

Impact of Hyperosmolar Sodium-Lactate Resuscitation on Lactate Clearance in Pediatric Severe Sepsis

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Abstract Background: Fluid resuscitation with normal saline (NS) could aggravate lactate production. Our objective was to compare the impact of small volume resuscitation using hyperosmolar sodium-lactate (HSL) versus NS in pediatric severe sepsis. The primary endpoint was the increased of lactate clearance after 1 and 6 hours of fluid resuscitation. The secondary endpoint was the incidence of fluid overload and serum sodium level. **Methodology and principal findings:** A clinical trial study on 34 severe sepsis children was conducted in Hasan Sadikin Hospital Bandung, Indonesia. Eligible subjects were newly diagnosed severe sepsis children (1–14 years old). Patients were resuscitated with either HSL (bolus of 5 mL/kgBW, repeated if no response and followed by 1 mL/kgBW/hour for 12 hours), or NS (bolus of 20 mL/kgBW, repeated if no response and followed by maintenance fluid requirement). If shock persisted, inotropes and/or catecholamine were commenced. HSL group had significant higher 1 hour and 6 hours lactate clearance compared to NS group ($p < 0.05$ and < 0.01 respectively). HSL group had significant lower incidence of fluid overload compared to NS group ($p < 0.001$). HSL and NS group had no significant difference serum sodium level after fluid resuscitation ($p = 0.601$). **Conclusions:** There was an impact of HSL on lactate clearance after 1 and 6 hours fluid resuscitation. As lower fluid overload incidence was observed in HSL group, HSL solution might likely to be a promising fluid for small volume resuscitation in severe sepsis children.

Keywords: children, hyperosmolar sodium-lactate, lactate clearance, normal saline, severe sepsis

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1. Introduction

Severe sepsis is a significant cause of morbidity and mortality of children in both developed and developing countries. Sepsis mortality were about 10% in developed countries and 60–80% in developing countries [1,2,3]. Severe sepsis occur through some changes that result in tissue hypoxia. Tissue hypoxia causes the formation of energy through glycolysis and lactate-pyruvate pathway through the Cori cycle, because depression of oxidative phosphorylation that produce lactate as alternative energy [4,5,6,7]. Lactate levels > 4 mmol/L indicate poor prognosis in severe sepsis [8]. Bai et al. found that initial lactate levels ≥ 5.55 mmol/L in critically ill pediatric patients could predict mortality with a sensitivity of 61% and a specificity of 86% [9].

Lactate clearance in children with severe sepsis reflects the recovery of tissue perfusion and oxygen supply within fluid resuscitation.

Lactate clearance $> 10\%$ within 1 hour after resuscitation can be used as monitoring of the successful resuscitation equivalent to central venous oxygen saturation (ScvO₂) [10]. High lactate clearance within 6 hours is significantly associated with decreased levels of

inflammatory biomarkers, improved organ function, and outcomes in severe sepsis [11,12]. Fluid resuscitation in children with severe sepsis according to Surviving Sepsis Campaign guidelines in 2012 using NS, but if given in large amount it could cause fluid overload and reperfusion injury that aggravate lactate levels [13]. The new type of liquid that can be used for small volumes resuscitation is HSL that contains lactate as an energy replacement for glucose that does not require oxygen and ATP in hypoxia condition. Hyperosmolar sodium-lactate has the advantage to improve microcirculation faster and avoid reperfusion

injury in pediatric dengue shock syndrome and bypass cardiac surgery, but there was no evidence in severe sepsis case. So in this study we expect HSL to increase the clearance of lactate higher than the NS in pediatric severe sepsis [14,15,16,17].

2. Methods

2.1. Patients Population

A clinical trial study on 34 severe sepsis children were conducted in Hasan Sadikin Hospital, Bandung, Indonesia. The children fulfilled the criteria of International pediatric sepsis consensus conference for severe sepsis [13] (1–14

years old) and had never received fluid resuscitation were eligible. No cardiovascular dysfunction, cyanotic heart disease, short gut syndrome, and gastric bypass history were excluded based on history taking, physical examination, and/or laboratory tests. Block permuted randomisation was used to allocate patients into each group. The enrollment and resuscitation of patients was performed by authors and four trained senior residents. Informed consent were obtained from the patient's parents and or guardian simultaneously while performing procedures of oxygenation, intravenous access, as shock condition required immediate management. The Ethics Committee of Hasan Sadikin Hospital had approved the protocol before the study. The intervention period ran for the first 6 hours of treatment and followed by a 48-hour observation period. The outcomes, complications, adverse events, and concomitant treatments were recorded throughout hospital stay until discharge.

2.2. Study Protocol

Patients were randomly assigned to receive intravenous bolus infusion of either HSL (5 mL/kgBW) or NS (20 mL/kgBW) for 10 minutes. Table 1 shows the comparison of both solutions composition. If shock did not recover with the first bolus, a second bolus with the same solution and dosage was infused once again. If the second bolus failed, then inotropes according to shock type was administered until shock reversed. If inotropes failed to reverse shock, then catecholamine was administered according to shock type according to our hospital guidelines for severe sepsis/septic shock and maintenance fluid HSL (1 mL/kgBW/hr) or NS (according to fluid requirement/kgBW) for 12 hours was given. If shock reversed, patients received maintenance dose of HSL (1 mL/kgBW/hr) or NS (according to fluid requirement/kgBW) for 12 hours. After 12 hours, solution was changed with dextrose 2.25%/NaCl 0.45%. Antibiotics were administered within 1 hour of shock septic. Blood samples for lactate level baseline measurement were drawn from patients simultaneously with fluid resuscitation.

2.3. Studied Parameters

Glasgow Coma Scale (GCS), blood pressure (systolic and diastolic), pulse rate, were measured before and after boluses. Shock recovery, fluid balance, and outcome were observed. Laboratory parameters of blood including haemoglobin, hematocrit, leukocytes, thrombocyte, C-reactive protein, and glucose, before and after bolus according to patient's condition. Lactate values were measured before (T₀), 1 hours (T₁), and 6 hours (T₆) after fluid boluses with HSL or NS.

Lactate clearance was calculated as follow:

- 1-hour lactate clearance (%) = $(0\text{-hour lactate} - 1\text{-hour lactate}) / 0\text{-hour lactate} \times 100$
- 6-hour lactate clearance (%) = $(0\text{-hour lactate} - 6\text{-hour lactate}) / 0\text{-hour lactate} \times 100$

2.4. Study Endpoints

The primary endpoint was the increased of lactate clearance after 1 and 6 hours of fluid resuscitation. Secondary endpoint were fluid overload and serum sodium level between groups.

2.5. Sample-size Determination and Statistical Analysis

To calculate the sample size for measuring and comparing the mean lactate clearance on two groups, then the sample size is determined based on the formula to examine the differences of mean with significance level $\alpha = 5\%$ ($Z_{\alpha} = 1.65$), $\beta = 20\%$ ($Z_{\beta} = 0.84$) and $SD=5.8$. We included 17 patients for each group. The impact of solution on lactate clearance levels over time in each group was analysed. The mean of lactate clearance in each group will be analyzed and compared between groups by unpaired t test for normal distribution data and the Mann-Whitney test for non-normal distribution data. The number of subjects who experienced fluid overload will be analyzed and compared between groups by unpaired t test. The mean of serum sodium level in each group will be analyzed and compared between groups by unpaired t test. P value <0.05 was considered as statistically significant.

3. Results

3.1. Studied Population

Since December 2014 to February 2015, 85 patients were assessed for eligibility, 39 patients were excluded due to inclusion criteria. Of the 46 randomised patients, each 23 patients were allocated to HSL or NS group. Only 17 patients in each group could be analyzed as death occurred. One patient in HSL group experienced hypernatremia 150 mEq/L, treatment was discontinued, and hypernatremia protocol was given. Figure 1 depicts participants' flow diagram.

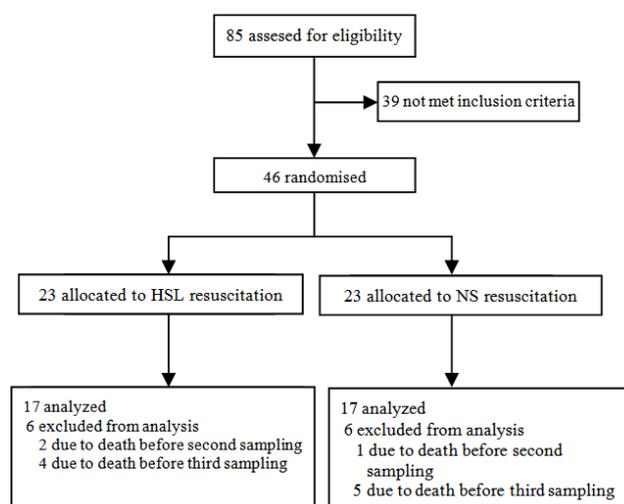


Figure 1. Participant's Flow Diagram

Patients consisted of 34 severe sepsis. As shown in Table 1, characteristic of study patients were homogen between two groups.

3.2. Impact on Lactate Level and Lactate Clearance

Baseline serum lactate levels were not significantly different between groups. Mann-Whitney test demonstrated significant difference of 1 hour-lactate clearance median between groups ($p<0.05$), Mann-

Whitney test demonstrated high significant difference of 6 hour-lactate clearance median between groups ($p < 0.01$) (Table 2).

Table 1. Characteristics of Study Patients

	HSL (n=17)	NS (n=17)
Age		
1 year	2	7
>1–2 years	3	3
3–<5 years	3	4
5–<10 years	5	2
≥10–14 years	4	1
Sex		
Male	10	11
Female	7	6
Nutritional status		
Normal	7	12
Moderate malnutrition	6	3
Severe malnutrition	4	2
Hemodynamic parameter		
Glasgow coma scale (GCS)	11.3 (3.1)	10.7 (3.0)
Systolic (mmHg)	70 (70–110)	80 (60–100)
Diastolic (mmHg)	38.2 (17.2)	47 (10.5)
Heart rate (x/minutes)	159.1 (28.2)	167.1 (14.9)
Duration of shock prior to fluid resuscitation		
<6 hours	13	13
6–12 hours	4	4
Shock type		
Cold shock	13	14
Warm shock	4	3
PELOD score on admission	21 (2–41)	22 (1–41)
Laboratory Parameters		
Haemoglobin (g/dL)	9.0 (2.3)	9.6(1.8)
Hematocrit (%)	26.8 (6.8)	29.4(6.6)
White blood cell (cell/mm ³)	9.100 (100–24.000)	14.700 (100–53.900)
Platetet (sel/mm ³)	96.000 (2.000–617.000)	217.000 (26.000–553.000)
CRP (U/L)	61.6 (6.7–242.7)	45.8 (1.5–308.5)
GDS (mg/dL)	101(52–260)	102 (45–124)

Table 2. Impact of Fluid Resuscitation on Lactate Clearance

Parameter	HSL Group (n=17)	NS Group (n=17)	p value
1 Hour Lactate Clearance (%)	20.5 (-228.5–80.3)	-15.5 (-185.7–44.4)	<0.05*
6 Hour Lactate Clearance (%)	33.3 (-71.4–90.9)	-16.7 (-1350–62.5)	<0.01*

Note : *) Mann-Whitney test, decrement was calculated based on the formula : 100*(value before – value after)/value before.

3.3. Impact on Fluid Overload

There was no statistically significant difference of response to fluid resuscitation, 48 hours outcome between groups, except fluid overload ($p < 0.001$). Total fluid intake was calculated in 6 hours as some patients could not survive for 24 hours. Fluid overload was calculated in similar way. Fluid intake and overload were significantly lower in HSL group. Time of achieving shock recoveries were not statistically different between groups (Table 3).

Table 3. Evaluation of Study Patients after Resuscitation

Variable	HSL Group (n=17)	NS Group (n=17)	P Value
	Shock recovered/not recovered		
Recovered	11	8	0.245*
Not recovered	6	9	
48 hours Outcome			
Survived	8	8	0.634*
Perished	9	9	
Fluid overload (>10%)	0	15	<0.01*

*non-pairwise t test.

3.5. Impact on Serum Sodium Level

As shown in Table 4, sodium level prior to resuscitation were low in both groups, although this was not statistically significant. There were significant increase of sodium level by the time but the increase were not significantly different between groups ($p = 0.610$). Only 1 subject in the HSL group experienced hypernatremia after fluid resuscitation (150 mEq/L) with no clinical manifestasion.

Table 4. Impact of Fluid Resuscittion on Serum Sodium level

Group	Sodium level (mEq/L)		
	0 hour	1 hour	6 hours
NS	129.41	131.88	133.82
HSL	128.65	133.41	136.65
Mean	129.03	132.65	135.24

notes : F calculate (between time) = 34.040; $p < 0.001$

F calculate (between treatment) = 0.265; $p = 0.610$

F calculate (time and treatment interaction) = 2.892; $p = 0.063$.

4. Discussions

This is the first study assessing the effects of HSL to lactate clearance in children with severe sepsis. Significant decrease of serum lactate occurred 6 hours after resuscitation in the HSL group, whereas in NS group, the serum lactate tended to increase. One hour-lactate clearance in the HSL group was significantly higher compared to the NS group ($p < 0.05$). Six hour-lactate clearance in the HSL group was significantly higher compared to the NS group ($p < 0.01$). Serum lactate level depicts the balance of lactate production and clearance. In this study, lactate clearance was higher in the HSL group as HSL improves microcirculation and organ perfusion better than NS. In NS administration, reperfusion injury leads to disturbance of intracellular signalling mechanism, which in turn activates the inflammation cascade, increase proinflammatory cytokine, reactive oxygen spesies (ROS) and reactive nitrogen spesies (RNS) release which boosts the lactate production [13].

HSL administration doesnt cause hyperlactatemia, in contrast, it reduces serum lactate level which depicts the improvement of cell metabolism after resuscitation. This is due to the fact that lactate contained in HSL is an organic anion metabolized as energy source by mitochondria-rich cells into piruvate, carbondioxide (CO₂), and water (H₂O). This is in accordance to the primary hypothesis.

In this study, we found a significant difference in fluid overload between the groups. Fifteen out of 17 subjects in the NS group had fluid overload >10%, whereas none of

the HSL group had fluid overload >10%. This is probably due to the limited monitoring resources and invasive hemodynamic monitoring. Hypertonic crystalloids such as HSL produce high osmotic gradient which will increase the plasma volume 3-4 times when using small volume resuscitation.

Small volume resuscitation using hypertonic HSL could cause hypernatremia, but only 1 patient in this study experienced hypernatremia after fluid resuscitation using HSL (Na:150 mEq/L). This result is similar to the study by Situmorang about the effect of HSL to the level of IL-6 in children with severe sepsis, which yields 1 hypernatremic subject (Na 162 mEq/L) in 12 hours after resuscitation, without coma, limb weakness or cranial nerve dysfunction [19]. Small volume resuscitation with HSL has the advantage of improving microcirculatory hemodynamics faster, modulating immune response, and preventing reperfusion injury, oxidative and nitrosative stress due to RNS and ROS production. This advantage have a protective effects in vital organs from hypoxia, ischemia and reperfusion [14,15,16,17].

The subject of this study had a mean age of 53,26 months predominantly males. This was in accordance with an epidemiological study in the USA which reported that the incidence of severe sepsis in 1 to 4 years-old group was 0.49 per 1000 population, and the <5years-old group had the highest morbidity and mortality. Cold shock is the most prominent type of shock in this study, which comprises 27 subjects, 13 from the HSL group and 14 from the NS group. This also corresponds with previous studies which state that almost 50% of septic shock in children were manifested as cold shock [18].

The number of surviving subjects in 48 hours is similar in both groups, however the number of subjects survived until 28 days or recovered is higher in HSL group (4 vs 2 in NS group) although the difference is statistically insignificant. The high mortality rate in this study is partially due to lack of intensive care unit, ventilator, monitor and invasive hemodynamic monitoring resources. Only 3 out of 34 subjects were admitted to the pediatric intensive care unit, and only 2 out of 18 patients subjects indicated for mechanical ventilation were put on ventilator, while the rest only received bag-valve-mask mechanical ventilation.

The limitation of this study is that it wasn't double blinded as the gold standard for clinical trials. This study is single blinded due to the difference of packaging between HSL 250 ml and RL 500ml in flexi bags although the label were covered, and the significant difference of fluid resuscitation volume between the two groups (1:4). In this study, serial 24-hour lactate level was not examined, which could be associated with severe sepsis outcome. Multicenter study with larger sample size and adequate fluid monitoring is needed.

5. Conclusions

Lactate clearance in severe sepsis children who received HSL is higher than those received NS. There are significant smaller volume intake and lower fluid overload in HSL group. Hyperosmolar sodium-lactate is a promising fluid for resuscitation in severe sepsis children who are at risk of fluid overload.

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