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Variable Saline Concentrations for Initial Resuscitation Following Polytrauma

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14. ABSTRACT

Optimal resuscitation fluid of the injured patient has yet to be established. We investigated the utility of standard variable saline concentrations (0.9%, 3%, 23.4%) in a murine polytrauma model of traumatic brain injury and hemorrhagic shock. Animals were evaluated for survival, hemodynamics, physiologic, and inflammatory response following injury and resuscitation. Our results demonstrated that high-concentration, low-volume saline resuscitation leads to increased mortality despite decreased posttraumatic cerebral edema. In addition, 3% saline may be the optimal crystalloid fluid to resuscitate in the setting of hypotension after head injury, as it limits ongoing inflammation, cerebral edema, and neurologic injury while preserving blood pressure and survival.

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1.0 SUMMARY

Optimal resuscitation fluid of the injured patient has yet to be established. We investigated the utility of standard variable saline concentrations (0.9%, 3%, 23.4%) in a murine polytrauma model of traumatic brain injury and hemorrhagic shock. Animals were evaluated for survival, hemodynamics, physiologic, and inflammatory response following injury and resuscitation. Our results demonstrated that high-concentration, low-volume saline resuscitation leads to increased mortality despite decreased posttraumatic cerebral edema. In addition, 3% saline may be the optimal crystalloid fluid to resuscitate in the setting of hypotension after head injury, as it limits ongoing inflammation, cerebral edema, and neurologic injury while preserving blood pressure and survival.

2.0 BACKGROUND

Optimal resuscitation of the far-forward casualty has yet to be established. Challenges in the resuscitation of a patient in an austere environment include transportable fluid volume and selecting the ideal fluid to improve end-organ perfusion in the presence of polytrauma, including traumatic brain injury (TBI) [1]. Current literature demonstrates the use of either 3% or 7.5% hypertonic saline for prehospital resuscitation of hemorrhagic shock with conflicting results [2-9]. Although 3% saline is used as a 250-mL bolus or continuous drip for patients with elevated intracranial pressure after TBI, 7.5% saline is not stocked as a standard fluid in most institutions for either treatment of TBI or hemorrhage. However, 23.4% saline is currently used clinically to rapidly decrease elevated intracranial pressure and is stocked as a standard concentration fluid. The advantage of using 23.4% saline, especially in a far-forward environment, is that it is a small volume (15-30 mL), allowing ease of transport and administration by first responders even in a far-forward environment [10]. Despite its efficacy in reducing intracranial hypertension with small volume boluses, 23.4% saline has not yet been investigated for its hemodynamic and resuscitative effects.

3.0 METHODS

3.1 Mouse Model of Mild TBI

Closed head injury was performed utilizing a weight drop device. Each mouse was anesthetized for 2 minutes with 2% isoflurane in 100% oxygen at 1 L/min. Animals were placed in a prone position on the platform below the weight drop device so the device was centered along the sagittal suture between the coronal and lambdoid suture lines. Head injury was induced by dropping a cylindrical rod weighing 400 grams from 1.5 cm. Sham TBI mice were anesthetized with isoflurane, but not subjected to the head injury.

3.2 Mouse Model of Hemorrhagic Shock

Ten minutes after TBI, mice were anesthetized with intraperitoneal pentobarbital (0.1 mg/g body weight) and the femoral artery was cannulated. Mice were placed on continuous hemodynamic monitoring (Harvard Apparatus) on a circulating water warming pad to maintain normothermia. After an initial period of equilibration, mice were hemorrhaged to a systolic

blood pressure (SBP) of 25 mmHg by rapidly withdrawing blood volume. After pressure-controlled hemorrhagic shock of 60 minutes, mice were resuscitated with varying saline resuscitation strategies to a targeted SBP of 80 mmHg. After adequate resuscitation, mice were decannulated, recovered, and then sacrificed at intervals for blood and tissue harvesting. Sham mice underwent anesthesia and femoral cannulation without hemorrhage. Resuscitation strategies included 0.9% saline, 3% saline, or 0.1 mL 23.4% saline given as a sole resuscitation fluid or as an initial 0.1-mL bolus followed by 0.9% saline (23.4% & 0.9%).

Shed blood volumes, resuscitation fluid volumes administered, and resulting SBPs were recorded. Survival was followed for 6 hours following hemorrhagic shock.

3.3 Electrolyte and Physiologic Evaluation

At 30 minutes and 4 hours post-resuscitation, blood samples were obtained by cardiac puncture following intraperitoneal pentobarbital anesthesia. Samples were analyzed on an iSTAT to determine hemoglobin, hematocrit, blood urea nitrogen (BUN), glucose, chloride, sodium, potassium, pH, partial pressure of carbon dioxide, bicarbonate (HCO_3), anion gap, lactate, and base excess.

3.4 Serum/Tissue Analysis

Blood samples were obtained by cardiac puncture. Brain tissue was harvested after decapitation. Brain cortical samples were homogenized in 1 mL of phosphate-buffered solution containing a complete protease inhibitor (Roche, IN). Supernatents were centrifuged three times at 12,000 rpm for 15 minutes each. Blood samples underwent centrifugation of 8000 rpm for 10 minutes in serum separator tubes. All samples were stored at -80°C until analysis. Serum and cerebral samples were evaluated at 30 minutes and 4 hours after resuscitation for multiple cytokines and chemokines by multiplex enzyme-linked immunosorbent assay (ELISA) (Quansys, UT), including interleukin-1 alpha and beta (IL-1α and IL-1β), IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, monocyte chemoattractant protein (MCP)-1, interferon-gamma (IFN-γ), macrophage inflammatory protein (MIP)-1α, regulated on activation, normal T-cell expressed and secreted (RANTES), granulocyte macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor alpha (TNFα). Serum samples were additionally analyzed by ELISA for neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) concentration as indicators of cerebral cellular injury. Brain samples were perfusion fixed and evaluated for extent of injury with hematoxylin and eosin staining.

3.5 Capillary Leak and Blood Brain Barrier Integrity

Integrity of the blood brain barrier was assessed by injecting 20 mg/kg 4% Evans blue dye via femoral artery catheter at the end of resuscitation. One hour after the completion of resuscitation, mice were anesthetized with intraperitoneal pentobarbital (0.1 mg/g body weight). The right ventricle was cannulated and inferior vena cava divided. The mice were then perfused with 10 mL heparinized (20 units/mL) phosphate-buffered saline at a continuous infusion rate of 3 mL/min by perfusion pump. Cerebral tissue was placed in 2 mL formamide, homogenized, and placed at 60°C for 24 hours. The specimens were centrifuged at 13,000 rpm for 10 minutes and

the supernatant was collected and centrifuged again at 13,000 rpm for 10 minutes. The supernatant was then analyzed in duplicate for Evans blue concentration by measuring the absorbance against a standard curve at 620 nm. Additional analysis of capillary leak and cerebral edema was performed using wet-to-dry brain weight ratios. At 1 or 4 hours after end of resuscitation, the mice were euthanized and decapitated. Cerebral tissue was weighed for wet weight, then dried at 55°C for 7 days. Dry weight was then measured and a wet-to-dry ratio was calculated.

3.6 Statistical Analysis

Student's t-tests were used when comparisons were made between two treatment groups. One-way analysis of variance with Tukey post hoc test was used to compare multiple groups.

4.0 RESULTS

4.1 Shed Blood Volume

All groups undergoing hemorrhagic shock had a shed blood volume significantly higher than animals that did not undergo hemorrhagic shock (sham) (Figure 1). In addition, the amount of blood withdrawn to reach 25 mmHg was not different between resuscitation groups with or without preceding TBI.

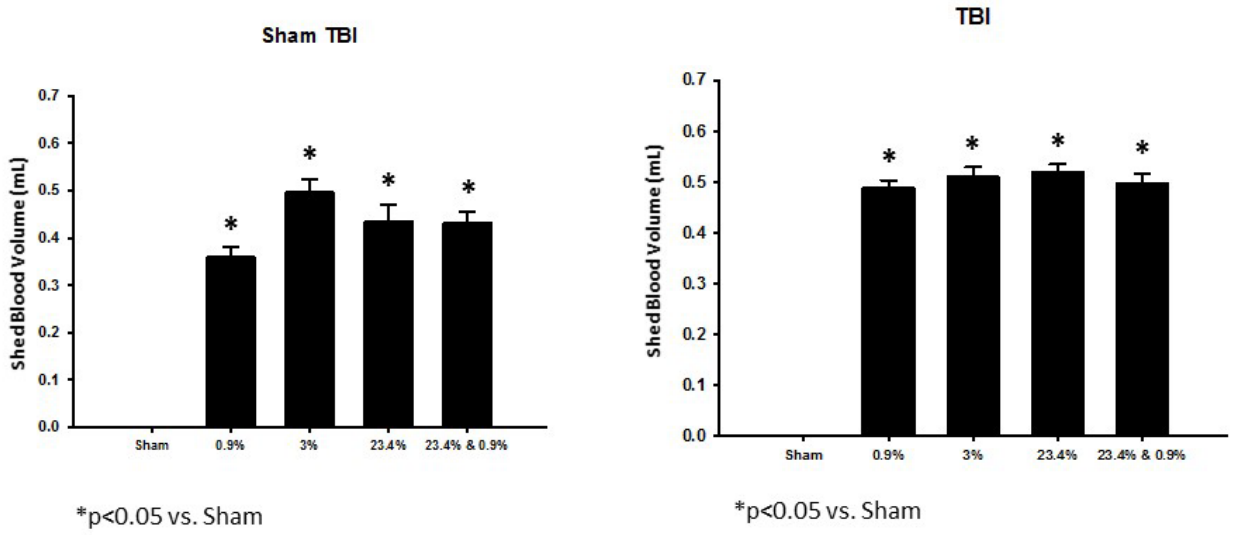

Figure 1. Shed blood volume.

4.2 Resuscitation Volume Administered

Mice resuscitated with 23.4% saline received the lowest amount of fluid, consistent with experimental design. When 0.9% saline was added to 23.4% saline for blood pressure-directed resuscitation, the total amount of resuscitation required was still below that of 0.9% saline alone. This difference persisted for animals undergoing hemorrhagic shock with and without preceding TBI. Although mice receiving 3% saline resuscitation after undergoing hemorrhagic shock with preceding TBI received less total volume than those receiving 0.9% saline resuscitation, this difference was not seen in the sham TBI/hemorrhage groups. Compared to sham TBI/hemorrhage animals, the addition of preceding TBI did not significantly change saline volumes received in any of the resuscitation groups (Figure 2).

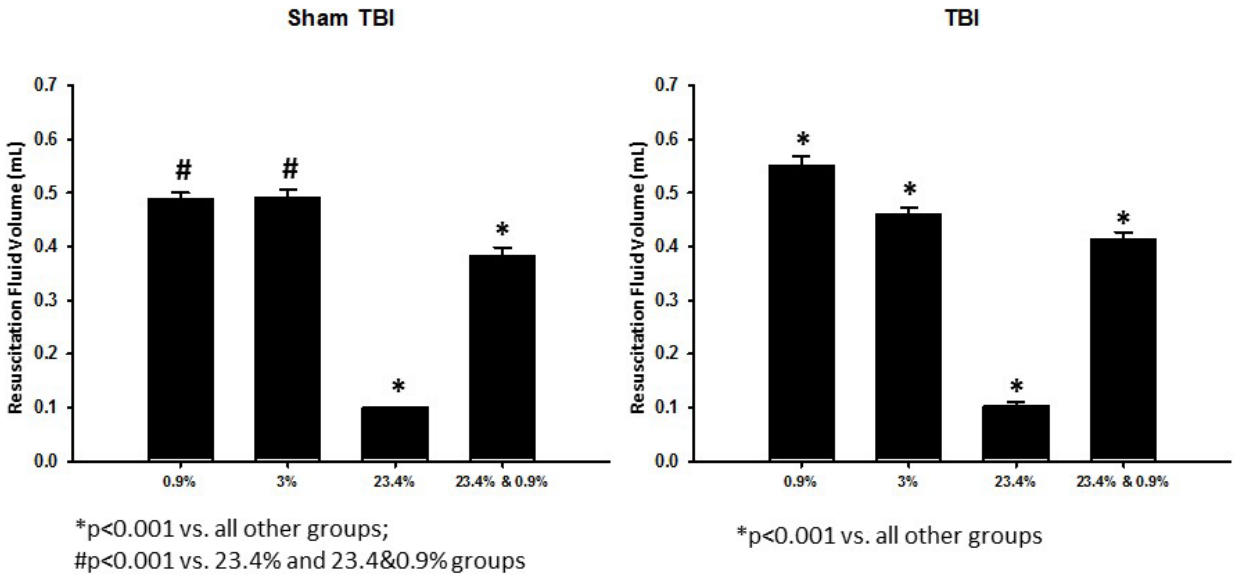

Figure 2. Resuscitation volumes.

4.3 Survival

For sham TBI/hemorrhage mice, there was no difference in post-injury survival between groups. By contrast, TBI/hemorrhage mice that received 0.9% saline had a higher survival than those receiving 23.4% saline or 23.4% & 0.9% saline. There were no deaths in mice undergoing sham injury without subsequent hemorrhagic shock (Figure 3).

4.4 Systolic Blood Pressure

For sham TBI/hemorrhage mice (Figure 4A), there were no differences in end-resuscitation blood pressure between resuscitation strategy groups. All four groups had a lower ending SBP than sham TBI/sham hemorrhage mice. Similarly, TBI/sham hemorrhage (Figure 4B) mice maintained a higher end-resuscitation SBP than the four TBI/hemorrhage groups. TBI/hemorrhage mice resuscitated with 0.9% saline maintained a higher end-resuscitation blood pressure than those receiving 23.4% or 23.4% & 0.9% saline ($p<0.001$). There were no blood pressure differences between 0.9% and 3% groups.

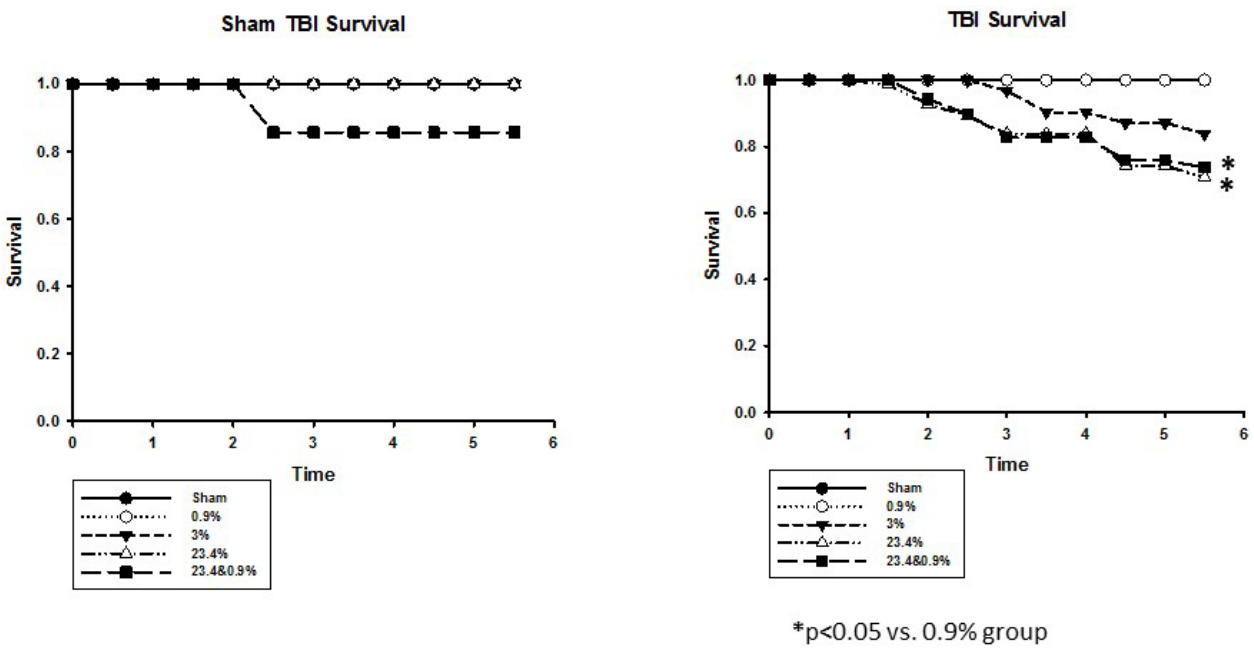

Figure 3. Survival.

Interestingly, TBI/sham hemorrhage mice had a lower end-resuscitation blood pressure than sham TBI/sham hemorrhage mice (p=0.003), indicating that TBI preceding hemorrhagic shock contributed to a lower final SBP. This difference also persisted across groups resuscitated with 0.9% (p=0.002), 3% (p=0.04), and 23.4% (p=0.02) saline.

4.5 Physiologic Markers of Resuscitation

The model of TBI ± hemorrhagic shock did not demonstrate any changes in serum lactate at the 30-minute or 4-hour time points after the end of resuscitation. By contrast, HCO_3 and base deficit were persistently lower in all TBI/hemorrhage groups at 4 hours after the end of resuscitation compared to those animals undergoing TBI/sham hemorrhage (p<0.001). There were no differences between resuscitation strategies in lactate, HCO_3, or base deficit (Figures 5A-C).

4.6 Metabolic Profile

Serum sodium (Figure 6) remained higher in the 23% & 0.9% saline resuscitation group compared to all other groups at both 30 minutes and 4 hours following resuscitation. The mean amount of sodium received in each group, based on resuscitation volume, was 0.08 mEq for the 0.9% saline group, 0.26 mEq for the 3% saline group, 0.4 mEq for the 23.4% saline group, and 0.45 mEq for the 23.4% & 0.9% saline group. By contrast, there were no significant differences in serum chloride concentration in any group (Figure 7). BUN, as a marker of potential hypovolemia, was significantly higher in the 23% group at 30 minutes and 4 hours after resuscitation compared to TBI/sham, 0.9%, and 3% groups, but higher in the 23.4% & 0.9% group compared to TBI/sham only at 30 minutes (Figure 8). Additionally, there were no differences in hematocrit among resuscitation strategies in either TBI or sham TBI animals sacrificed at 30 minutes or 4 hours.

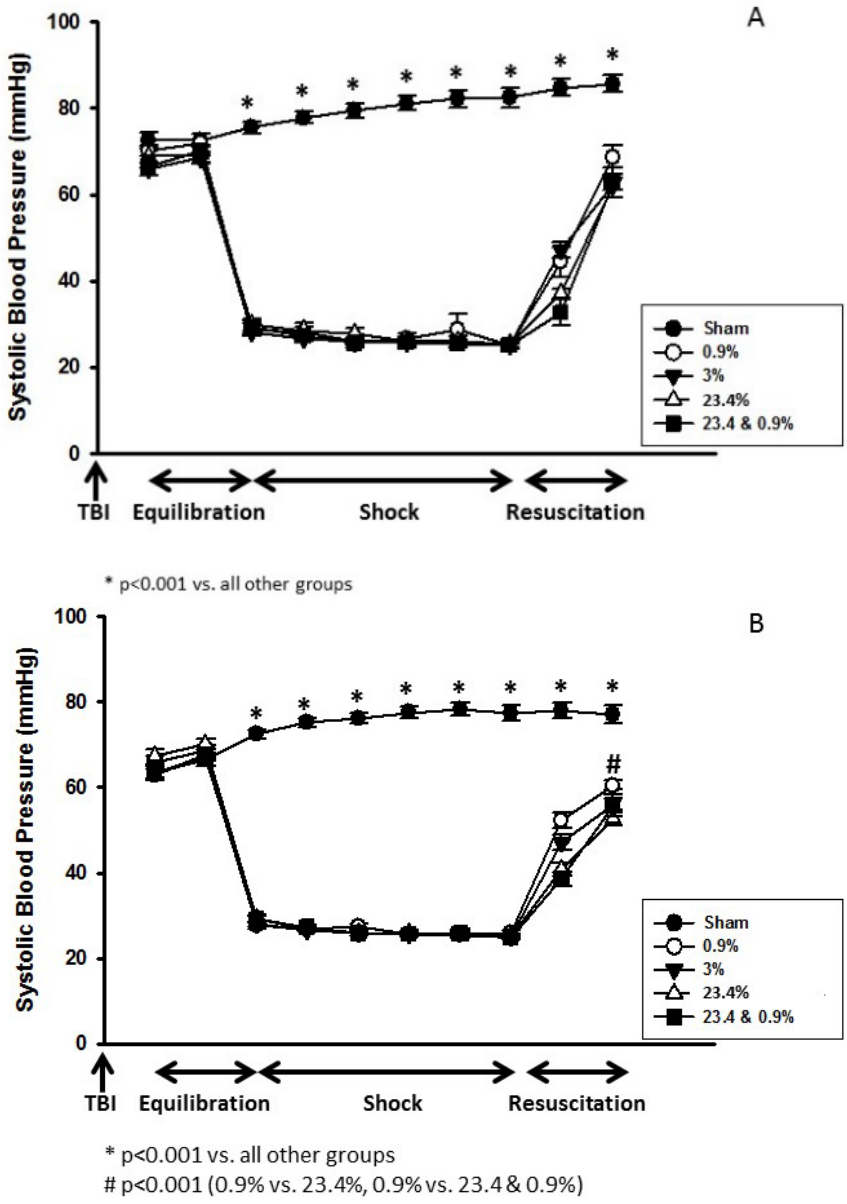

Figure 4. Systolic blood pressure. *(A) Sham TBI; (B) TBI.*

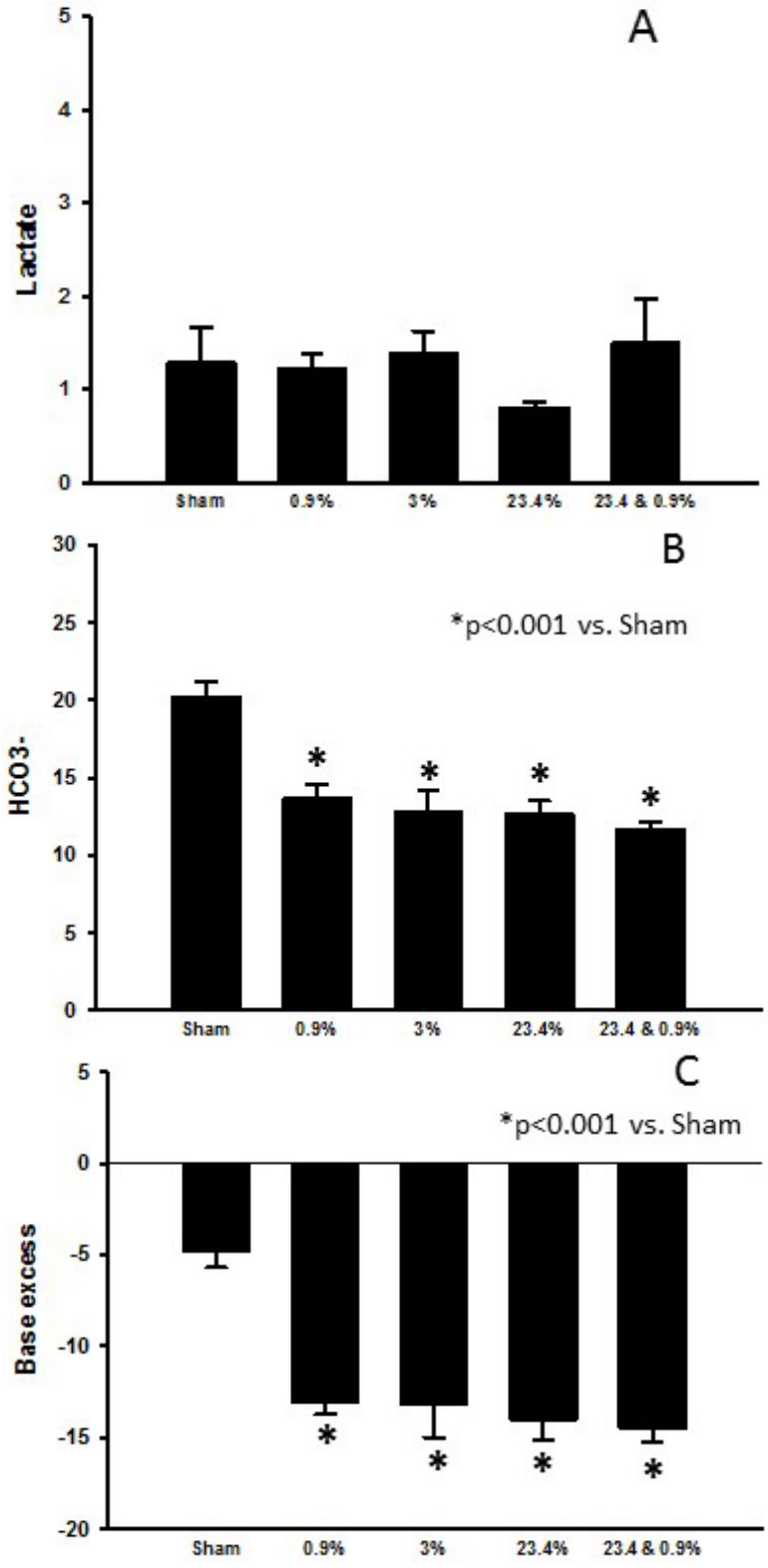

Figure 5. Physiologic markers of resuscitation. *(A) Lactate – TBI 30 min; (B) HCO_3 – TBI 4 h; (C) Base excess – TBI 4 h.*

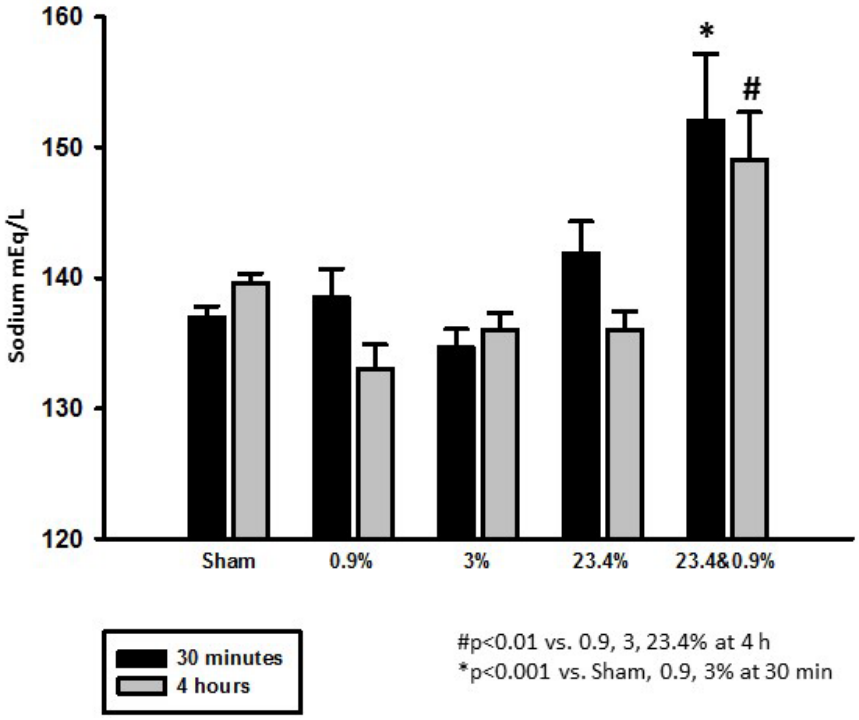

Figure 6. Sodium.

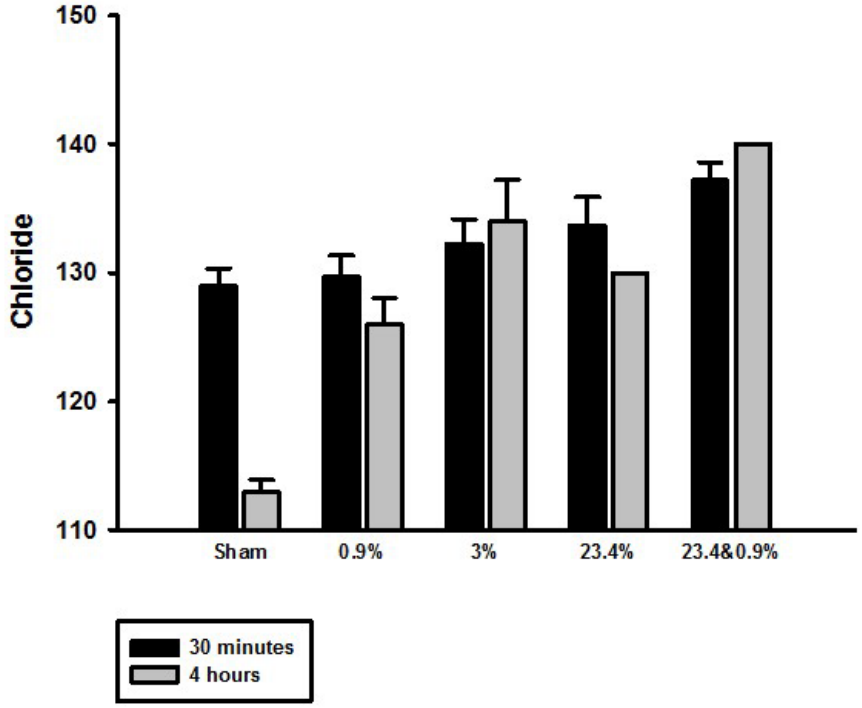

Figure 7. Chloride.

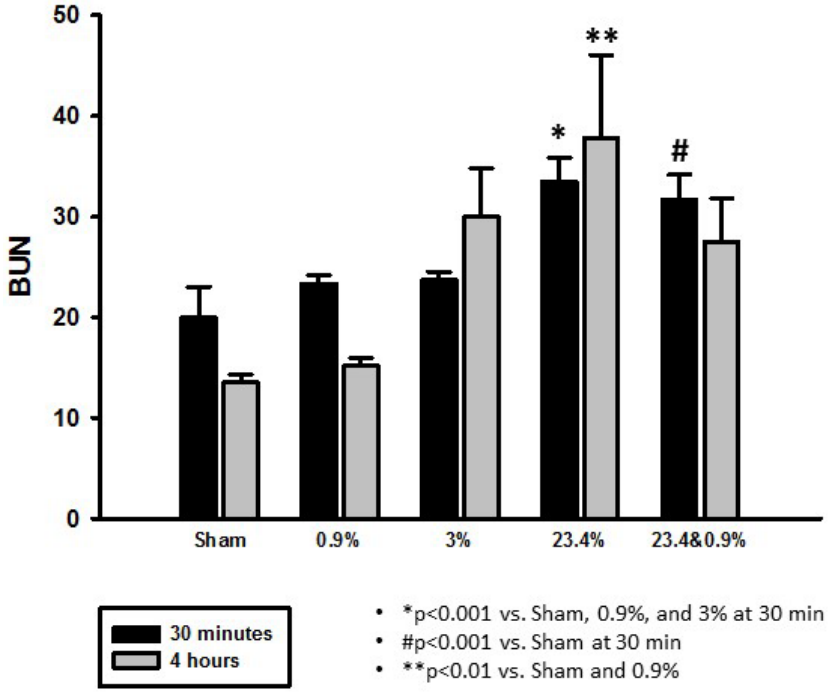

Figure 8. BUN.

4.7 Serum and Cerebral Cytokine Profiles

Sixteen cytokines and chemokines were analyzed from serum and brain tissue. There were no significant differences among all injury groups for serum and cerebral IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-12, IL-17, IFN-γ, RANTES, and GM-CSF at 30 minutes or 4 hours after resuscitation. For IL-6, serum levels were higher in 0.9%, 23.4%, and 23.4% & 0.9% groups compared to 3% saline at 30 minutes, with prolonged elevation remaining in the 23.4% & 0.9% group compared to 0.9% and 3% groups (Figure 9). Cerebral IL-6 levels were increased only in the 0.9% saline group compared to TBI/sham at 30 minutes. While serum IL-10 was increased only in the 23.4% group compared to TBI/sham at the 30-minute time point, cerebral IL-10 levels were elevated in the 0.9% saline group at both 30 minutes and 4 hours compared to the 3% saline group (Figure 10). MCP-1 serum levels demonstrated a delayed increase in the 23.4% & 0.9% group at 4 hours compared to all other groups. By contrast, cerebral MCP-1 levels were transiently increased in the 0.9% saline group compared to TBI/sham and 3% saline at 30 minutes (Figure 11). TNFα analysis demonstrated increased serum levels in the 3% group at 30 minutes compared to TBI/sham; however, cerebral levels were increased in 0.9% and 23.4% saline groups at 30 minutes compared to TBI/sham and 3% groups (Figure 12). MIP-1α demonstrated serum and cerebral levels similar to the profile seen in TNFα, with the 0.9% and 23.4% saline groups having elevated serum levels at 30 minutes compared to TBI/sham and elevated cerebral levels at 30 minutes compared to TBI/sham and 3% (Figure 13).

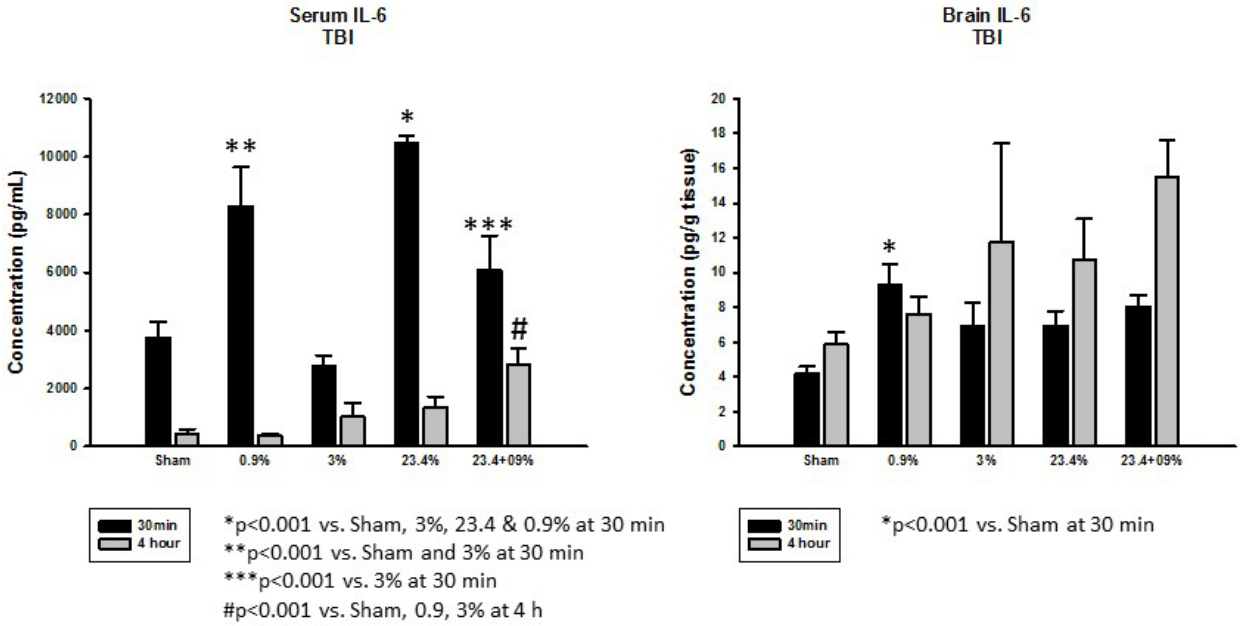

Figure 9. IL-6.

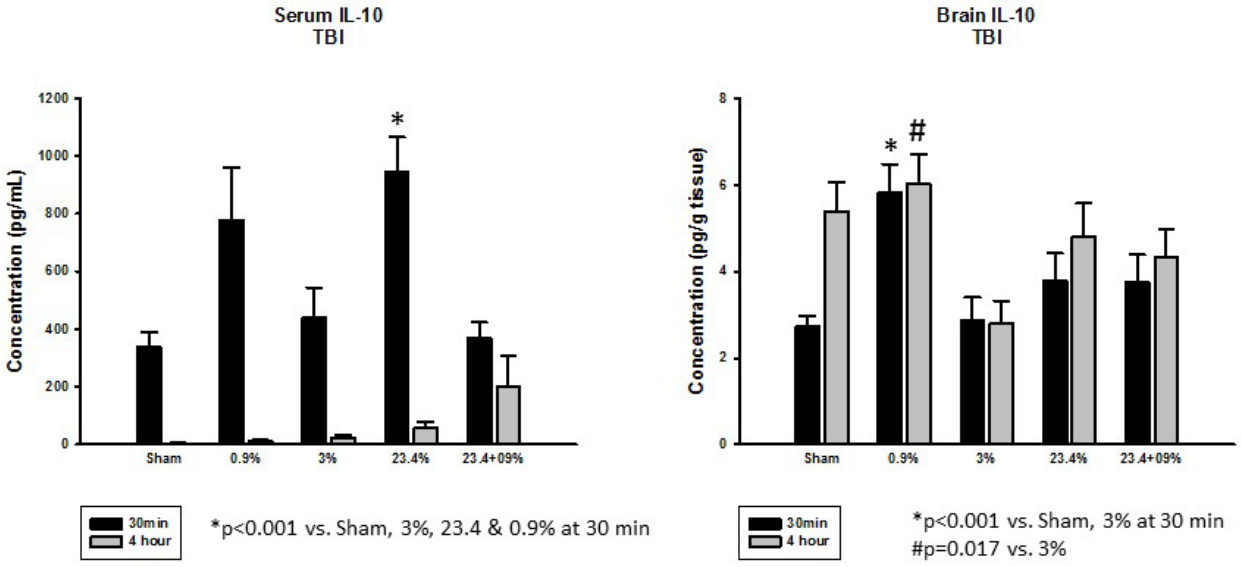

Figure 10. IL-10.

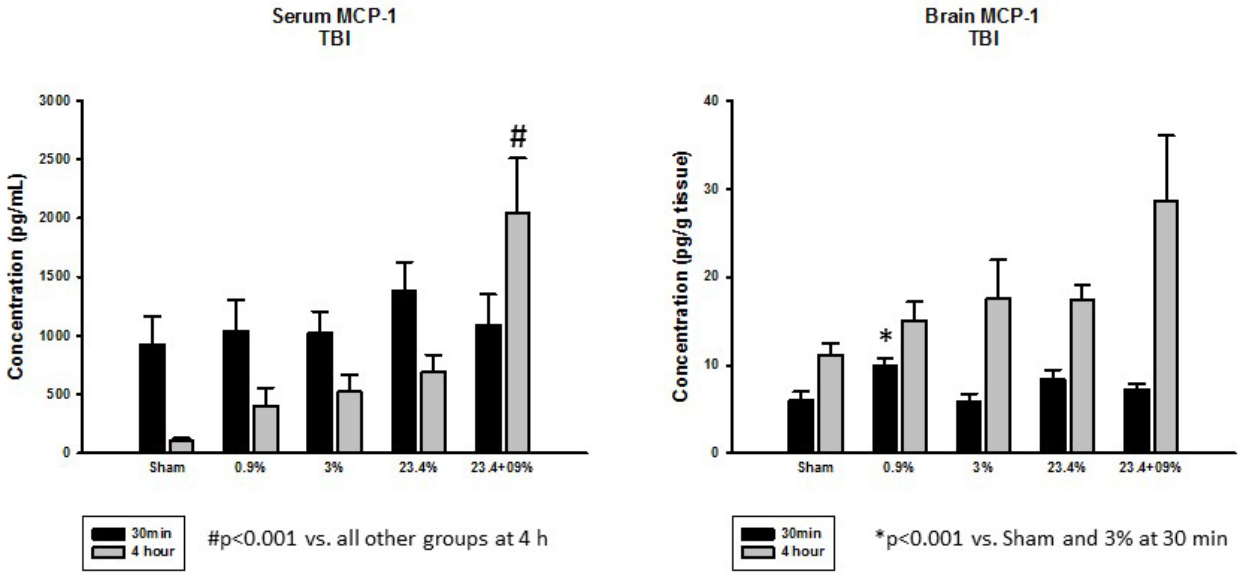

Figure 11. MCP-1.

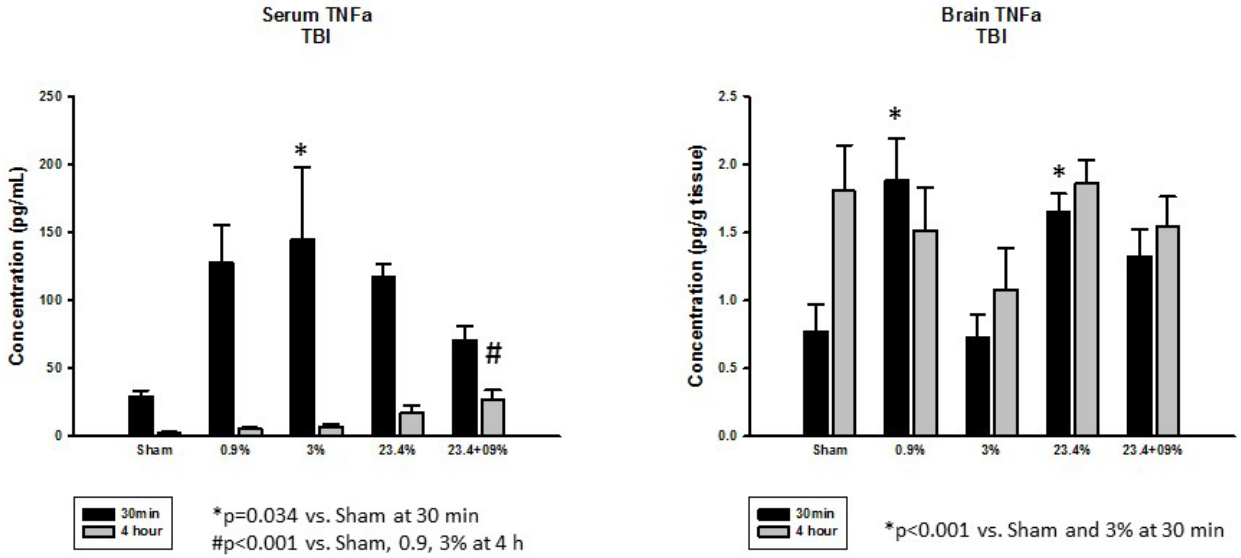

Figure 12. TNFα.

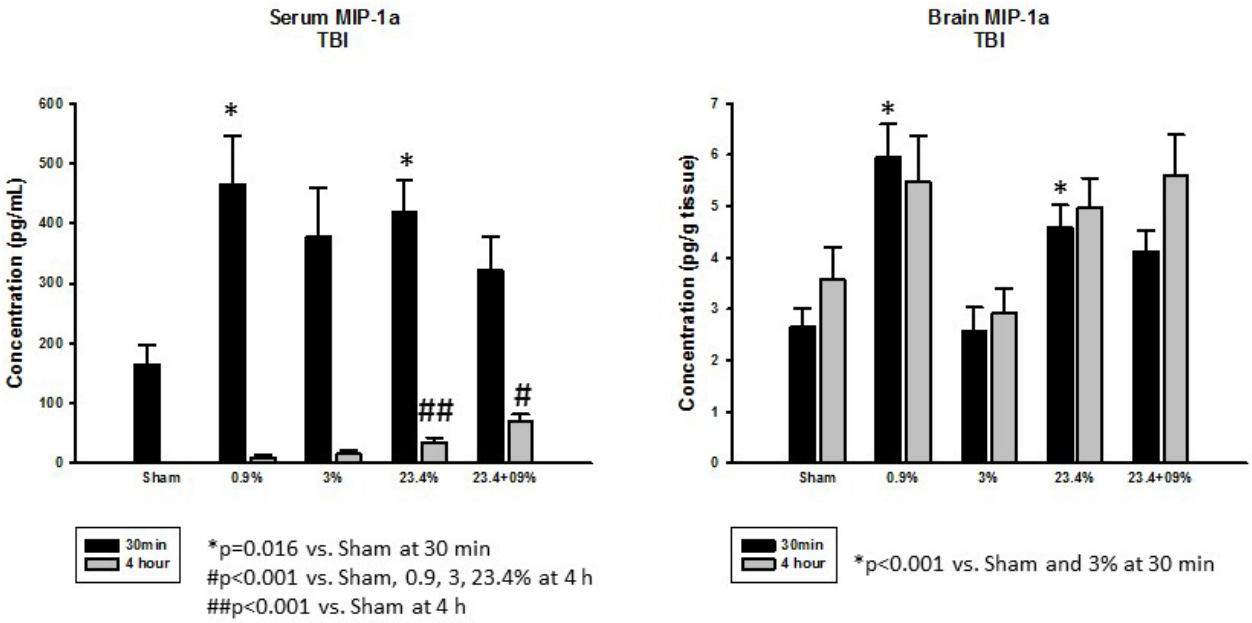

Figure 13. MIP-1*α*.

4.8 Histology

Hematoxylin and eosin staining demonstrated no differences between groups for evidence of cerebral injury.

4.9 Serum Biomarkers of Neurologic Injury

Three potential markers of neurologic injury were analyzed: NSE, GFAP, and UCHL1. There were no differences between injury groups for serum GFAP concentration. UCHL1 serum levels were higher in the 0.9% group compared to TBI/sham at 30 minutes, with persistently higher levels in 0.9%, 23.4%, and 23.4% & 0.9% groups at 4 hours (Figure 14). However, when comparing 4-hour levels to 30-minute levels, all groups showed increases in UCHL1 ($p<0.001$). Furthermore, these differences were demonstrated in the sham TBI groups as well, suggesting that UCHL1 is not specific for brain injury and may reflect nerve ischemia in the cannulated hindlimb that is exacerbated by hypotension associated with hemorrhagic shock (Figure 15). By contrast, NSE was able to distinguish between TBI and sham TBI in all resuscitation groups (Figure 16). Although 3% saline resuscitation showed higher NSE levels at 30 minutes compared to 23.4% saline, further analysis demonstrated that while 0.9%, 23.4%, and 23.4% & 0.9% saline groups increased NSE levels over time, there was no significant change in NSE levels following TBI/sham or TBI with 3% saline resuscitation (Figure 17). These results suggest that higher concentrations of resuscitative saline may lead to lower initial serum injury biomarker levels, but these benefits are transient and neurologic injury may continue to occur over time for 23.4% and 23.4% & 0.9% groups similar to 0.9% saline.

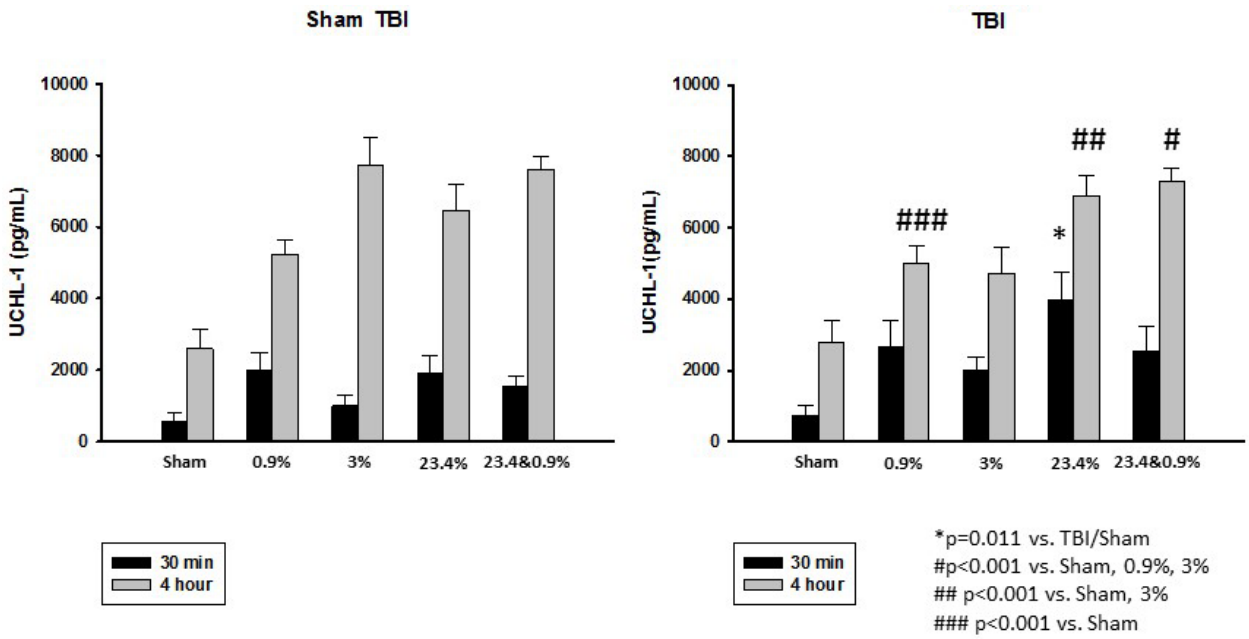

Figure 14. UCHL1 by injury.

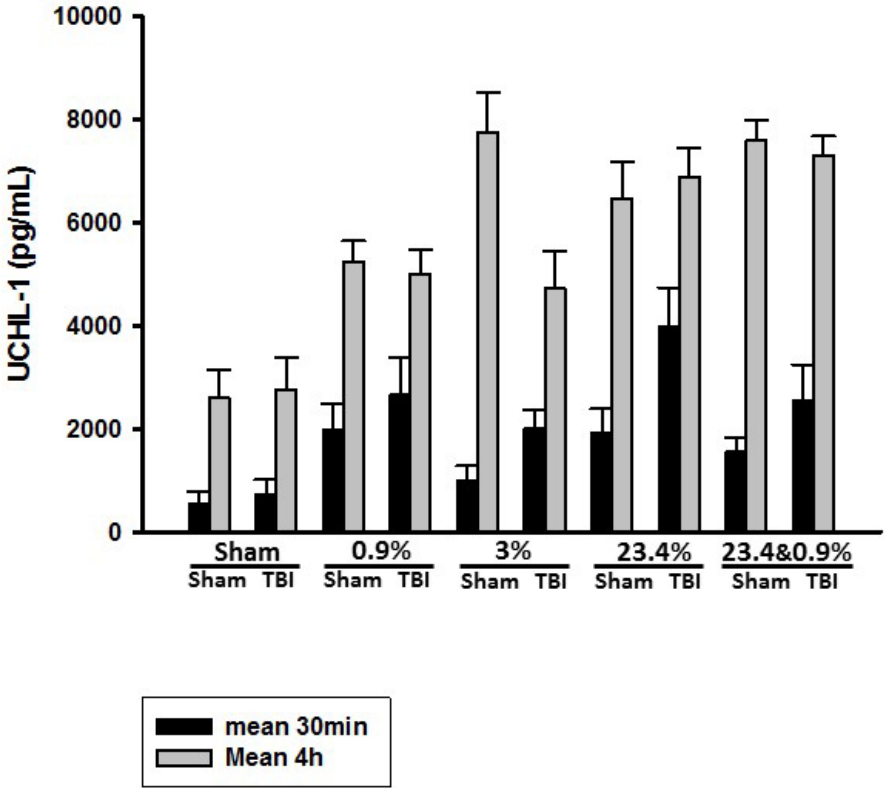

Figure 15. UCHL1 combined.

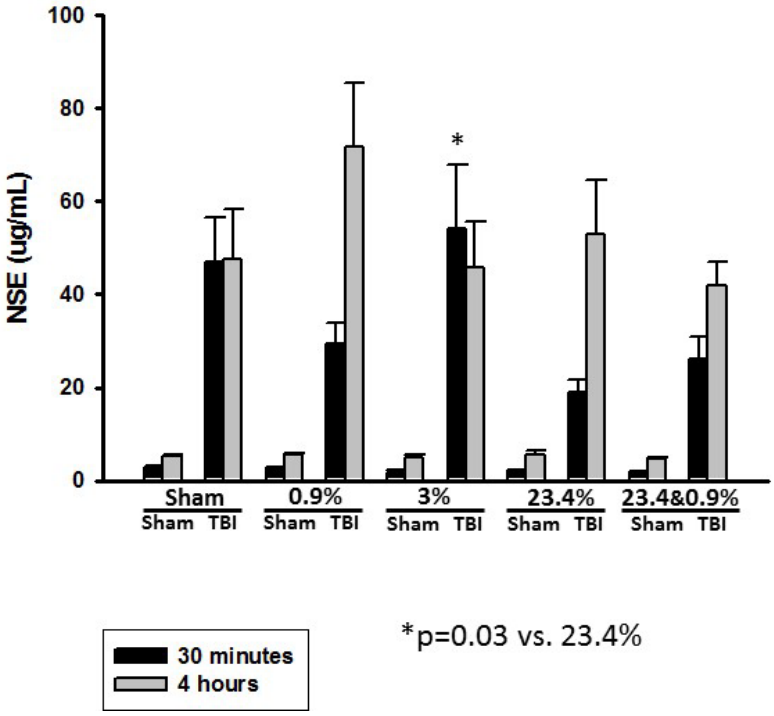

Figure 16. NSE.

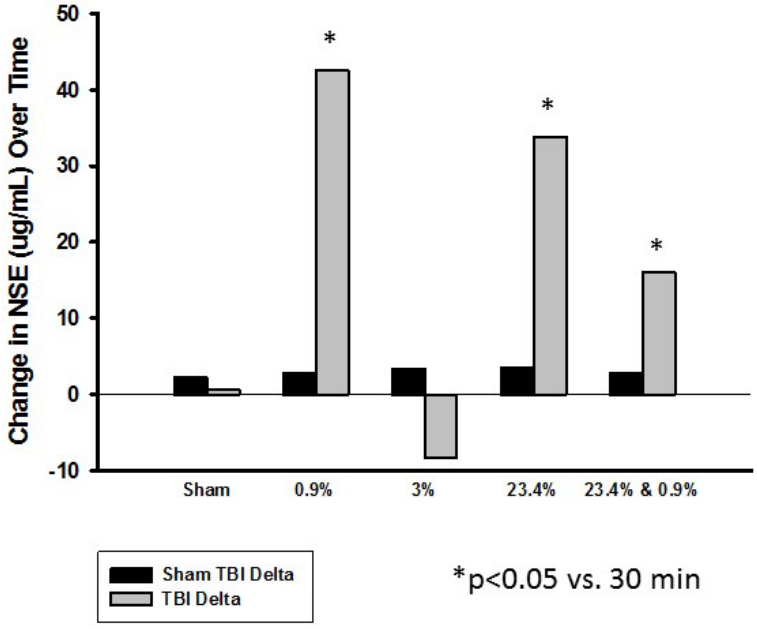

Figure 17. Delta NSE.

4.10 Blood Brain Barrier Integrity and Cerebral Edema

Blood brain barrier integrity, as measured with Evans blue extravasation into the cerebral tissue, demonstrated increased capillary leak and tissue Evans blue concentration for TBI/0.9% compared to sham/sham and TBI/23.4%. Resuscitation with 3%, 23.4%, and 23.4% & 0.9% saline led to similar low levels of capillary leak that were no different than TBI/sham (Figure 18). Further analysis of cerebral edema by tissue wet-to-dry ratio demonstrated similar levels of cerebral water content for TBI/sham, TBI/0.9%, TBI/3%, and TBI/23.4% groups. Resuscitation with 23.4% & 0.9% saline after TBI led to a transient cerebral volume contraction (Figure 19), likely associated with the higher sodium levels seen in Figure 6.

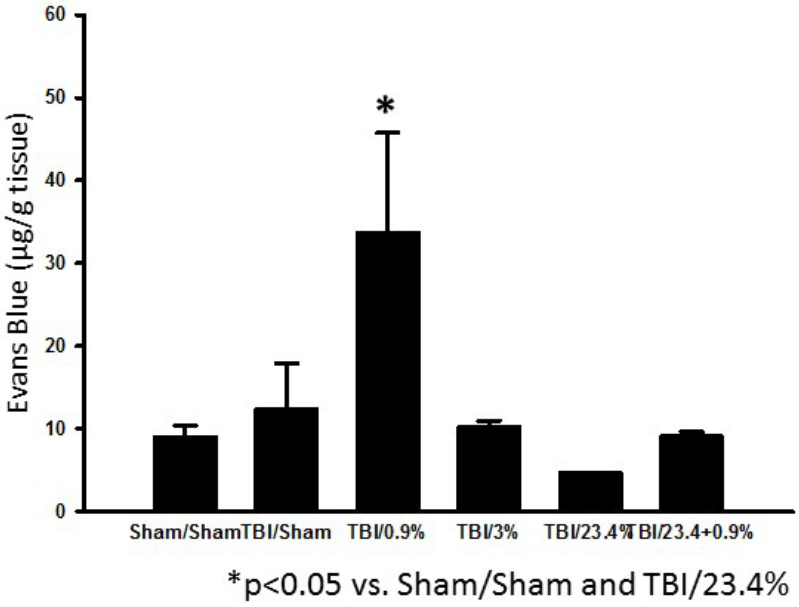

Figure 18. Evans blue – brain.

5.0 DISCUSSION

Compared to 0.9% saline as the standard of care with isotonic resuscitation, 23.4% saline either alone or in combination with additional 0.9% to ensure restoration of adequate SBP resulted in the following findings:

Pro:

- Decreased volume needed for resuscitation
- Reduced initial neurologic injury by serum biomarker
- Reduced cerebral edema

Con:

- Increased mortality
- Inability to maintain SBP following resuscitation
- Increased serum sodium levels
- Worsened azotemia, dehydration

- Higher sustained systemic and transient cerebral inflammation by several cytokine markers

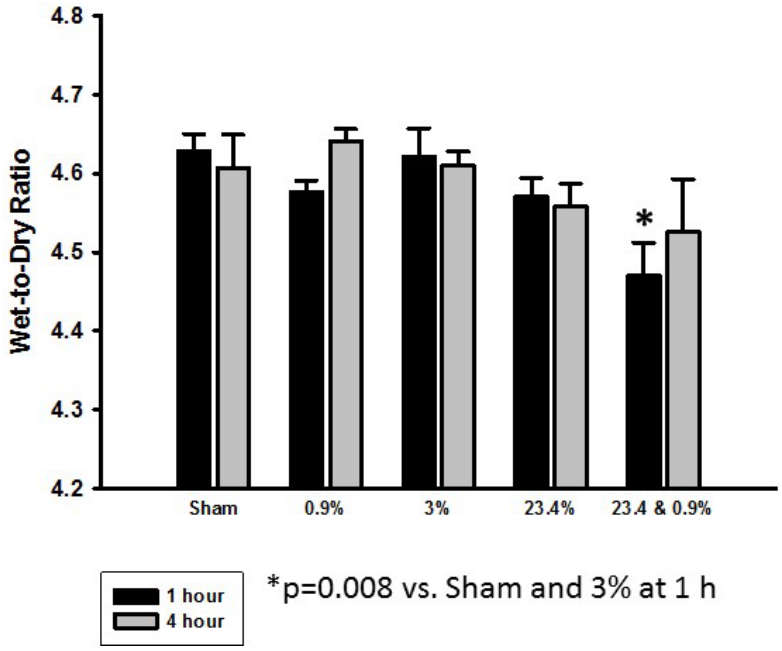

Figure 19. Brain wet-to-dry ratios.

By contrast, 3% may be the optimal saline concentration for resuscitation from combined TBI and hemorrhagic shock, as this study demonstrated 3% to:

- Not decrease survival
- Sustain post-resuscitation blood pressure
- Not appreciably change serum sodium concentration, chloride level, or azotemia
- Reduce systemic and cerebral pro-inflammatory cytokine response compared to 0.9% saline
- Prevent ongoing neurologic injury compared to 0.9% saline
- Minimize post-traumatic cerebral capillary leak and edema

6.0 CONCLUSIONS

Following TBI with hemorrhagic shock, 3% saline resuscitation may lead to the most favorable balance of survival, blood pressure restoration, minimization of systemic and cerebral inflammation, and prevention of ongoing neurologic injury without contributing to significant physiologic or metabolic derangements. Resuscitation with higher concentrations of saline may acutely limit cerebral edema but may not be appropriate in the setting of concomitant hemorrhagic shock.

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

α	alpha
β	beta
BUN	blood urea nitrogen
ELISA	enzyme-linked immunosorbent assay
GFAP	glial fibrillary acidic protein
GM-CSF	granulocyte macrophage colony-stimulating factor
HCO_3	bicarbonate
IFN-γ	interferon-gamma
IL	interleukin
MCP	monocyte chemoattractant protein
MIP	macrophage inflammatory protein
NSE	neuron-specific enolase
SBP	systolic blood pressure
TBI	traumatic brain injury
TNFα	tumor necrosis factor alpha
UCHL1	ubiquitin carboxyl-terminal hydrolase L1