Effects of Fluid Volume of Resuscitation Following Induction of Hemorrhagic Shock

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Abstract

One standard of resuscitation while using fluids to resuscitate for hemorrhagic shock is the infusion of three times lost blood volume (LBV) with crystalloid fluids. During a rat hemorrhage study, hematuria was observed after infusion of 3 times lost blood volume of crystalloids, indicating possible over-perfusion. It was hypothesized that infusion of a lower rate would ameliorate this effect and improve outcomes. In this study, shock was induced by performing a controlled bleed of approximately 40% blood loss in two groups of study rats (each n=5), and resuscitated them with normal saline. One group was resuscitated with an infusion of 1.5 times LBV and the other with 3 times LBV. The results did not support the hypothesis, as both groups (n=5) had a similar mortality rate, although the cause of death was different in each group. The rats infused with 3 times LBV died of complications relating to overperfusion, and those infused with 1.5 times LBV died of complications relating to hemorrhage. This likely indicates that an ideal reperfusion volume of crystalloid solution lies somewhere between 1.5 and 3 times LBV.

INTRODUCTION:

Traumatic hemorrhage is the leading cause of preventable death in both civilian and military settings. (Champion HR, 2003). The American College of Surgeons (ACS) has established 4 classes of hemorrhage:

- **Class I Hemorrhage** involves up to 15% of blood volume. There is typically no change in vital signs and fluid resuscitation is not usually necessary.
- **Class II Hemorrhage** involves 15-30% of total blood volume. A patient is often tachycardic (rapid heart beat) with a reduction in the difference between the systolic and diastolic blood pressures. The body attempts to compensate with peripheral vasoconstriction. Skin may start to look pale and be cool to the touch. The patient may exhibit slight changes in behavior. Volume resuscitation with crystalloids (normal saline solution or Lactated Ringer's solution) is all that is typically required. Blood transfusion is not usually required.
- **Class III Hemorrhage** involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral hypo-perfusion (shock) with diminished capillary refill occurs, and the mental status worsens. Fluid resuscitation with crystalloid and blood transfusion are usually necessary.
- **Class IV Hemorrhage** involves loss of >40% of circulating blood volume. The limit of the body's compensation is reached and aggressive resuscitation is required to prevent death.

(American College of Surgeons Committee on Trauma, 2018)

ATLS Guidelines refer to the “3-to-1 rule,” which refers to the fact that patients in hemorrhagic shock can require up to 300 mL of crystalloid for every 100 mL of blood loss. (American College of Surgeons, 2008) This rule of thumb grew out of observations made during the Vietnam war that showed that patients in prolonged hemorrhagic hypotension required isotonic crystalloid infusion of two to three times the estimated volume of blood loss in order to survive. (Krausz, 2006) Application of this rule should be tempered by the knowledge that volume replacement needs to be be adjusted to the patient’s response to therapy, not just their initial classification. (American College of Surgeons, 2008)

Veterinary literature recommends treating shock with crystalloids based on the animal’s weight in kg and species (90 ml/kg for a dog, 55 ml/kg for a cat – no data found for rodents). (DiBartola, 2000) Other therapies exist (Hildebrand, 2013) (Rasmussen KC, 2016), however the original intent of this study was to explore the treatment of hemorrhage / shock with the infusion of 3 times lost blood volume of crystalloid solution.

The initial resuscitation of moderate/severe hemorrhagic shock includes the administration of isotonic crystalloids, colloids, or blood products to increase the blood volume to allow the circulatory system to deliver the remaining blood to the organs and tissues. Toward this end, both crystalloids and colloids replace the volume of blood lost, but provide no other support. For Class III hemorrhage, the ACS recommends a crystalloid (Lactated Ringers solution (LRS), normal saline (NS) etc.) and blood (American College of Surgeons Committee on Trauma, 2018). Tactical Combat Casualty Care (TCCC) guidelines for resuscitation of shock recommend resuscitation fluids to be given in descending order of preference: whole blood; plasma, red blood cells (RBC's) and platelets in a 1:1:1 ratio; plasma and RBC's in a 1:1 ratio; plasma or RBC's alone; Hextend; and crystalloid (Lactated Ringer's or Plasma-Lyte A) (National Association of Emergency Medical Technicians (NAEMT), 2018).

Additionally, after work on this study was completed, Tactical Combat Casualty Care (TCCC or TC3) guidelines changed and no longer include NS, substituting instead Lactated Ringers (LR) or Plasma-Lyte A as crystalloids for volume resuscitation (National Association of Emergency Medical Technicians (NAEMT), 2018). This is likely because Lactated Ringers has been found to be superior to NS for fluid resuscitation, although there were not significant differences in outcomes between patients resuscitated with each. (Mane, 2017 November) Several studies have shown that NS can induce hyperchloremic acidosis (Burdett, 2003 October), (Eisenhut, 2006 September), (Mellor, 1999) and often requires the administration of bicarbonates to counteract this response. This then can induce a cascade of other adverse sequelae, such as volume overload, exacerbation of hypertension and reduction in ionized calcium (Kraut, 2014) which can cause further patient decompensation. Lactated Ringers solution contains other electrolytes such as potassium, calcium and lactate, which can enter the Krebs cycle and form bicarbonates as an end product and can correct the acidosis induced by the saline components of the solution. Furthermore, there is evidence that the extravasation of fluid into the tissues is higher with NS. (Laszlo, 2017)

Normal saline was chosen due to its long history and the fact that it is still a common and viable option and remains a standby for daily use in animal and human medicine. Normal saline is believed to have originated as a primary resuscitation fluid during the European cholera epidemic of 1831 and is still a leading choice today. (Awad S, 2008 April). It is remains a commonly used and readily available resuscitation fluid and may be the only crystalloid available to a combat medical provider in an austere environment or on the front lines. Additionally, providers in the environments described may not have access to blood and blood products, or may not have these products in sufficient quantity, and thus may be limited in their choices to prolong survival for the first 72 hours or even longer. In these circumstances, NS, if available, can and should be used to prolong life until definitive care is available.

Given our concerns about hematuria and possible over-perfusion, we hypothesized that an infusion of NS equal to 1.5 times the LBV would be superior in resuscitation of the subject to an infusion of 3 times LBV.

METHODS:

Animals: 10 male Sprague-Dawley rats (Hilltop Animal Laboratory, Scottdale, PA) weighing 300–400 g were used in this study. The animals were kept in an AAALAC accredited facility with a 12-hour light/dark cycle with free access to food and water until the day of the experiment. The experiments were conducted at Hilltop Animal Laboratories in Scottdale, PA under an approved US Army Medical Research and Material Command, Animal Care and Use Review Office Protocol.

Surgical procedure: The animals were anesthetized with an intramuscular injection of Telazol (25mg/kg)/Dexdomitor (1.5mg/kg) and given Buprenex (0.05 mg/kg sc) for pain prophylaxis. The neck and inner leg were shaved, and then swabbed with Betadine and then a 70% ethanol scrub. Lidocaine 1% was locally applied before performing surgical cut downs for vascular access. Animals were kept in a supine position throughout the experiment. Silicone catheters (30cm x 3fr) were placed into the carotid artery, external jugular vein, and femoral artery and secured with 4.0 silk ties.

Monitoring: The rats were maintained on a heating pad throughout the study. Continuous mean arterial pressures (MAP) and heart rate were monitored with a Biopac Mp160 signal amplifier connected to a pressure transducer attached to the carotid artery catheter. ABG measurements were taken at Time = 0, 70 minutes (end of shock), 2 hours, and 6 hours.

Hemorrhage/Shock: The animals were bled into heparinized 10 cc syringes using a 2-stage syringe pump (New Era Pump Systems, Farmingdale, NY) at a rate of 0.64 ml/min until a

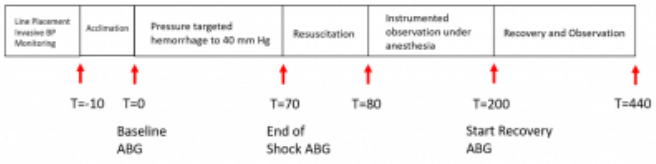
MAP of 40 mm Hg was reached. The total blood loss was approximately 40%. The animals were held at a MAP of 40 mm Hg with subsequent withdrawals or infusions of blood during the 1-hour shock period prior to start of fluid resuscitation.

Fluid Resuscitation: The animals were randomized into two groups. One group (n=5) received 3 times the lost blood volume of NS. The other group (n=5) received 1.5 times the blood loss volume of NS. The fluid was infused over 10 minutes using the syringe pump, at a rate calculated to replace the lost blood volume of each individual animal in that time period. Once administration of resuscitation fluids was completed, animals were observed and arterial blood gas measurements were taken under anesthesia at end of shock (70 minutes) end of resuscitation (80 minutes) and again after 2 hours. At the end of this period, the catheters were tied off and the incision closed with surgical clips. The animals were then recovered and observed for an additional 4 hours. At the completion of the 4 hour observation period, the knot was clipped and a final ABG was collected with a 23g needle before the rats were euthanized. During the observation period, the animals were observed for signs of regaining consciousness - righting response, gross movement, etc. Although none recovered consciousness, it was during the recovery / observation phase that hematuria was noted in all the 3 times LBV group.

Arterial Blood Gas Measurements: Arterial blood gas (ABG) was measured using an ABL90 Flex (Radiometer) at 4 time points: Pre-hemorrhage (baseline; T= 0), Post-hemorrhage (end of shock; T = 70 minutes), 2 hours post-resuscitation and at the end of the study period (440 minutes).

Figure 1

Rat Pressure Targeted Hemorrhage Model

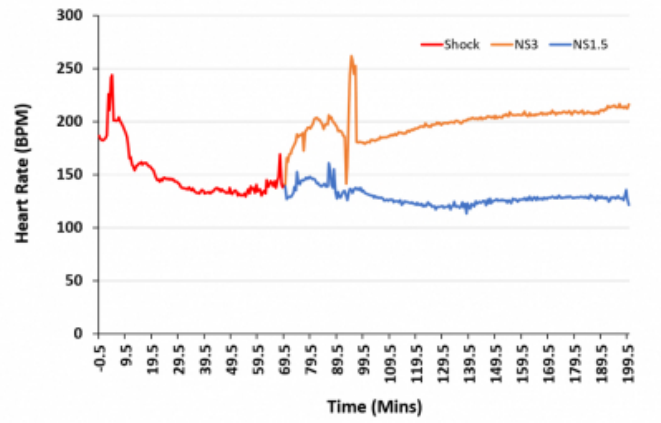


RESULTS:

Both groups had a pre-shock heart rate of approximately 200 bpm, and a heart rate of approximately 130 bpm during the pressure-targeted portion of the study. After resuscitation, the In the 1.5 times LBV group, the heart rate remained at or slightly below the shock heart rate, while the post-resuscitation heart rate of the 3 times LBV group returned to at or slightly above their pre-resuscitation heart rate of 200 bpm.

Figure 2

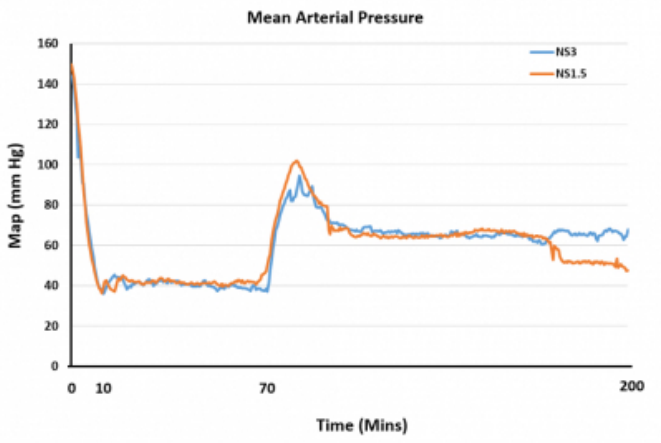
Rat Heart Rates by Group



Both groups had similar MAPs throughout most of the study, which was expected in the first portion as it was pressure-targeted with a goal MAP of 40mm Hg. During most of the post-resuscitation phase in which the animals were instrumented and under anesthesia (T = 80 minutes to T = 200 minutes), both groups had similar MAPs. However the 1.5 times LBV group's MAP dropped from approximately 65mm Hg to approximately 50mm Hg within the last 30 minutes prior to the beginning of the recovery and observation phase (from approximately T=170 to T=200). This end-of-study drop was still above the MAP of 40 mm Hg at 70 minutes, when resuscitation was initiated.

Figure 3

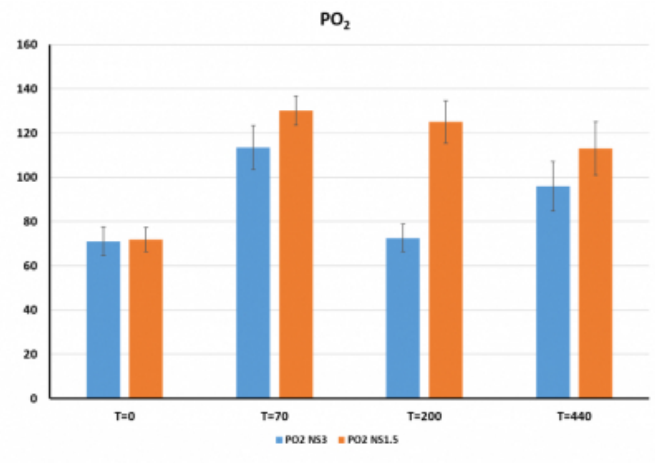
Mean Arterial Pressure by Group



The PO2 (mm Hg) and sO2 (%) of the 1.5 times LBV group was higher on average than the NS3 group throughout the study. This is expected, as the blood of the 1.5 times LBV group was less diluted and thus had a higher O2 carrying capacity.

Figure 4

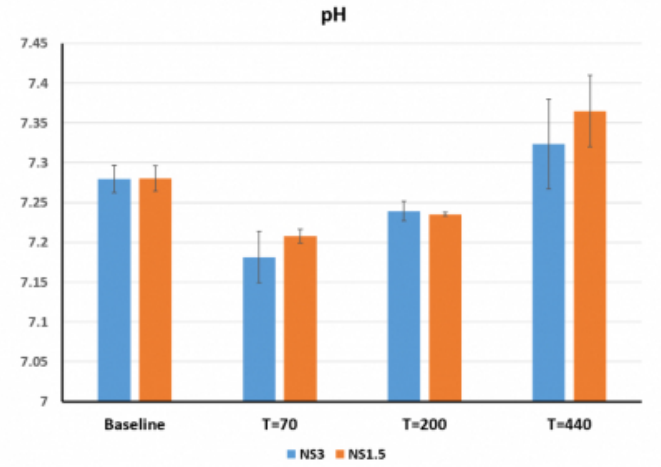
PO2 by Group



Furthermore, although the bloodwork indicates a metabolic acidosis in both groups, it was determined to be more severe in the 3 times LBV group, with a lower pH and higher base deficit, indicating that the degree of acidosis did in fact correlate with the volume of resuscitation.

Figure 5

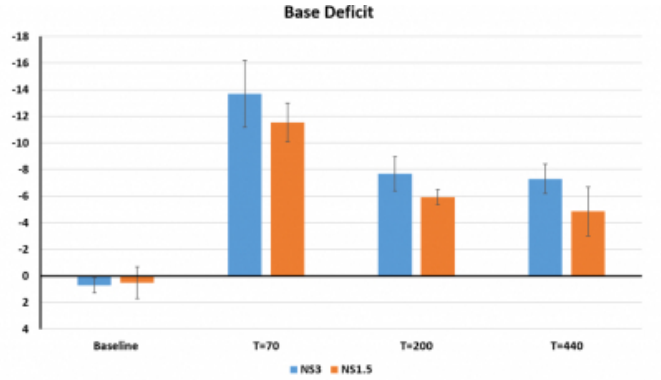
pH by Group



The lactate of the 1.5 times LBV group was lower than that of the 3 times LBV group throughout the study, and this was the only marker that was statistically significant at 200 and 440 minutes. The other markers showed trends but did not reach significance between the groups, likely due to the small number of animals in each group.

Figure 6

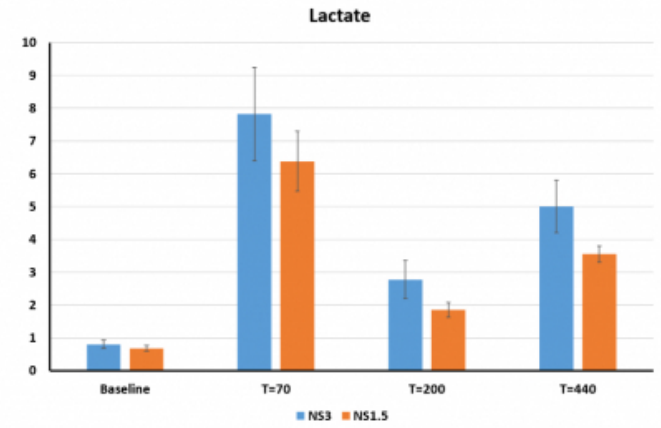
Base Deficit by Group



The data was analyzed by a 2 tailed T-test using the Graphpad Prism software. Overall survival was not significantly different between the 2 treatment groups based on analysis by Log rank test. A sample size of 5 per group allowed us to still reach 80% power while maintaining an alpha of 0.05.

Figure 7

Lactate by Group



DISCUSSION:

Results did not support the hypothesis that infusion of a lower rate would ameliorate the negative physiologic effects and improve outcomes. Instead, it was determined that death rates were similar for both groups. Interestingly, though, the cause of death appeared to be different for each group. It appeared that the rats re-perfused with 1.5 times LBV were more likely to die of hemorrhagic / hypovolemic shock and its sequelae. However, all of the animals re-perfused with 3 times LBV developed hematuria post-perfusion, therefore they most likely died of over-perfusion / hyper-volemic sequelae.

Over-perfusion is a pathological entity by itself, potentially

resulting in coagulopathy secondary to hemodilution (St. John A, 2018). Furthermore, over-perfusion with NS can result in hyperchloremic acidosis (Burdett, 2003 October), (Eisenhut, 2006 September), (Mellor, 1999). Given that coagulopathy and acidosis are two thirds of the "deadly triad" which consists of coagulopathy, acidosis and hypothermia, preventing or avoiding these sequelae are important therapeutic considerations. Current fluid resuscitation algorithms attempt to focus on replacing lost volume in order to improve and sustain tissue oxygenation without over-perfusing the patient. This can be a delicate balance to strike, and in these rats, the balance between hypovolemic shock and over-perfusion seemed to favor neither group, although the 3 times LBV group did have a slightly higher survival rate beyond 250 minutes.

CONCLUSION:

More fluid is not always better. As a single therapeutic option, crystalloids alone in rats may be associated with suboptimal outcome as compared to polytherapy or whole blood replacement. However, as a sole therapy option, an optimal balance may be reached by reperfusing somewhere between 1.5 and 3 times the calculated LBV. This data may be extrapolated to larger animal species and humans, and if so may affect emergency practices, particularly in situations where crystalloid replacement is the only resuscitation fluid available, as may be the case in battlefield conditions where a combat medic will have limited fluid replacement options. In this study, although the parameters measured did appear to favor the 1.5 times LBV group, survival rates did not favor either group. Furthermore, although other factors may be at play, it appears that for NS and perhaps for other crystalloids, optimal resuscitation volume may lie between 1.5 and 3 times lost blood volume. Further study would be required to clarify what, if any, difference there is and where the optimum resuscitation volume lies. Further studies should also investigate the effect of different resuscitation fluids (i.e. fresh whole blood, Hextend, LRS, etc.) on survival in a rat 40% hemorrhage model.

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