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Comparison of Lactate Clearance after Resuscitation with Lactated vs. Acetated Crystalloid in Septic Shock.

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Abstract: **Background**: Buffered crystalloid solutions are often recommended as the first choice for intravenous resuscitation. Sepsis-related morbidity and mortality are lower when patients with septic shock are resuscitated early. **Purpose**: To compare the efficacy and potency of lactate clearance, resolution of metabolic acidosis, improvement in hemodynamic status, and resolution of shock after resuscitation with lactate- and acetate-buffered solutions in septic shock. **Methods**: Of the 60 patients with septic shock and sepsis, 30 were recruited for lactate solution and 30 for acetate solution. After admission of these patients to the ICU, we perform ABG of the patient to determine baseline PH, PCO2, PO2, bicarbonate, and lactate. After 12 hours of resuscitation, we repeat the ABG to determine the improvement in sepsis/septic lactate clearance and resolution of metabolic acidosis in both groups. **Results**:The mean change in pH and pO2 was significantly increased and pCO2 significantly decreased in the acetate group from admission to 12 hours after admission, whereas only pO2 was significantly increased in the lactate group. Mean lactate values at admission and after 12 hours were 6.20±2.67 and 4.60±2.13, respectively, in the acetate group and 5.24±1.44 and 2.98±0.53, respectively, in the lactate group. Mean SBP (mmHg) and DBP (mmHg) were significantly increased, and HR (beats/min) and RR (/min) were significantly decreased from admission to 12 hours after admission in the acetate group and the lactate group. **Conclusion**: Mean lactate was significantly decreased more in the lactate group (2.26) than in the acetate group. In addition, SBP (mmHg) and DBP (mmHg) were increased more and HR (beats/min) decreased more in the acetate group than in the lactate group.

Keywords: Schock, Septic,Resuscitation Fluid therapy; Colloids,Lactate

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INTRODUCTION

A dysregulated host response to infection leads to sepsis, which has been described as a life-threatening organ failure [1]. By definition, septic shock is a subtype of sepsis in which particularly severe metabolic, cellular, and circulatory disturbances are associated with a higher risk of death than sepsis alone [1]. A systemic inflammatory response syndrome known as septic shock is described as refractory hypotension despite a fluid intake of 30 ml/kg body weight and is triggered by infection [2]. With a mortality rate of 20% to 45%, septic shock remains a major cause of morbidity and mortality in critically ill patients [3,4]. The mystery of sepsis-related organ dysfunction and failure remains unsolved, although progression to a syndrome of multiple organ failure has been blamed for the majority of deaths in septic shock [5].

As a symptom of anaerobic metabolism and inadequate perfusion, lactate frequently occurs in sepsis and septic shock. Lactate clearance or normalisation of lactate levels is considered a sign of adequate resuscitation in septic shock, according to the Surviving Sepsis Campaign 2021. Lactate, a byproduct of numerous cell types, is released into the blood and either oxidised directly by the liver and kidneys or used as a source of glucose. There are several possibilities that may be responsible for sepsis-related hyperlactatemia, including tissue hypoxia. An important predictor of mortality is lactate formation, which is associated with increased sympathetic activity (HR 90) and hypotension (MAP 65 mmHg) [6,7].
Effective lowering of lactate levels can reduce mortality at 28 days when initial serum lactate is higher than 2 mmol/L [8]. In one study, lactate clearance was found to be greater than 10% after 2 hours of fluid resuscitation, indicating a good

response to treatment or at least can be used as a therapeutic target in the early stages of treatment of a septic patient [9]. According to the Surviving Sepsis Campaign Bundle 2018, one of the resuscitation methods to treat sepsis is intravenous fluid administration, as it can lower serum lactate levels. It is recommended to monitor serum lactate levels within 2-4 hours if the initial serum lactate level is above 2 mmol/L before intravenous fluid infusion [10].

The recommended fluid is an isotonic mixture of balanced crystalloid solutions and normal saline solution (NSS). the NSS consists of 154 mmol/L sodium and 154 mmol/L chloride ions. The pH of the patient's blood can be corrected with balanced crystalloid solution by replacing the chloride ions with bicarbonate or another buffer, such as lactated Ringer's solution (LRS) [11].

Crystalloid fluids are recommended when resuscitating septic patients [12]. Crystalloid solutions are divided into balanced and unbalanced solutions, such as Lactated Ringer (LR) or Plasmalyte, and unbalanced solutions, such as 0.9% saline (NS) [13]. Compared with NS, balanced fluids have electrolyte levels that are more physiologic and closer to plasma [13]. NS has been associated with acute kidney injury and can cause hyperchloremic metabolic acidosis (AKI).In this study we aim to compare following Comparison the efficacy and potency for lactate clearance, resolution of metabolic acidosis and improvement of hemodynamic status/ resolution of shock after resuscitation with Lactate and acetated Buffered solutions in septic shock.

MATERIAL AND METHODS:

In this pragmatic, blinded, comparative, randomized study, a total of 60 patients with septic shock and sepsis patients admitted to the intensive care unit were enrolled. Written informed consent was obtained from each patient. Of the 60 patients, 30 were enrolled for the lactate solution and 30 for the acetate solution based on welldefined inclusion and exclusion criteria. Included were patients with septic shock (as defined by the Surviving Sepsis Guidelines 2021) at > 18 years of age, an initial lactate level >2 mmol/L, a metabolic acidosis pH <7.35, and a bicarbonate level <20 Eq/L. Patients with cardiogenic shock/hemorrhagic shock, respiratory acidosis, CKD, and high baseline APACHE were excluded from the study.

Patients in the lactate group received Ringer's lactate, while those in the acetate group received plasma LyteA (Physiomax). The composition of Physiomax is the same as that of plasma. It is lactate and calcium free and has a similar pH to plasma. This study was conducted in patients with a suspected or confirmed diagnosis of sepsis or septic shock, in patients with high lactate levels and metabolic acidosis. After admission of such patients to the ICU, we order an ABG of the patient to establish baseline pH, pCO2, pO2, Bicarbonate, and lactate. According to the guideline for surviving sepsis, we resuscitate the patient with an infusion of 30 ml/kg buffered (lactate and acetate) in the first 3 hours after recognition of septic or sepsis shock. After 12 hours of resuscitation, we order a repeat ABG to determine improvement in sepsis/septic lactate clearance and resolution of metabolic acidosis in both groups.

Statistical Analysis:

SPSS version 21.0 was used for statistical analysis. Data were expressed as mean (standard deviation) and percentage (%). The chi-square test was used to compare categorical variables and the independent t test was used to compare discrete variables between groups. The paired t-test was used to analyse changes from admission to 12 hours after admission. The p value 0.05 was considered significant.

RESULTS:

Mean age did not differ significantly between the acetate group (44.87±16.45) and the lactate group (38.33±12.32). The percentages of males and females were 83.33% and 16.67% in the acetate group and 70.00% and 30.00% in the lactate group. In terms of gender, both groups were comparable.

Table 1: Comparisons of baseline characteristics in between acetate group and lactate group

	Acetate group (n=30)		**Lactate group (n=30)**		**t**	**p-Value**
	Mean	**±SD**	**Mean**	**±SD**		
Age (years)	44.87	16.45	38.33	12.32	1.74	0.087
Gender	n	%	n	%	chi sq.	p-Value
Male	25	83.33	21	70.00	0.84	0.360
Female	5	16.67	9	30.00		

Table 2 shows the comparison of ABG values at the time of admission in between the acetate group and the lactate group. Mean pH, pCO2, pO2, bicarbonate, and lactate were 7.15±0.15, 42.51±7.12, 131.91±58.79, 16.17±4.84, and 6.20±2.67 in the acetate group and 7.23±0.22, 32.63±11.48, 126.22±35.55, 19.46±4.10, and 5.24±1.44 in the lactate group, respectively. The mean pCO2 was significantly lower and bicarbonate was significantly higher in the lactate group than in the acetate group. Mean pH, pO2, and lactate were not significantly different between the acetate group and the lactate group.

Table 2:Comparisons of ABG at the time of admission in between acetate group and lactate group

	Acetate group (n=30)		**Lactate group (n=30)**		**t**	**p-Value**
	Mean	±SD	Mean	±SD		
pH	7.15	0.15	7.23	0.22	-1.74	0.086
pCO2	42.51	7.12	32.63	11.48	4.01	<0.001*
pO2	131.91	58.79	126.22	35.55	0.45	0.652
Bicarbonate	16.17	4.84	19.46	4.10	-2.84	0.006*
Lactate	6.20	2.67	5.24	1.44	1.73	0.089

*=Significant ($p<0.05$)

Table 3 shows the comparisons of hemodynamics at admission in between acetate group and lactate group. The mean SBP (mmHg), DBP (mmHg), HR (beats/min), RR (/min) and SPO2 (%) were 104.37±17.56, 63.40±11.94, 124.77±25.04, 23.00±6.92 and 94.13±8.73in the acetate group and 103.93±15.64, 68.77±9.91, 102.37±12.26, 19.67±2.97 and 96.23±5.26 in the lactate group, respectively. The mean HR (beats/min) and RR (/min) were significantly lower in the lactate group than in the acetate group. Mean SBP (mmHg), DBP (mmHg), and SPO2 (%) were not significantly different between the acetate group and the lactate group.

Table 3:Comparisons of hemodynamics at admission in between acetate group and lactate group

	Acetate group (n=30)		**Lactate group (n=30)**		**t**	**p-Value**
	Mean	±SD	Mean	±SD		
SBP (mmHg)	104.37	17.56	103.93	15.64	0.10	0.920
DBP(mmHg)	63.40	11.94	68.77	9.91	-1.89	0.063
HR (beats/min)	124.77	25.04	102.37	12.26	4.40	<0.001*
RR (/min)	23.00	6.92	19.67	2.97	2.42	0.019*
SPO2 (%)	94.13	8.73	96.23	5.26	-1.13	0.264

*=Significant ($p<0.05$)

Mean pH, pCO2, pO2, bicarbonate, and lactate were 7.31±0.15, 38.67±7.29, 151.45±30.17, 20.38±4.41 and 4.60±2.13 in the acetate group and 7.30±0.19, 30.62±5.80, 141.00±36.35, 20.47±2.65 and 2.98±0.53 in the lactate group, respectively. The mean pCO2 and lactate were significantly lower in the lactate group than in the acetate group. Mean pH, pO2, and bicarbonate were not significantly different between the acetate group and the lactate group (Table 4).

Table 4:Comparisons of ABG at the time after 12 hrs of admission in between acetate group and lactate group

	Acetate group (n=30)		**Lactate group (n=30)**		**t**	**p-Value**
	Mean	**±SD**	**Mean**	**±SD**		
pH	7.31	0.15	7.30	0.19	0.03	0.977
pCO2	38.67	7.29	30.62	5.80	4.74	<0.001*
pO2	151.45	30.17	141.00	36.35	1.21	0.230
Bicarbonate	20.38	4.41	20.47	2.65	-0.09	0.927
Lactate	4.60	2.13	2.98	0.53	4.05	<0.001*

*=Significant ($p<0.05$)

The mean SBP (mmHg), DBP (mmHg), HR (beats/min), RR (/min) and SPO2 (%) were 126.33±21.15, 77.27±11.20, 97.40±20.83, 18.07±4.75, and 94.80±9.47 in the acetate group and 111.43±7.57, 75.33±6.00, 84.23±8.78, 15.17±2.48 and 99.07±0.78 in the lactate group, respectively. The mean SBP (mmHg), HR (beats/min), RR (/min) were significantly lower and SpO2 was significantly higher in the lactate group than in the acetate group. DBP (mmHg) was not significantly different between the acetate group and the lactate group (Table 5).

Table 5:Comparisons of hemodynamics after 12 hrs of admission in between acetate group and lactate group

	Acetate group (n=30)		Lactate group (n=30)		t	p-Value
	Mean	±SD	Mean	±SD		
SBP (mmHg)	126.33	21.15	111.43	7.57	3.63	0.001*
DBP(mmHg)	77.27	11.20	75.33	6.00	0.83	0.408
HR (beats/min)	97.40	20.83	84.23	8.78	3.19	0.002*
RR (/min)	18.07	4.75	15.17	2.48	2.97	0.004*
SPO2 (%)	94.80	9.47	99.07	0.78	-2.46	0.017*

*=Significant ($p<0.05$)

Table 6 shows the changes in mean ABG from admission to 12 hours after admission in the acetate and lactate groups. The mean change in pH, pO2, bicarbonate, SBP (mmHg), and DBP (mmHg) was significantly increased, and pCO2, lactate, HR (beats/min), and RR (/min) were significantly decreased from admission to 12 hours after admission in the acetate group. The mean change in pO2, SBP (mmHg), DBP (mmHg), and SpO2 was significantly increased, and pCO2, lactate, HR (beats/min), and RR (/min) were significantly decreased from admission to 12 hours after admission in the lactate group.

Table 6: Changes of mean ABG from admission to 12 hrs after admission in acetate group and lactate group

	Acetate group (n=30)		Lactate group (n=30)	
	Mean difference	p-Value	Mean difference	p-Value
pH	-0.16	<0.001*	-0.07	0.089
pCO2	3.84	0.016*	2.01	0.255
pO2	-19.54	0.047*	-14.78	0.017*
Bicarbonate	-4.21	0.001*	-1.00	0.160
Lactate	1.69	<0.001*	2.26	<0.001*
SBP (mmHg)	-21.96	<0.001*	-7.50	0.015*
DBP(mmHg)	-13.86	<0.001*	-6.57	0.001*
HR (beats/min)	27.37	<0.001*	18.13	<0.001*
RR (/min)	4.93	0.005*	4.50	<0.001*
SPO2 (%)	-0.67	0.753	-2.83	0.007*

*=Significant ($p<0.05$)

DISCUSSION

Although patients have received balanced crystalloid fluids and saline in clinical practise for decades [14,15]. The few studies have addressed the effects of crystalloid composition on clinical outcomes. Preclinical models have shown that the high chloride content of saline has deleterious effects on the body, including hyperchloremia, acidosis, inflammation, renal vasoconstriction, acute kidney injury, hypotension, and death [16-20]. Studies in healthy volunteers suggest that saline may impair renal blood flow through chloride-mediated renal vasoconstriction [21]. Observational studies in critically ill patients have yielded conflicting results, although they have shown that saline has a higher rate of acute kidney injury [22], renal replacement therapy, and death than balanced crystalloids. Two recent pilot studies in critically ill patients showed an absolute difference of 1 percentage point in mortality in favour of balanced crystalloid solutions [23,24], although they were underpowered for clinical outcomes.

Today, crystalloid solutions are commonly administered in the United States and recommended as the first line of treatment for patients with septic shock [14,25]. The term most commonly used to describe solutions composed of water, inorganic ions, and small organic molecules is "crystalloid" Crystalloids are composed of glucose or sodium chloride solutions and may be hypotonic, isotonic, or hypertonic. To mimic plasma, some may contain buffers such as lactate or acetate, and some may contain other components such as potassium or calcium [259]. Since normal saline (0.9% NaCl) is closest to the osmolality of plasma (287 mOsm/kg) and has an osmolality 1.5 times greater than the physiologic chloride content of serum, it is considered an isotonic solution. 154 mEq/L sodium and 154 mEq/L chloride are also present. Normal saline is therefore considered an imbalanced solution [25]. Because normal saline has a higher chloride concentration, the strong ion difference technique (SID) explains why large-volume infusions can cause hyperchloremic acidosis, also known as dilutionalhyperchloremic acidosis [26].

In our study, mean pH and pO2 at admission were not significantly different between the acetate and lactate groups. In contrast, pCO2 at admission was significantly lower in the lactate group compared with the acetate group. The mean change in pH and pO2 was significantly increased and pCO2 was significantly decreased from admission to 12 hours after admission in the acetate group, whereas only pO2 was significantly increased in the lactate group.Previous studies found that the pH was significantly lower in the acetate as compared to lactate-buffered groups [27,28].Whereas another two studies reported that the pH was significantly lower in the lactate as compared to acetate-buffered groups [29,30]. Various studies found no difference in pH in the acetate- vs lactate-buffered groups [31,32].According to Park et al (2011), after administration of normal saline, pH decreased along with an increase in PCO2 and a decrease in standard base excess [33]. This decrease in standard base excess was attributed to the acidifying and alkalizing effects, respectively, of the strong ion difference and the strong ion gap increase, which was offset by the loss of albumin. Only the differences in albumin and the standard base excess were significant, despite the numerical changes in the parameters. Regarding the nonsignificant decrease in the strong ion difference, several electrolyte values were significantly different between the two measurement time points; however, this difference was mainly caused by significant increases in chloride, sodium, and calcium with only minor changes in potassium and magnesium. Patients with severe sepsis and septic shock often experience a decrease in pH under these conditions [34,35]. An increase in arterial PCO2 often occurs within a few days [35]. Park et al. (2011) found that PCO2 increased by approximately 2 mmHg in the first 30 minutes after resuscitation despite a constant respiratory rate [33]. Reduced anxiety, increased blood pressure, and improved systemic perfusion may at least partially explain this finding (which may have optimised the removal of CO2 from tissues, thereby increasing its partial blood pressure).

In our study, mean lactate values at admission and after 12 hours were 6.20±2.67 and 4.60±2.13, respectively, in the acetate group and 5.24±1.44 and 2.98±0.53, respectively, in the lactate group. The mean lactate change was significantly decreased from admission to 12 hours after admission in the acetate and lactate groups. In addition, the mean lactate value had decreased more in the lactate group (2.26) than in the acetate group (1.69). Different lactate-containing solutions have different effects on plasma lactate levels. A review and meta-analysis of 29 studies examining the effects of acetate- versus lactate-containing solutions in humans found that administration of lactate-containing solutions resulted in higher plasma lactate levels in 14 studies, whereas no significant difference was found in the other five studies (36). In one study in humans, both Ringer's lactate (LR) and normal saline (NS) were administered as intravenous boluses to healthy participants. Plasma lactate was measured before and 5 minutes after administration of the bolus, but the administration itself took an average of 47 minutes. There was no discernible difference between the increase in plasma lactate in the NS group and the increase in the LR group (37). In a related experiment, 24 healthy subjects received 1 L of Ringer's lactate or saline over the course of 1 hour, with no differences in plasma lactate levels. Plasma lactate was determined before, during, and up to 240 min after bolus injection (38). In these two studies, similar volumes of fluid were used as in the present study, but measurements of plasma lactate were made over a much longer period of time. In a study of patients undergoing major surgery, patients receiving 10 ml/kg/h of a lactate-containing solution had higher intraoperative lactate values than patients receiving the same amount of an acetate-containing solution. Measurements were taken every 2 h from baseline to 8 h after the start of infusion (39).

The mean change in pH and pO2 was significantly increased, as was pCO2, and lactate was significantly decreased from admission to 12 hours after admission in the acetate group, whereas only pO2 was significantly increased and lactate was significantly decreased in the lactate group. SBP (mmHg) and DBP (mmHg) were higher in the acetate group, and HR (beats/min) was lower than in the lactate group.

CONCLUSION:

The mean change in pH and pO2 was significantly increased, as was pCO2, and lactate was significantly decreased from admission to 12 hours after admission in the acetate group, whereas only pO2 was significantly increased and lactate was significantly decreased in the lactate group. SBP (mmHg) and DBP (mmHg) were higher in the acetate group, and HR (beats/min) was lower than in the lactate group.

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