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The Impact of Pre-Hospital Administration of Lactated Ringer's Solution versus Normal Saline in Patients with Traumatic Brain Injury

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Abstract

Lactated Ringer's (LR) and normal saline (NS) are both used for resuscitation of injured patients. NS has been associated with increased resuscitation volume, blood loss, acidosis, and coagulopathy compared with LR. We sought to determine if pre-hospital LR is associated with improved outcome compared with NS in patients with and without traumatic brain injury (TBI). We included patients receiving pre-hospital LR or NS from the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study. Patients with TBI (Abbreviated Injury Scale [AIS] head ≥3) and without TBI (AIS head ≤2) were compared. Cox proportional hazards models including Injury Severity Score (ISS), AIS head, AIS extremity, age, fluids, intubation status, and hospital site were generated for prediction of mortality. Linear regression models were generated for prediction of red blood cell (RBC) and crystalloid requirement, and admission biochemical/physiological parameters. Seven hundred ninety-one patients received either LR ($n = 117$) or NS ($n = 674$). Median ISS, AIS head, AIS extremity, and pre-hospital fluid volume were higher in TBI and non-TBI patients receiving LR compared with NS ($p < 0.01$). In patients with TBI ($n = 308$), LR was associated with higher adjusted mortality compared with NS (hazard rate [HR] = 1.78, confidence interval [CI] 1.04–3.04, $p = 0.035$). In patients without TBI ($n = 483$), no difference in mortality was demonstrated (HR = 1.49, CI 0.757–2.95, $p = 0.247$). Fluid type had no effect on admission biochemical or physiological parameters, 6-hour RBC, or crystalloid requirement in either group. LR was associated with increased mortality compared with NS in patients with TBI. These results underscore the need for a prospective randomized trial comparing pre-hospital LR with NS in patients with TBI.

Key words: adult brain injury; clinical management of CNS injury; head trauma; traumatic brain injury

Introduction

Historically, intravenous fluid administration has been one of the few interventions available prior to hospital arrival. The administration of intravenous fluids is intended to restore effective circulating volume, improve oxygen delivery, and correct shock at the cellular level. The Advanced Trauma Life Support course recommends administering either lactated Ringer's (LR) or normal saline (NS) for the initial resuscitation of injured patients.[1] However, controversy exists regarding both the optimal type as well as volume of fluid to be administered. A recent practice management guideline published by the Eastern Association for the Surgery of Trauma concluded that there is insufficient evidence to recommend one crystalloid solution over another in the pre-hospital setting.[2]

No randomized controlled trials comparing the pre-hospital use of LR and NS in injured patients have been conducted to date. The purpose of this study was to compare the effects of pre-hospital administration of LR and NS on outcomes in patients with and without significant traumatic brain injury (TBI). Previously, an animal study comparing blood loss and coagulation in a validated swine polytrauma model revealed that administration of LR rather than NS led to less blood loss and greater hypercoagulability in uncontrolled hemorrhagic shock.[3] Further, a small prospective study of patients with severe TBI demonstrated that exogenously administered lactate can be utilized as an substrate for aerobic

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metabolism in the human brain, leading to sparing of cerebral glucose.[4] Given previous findings of the protective effects of lactate in trauma and severe TBI patients, our hypothesis was that pre-hospital administration of LR would be associated with improved outcome compared with NS.

Methods

Data were obtained from a database created by the Center for Clinical and Translational Sciences at the University of Texas Health Science Center at Houston for the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study.[5] PROMMTT enrolled 1245 injured patients who required the highest level activation at one of 10 level 1 trauma centers who subsequently received one or more units of red blood cells (RBC) within 6 hours of hospital admission. Exclusion criteria included age <16 years, transfer from another hospital, pregnancy, >20% burn injury, inhalation injury, incarceration, and death within 30 minutes of hospital admission. Data were collected in real time on fluid and blood product infusions. The time of mortality or hospital discharge was recorded. Approval was obtained from the institutional review board (IRB) at each center and from the U.S. Army Human Research Protections Office. Because PROMMTT was an observational study, waiver of consent was granted by the IRB at the Data Coordinating Center, 9 of 10 clinical sites, and by a secondary review by the U. S. Army Medical Research and Materiel Command Office of Research Protections. One site IRB requested consent from surviving subjects, but allowed retention of data on all patients unable to consent as long as consent attempts were documented. No patient or legal representative refused consent.[6]

Collected data included age, gender, mechanism of injury, ISS, AIS by body region, vital signs upon emergency department arrival and initial laboratory values. The volume of LR or NS administered prior to hospital arrival was recorded. Patients who received any other type of fluid or blood products and those who received both LR and NS were excluded. Patients receiving a small volume of pre-hospital fluid (<200 mL) and those with minor injuries (ISS <9) were also excluded. Mean or median values for each variable were calculated in the LR and NS subgroups for both brain-injured (AIS head ≥3) and non-brain injured (AIS head ≤2) patients. Comparisons were made with the Mann-Whitney U test or Pearson's χ^2 test, as appropriate. Time of death or hospital discharge was available for all patients. Our primary outcome was mortality at 30 days. Secondary outcomes were RBC and crystalloid use in the first 6 hours after admission. Admission physiological and biochemical variables, including systolic blood pressure (SBP), heart rate, International Normalized Ratio (INR), hemoglobin, base deficit, pH, and lactate were also treated as secondary outcomes because they were measured after pre-hospital LR or NS was administered.

Statistical analysis

To determine the effect of pre-hospital fluid type on mortality, a Cox proportional hazards model with random effects was created that included pre-hospital fluid type, pre-hospital fluid volume, ISS, AIS head, AIS extremity, age, pre-hospital intubation status, and study site. The Cox proportional hazards model with random effects is utilized for analysis of time-to-event data with covariates whose values may change over time.[7] The random effects method assumes a single hazard factor for each trauma center that adjusts for unmeasured clinical practices that affect all patients from the center, thus controlling for some of the bias introduced by the heterogeneity of practices at each clinical site. Separate models were created for patients with and without brain injuries. Linear regression models were created using the same covariates to examine the impact of pre-hospital fluid type on each of the secondary outcome variables. Statistical analyses were carried out with Stata version 12.1, 2012 (StataCorp., College Station, TX). *P* values ≤0.05 were considered significant.

Table 1. Baseline Characteristics for Patients with AIS Head ≥3

	LR (n = *52*)	*NS* (n = *256*)	P *value*
ISS	42 (32–57)	34 (26–43)	<0.001
AIS head	5 (4–5)	4 (3–5)	<0.001
AIS chest	3 (0–4)	3 (0–4)	0.896
AIS abdomen	0 (0–2)	2 (0–3)	0.075
AIS extremity	3 (0–3)	2 (0–3)	0.011
Age (year)	45.2 ± 20.8	42.8 ± 18.4	0.453
Sex (%male)	65.4	71.9	0.348
Mechanism			
Blunt (%)	84.6	84.0	0.509
Penetrating (%)	15.4	16.0	–
Pre-hospital intubation (%)	92.3	57.0	<0.001
Pre-hospital transport time (min)	57 ± 21	69 ± 62	0.599
Pre-hospital fluid volume (mL)	1540 ± 1030	970 ± 770	<0.001

AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; LR, lactated Ringer's; NS, normal saline.

Results

The database included 791 patients with ISS ≥9 who received ≥200 mL of LR ($n = 117$) or NS (n = 674) prior to hospital arrival; 308 patients had an AIS head ≥3 and 483 patients had an AIS head ≤2. Demographics and injury scoring information for brain-injured and non-brain-injured patients are shown in Tables 1 and 2. In both groups, patients receiving LR had a higher ISS, AIS head, AIS extremity, pre-hospital fluid volume, and pre-hospital intubation rate than patients receiving NS (Tables 1 and 2). Reported causes of death for the overall cohort are listed in Table 3.

In patients with AIS head ≥3, unadjusted 30-day mortality was 50% in the LR group and 28% in the NS group. In patients with AIS

Table 2. Baseline Characteristics for Patients with AIS Head ≤2

	LR (n = *65*)	*NS* (n = *418*)	P *value*
ISS	26 (17–35)	19 (13–29)	<0.001
AIS head	0 (0–1)	0 (0–0)	<0.001
AIS chest	3 (0–4)	3 (0–3)	0.831
AIS abdomen	2 (0–4)	2 (0–4)	0.656
AIS extremity	3 (0–4)	2 (0–3)	<0.001
Age (year)	41.1 ± 20.1	38.8 ± 17.8	0.492
Sex (% male)	73.8	77.3	0.543
Mechanism			
Blunt (%)	56.9	56.5	0.944
Penetrating (%)	43.1	43.5	–
Pre-hospital intubation (%)	70.8	20.7	<0.001
Pre-hospital transport time (min)	57 ± 34	51 ± 29	0.283
Pre-hospital fluid volume (mL)	1520 ± 1280	890 ± 650	<0.001

AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; LR, lactated Ringer's; NS, normal saline.

Table 3A. Reported Causes of Death in All Subjects

Cause	*LR* (n = *42*)	*NS* (n = *119*)	P *value*
Exsanguination	22 (52.4%)	49 (41.2%)	0.217
Brain injury	19 (45.2%)	49 (41.2%)	0.719
Cardiovascular	14 (33.3%)	24 (20.1%)	0.095
Multiple organ failure	3 (7.1%)	16 (13.4%)	0.406
Airway/respiratory	7 (16.7%)	15 (12.6%)	0.602
Sepsis	1 (2.4%)	7 (5.9%)	>0.99
Other causes	5 (11.9%)	14 (11.7%)	>0.99

Percentages do not add to 100 because centers were allowed to list more than one cause of death.

LR, lactated Ringer's; NS, normal saline.

head ≤2, unadjusted 30-day mortality was 25% in the LR group and 11% in the NS group. Survival analysis of patients with AIS head ≥3 using a Cox proportional hazards model with random effects showed increased mortality in the LR group compared with the NS group at 30 days (HR 1.78, CI 1.04–3.04, $p = 0.035$). No difference in 30-day mortality was observed in patients with AIS head ≤2 (HR 1.49, CI 0.757–2.95, $p = 0.247$). Comparison of the dominant LR center versus all other centers also revealed no difference in 30-day mortality using Cox regression modeling (HR 1.86, $p = 0.890$).

Secondary outcomes are listed in Table 4 (AIS head ≥3) and Table 5 (AIS head ≤2). In both brain-injured and non-brain-injured patients, no differences were observed between patients receiving LR and NS in any of the measured biochemical or physiological variables after adjustment using linear regression. Pre-hospital fluid type also had no significant impact on RBC or total crystalloid requirement during the first 6 h after injury in either group.

Discussion

In recent years there have been a number of studies investigating the impact of LR and NS on biochemical and physiological parameters. Animal models of uncontrolled hemorrhagic shock have demonstrated that administration of LR resulted in improved physiological outcomes. [8–10] LR and NS may also have different effects on coagulation.[11,12] One animal study using a hemorrhagic shock model showed that resuscitation with LR was associated with decreased secondary bleeding.[3] Other studies have suggested that the use of LR may lead to a hypercoagulable state.[3,12] A clinical trial in patients undergoing aortic aneurysm repair showed that patients receiving NS required more platelets than those receiving LR.[13]

Table 3B. Reported Causes of Death in Patients with AIS Head ≥3

Cause	*LR* (n = *27*)	*NS* (n = *73*)	P *value*
Exsanguination	9 (33.3%)	15 (20.5%)	0.197
Brain injury	19 (70.4%)	47 (64.4%)	0.641
Cardiovascular	10 (37.0%)	9 (12.3%)	0.009
Multiple organ failure	2 (7.4%)	8 (11.0%)	0.725
Airway/respiratory	6 (22.2%)	12 (16.4%)	0.561
Sepsis	0 (0%)	3 (4.1%)	0.561
Other causes	1 (3.7%)	6 (8.2%)	0.671

Percentages do not add to 100 because centers were allowed to list more than one cause of death.

LR, lactated Ringer's; NS, normal saline.

Table 4. Secondary Outcomes for Patients with AIS Head ≥3

	LR (n = *52*)	*NS* (n = *256*)	P *value*[a]
SBP (mm Hg)[b]	120 ± 32	107 ± 29	0.264
HR[b]	105 ± 30	103 ± 28	0.827
INR	1.9 ± 1.7	1.4 ± 1.1	0.559
Base deficit	6.5 ± 5.0	7.3 ± 5.7	0.406
pH	7.26 ± 0.14	7.24 ± 0.14	0.142
Hemoglobin (g/dL)	10.5 ± 2.6	11.7 ± 2.1	0.113
Lactate (mEq/L)	5.7 ± 3.5	4.5 ± 2.8	0.753
6-h fluid requirement (L)	5.4 ± 2.9	3.8 ± 3.1	0.256
6-h RBC requirement (units)	4.5 ± 3.7	5.8 ± 7.0	0.161

[a]Linear regression model including pre-hospital fluid type, pre-hospital fluid volume, ISS, AIS head, AIS extremity, age, hospital site, and pre-hospital intubation status.

[b]Initial value measured on arrival to the emergency department.

AIS, Abbreviated Injury Scale; HR, hazard rate; INR, International Normalized Ratio; ISS, Injury Severity Score; LR, lactated Ringer's; NS, normal saline; RCB, red blood cells; SBP, systolic blood pressure.

Additionally, the use of NS may also lead to increased acidosis as compared with LR.[11–14] NS contains 154 milliequivalents per liter (mEq/L) of sodium and chloride with a pH of approximately 4.6, whereas LR contains 130 mEq/L of sodium, 4 mEq/L of potassium, 3 mEq/L of calcium, 109 mEq/L of chloride, and 28 mEq/L of lactate with a pH of 6.6.[15] This hyperchloremic acidosis may lead to systemic vasodilation, coagulopathy, and increased extravascular lung water.[11] In patients with hemorrhagic shock, it has been speculated that the lactate in LR has minimal effect on blood pH.[8,11]

Despite its theoretic advantages, LR has not been widely accepted in the pre-hospital environment. LR is currently not approved by the Association of American Blood Banks for simultaneous infusion with packed RBC due to concerns over clotting of filters.[11] These concerns, however, have not been supported by clinical trials. Further, NS is often considered to be the preferred fluid for patients with TBI due to its relative hyperosmolarity compared with LR. However, randomized clinical trials on pre-hospital fluid resuscitation in patients with TBI have largely

Table 5. Secondary Outcomes for Patients with AIS Head ≤2

	LR (n = *65*)	*NS* (n = *418*)	P *value*[a]
SBP (mm Hg)[b]	118 ± 28	104 ± 28	0.271
HR[b]	112 ± 26	107 ± 2827	0.392
INR	1.6 ± 0.7	1.4 ± 1.3	0.976
Base deficit	7.7 ± 6.1	7.0 ± 5.4	0.401
pH	7.24 ± 0.17	7.25 ± 0.13	0.921
Hemoglobin (g/dL)	10.5 ± 2.8	11.6 ± 2.2	0.998
Lactate (mEq/L)	4.8 ± 3.0	7.1 ± 4.9	0.100
6-h fluid requirement (L)	6.7 ± 4.1	4.1 ± 3.3	0.368
6-h RBC requirement (units)	8.3 ± 8.7	7.3 ± 9.7	0.287

[a]Linear regression model including pre-hospital fluid type, pre-hospital fluid volume, ISS, AIS head, AIS extremity, age, hospital site, and pre-hospital intubation status.

[b]Initial value measured on arrival to the emergency department.

AIS, Abbreviated Injury Scale; HR, heart rate; INR, International Normalized Ratio; ISS, Injury Severity Score; LR, lactated Ringer's; NS, normal saline; RCB, red blood cells; SBP, systolic blood pressure.

focused on comparing the use of hypertonic solutions with NS. These studies have not consistently shown a benefit for hypertonic solutions.[16–18] No randomized controlled clinical trials directly comparing the pre-hospital use of LR and NS in injured patients have been conducted to date.

Our results demonstrate that the use of LR for pre-hospital resuscitation in patients with significant brain injury was associated with increased mortality at 30 days. The reasons for this are not entirely clear. The slight hyperosmolarity of NS compared with LR may be a contributing factor. NS has been thought to decrease cerebral edema to a greater extent than LR; however, studies comparing NS with hypertonic saline have been equivocal.[11,19] Thus, the clinical relevance of the osmolarity difference is uncertain. Only a few studies have been performed comparing the effect of LR with other resuscitation fluids on intracranial pressure and clinical outcomes. In animal studies, large volumes of LR lead to a decrease in the serum osmolality, which may contribute to increased cerebral edema via passage of water across the blood –brain barrier.[20] One study in dogs using a hemorrhagic shock model demonstrated that resuscitation with LR led to increased intracranial pressure (ICP) as compared with resuscitation with hypertonic saline.[21] Another study in rabbits using an isovolumic hemodilution model demonstrated only a transient, mild increase in ICP after LR infusion that dissipated within 4 h.[22] Using a rat brain-injury model, Feldman and colleagues demonstrated that the rapid infusion of a large volume of LR for resuscitation did not lead to increased brain edema, as measured by direct histological examination.[23]

A small study of 18 healthy human volunteers receiving large volumes of either LR or NS determined that LR led to small, transient changes in serum osmolality, whereas NS led to decreases in serum pH but not osmolality.[20] One clinical study randomized brain-injured children to receive either LR or hypertonic saline as the main resuscitation fluid during the first 72 h of hospitalization.[24] In this study, the LR group required a greater number of interventions to decrease ICP, but clinical outcomes were unchanged. In another randomized clinical trial in which brain-injured patients were administered either 250 mL LR or hypertonic saline prior to hospital arrival, no significant differences in mortality or neurological outcome were observed.[25] However, pre-hospital fluid volumes >250 mL were not given and multivariate analysis was not performed. No studies have directly compared clinical outcomes in brain-injured patients receiving LR and NS in the pre-hospital setting.

Another possible explanation for the observed mortality difference between LR and NS in brain-injured patients is the difference in their inflammatory profiles. Administration of LR has been shown to activate neutrophils and upregulate the inflammatory response, though this is attenuated by the use of LR solutions that contain only the L-isomer of lactate.[26–28] In animal models, resuscitation with hypertonic saline has been demonstrated to lead to attenuated liver, pulmonary and intestinal inflammatory responses after hemorrhagic shock as compared with LR.[29–31] Similar findings have not been demonstrated for NS. However, in one study using an uncontrolled hemorrhagic shock model, animals resuscitated with NS had a similar inflammatory response to those resuscitated with LR.[9]

There are a number of limitations in this study. It has all of the weaknesses associated with a retrospective analysis of prospectively gathered data. The absence of a significant difference in mortality between LR and NS in patients without significant brain injury may be due to a lack of power. Although this subgroup had more patients ($n = 483$) than the brain-injured group ($n = 308$), the mortality rate was comparatively lower, making differences more difficult to identify. There were significant baseline differences in the patients in the LR group versus the NS group with respect to rate of pre-hospital intubation and volume of resuscitation. We included these variables in our multivariate analysis to control for them, but this may suggest heterogeneity of pre-hospital and subsequent care at various centers.

The proportion of patients receiving LR between centers varied considerably, with more than half coming from a single center. This center administered a higher pre-hospital fluid volume and had a higher mortality rate than other centers but also had more severely injured patients. The addition of injury severity scoring data to the Cox proportional hazards models can only account for this to an extent given the known limitations inherent to the ISS and AIS design. We attempted to adjust for the center effect by generating a Cox model with random effects. This is a technique designed to account for unmeasured clinical factors at each center that theoretically affect all patients from the center. This may be more accurate than a fixed effects model. The statistical methods we employed may increase the accuracy of our results, but they still cannot fully compensate for the many differences in practice patterns and patient populations among centers. Thus, the matching between the LR and NS groups remains imperfect. Due to limitations of our study design, the true difference in mortality between groups remains unclear.

A randomized clinical trial examining this issue cannot realistically be conducted at a single center because it would be underpowered. Any future multi-center trial of this nature will have significant variations in injury severity and patient population between centers. In fact, PROMMTT was specifically designed to have a degree of heterogeneity among centers.[5] If patients from a given center only receive fluid of a single type, then the difficulties we encountered with creating a model to adequately match the LR and NS groups will remain. The only way to compare the two groups in a satisfactory manner is by randomization.

Administration of pre-hospital LR was associated with increased adjusted mortality compared with NS in patients with significant TBI. These findings justify the need for a randomized clinical trial comparing pre-hospital administration of LR and NS in patients with TBI.

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