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CLINICAL INVESTIGATIONS

Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: Improved short-term survival and acid-base balance with Hextend compared with saline

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In the absence of clinical data in patients with septic shock, this study suggests that a balanced colloid solution may be superior to saline or lactated Ringer's for fluid resuscitation.

Objective:

To compare resuscitation with 0.9% saline with Hextend, a synthetic colloid in a balanced electrolyte solution, in terms of acid-base status and survival time in an experimental model of septic shock in the rat.

Design:

Randomized, open-label, controlled experiment.

Setting:

University research laboratory.

Subjects:

Sixty adult, male Sprague-Dawley rats.

Intervention:

Animals were studied for 12 hrs after intravenous infusion of *Escherichia coli* endotoxin (20 mg/kg). Animals were volume resuscitated to maintain a mean arterial pressure >60 mm Hg using either 0.9% saline (n = 25), Hextend (n = 25), or lactated Ringer's (n = 10).

Measurements:

Arterial blood gases and electrolytes were measured before and after resuscitation (0, 180, 360, and 540 mins after endotoxin infusion). Survival time was measured, up to 12 hrs.

Results:

Mean survival time among animals treated with saline or Ringer's was 45% less compared with Hextend-treated animals: 391 ± 151 mins and 362 ± 94 mins vs. 567 ± 140 mins, respectively, $p < .0001$. Overall survival (at 12 hrs) was 0% with saline or Ringer's vs. 20% with Hextend, $p = .05$. After resuscitation with saline, arterial standard base excess and plasma apparent strong ion difference were both significantly lower (−19.3 ± 5.2 vs. −12.1 ± 5.7, $p < .001$, and 23.0 ± 6.2 vs. 30.3 ± 2.9, $p < .0001$, respectively) and plasma Cl^- was significantly higher (123 ± 7 vs. 115 ± 3 mmol/L, $p < .0001$) compared with Hextend. Resuscitation with Ringer's solution resulted in a standard base excess, and Cl^- between that of saline and Hextend (−15.4 ± 3.1, and 117 ± 3, respectively).

Conclusion:

Compared with 0.9% saline, volume resuscitation with Hextend was associated with less metabolic acidosis and longer survival in this experimental animal model of septic shock.

Key Words: sepsis; septic shock; fluid resuscitation; acid-base balance; metabolic acidosis; chloride; saline; hetastarch; colloids

Introduction

The initial treatment for septic shock includes volume resuscitation [1] . However, controversy exists as to what type of fluid resuscitation is best, both in terms of effectiveness as well as safety. In North America, 0.9% NaCl (normal saline) is the most commonly used resuscitation fluid, especially for those patients with sepsis. Large volume saline infusion produces metabolic acidosis by increasing the plasma

chloride concentration relative to the plasma sodium concentration [2] [3] [4] [5] [6] [7] . The result is a reduction in the strong ion difference (SID), the difference between positive and negative charged electrolytes, which in turn produces an increase in free hydrogen ions to preserve electrical neutrality [8] . However, the clinical consequences of metabolic acidosis are not well understood. Transient acidosis in otherwise healthy subjects is a common result of exercise and is well tolerated without any significant long-term sequelae. Recent experimental evidence suggests that acidosis may be protective, particularly during conditions of decreased metabolic substrate availability [9] . By contrast, metabolic acidosis in resuscitated, critically ill patients seems to be associated with significant morbidity and mortality [10] [11] , although causality has not been established.

Given this and other disadvantages of saline, alternative fluids are sometimes used for resuscitation of patients with septic shock. Unfortunately, alternative fluids also have disadvantages. Evidence from animal models of hemorrhagic shock suggests that survival is improved with lactated Ringer's compared with saline [12] . However, this finding has not been consistent across all studies and some authors have raised concerns about the hypotonicity of Ringer's solution [13] . Until recently, colloid solutions have either been prepared in 0.9% saline (hetastarch) or contain gelatins or human proteins or albumin—the latter being the subject of recent controversy over safety [14] . Therefore, the purpose of this study was to compare survival time and acid-base balance after resuscitation with Hextend (Abbott, Chicago, IL; 6% hetastarch in a balanced electrolyte solution) or 0.9% saline in animals with endotoxin-induced shock. Hextend has significantly less chloride compared with 0.9% saline (124 vs. 154 mmol/L) and does not produce metabolic acidosis in humans [15] .

METHODS

Surgical Preparation.

Following approval by the Animal Care and Use Committee of the University of Pittsburgh Medical Center, 60 adult, male Sprague-Dawley rats were anesthetized with pentobarbital sodium (40 mg/kg intraperitoneally). Each animal was then intubated with a beveled 16-guage angiocatheter and ventilated with room air using a Harvard rodent ventilator (Holliston, MA) at a tidal volume of 10 mL/kg and a frequency sufficient to maintain an arterial P_{co_2} between 35 and 45 mm Hg. Arterial blood gases were monitored frequently using an ABL-725 blood gas analyzer (Radiometer, Copenhagen, Denmark). The right femoral vein and right carotid artery were isolated by dissection and cannulated with 1.27-mm PE 90 catheters. Blood sampling and continuous arterial pressure monitoring was achieved using the carotid arterial catheter. The venous catheter was used for administration of endotoxin and for fluid resuscitation.

Experimental Protocol.

Before the administration of endotoxin, the animals were maintained in a steady state as defined by stable hemodynamics, and arterial blood gas values for at least 30 mins. Arterial pressure was measured continuously and recorded in real time on a strip-chart recorder (Gould, Cleveland, OH). *Escherichia coli* endotoxin (O111:B4, Sigma Chemical, St. Louis, MO) was administered intravenously at a dose of 20 mg/kg. This dose and strain of endotoxin was selected because it results in physiologic conditions that closely resemble human septic shock. These conditions include hemodynamic instability, diffuse capillary leak syndrome, and metabolic acidosis. Animals were then resuscitated with 3–5-mL boluses of fluid, as needed to maintain a mean arterial pressure of >60 mm Hg using 0.9% saline (n = 25) or

Hextend (n = 25). The chemical composition of the resuscitation fluids is shown in Table 1. No other therapy (e.g., vasopressors) was provided. At the conclusion of these experiments, an additional ten animals were studied using the same methods but resuscitating with lactated Ringer's solution.

Table 1. Composition of resuscitation solutions

Component	0.9% Saline	Hextend	Lactated Ringer's
Na^+ , mmol/L	154	143	130
Cl^- , mmol/L	154	124	109
K^+ , mmol/L	0	3	4
Ca^{2+} , mmol/L	0	2.5	1.5
Mg^{2+} , mmol/L	0	0.5	0
Lactate, mmol/L	0	28	28
Hetastarch, g/dL	0	6	0
SID, mEq/L	0	28	28

SID, strong ion difference once lactate is metabolized.

Measurements and Calculations.

Survival time was recorded in minutes. Blood work including, blood gas analysis, whole blood lactate, and electrolytes necessary to calculate strong ion difference, were obtained at baseline (t = 0 min) and after initial resuscitation (t = 180 mins). The primary analysis was restricted to these two time points. However, the same measurements were also obtained on surviving animals at 360 and 540 mins. Standard base excess (SBE) was calculated as previously described [16] . The apparent strong ion difference (SIDa) was calculated from arterial plasma as: $SIDa = Na^+ + K^+ + Mg^{2+} + Ca^{2+} - Cl^- -$ lactate, all expressed in mEq/L [17] [18] .

Statistical Analysis.

The primary analysis was between saline- and Hextend-treated animals and was based on the time to death in both groups (Kaplan-Meier). All animals were observed for 12 hrs, and those that were alive at 12 hrs were considered survivors. Overall survival was analyzed using Fisher's exact test. Mean differences between groups were analyzed using individual *t*-tests and then by analysis of variance. Correlations were tested using Spearman's correlation test. Univariate and multivariate regression analyses were performed. A power calculation was based on an 80% power to detect a 20% difference in survival time. A sample size of 50 was sufficient to achieve this power. As a secondary exploratory analysis, survival time and acid-base values were analyzed using the same methods (without regression) for ten animals resuscitated with lactated Ringer's solution. Error values given in the text are standard deviations. Kaplan-Meier curves were compared using a Bonferroni adjustment. Statistical analysis was performed using MedCalc (version 4.2, Mariakerke, Belgium) and Stata (version 6.0, College Station, TX) software. A $p < .05$ was considered statistically significant.

RESULTS

Mean survival time among saline-treated animals was 45% less compared with Hextend-treated animals: 391 ± 151 mins vs. 567 ± 140 mins, $p < .0001$ (Fig. 1). Overall, short-term, survival was defined as being alive at study end point (12 hrs) and was 0% with saline vs. 20% (five animals) with Hextend, $p = .05$. Saline-treated animals received almost twice as much volume (titrated to maintain a mean arterial pressure >60 mm Hg) compared with Hextend-treated animals (0.19 ± 0.04 mL/kg/min vs. 0.12 ± 0.09 mL/kg/min, $p < .001$). There were no differences between groups in baseline values for any of the measured or calculated variables. However, at 180 mins after endotoxin and after initial resuscitation with saline, mean values for arterial SBE (−19.3 ± 5.2 vs. −12.1 ± 5.7 $p < .001$), arterial pH (7.02 ± 0.13 vs. 7.15 ± 0.12, $p < .01$), and plasma SIDa (23.0 ± 6.2 vs. 30.3 ± 2.9, $p < .0001$) were all significantly lower, whereas plasma Cl^- was significantly higher (123 ± 7 vs. 115 ± 3 mmol/L, $p < .001$) compared with Hextend. Values for each variable at 0 min and after initial resuscitation at 180 mins are shown in Table 2. In both groups, SBE and SIDa decreased whereas Cl^- increased. However, a much greater change was seen in the saline-treated animals compared with Hextend. A small but statistically significant decrease in plasma Ca^{2+} was also seen in the saline group. Interestingly, small differences were also seen in gas exchange between groups. In the saline group, Pa_{o_2} increased by 8.6 mm Hg and Pa_{co_2} remained constant. By contrast, in the Hextend group, Pa_{o_2} decreased by 7.8 mm Hg and Pa_{co_2} increased by 9.6 mm Hg. However, only the differences in Pa_{co_2} were statistically significant. For the duration of the experiment, in surviving animals, the differences in plasma Cl^- , Ca^{2+} , SBE, SIDa, pH, and Pa_{co_2} , persisted between groups. The values for Cl^- , SBE, and lactate are shown in Figure 2.

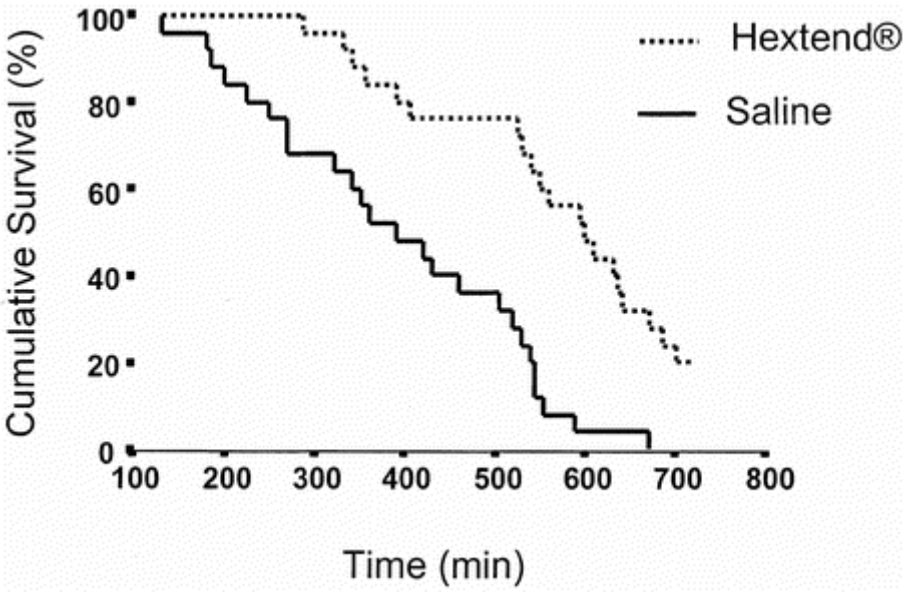

Figure 1. Mean survival time among saline-treated animals was less compared with Hextend-treated animals.

Table 2. Mean values for study variables before and after resuscitation

Variable	Group	Baseline	Postresuscitation [a]	Change
pH	Saline	7.39 ± 0.08	7.02 ± 0.13 [b c]	−0.37 ± 0.19
	Hextend	7.43 ± 0.08	7.15 ± 0.12 [b]	−0.28 ± 0.14
Po_2 , mm Hg	Saline	104.5 ± 18.1	113.1 ± 48.8	+8.5 ± 38.0

	Hextend	103.7 ± 22.8	95.9 ± 34.3	−7.8 ± 26.1
Pco_2 , mm Hg	Saline	38.2 ± 9.8	38.5 ± 16.3	+0.3 ± 14.2 [c]
	Hextend	36.9 ± 8.4	46.6 ± 14.1 [b]	+9.64 ± 11.8
K^+ , mmol/L	Saline	4.3 ± 1.1	5.4 ± 2.4	+1.1 ± 2.3
	Hextend	4.1 ± 1.7	5.0 ± 2.2	+0.7 ± 2.1
Na^+ , mmol/L	Saline	141.1 ± 2.9	143.7 ± 4.9	+2.6 ± 4.4
	Hextend	142.2 ± 2.6	143.5 ± 3.7	+1.3 ± 3.5
Ca^{2+} , mmol/L	Saline	1.15 ± 0.10	1.04 ± 0.17 [b c]	−0.13 ± 0.17 [c]
	Hextend	1.14 ± 0.11	1.16 ± 0.14	+0.03 ± 0.09
Cl^- , mmol/L	Saline	111.2 ± 3.9	123.1 ± 6.9 [b c]	+11.9 ± 7.3 [c]
	Hextend	110.3 ± 3.2	115.2 ± 3.3 [b]	+4.9 ± 3.0
Glucose, mg/dL	Saline	157.9 ± 56.0	249.5 ± 172.5	+91.6 ± 160.5
	Hextend	131.7 ± 12.4	201.9 ± 128.6	+70.2 ± 127.3
Lactate, mmol/L	Saline	2.8 ± 1.6	6.6 ± 3.6 [b]	+3.7 ± 4.1
	Hextend	2.3 ± 0.7	6.7 ± 4.3 [b]	+4.4 ± 4.3
SBE, mEq/L	Saline	−2.15 ± 5.5	−19.3 ± 5.2 [b c]	−17.2 ± 7.6 [c]
	Hextend	−0.05 ± 2.2	−12.1 ± 5.7 [b]	−12.1 ± 5.9
SIDa, mEq/L	Saline	35.0 ± 6.4	23.0 ± 6.2 [b c]	−11.9 ± 7.1 [c]
	Hextend	37.7 ± 3.1	30.3 ± 2.9 [b]	−7.4 ± 2.5

SBE, standard base excess; SIDa, apparent strong ion difference.

[a] Postresuscitation values were obtained after initial fluid resuscitation at 180 mins;

[b] $p < .05$ compared with baseline;

[c] $p < .05$ compared with Hextend group.

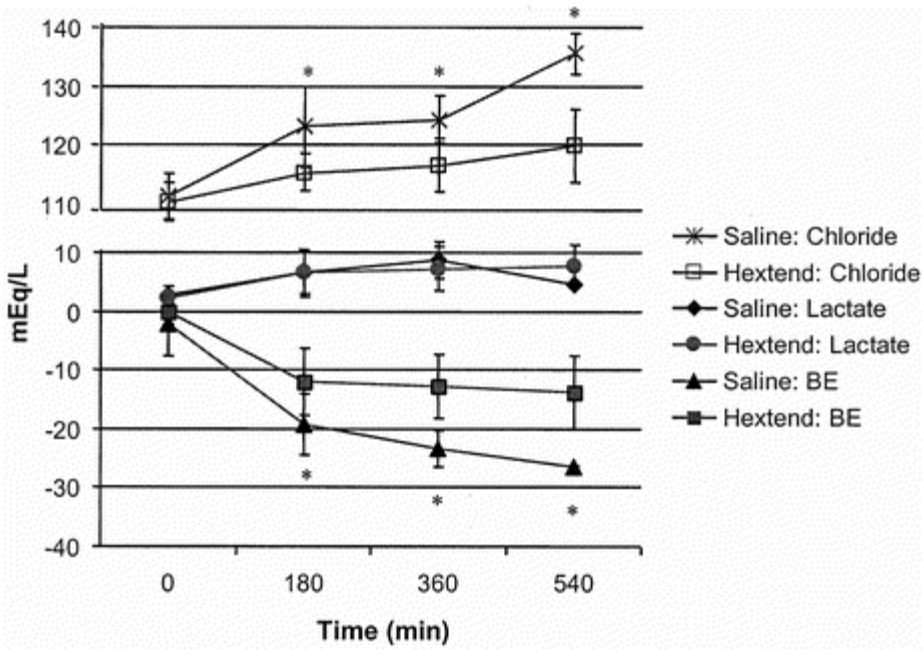

Figure 2. Values for Cl^- , SBE, and lactate.

Because of the significant interactions present between the variables listed in Table 2, both univariate and multivariate analyses were performed. A multivariate regression model was employed using the following variables: treatment group, change (from 0 to 180 mins) in Ca^{2+} , Cl^- , lactate, $Paco_2$, and pH. Only treatment group and pH were independent predictors of survival time ($p < .05$). A second multivariate regression model was used to explore the variables associated with the change in pH occurring with resuscitation. Ca^{2+} , Cl^- , K^+ , Na^+ , lactate, and $Paco_2$ were included in the model. For the entire group, only Cl^- , lactate, and $Paco_2$ were independent predictors of pH ($p < .001$). These same variables were significant when the analysis was restricted to the saline group, whereas only $Paco_2$ was significant for the Hextend group.

Next, a series of univariate analyses was performed for all animals together and for each treatment group separately. The results are shown in Table 3. The changes from baseline for SBE, SIDa, Ca^{2+} , and pH were positively correlated with survival time whereas changes in Cl^- and lactate were negatively correlated. Changes from baseline values in $Paco_2$, were not correlated with survival time in any group. The relationship between the change in Cl^- and survival time is further illustrated in Figure 3. A strong negative correlation is seen between the change in Cl^- and survival time for all animals and for the saline group, but this association is lost in the Hextend group.

Table 3. Univariate correlation between study variables and survival time

Variable	All Animals		Saline Only		Hextend Only	
	r	*p* Value	*r*	*p* Value	*r*	*p* Value
SBE	.61	<.001 [a]	.66	.002 [a]	.36	.12
Cl^-	−.64	<.001 [a]	−.70	<.001 [a]	−.17	.48
Lactate	−.37	.02 [a]	−.59	.008 [a]	−.39	.08
Ca^{2+}	.56	.002 [a]	.52	.08	.27	.34
$Paco_2$	.07	.68	−.12	.63	−.15	.50

pH	.69	<.0001 [a]	.82	<.0001 [a]	.51	.03 [a]
SIDa	.48	.002 [a]	.57	.01 [a]	−.11	.64

SBE, standard base excess; SIDa, apparent strong ion difference.

[a] $p < .05$. Correlation coefficients are shown for each variable on the basis of the net change in each variable from baseline related to survival time.

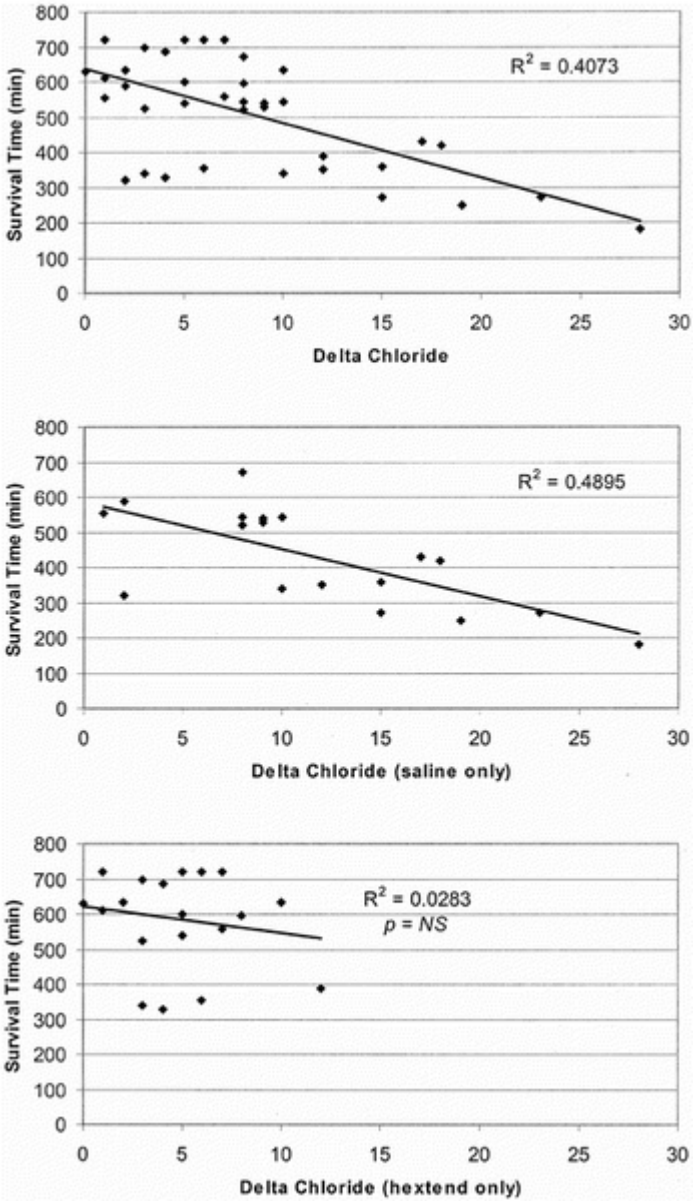

Figure 3. Relationship between change in Cl^- and survival time.

Survival time for the additional ten animals resuscitated with lactated Ringer's solution was 362 ± 94 mins and quite similar to saline-treated animals ($p = .23$) but significantly less than Hextend-treated animals ($p < .0001$). Resuscitation with Ringer's solution resulted in an arterial SBE and plasma Cl^- between that of saline and Hextend (Table 4). At 180 mins after endotoxin, mean values for arterial SBE

were −15.4 ± 3.1 (p = .04 vs. saline), 22.4 ± 3.0 (p < .0001 vs. Hextend) for plasma SIDa, and 117 ± 3.0 mmol/L (p = .01 vs. saline) for plasma Cl^- . Surprisingly, Ringer's yielded the highest arterial pH, 7.16 ± 0.05 (p = .004 vs. saline), owing in large part to a lower observed arterial P_{co_2} of 33.5 ± 8.5 mm Hg (p = .01 vs. Hextend). Plasma Ca^{2+} concentrations were also highest in the Ringer's-treated animals (1.2 ± 0.1 mmol/L, p = .005 vs. saline). Surprisingly, Ringer's solution resulted in changes in SBE and SIDa that were more like those seen with saline than with Hextend. Indeed, the change in SIDa with Ringer's, −10 ± 3, was similar to the −11.9 ± 7.1 with saline and quite different from the −7.4 ± 2.5 (p = .02). Even the change in plasma Cl^- with Ringer's resuscitation (+7.7 ± 2.7) was greater than with Hextend (p = .02). However, unlike in saline-treated animals, there was no correlation between the change in plasma Cl^- and survival time for Ringer's-treated animals (r = .09).

Table 4. Effects of lactated Ringer's on study variables

Variable	Baseline	Postresuscitation [a]	Change
pH	7.45 ± 0.08	7.16 ± 0.05 [b] [c]	−0.27 ± 0.07
Po_2 , mm Hg	93.1 ± 19.2	104 ± 24.5	+14.4 ± 28.9 [d]
Pco_2 , mm Hg	37.5 ± 10.8	33.5 ± 8.5 [d]	−3.7 ± 9.0 [d]
K^+ , mmol/L	3.8 ± 0.3	4.4 ± 0.8	+0.6 ± 0.9
Na^+ , mmol/L	137.4 ± 1.3 [c] [d]	139.5 ± 2.6 [c] [d]	+2.0 ± 1.6
Ca^{2+} , mmol/L	1.20 ± 0.03	1.22 ± 0.06 [c]	+0.04 ± 0.09 [c]
Cl^- , mmol/L	108.2 ± 2.1	116.7 ± 3.0 [b] [c]	+7.7 ± 2.7 [d]
Lactate, mmol/L	1.9 ± 0.6	7.3 ± 2.2 [b]	5.0 ± 2.1
SBE, mEq/L	1.18 ± 1.74	−15.4 ± 3.1 [b] [c]	−15.7 ± 2.4
SIDa, mEq/L	33.5 ± 2.0 [d]	22.4 ± 3.0 [b] [d]	−10.0 ± 3.0 [d]

SBE, standard base excess; SIDa, apparent strong ion difference.

[a] Postresuscitation values were obtained after initial fluid resuscitation at 180 mins;

[b] p < .05 compared with baseline;

[c] p < .05 compared with saline group;

[d] p < .05 compared with Hextend group.

DISCUSSION

The long-existing controversies over the composition of resuscitation fluid will not likely be settled soon. Resuscitation research in humans with septic shock is extremely difficult because of the problems associated with obtaining informed consent in a timely fashion. Recent studies in patients undergoing surgery [3] [4] [5] [6] [7] have provided clear evidence that solutions that contain supraphysiologic concentrations of Cl^- , such as saline, produce hyperchloremia and metabolic acidosis whereas solutions with more physiologic concentrations of strong ions do not. The physiologic and chemical mechanisms for these effects have been well described [2] [8] [19] , even if they are still disputed [20] [21] . What is even more controversial is whether these effects are deleterious to patients [20] [22] . Although most clinicians

practice as though they believe that acidosis is harmful, there is little evidence that treating metabolic acidosis improves clinical outcomes [22] [23] . However, this fact does not address the issue of whether the iatrogenic acidosis that occurs from saline resuscitation is harmful or whether avoiding it can be helpful.

The present study was designed to test the hypothesis that fluid resuscitation with a solution that more closely approximates blood plasma would result in improved acid-base balance and prolong short-term survival compared with saline resuscitation in animals with septic shock. The results of this investigation reveal that, compared with saline-resuscitated animals, animals resuscitated with Hextend survived 45% longer and had significantly less metabolic acidosis. Furthermore, survival time was correlated with the change in pH and negatively correlated with the increase in serum Cl^- after initial resuscitation. The decrease in pH appears to have been brought on by changes in Cl^- , lactate, and Pa_{co_2} . However, lactate values were not different between groups and changes in Pa_{co_2} were not correlated with survival time. Thus, hyperchloremia and the resulting metabolic acidosis were strongly associated with early mortality in these endotoxemic animals. Although the plasma Cl^- concentration increased in the Hextend group (4.9 ± 3.0 mmol/L), the increase in the saline group was much greater (11.9 ± 7.3 mmol; $p < .001$) and the association with decreased survival time was only apparent for saline-treated animals (Fig. 2).

The mechanisms responsible for the observed decrease in short-term survival time in association with hyperchloremic metabolic acidosis are not known. Acidemia might have influenced survival through a variety of mechanisms. For example, acidemia may result in decreased myocardial contractility [24] , although this effect does not appear to be very great during moderate levels of acidemia (e.g., >7.0) [23] . It is not known how much this effect might have contributed to the worsening of shock seen in this study. Acidemia may also influence the inflammatory response through at least two mechanisms. First, acidemia increases endogenous catecholamine release, which induces the production of both pro- and anti-inflammatory cytokines [25] . Second, there may be a direct effect of acidemia on cytokine production by inflammatory cells. Jensen [26] has shown that adding acid to macrophages (to a pH of 6.75) increases tumor necrosis factor secretion by increasing gene transcription. If these effects occurred, they might have influenced short-term (<12 hr) survival either by the direct vasoactive properties of these molecules, which could have contributed to the worsening of shock, or via direct tissue injury. The present study does not permit testing of these hypotheses.

A surprising finding of this study was that in saline-treated animals, a small but significant decrease in plasma Ca^{2+} concentration (0.13 ± 0.17) was independently associated with survival time, although apparently not through any change in pH. This association with Ca^{2+} is notable because postresuscitation Ca^{2+} concentrations were not much different from baseline (1.15 ± 0.10 vs.1.04 ± 0.17), nor were they significantly outside the range typically considered normal for critically ill humans. Little is known about the effects of this degree of change in plasma Ca^{2+} . A speculative explanation for this finding might be that even mild hypocalcemia is poorly tolerated in the face of severe acidosis and shock. Of interest is the finding that, despite improved acid-base balance and Ca^{2+} homeostasis with lactated Ringer's solution, survival time was not improved relative to saline. Thus, it does not appear to be sufficient merely to correct the arterial pH and Ca^{2+} . Some investigators have proposed that the hypotonicity of Ringer's solution may be detrimental [13] ; if so, this effect may have been sufficient to offset any benefit attributable to improved pH and Ca^{2+} levels. It is also apparent that Ringer's solution did not improve the metabolic acid-base picture as expected and the effect on arterial pH was mediated by a lower arterial P_{co_2} rather than by a corresponding change in SBE and SIDa. Compared with the Hextend, Ringer's solution resulted in a much lower SBE and SIDa even though the pH was similar. This finding may have implications for the many differences noted between metabolic and respiratory acid-base changes.

There are several limitations to the present study. First, patients with septic shock are rarely treated with fluid resuscitation alone. Vasopressors such as norepinephrine are needed in a large percentage of such patients and, thus, fluid resuscitation volumes are presumably less. Clinically, fluid management should also be guided by at least central venous monitoring if not by pulmonary arterial pressure. However, the rates of saline infusion in this study (0.19 mL/kg/min) are equivalent to approximately 2.5 L over a 3-hr period in a 70-kg man, and, as such, are not different from volumes commonly used in clinical practice. Furthermore, there are situations (e.g., evacuation of trauma victims) when volume resuscitation is the only treatment available for shock. A second limitation is the use of intravenous endotoxin infusion to produce shock. Although endotoxemia does mimic many of the hemodynamic and inflammatory characteristics of sepsis, there are important differences between endotoxemia and human sepsis [27] . In addition, rats are very endotoxin-resistant animals and require much higher doses to induce clinical effects compared with endotoxin-sensitive species such as humans. A third limitation is the use of survival time rather than survival to a fixed time point (e.g., 30 days) as the primary outcome measure. This was down for two reasons. First, a lethal model of septic shock was more desirable to study the effects of resuscitation on severe acidosis; and, second, because survival time allowed for significantly higher statistical power to detect a difference between each group. Finally, the protocol used in this study does not permit one to determine which of the specific attributes of each fluid, saline or Hextend, are responsible for the observed differences in survival time. Hextend may be superior to saline because of its lower Cl^- content, higher Ca^{2+} content, or higher tonicity, or for some other reason possibly influenced by its colloid composition. The lactated Ringer's group was added in an effort to explore these potential mechanisms. Although the data from these experiments are not as comparable because these animals were not randomized, the results suggest that neither pH nor Ca^{2+} correction is sufficient to improved short-term survival time in crystalloid-resuscitated rats. However, the observed differences in chloride-induced acidosis and the observed association between these differences and survival time in the saline-treated group suggest that the strong ion composition of the solution plays an important role.

There is some evidence that endogenous hyperchloremia also occurs with sepsis [28] [29] . In animals, endotoxemia results in hyperchloremic metabolic acidosis that is only partially explained by saline resuscitation [2] . The mechanisms for development of this type of acidosis are not well known. Capillary leak and partial loss of Donan equilibrium with loss of albumin from the intravascular space, might result in back-leak of chloride from the interstitial space to balance the loss of negative charge. It possible that crystalloids and colloids have different effects on development and propagation of capillary leak such that endogenous hyperchloremia might also have played a role in genesis of metabolic acidosis seen in these animals, including those resuscitated with lactated Ringer's.

CONCLUSION

Saline resuscitation produces hyperchloremic metabolic acidosis and is associated with decreased short-term survival time compared with volume resuscitation with Hextend (6% hetastarch in a balanced electrolyte solution). Resuscitation with lactated Ringer's solution results in improved arterial pH and plasma Ca^{2+} levels but fails to improve survival time. In this murine model of septic shock, short-term survival appears to be influenced by changes in Cl^- and Ca^{2+} occurring with fluid resuscitation. In the absence of clinical data in patients with septic shock, this study suggests that a balanced colloid solution may be superior to saline or lactated Ringer's for fluid resuscitation.

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REFERENCES

1. Task Force of the American College of Critical Care Medicine, SCCM : Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med 1999; 27: 639–660 Full Text

2. Kellum JA, Bellomo R, Kramer DJ, et al: Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock 1998; 9: 364–368 Abstract

3. Scheingraber S, Rehm M, Sehmisch C, et al: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90: 1265–1270 Full Text

4. Waters JH, Miller LR, Clack S, et al: Cause of metabolic acidosis in prolonged surgery. Crit Care Med 1999; 27: 2142–2146 Full Text

5. Waters JH, Bernstein CA: Dilutional acidosis following hetastarch or albumin in healthy volunteers. Anesthesiology 2000; 93: 1184–1187 Full Text

6. Liskaser FJ, Bellomo R, Hayhoe M, et al: Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. Anesthesiology 2000; 93: 1170–1173 Full Text

7. Rehm M, Orth V, Scheingraber S, et al: Acid-base changes caused by 5% albumin versus 6% hydroxyethyl starch solution in patients undergoing acute normovolemic hemodilution: A randomized prospective study. Anesthesiology 2000; 93: 1174–1183 Full Text

8. Stewart P: Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983; 61: 1444–1461 Abstract

9. Laffey JG, Engelberts D, Kavanagh BP: Injurious effects of hypocapnic alkalosis in the isolated lung. Am J Respir Crit Care Med 2000; 162: 399–405 Abstract

10. Stacpoole PW, Wright EC, Baumgartner TG, et al: Natural history and course of acquired lactic acidosis in adults. DCA-Lactic Acidosis Study Group. Am J Med 1994; 97: 47–54 Abstract

11. Hickling KG, Henderson SJ, Jackson R: Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990; 16: 372–377 Abstract

12. Healey M, Davis RE, Liu G: Lactated Ringers is superior to normal saline in a model of massive hemorrhage and resuscitation. J Trauma-Injury Infect Crit Care 1998; 45: 894–889

13. Prough DS, Bidani A: Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999; 90: 1247–1249 Full Text

14. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: A systematic review of randomised trials. BMJ 1998; 316: 961–964 Abstract

15. Wilkes NJ, Woolf R, Mutch M, et al: The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001; 93: 811–816 *Full Text*

16. Christiansen TF: An algorithm for calculating the concentration of the base excess of blood. *In:* Proceedings of the IFCC Expert Panel on pH and Blood Gases. Siggard-Andersen O (Ed). Copenhagen, Radiometer Medical A/S, 1981, pp 77–81

17. Kellum JA, Kramer DJ, Pinsky MR: Strong ion gap: A methodology for exploring unexplained anions. J Crit Care 1995; 10: 51–55 Abstract

18. Figge J, Mydosh T, Fencl V: Serum proteins and acid-base equilibria: A follow-up. J Lab Clin Med 1992; 120: 713–719 Abstract

19. Kellum JA: Metabolic acidosis in the critically ill: Lessons from physical chemistry. Kidney Int 1998; 66: S81–S86

20. Prough DS: Acidosis associated with perioperative saline administration: Dilution or delusion? Anesthesiology 2000; 93: 1167–1169 Full Text

21. Siggard-Andersen O, Fogh-Andersen N: Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthiol Scand 1995; 39: 123–128

22. Forsythe SM, Schmidt GA: Sodium bicarbonate for the treatment of lactic acidosis. Chest 2000; 117: 260–267 Full Text

23. Cooper D, Herbertson M, Werner H, et al: Bicarbonate does not increase left ventricular contractility during L-lactic acidemia in pigs. Am Rev Resp Dis 1993; 148: 317–322

24. Opie L: Effect of extracellular pH on function and metabolism of isolated perfused rat heart. J Appl Physiol 1965; 209: 1975–1980

25. Tulzo YL, Shenkar R, Kaneko D: Hemorrhage increases cytokines expression in lung mononuclear cell in mice, involvement of catecholamines in nuclear factor-B regulation and cytokine expression. J Clin Invest 1997; 99: 1516–1524 Abstract

26. Jensen JC, Buresh C, Norton JA: Lactic acidosis increases tumor necrosis factor secretion and transcription *in vitro*. J Surg Res 2000; 49: 350–353

27. Martich GD, Boujoukos AJ, Suffredini AF: Response of man to endotoxin. Immunobiology 1993; 187: 403–416 Abstract

28. Mecher C, Rackow EC, Astiz ME, et al: Unaccounted for anion in metabolic acidosis during severe sepsis in humans. Crit Care Med 1991; 19: 705–711 Abstract

29. Gilbert EM, Haupt MT, Mandanas RY, et al: The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis 1986; 134: 873–878 Abstract