maintain normothermic core body temperature (37°C to 38°C [98.6°F to 100.4°F]) and was monitored using a pulmonary artery catheter.

Animals were instrumented as previously described with ECG leads, left femoral artery and vein catheters, and a right carotid artery sheath for continuous blood pressure measurement and arterial blood sampling. Vital signs and hemodynamics were monitored continuously (Biopac Systems, Goleta, CA). In addition, a 5-French pig-tail catheter was placed into the left ventricle for pressure monitoring and injection of colored microspheres, and a pulmonary artery thermodilution catheter (Edwards Life Sciences, Irvine, CA) was inserted via the right external jugular vein into the pulmonary artery for cardiac output (CO), and core temperature monitoring.

A midline laparotomy was performed for splenectomy to prevent autotransfusion, and an infrarenal aortotomy wire was placed to induce an aortic tear of 4-mm internal luminal length. The wire was exteriorized through the abdominal incision, and the incision was closed at the skin using surgical staples. The right anterior mid femur was then exposed after incising the skin and performing blunt dissection to prepare for percussive femoral fracture.

To induce TBI, pigs were then rotated to the prone position, a scalp incision was made, and the cranium was exposed. A 16mm-diameter craniotomy hole was placed rightward of the sagittal suture and anterior to the coronal suture. A bolt was then placed firmly into the craniotomy site, approximating the intact dura and connected to the fluid percussion device. Additional small craniotomies were made to place a neonatal intraventricular catheter (Phoenix Biomedical, Valley Forge, PA) for intracranial pressure (ICP) monitoring (SenSym pressure sensor, Sunnyvale, CA). All craniotomy sites were sealed completely with dental cement.

Injury and Hemorrhage Protocol

The pigs then underwent a stabilization period after instrumentation for at least 30 minutes, during which baseline measurements were recorded. TBI was then induced using a fluid percussion device delivering a 15msec pressure wave of 3 to 3.5 atmospheres to the intact dura, as previously described.[11] The pigs were then rotated to the supine position, and an open comminuted diaphyseal femoral fracture was induced by firing a captive bolt pistol (Schermer Stunner, Model MKL, Karl Schermer, Karlsruhe, Germany) directly against the exposed femur using a 0.22-caliber blank round. Simultaneously, catheter hemorrhage was started via the left femoral arterial catheter and controlled by computer-driven roller pump, as previously described.[13–15] At mean arterial pressure (MAP) equal to 50mmHg, the aortic tear injury was created by pulling the aortotomy wire. Catheter hemorrhage was titrated to achieve MAP equal to 30mmHg until hemorrhagic shock was confirmed by an arterial lactate concentration >2.0mmol/L, typically after 15 minutes had elapsed.

Resuscitation Protocol

One dose of the DCR cocktail consisted of 7mL/kg of 6% hydroxyethyl starch in Ringer's lactate solution (Hextend), vasopressin (0.4U/kg), and fibrinogen concentrate (50mg/kg, RiaSTAP®, CSL Behring) in a total fluid volume of 10mL/kg and infused together over 10 minutes using an infusion pump. Over the first hour of fluid resuscitation, the bolus group received two 10mL/kg boluses, for a total of 20mL/kg of DCR cocktail volume. Each individual bolus was infused over 10 minutes using a roller pump, and boluses were separated by 30 minutes. The infusion group received the same total volume

of DCR cocktail infused at a constant 0.33mL/kg/min rate to achieve an equivalent total volume of 20mL/kg over 1 hour.

No other fluid resuscitation was given, and pigs were monitored for up to 3 hours after the start of fluid resuscitation or until the time of spontaneous death, defined as a loss of pulsatile arterial blood pressure waveform and MAP <20mmHg for at least 1 minute. Animals were euthanized under anesthesia with an overdose of pentobarbital (100mg/kg) (Med-Pharmex, Pomona, CA).

Outcome Measurements

Primary outcome measurements were intraperitoneal blood loss measured at the time of death or at 3 hours using preweighed laparotomy sponges, reported in mL/kg and as the bleeding rate adjusted for survival time in mL/kg/min, and time-to-event survival to 3 hours. Secondary outcomes included hemodynamics, metabolic markers of resuscitation (Radiometer Medical ABL 505, EML 100, and OSM3, Brønshøj, Denmark), complete blood counts (VetScan HM2, Allied Analytic, Tampa, FL), rotational thromboelastometry (ROTEM; Instrumentation Laboratory, Bedford, MA) with whole blood and fibrin-specific clot measurements using platelet-poor plasma obtained by centrifugation, and vital organ microvascular blood flow measured using colored microsphere injection (Dye-Trak® Microspheres, Triton Technology, Seattle, WA) (intravenous, 1mL, 3 million/mL) at the predetermined time points at baseline, 60, 120, and 180 minutes, as previously described in detail.[11]

Statistical Analysis

Data from 18 animals divided into two groups of nine per group were summarized using mean and standard deviation (SD) when normally distributed, or median with interquartile range (IQR) when significantly skewed. Student's *t*-test, analysis of variance (ANOVA), or Wilcoxon rank sums were used to compare continuous outcomes at single points, as indicated. Serial continuous data were compared using repeated measures (RM) ANOVA using effects of protocol time and treatment group, with Tukey-Kramer adjustment for multiple comparisons. Pearson product-moment correlations were used to examine for significant associations between continuous outcome variables. Time-to-event Kaplan-Meier survival analysis was used to compare survival to 3 hours. All differences were considered statistically significant at $p < .05$. All statistical analysis was performed with SAS JMP, version 15 (SAS, Cary, NC). Based on our previous work using similar polytrauma models, a decrease of approximately 15mL/kg of intraperitoneal blood volume from 30mL/kg (SD, 10mL/kg) improved survival. Therefore, to detect a difference in survival related to a 15mL/kg decrease in intraperitoneal bleeding, nine pigs in each group were required to achieve 80% power to detect differences with alpha = 0.05

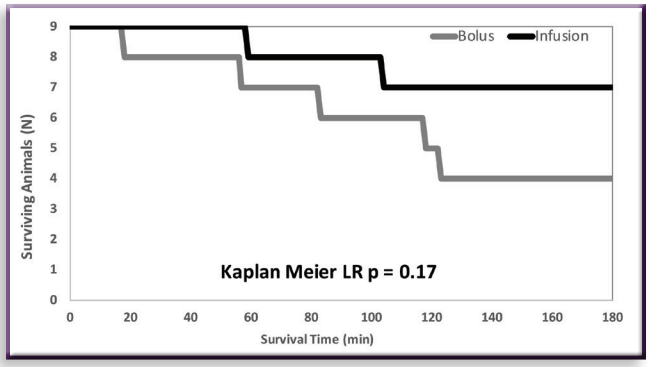
Results

There were no baseline differences in weight, TBI percussion, catheter hemorrhage volume, and lactate at the start of resuscitation between bolus and infusion groups (Table 1). All animals in all groups received a total of 20mL/kg of DCR cocktail.

Blood Loss, Survival, and Coagulation

Internal hemorrhage volume was significantly decreased by 42% with infusion versus bolus (t-test, $p = .038$) (Table 1.) Median (IQR) intraperitoneal bleeding rate adjusted for survival time was 0.26 (0.06, 0.56) mL/kg/min with bolus and 0.058 (0.03, 0.22) with infusion (Wilcoxon $p = .09$). Internal hemorrhage volume was also significantly and negatively correlated with survival time ($r = –0.85$; $p < .001$). Survival to 3 hours was 80% with infusion versus 40% with bolus. However, survival was not statistically different between treatment groups (Kaplan Meier log-rank, $p = .17$) (Figure 1).

FIGURE 1 *Kaplan-Meier survival plot comparing time-to-event survival to 180 minutes for bolus versus infusion groups. There was a nonsignificant increase of survival from 40% with bolus to 80% with slow infusion (Kaplan-Meier log-rank [LR], p = .17).*



ROTEM was measured using the EXTEM assay in whole blood and in platelet-poor plasma. Maximal clot firmness decreased significantly from baseline in plasma and was not different between treatment groups. Whole blood ROTEM parameters did not change significantly over time or between treatment groups (Table 2). These data indicate that differences in hemorrhage between groups could not be attributed to differences in coagulation state.

Hemodynamics and Resuscitation

Overall MAP was increased during resuscitation with infusion compared with bolus (RM ANOVA treatment group effect,

TABLE 1 *Outcomes*

Factor	Bolus			Infusion			*t*-test
Variable	N	Mean	SD	N	Mean	SD	*p* value
Weight (kg)	9	21.7	2.6	9	20.8	1.7	0.391
Percussion (Atm)	9	3.5	0.3	9	3.5	0.3	0.852
Cath. Hemorrhage Volume at T0 (mL/kg)	9	16.0	1.3	9	16.6	2.9	0.566
Intraperitoneal Hemorrhage Volume (mL/kg)	9	26.1	13.4	9	15.0	11.2	0.038
Total Hemorrhage Volume (mL/kg)	9	42.2	13.9	9	31.7	11.2	0.049
T0* Arterial Lactate	9	2.3	0.6	9	2.6	0.6	0.369
Survival Time (min)	9	124.3	61.2	9	158.1	44.9	0.202

*T0 denotes time of onset of fluid resuscitation.

TABLE 2 *ROTEM Clot Formation Parameters for Bolus and Infusion Groups Measured Using EXTEM at Baseline and During Resuscitation Using Whole Blood and Plasma**

		Baseline		T0		T30		T60		T120		T180	
Whole Blood EXTEM		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Bolus	CT (s)	59.6	7.5	53.8	7.4	57.4	11.1	97	31.6	56.6	10.1	58.8	12.4
	CFT (s)	56.6	10.4	53.2	9.7	76	7.3	61.3	17.3	92.4	15.7	84.8	12.6
	MCF (mm)	73	3.3	72.7	4.1	70	2.4	61.3	2.6	68.4	4.6	69.8	3.6
	LI30 (%)	99.4	0.9	99.6	0.7	100	0	69.1	8.4	100	0	100	0
Infusion	CT (s)	57.8	5.2	56.2	8.9	61.7	6.9	93.7	21.5	57.1	11.3	61.9	7.8
	CFT (s)	58.3	11.8	87.8	102.7	80.2	10.7	69.3	4.3	84.7	13.8	77.6	13.8
	MCF (mm)	72.8	4.2	68.6	12.6	70.9	3	61.3	2.4	71.1	3.3	71.4	3.7
	LI30 (%)	100	0	99.8	0.4	100	0	—	—	100	0	100	0
Plasma EXTEM		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Bolus	CT (s)	56.9	5.3	49.4	4.8	52.4	7.5	55.4	6.7	55.4	6.7	49.5	6.8
	CFT (s)	272.9	177.1	542.8	551.5	2945.5	1131	1810	0	3253.5	1979	1957	0
	MCF (mm)	24.8	4.5	22.9	3.7	17.1	2.5	16.5	2.4	16.2	3.4	17.8	3.3
	LI30 (%)	99.9	0.3	100	0	99.9	0.4	98.4	3.8	100	0	99.8	0.5
Infusion	CT (s)	58.6	5.7	49.8	5.4	54.2	9	59.4	4.3	58.4	6.1	54.9	5.4
	CFT (s)	641.6	329.2	973.8	641.8	2235.5	874.7	—	—	2580.3	890.8	1318.3	643.6
	MCF (mm)	22.9	2.3	19.7	2.8	16.4	2	15.2	1.0	18.1	1.5	19.3	2.8
	LI30 (%)	100	0	99.7	1	98.8	1.9	100	0	99.9	0.4	100	0

*Two-way repeated measures ANOVA with Tukey adjustment revealed no statistical difference between bolus and infusion group ROTEM parameters at individual time points.

T# denotes time after onset of fluid resuscitation in minutes.

ANOVA, analysis of variance; CFT, clot formation time; CT, clotting time; LI30%, lysis index at 30 minutes after MCF; MCF, maximal clot firmness; ROTEM, rotational thromboelastometry

$p < .001$). This difference was attributable to significantly increased MAP at 30 and 60 minutes specifically (RM ANOVA treatment group interaction effect, $p = .002$), where MAP was increased by an average of 18.6mmHg and 30.2mmHg with infusion compared with bolus, respectively (Figure 2A). Overall mean cardiac output measured by thermodilution during resuscitation peaked later with infusion compared with bolus but was not statistically different between treatment groups (RM ANOVA treatment group effect, $p = .28$) (Figure 2B). Overall mean (SD) arterial lactate concentration during resuscitation was decreased with infusion at 2.6 (2.5) mmol/L compared with bolus at 4.2 (3.5) mmol/L (RM ANOVA treatment group effect, $p < .001$). There were no significant individual differences in lactate concentration between groups at specific time points (RM ANOVA interaction effect, $p = .32$) (Figure 2C). These data suggest that improvements in hemodynamics with infusion translated to improved metabolic resuscitation compared with bolus.

Cerebral Resuscitation

Mean ICP was increased overall during resuscitation with infusion at 10.6mmHg compared with bolus at 5.9mmHg (RM ANOVA treatment group, $p < .001$). However, elevations of ICP did not reach the critical threshold of >20mmHg, and there were no individual times when ICP was different during resuscitation (RM ANOVA treatment group × protocol time interaction, $p = .26$) (Figure 3). Mean overall cerebral perfusion pressure, calculated as MAP minus ICP, was also significantly increased during resuscitation at 36.4mmHg with infusion versus 31.3mmHg with bolus treatment (RM ANOVA treatment group, $p = .015$). Again, there were no individual differences at specific time points measured for cerebral perfusion pressure (RM ANOVA treatment group × protocol time interaction, $p = .43$). These results suggest that infusion supported cerebral hemodynamics marginally better than bolus did.

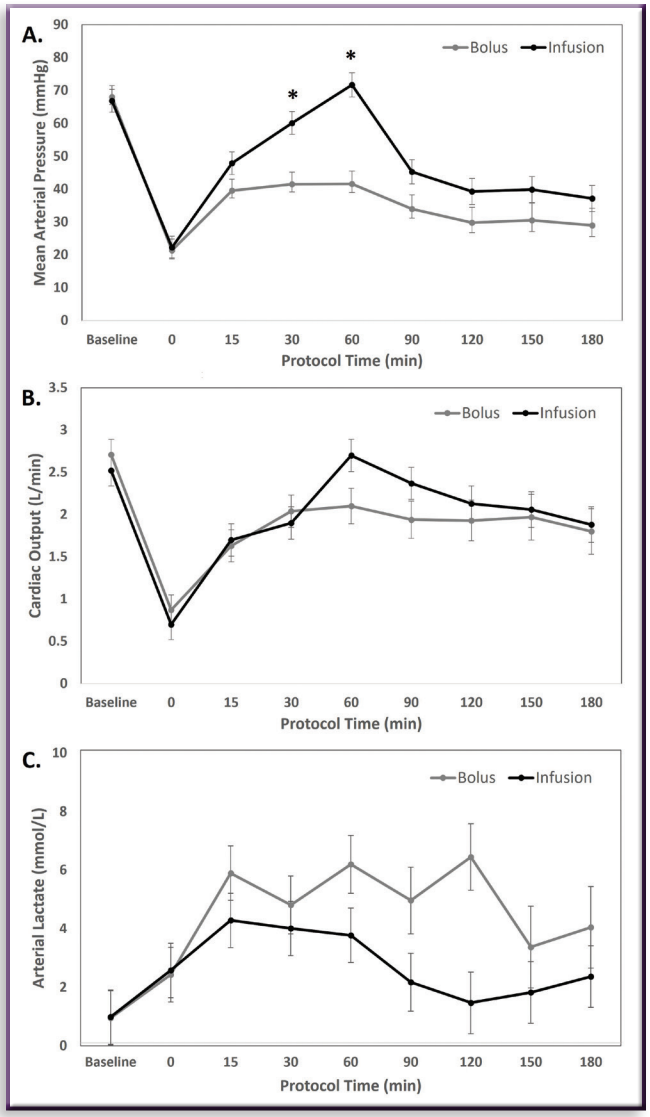
Vital Organ Blood Flow

Vital organ blood flow was measured using colored microsphere injection and reported in mL/min/g tissue for brain, ileum, kidney, and myocardium (Figure 4). Vital organ blood flow tended to decrease from baseline during hemorrhage in all groups, and there was no significant effect of treatment group on vital organ blood flow during resuscitation (RM ANOVA treatment group p values >.09). Overall, there were no detrimental effects of infusion on vital organ blood flow compared with bolus.

The First 60 Minutes

Using the same polytrauma model, we previously reported that adding vasopressin to Hextend boluses had the effect of increasing systemic blood pressure and intraperitoneal blood loss.[12] However, this behavior was different with the current experiments where MAP was paradoxically increased, and blood loss decreased in the infusion group. To investigate this finding in more detail, we resampled MAP data from available continuous Biopac Systems data every 30 seconds for the first 60 minutes of fluid resuscitation and compared the MAP differences between the infusion and bolus groups (Figure 5). We found that during the first bolus, from 0 to 10 minutes, mean (SD) MAP was significantly increased, with bolus at 33.2 (11.8)mmHg versus infusion at 28.8 (12.7)mmHg (ANOVA group, $p = .001$). During the 10- to 40-minute period following the first bolus, MAP was significantly decreased, with bolus at 41.4 (13.8)mmHg versus infusion at 52.0 (17.1) mmHg (ANOVA group, $p < .001$). During the second bolus at 40 to 50 minutes, MAP remained significantly decreased, with bolus at 54.1 (20.5)mmHg versus infusion at 58.5 (19.4) mmHg (ANOVA group, $p = .038$). MAP remained decreased, with bolus at 48.4 (20.7)mmHg versus infusion at 59.4 (22.0) mmHg, until the end of infusion at 60 minutes (ANOVA group, $p < .001$). These data suggest that increased systemic blood

FIGURE 2 *Hemodynamics and metabolic resuscitation.* **(A)** *Average mean arterial pressure (MAP),* **(B)** *cardiac output measured by thermodilution, and* **(C)** *arterial lactate concentration for bolus and infusion groups plotted over time.*



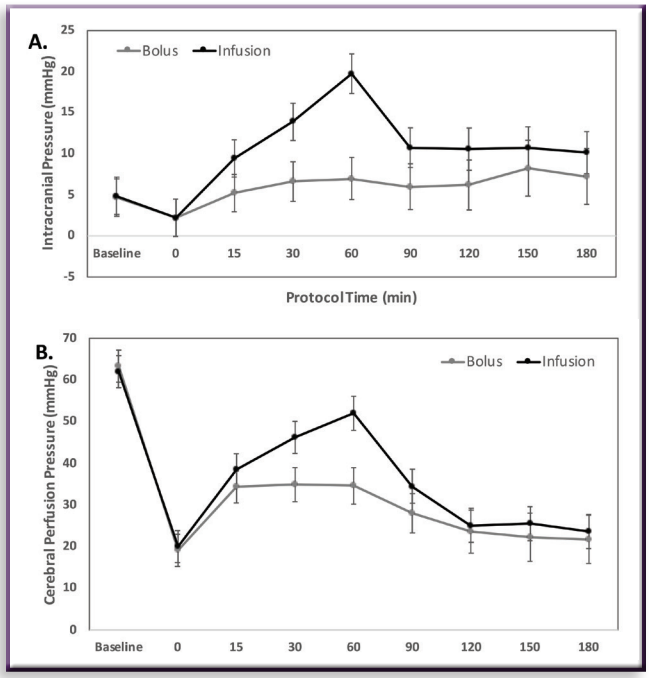
*Indicates significant individual difference vs bolus group at designated time after Tukey adjustment for multiple comparisons.
Error bars = 95% confidence interval.

pressure during the first DCR cocktail bolus is the likely culprit that increased internal blood loss in the bolus group, despite inducing overall lower blood pressure during the first 60 minutes.

Discussion

The primary result of this study is that slow infusion of the DCR cocktail decreased internal hemorrhage compared with bolus administration in a swine model of polytrauma with TBI and NCTH. We attribute the increased hemorrhage volume with the bolus group to early increased systemic blood pressure during the first bolus. Alternative explanations, including differences in overall fluid infusion volumes, initial blood loss, or clot formation, do not appear to apply because they were similar between groups. In addition, slow infusion of the DCR cocktail provided improved hemodynamic, metabolic, and cerebral resuscitation parameters without negatively affecting vital organ perfusion.

FIGURE 3 *Intracranial pressure and cerebral perfusion pressure. ICP was increased overall during resuscitation with infusion, averaging 10.6mmHg compared with bolus at 5.9mmHg (RM ANOVA treatment group, p < .001). However, there were no individual differences during resuscitation (RM ANOVA interaction, p = .26). Mean CPP was als o significantly increased overall during resuscitation at 36.4mmHg with infusion versus 31.3mmHg with bolus treatment (RM ANOVA treatment group, p = .015). Again, there were no individual differences at specific time points measured for CPP (RM ANOVA treatment group*protocol time interaction, p = .43).*

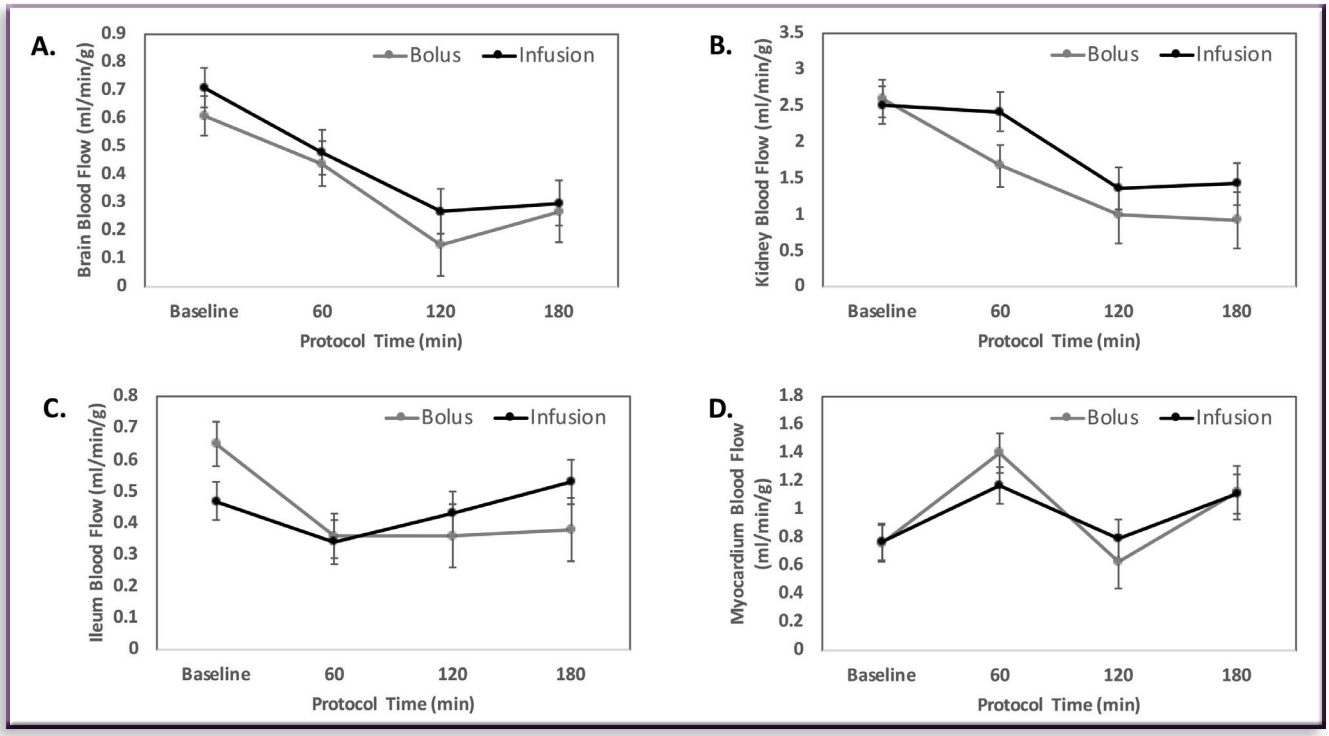


CPP, cranial perfusion pressure; ICP, intracranial perfusion pressure; RM ANOVA, repeated measures analysis of variance
Error bars = 95% confidence interval

It is notable that the blood pressure within the bolus group was increased only with the first bolus compared with infusion, suggesting that early increased blood loss induced an inability to recover hemodynamics during subsequent fluid boluses later during resuscitation. Similar results were seen in a previous porcine NCTH model reported by Stern et al[16] using 7.5% NaCl/6% dextran-70 (dextran-70, Rugby® Laboratories, Livonia, MI). The authors found that infusing the resuscitation fluid at one-third the control rate improved 90-minute survival and decreased intraperitoneal blood loss. Systemic blood pressure was increased during the first 15 minutes of resuscitation in the faster infusion group.[16] These results point toward the first 10 to 15 minutes of fluid resuscitation of NCTH as being a critical time that should be managed very carefully to avoid inducing rebleeding events. Therefore, a more measured approach to fluid resuscitation of NCTH, given more slowly and over longer periods of time, may more readily achieve the goal of providing limited resuscitation without encouraging rebleeding.

Limited or delayed resuscitation of hemorrhagic shock is not a new concept and is a core tenant of damage control resuscitation, where the primary intent is to preserve life rather than provide full physiologic resuscitation.[17] Limiting fluid resuscitation has been operationalized with good effect in several different ways in clinical trials, including limiting the volume of resuscitation fluids given, decreasing goal blood-pressure targets, and delaying the onset of fluid resuscitation.[18–20] Our

FIGURE 4 *Vital organ blood flow. Least squares mean blood flow measured using colored microsphere injection in mL/min/g tissue for* **(A)** *brain,* **(B)** *ileum,* **(C)** *kidney, and* **(D)** *myocardium. There was no effect of treatment group on vital organ blood flow during resuscitation (RM ANOVA treatment group p values >.09).*



Error bars = 95% CI.

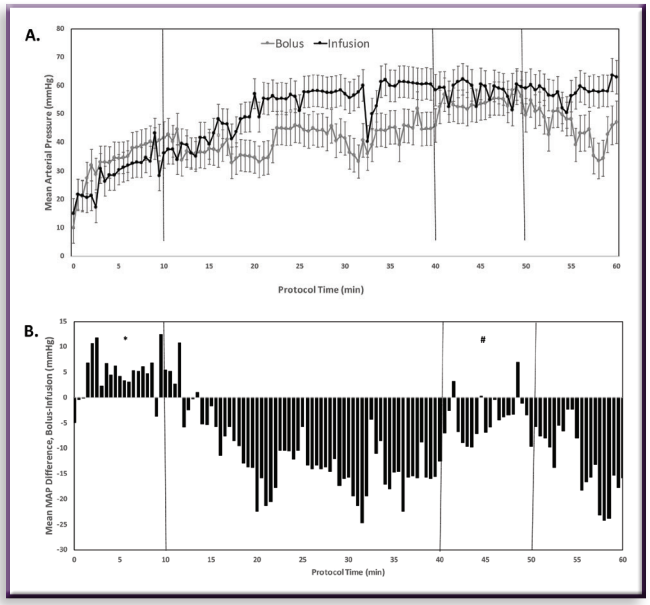
study adds to this evidence by supporting controlling the rate of fluid infusion as an additional strategy for use during damage control resuscitation.

Current TCCC guidelines prescribe the use of whole blood and blood products as the first-line fluids for resuscitation of hemorrhagic shock.[21] However, it is not clear that blood-based resuscitation can provide cardiovascular support required to overcome dysregulation of vascular tone after TBI.[22] Vasopressin was added as a component of the DCR cocktail precisely because volume expansion alone was incapable of restoring systemic blood pressure after TBI.[12] Stadlbauer et al[23] compared vasopressin alone versus fluid resuscitation and no resuscitation in a swine liver injury model. Vasopressin (0.4U/kg bolus and 0.08U/kg/min infusion) outperformed aggressive fluid resuscitation for a period of free bleeding lasting only 30 minutes prior to definitive surgical hemostasis and blood transfusion. In this case, blood pressure was increased with vasopressin without increased internal hemorrhage. However, lactate also increased during this time, indicating a lack of metabolic resuscitation with vasopressin alone.[23] Therefore, we might expect that vasopressin alone in our polytrauma model would enhance early survival but would likely lead to increased later mortality from shock. Conversely, whole blood and blood products may be favorable precisely because they may not induce the sharp spikes in blood pressure seen with colloids and vasopressors and may provide additional oxygen-carrying capacity. The DCR cocktail is intended to be used when blood products are not available, not to replace them. Therefore, further investigation comparing the DCR cocktail to blood-based resuscitation is planned and will be required to determine whether the same hemodynamic responses induced by our DCR cocktail also apply to blood-based fluid resuscitation strategies.

The primary clinical implication for these results is the potential extension of survivability of polytraumatized NCTH casualties until blood products become available. Whole blood transfusions are not always tactically feasible. Forward-operating elements are limited in the amount of blood that can be carried onto the battlefield because of weight and logistical requirements. Ideally, a 30-person element is equipped with 2 × Golden Minute containers, each holding two units of blood. On average, a patient overseas with noncompressible hemorrhage who is a transient responder will require a minimum of six units to survive transport to a hospital. Once a prepositioned supply is exhausted, medics must resort to a "walking blood bank" protocol, which can take up to an hour from point of injury, depending on battlefield conditions and the availability of a type O low-titer doner. Donors cannot be type-specific to a patient because blood in a Golden Minute container will be type O, and once introduced, it is against policy to transfuse a new blood type. Furthermore, donating blood on the battlefield reduces combat effectiveness for the duration of the procedure.

Given the small volume and portability of the DCR cocktail, it is a viable option for combat medics during TCCC's Tactical Field Care phase once intravenous access is established. The early use of vasopressin may also be advantageous. A systematic review of 433 animals in 15 preclinical studies of hemorrhagic shock demonstrated a mortality benefit for vasopressin compared with fluid resuscitation and other vasopressors.[24] A randomized controlled trial of vasopressin supplementation for resuscitation of mostly penetrating-trauma patients also reduced the overall quantity of blood products required in the first 48 hours.[25] These favorable effects of vasopressin may allow medics to extend survival and resuscitate patients while also conserving limited supplies of blood products. Similarly,

FIGURE 5 *Mean arterial pressure plotted during the first 60 minutes of fluid resuscitation.* **(A)** *Mean MAP was extracted every 30 seconds and plotted by group for the first 60 minutes of resuscitation.* **(B)** *The mean difference plotted. MAP was initially increased briefly with bolus compared with infusion at the onset of fluid resuscitation, but then decreased for the remainder of the first 60 minutes. Data in panel A are plotted as means with fitted smoothed line graph.*



*Denotes time period of first bolus, 0 to 10 minutes.
#Denotes time period of second bolus, 40 to 50 minutes.
Error bars = standard deviation
MAP, mean arterial pressure

such a DCR cocktail would be advantageous in the setting of civilian rural trauma, where prehospital transport times are often protracted and significantly longer compared with the urban setting.[26,27]

Limitations

Our study is limited in several ways. First, the DCR cocktail was tested in a preclinical porcine model of anesthetized polytrauma with hemorrhagic shock. Important contributions to coagulopathy and survival, including hypothermia, were not addressed in this study. Next, a single aortic-tear injury type was tested, so we cannot predict similar results for alternative injury profiles, such as solid organ injury. We did not do direct comparisons to vasopressin alone. In a previous study, [12] we found that vasopressin bolus spiked blood pressure and increased internal blood loss in this model. So, we do expect that infusing vasopressin more slowly would have similar beneficial effects in terms of reducing internal hemorrhage. Regardless, vasopressin should be viewed as a potential confounder because of its effects on blood pressure, bleeding, and the need for subsequent blood product transfusion. We also did not test the DCR cocktail in combination with whole blood transfusion but are planning such comparisons in future work. Finally, the number of anticipated animals tested per group (nine) was insufficient to provide reliable survival data because the anticipated 15mL/kg difference in intraperitoneal blood loss was not achieved.

Conclusion

Our results suggest that the rate of infusion is an important variable that should be considered and tested when designing resuscitative fluids for DCR of polytrauma with NCTH.

Author Contributions

NJW and SAS conceived the study concept and obtained funding. XW, KR, CYH, and JCB conducted experiments and provided critical input and revisions to the project. CA and AW provided key data analysis and interpretation. NJW wrote the first draft, and all authors provided critical revision and read and approved the final manuscript.

Financial Disclosure

The authors have indicated they have no personal financial relationships relevant to this article to disclose.

Funding

This work was supported by U.S. Department of Defense Award W81XWH-17-1-065, Defense Medical Research and Development Program—Prolonged Field Care Research Award. Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the Dept. of Defense.

References

1. **Kotwal RS, Janak JC, Howard JT, et al.** United States military fatalities during Operation Inherent Resolve and Operation Freedom's Sentinel. *Mil Med*. 2022 May 11:usac119.
2. **Holcomb JB, McMullin NR, Pearse L, et al.** Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001–2004. *Ann Surg*. 2007;245(6):986–991.
3. **Kotwal RS, Mazuchowski EL, Howard JT, et al.** United States Special Operations Command fatality study of subcommands, units, and trends. *J Trauma Acute Care Surg*. 2020;89(2S Suppl 2):S213–S224.
4. **McMahon CG, Yates DW, Campbell FM, Hollis S, Woodford M.** Unexpected contribution of moderate traumatic brain injury to death after major trauma. *J Trauma*. 1999;47(5):891–895.
5. **Chesnut RM, Marshall LF, Klauber MR, et al.** The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34(2):216–222.
6. **Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF.** Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)*. 1993;59:121–125.
7. **Wald SL, Shackford SR, Fenwick J.** The effect of secondary insults on mortality and long-term disability after severe head injury in a rural region without a trauma system. *J Trauma*. 1993;34(3):377–381.
8. **Stocchetti N, Furlan A, Volta F.** Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma*. 1996;40(5):764–767.
9. **Pietropaoli JA, Rogers FB, Shackford SR, Wald SL, Schmoker JD, Zhuang J.** The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. *J Trauma*. 1992;33(3):403–407.
10. **Butler FK Jr, Holcomb JB, Shackelford SA, et al.** Advanced resuscitative care in Tactical Combat Casualty Care: TCCC Guidelines Change 18-01:14 October 2018. *J Spec Oper Med*. 2018;18(4):37–55.
11. **St John AE, Wang X, Ringgold K, et al.** A multifunctional, low-volume resuscitation cocktail improves vital organ blood flow and hemostasis in a pig model of polytrauma with traumatic brain injury. *J Clin Med*. 2021;10(23):5484.
12. **Dickson JM, Wang X, St John AE, Lim EB, Stern SA, White NJ.** Damage control resuscitation supplemented with vasopressin in a severe polytrauma model with traumatic brain injury and uncontrolled internal hemorrhage. *Mil Med*. 2018;183(9-10):e460–e466.
13. **Stern SA, Dronen SC, Birrer P, Wang X.** Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. *Ann Emerg Med*. 1993;22(2):155–163.
14. **Stern SA, Dronen SC, Wang X.** Multiple resuscitation regimens in a near-fatal porcine aortic injury hemorrhage model. *Acad Emerg Med*. 1995;2(2):89–97.

15. **Zink BJ, Stern SA, McBeth BD, Wang X, Mertz M.** Effects of ethanol on limited resuscitation in a model of traumatic brain injury and hemorrhagic shock. *J Neurosurg*. 2006;105(6):884–893.
16. **Stern SA, Kowalenko T, Younger J, Wang X, Dronen SC.** Comparison of the effects of bolus vs. slow infusion of 7.5% NaCl/6% dextran-70 in a model of near-lethal uncontrolled hemorrhage. *Shock*. 2000;14(6):616–622.
17. **Velez DR.** The history of hemorrhagic shock and damage control resuscitation. *Am Surg*. 2022;88(11):2656–2659.
18. **Schreiber MA, Meier EN, Tisherman SA, et al; ROC Investigators.** A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. *J Trauma Acute Care Surg*. 2015;78(4):687–695.
19. **Safiejko K, Smereka J, Filipiak KJ, et al.** Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock: a systematic review and meta-analysis of randomized controlled trials. *Cardiol J*. 2022;29(3):463–471.
20. **Bickell WH, Wall MJ Jr, Pepe PE, et al.** Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331(17):1105–1109.
21. **Deaton TG, Auten JD, Betzold R, et al.** Fluid resuscitation in Tactical Combat Casualty Care; TCCC Guidelines Change 21-01. 4 November 2021. *J Spec Oper Med*. 2021;21(4):126–137.
22. **Varsos GV, Budohoski KP, Kolias AG, et al.** Relationship of vascular wall tension and autoregulation following traumatic brain injury. *Neurocrit Care*. 2014;21(2):266–274.
23. **Stadlbauer KH, Wagner-Berger HG, Raedler C, et al.** Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. *Anesthesiology*. 2003;98(3):699–704.
24. **Cossu AP, Mura P, De Giudici LM, et al.** Vasopressin in hemorrhagic shock: a systematic review and meta-analysis of randomized animal trials. *Biomed Res Int*. 2014;2014:421291.
25. **Sims CA, Holena D, Kim P, et al.** Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. *JAMA Surg*. 2019;154(11):994–1003.
26. **Gerhardt RT, Strandenes G, Cap AP; THOR Network and RemTORN Study Groups.** Remote damage control resuscitation and the Solstrand Conference: defining the need, the language, and a way forward. *Transfusion*. 2013;53 Suppl 1:9S–16S.
27. **Esposito TJ, Maier RV, Rivara FP, et al.** The impact of variation in trauma care times: urban versus rural. *Prehosp Disaster Med*. 1995;10(3):161–166.

PMID: 37224392; *DOI:* 10.55460/MB9O-LXOB

The Special Operations Medical Association's Official Journal

JSOM

JOURNAL *of* SPECIAL OPERATIONS MEDICINE™

Fall 2023
Volume 23, Edition 3

THE JOURNAL FOR OPERATIONAL MEDICINE AND TACTICAL CASUALTY CARE

Inside this Issue:

- FEATURE ARTICLES: DripAssist and Traditional Methods for Rate Infusions
- Military Physician Telemedicine in Turkey
- SOF Cognitive Assessments
- WWII Yugoslav Guerrilla Hospital › Combat Vascular Access
- Intranasal Analgesia in French Armed Forces
- Psychological Strategies in EOD Technicians
- IV Infusion of a DCR Cocktail Decreases Blood Loss in a Pig Model
- Unconventional Resilience › Artificial Blood Development
- Rib Fracture POC Ultrasound & Pain Control › Sympathoadrenal Activity in Cold Water Diving
- CASE REPORT: Phosphorus Burn Management
- ONGOING SERIES: Human Performance Optimization, Prolonged Casualty Care, Book Review, TECC for TEMS Updates, TCCC Updates, *and more!*

Dedicated to the Indomitable Spirit, Lessons Learned & Sacrifices of the SOF Medic

A Peer Reviewed Journal That Brings Together The Global Interests of Special Operations' First Responders