

A comparison of NSS vs balanced salt solution as a fluid resuscitation and impact of fluid balance on clinical outcomes in pediatric septic shock

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Abstract

Septic shock is a common condition affecting children worldwide. Initial resuscitation with crystalloid fluid is the first step in treatment of septic shock. However, there is increasing concern about side effects of using normal saline. Our objective was to compare the effectiveness of balanced salt solution vs 0.9% normal saline solution (NSS) on decreasing morbidity and mortality in pediatric septic shock. This was a prospective observational study enrolled septic children aged 1-15 years treated at the Department of Pediatrics, King Chulalongkorn Memorial Hospital. They were given fluids resuscitation according to Surviving Sepsis Campaign (SSC) guidelines. Thirty-five sepsis children were enrolled, 20 received normal saline as first line fluid resuscitation and 15 received balanced

salt solution (Ringer lactate solution [RLS]) as first line fluid resuscitation. Baseline characteristic of both groups were similar. RLS group received significantly less fluid resuscitation at 24 and 48 hours compared to NSS group (134.3 ± 42.9 vs 171.3 ± 49.5 ; $p=0.02$, 236.9 ± 75.7 vs 313.1 ± 115.3 ; $p=0.03$). Moreover, RLS group had significantly less metabolic acidosis and better base excess at 6 hours and 24 hours compared to NSS group (2.5 ± 4.1 vs -3.7 ± 4.1 ; $p<0.001$, 3.4 ± 3.2 vs -1.2 ± 3.9 ; $p=0.03$). There was no statistically significant difference in mortality between two groups (15% [n=3] NSS, 6.7% [n=1] RLS).

Conclusion: Using balanced salt solution for resuscitation decreased metabolic acidosis and tended to decrease fluid intake and fluid accumulation.

Introduction

Sepsis is a common clinical condition with a significant impact on healthcare resources and expense. Severe sepsis and septic shock is the leading cause of death in most of intensive care units worldwide. Data from the surviving sepsis campaign showed a mortality of 34.8% and the number

is higher in developing country. (1,2) Early resuscitation in severe sepsis and septic shock can modulate inflammation and result in significant reduction of morbidity and mortality. (3) The surviving sepsis guidelines currently recommend early aggressive fluid resuscitation during golden hours. Initial resuscitation with crystalloids fluid is the first step in treatment of severe sepsis and septic shock patients. (3,4) However, it does not indicate specific type of crystalloid or colloid fluid. Thus, choice of fluid is currently controversial.

Crystalloids can be characterized on the basis of tonicity and electrolyte content. The presence of an organic anion (eg lactate, acetate, or gluconate) with corresponding lower chloride content that more closely resembles the composition of plasma suggest that a crystalloid should be balanced. (5-7) The most commonly used crystalloid, normal saline (0.9% NaCl), is quite far from "normal" with a pH of less than 7 and a supraphysiologic chloride content of 154 mmol/l. Compared with a balanced crystalloid solution, normal saline predispose patients to hyperchloremic metabolic acidosis, decrease renal blood flow to glomerulus, and impair

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smooth muscle contractility. (7-11) In addition, there are only a few trials in adult sepsis compared clinical outcome between these two types of crystalloids. Uncontrolled fluid balance had significant impact on pediatric septic shock mortality. Thus, this study aimed to compare clinical efficacy of normal saline and balanced salt fluids resuscitation as well as the effect of fluid balance on clinical outcomes in pediatric septic shock.

Material and methods

Study design

Prospective observational study. Children aged between 1 month through 15 years with diagnosis of severe sepsis or septic shock who admitted at Pediatric Ward and PICU of King Chulalongkorn Memorial Hospital during June 2013 to March 2014 were enrolled in this study. Our institutional review board approved the study, and informed consent was obtained.

Exclusion criteria

- Congenital heart disease with CHF
- Shock from other causes
- End stage disease eg metastasis tumor
- Severe congenital anomaly

They were divided into two groups, first group was given 0.9% normal saline solution (NSS) 20 ml/kg as the first fluid resuscitation and the second group was given balanced salt solution (Ringer lactate solution [RLS]) 20 ml/kg as the first fluid resuscitation. Then, they were reassessed to give another dose of 0.9% NSS or RLS if clinical indicated. They were assigned to goal-directed therapy received step-by-step goal assessment per algorithm.

Outcome measurement

- 1 Clinical scoring: sequential organ failure assessment (SOFA) score, pediatric risk of mortality III (PRISM III) score, pediatric logistic organ dysfunction (PELOD) score, inotropic score, % fluid overload, ventilator free day.
- 2 Physiologic parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), heart rate (HR), fluid intake (type and amount), urine output, estimate fluid balance, medications requirement.
- 3 Laboratory parameters: complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), blood urea nitrogen (BUN), creatinin, electrolyte, calcium, albumin, liver function test (LFT), superior cava vein oxygen sat-

uration (ScvO₂), blood gas analysis.

Statistical analysis

Descriptive statistical analysis was used to examine the demographic characteristics of the study population. Data were expressed as mean±SD. The baseline clinical characteristics, physiologic parameters and laboratory parameters were compared between NSS group and RLS using the two-tailed student t test and chi-square test for continuous and categorical variables, respectively. $p < 0.05$ was considered statistically significant. All of the analysis was performed by using SPSS software version 14 (Chicago, ILL).

Results

Baseline clinical characteristics

During the study period, there were 35 children enrolled to our study. Almost all of the patients were admitted to PICU either from the ER or general pediatric ward. The baseline clinical characteristics of subjects were summarized in **Table 1**. Their mean age was 50.3 ± 58.9 months. Their baseline PRISM III score was 8.75 ± 4.6 , PELOD score 8.75 ± 8.8 , and SOFA score 8.3 ± 2.6 . Their baseline clinical characteristics were presented in **Table 2**.

Microorganism variables

The results of bacterial studies were summarized in **Table 3**.

Clinical outcomes

Their mean age and PELOD were not significantly different compared between NSS and RLS at baseline. The use of RLS resulted in significantly better base deficit at 6 hrs ($p < 0.001$) and 24 hrs after fluid resuscitation ($p = 0.002$) compared to 0.9% NSS. The NSS group tended to require more renal replacement therapy 3/20 (15%) than RLS group (none). Furthermore, septic children in RLS group received significantly less fluid resuscitation accumulation at 24 hrs and 48 hrs compared to NSS group (134.3 ± 42.9 vs 171.3 ± 49.5 ml/kg/d, $p = 0.02$; 236.9 ± 75.7 vs 313.1 ± 115.3 ml/kg/d, $p = 0.03$). However, there was no significant difference in mortality between two groups (8.5%, NSS vs 2.8%, RLS; $p = 0.3$) (**Table 4**). Moreover, there was a trend to have higher percentage of fluid overload ($5.4 \pm 4.04\%$) in historical control compared to our current study ($1.8 \pm 13\%$, $p = 0.08$). There was higher percentage of fluid overload in mortality of historical control ($8.4 \pm 3.8\%$) compared to current study ($3.9 \pm 3.7\%$) at 24 hrs, but did not reach statistically significant. Finally, there was a significant reduction of our

septic mortality from 19.1% in historical control to 11.4% in current study ($p < 0.01$) (**Table 5**).

Discussion

Fluid administration is the mainstay of sepsis resuscitation. It restores the intravascular volumes with the aim to improve tissue perfusion, lactate clearance, central venous oxygen saturation and to reduce vasopressor requirement. (11-13) There is however emerging evidence that NSS may be associated with adverse outcomes. (5,14-17) Our study demonstrated that the use of balanced salt solution (RLS) resulted in significantly improves in acid-base status compared to NSS. Infusion of 0.9% NSS is a common cause of normal anion gap metabolic acidemia. Moreover, the buffering capacity of saline is negligible. A mechanic approach of fluid resuscitation and acidemia is quite important. Administration of 0.9% NSS contains no buffer base and diluted the endogenous buffer system. A recent prospective study has associated administration of chloride-rich fluid with poor renal outcome. More use of NSS may also result in higher chloride effect on kidney. Higher chloride exposure could have more effect on renin activity and worsen GFR. (11,18,19) In contrast, infusion of RLS does not result in acidemia since the metabolism of lactate involves the generation of bicarbonate. Balanced salt solutions, based on the prototype compounded sodium lactate, are increasingly being recommended on the basis of physiologically approximate the constituents of extracellular fluid. (7)

This study also showed a trend of decreasing fluid balance in RLS compare to NSS group at 24 hrs and 48 hrs (3.77%/4.77%, 4.1%/6%) although no statistically significance. Fluid overload has been independently associated with increased morbidity and mortality. The excessive use of fluids during resuscitation was associated with increased cumu-

lative fluid balance. Recent study demonstrated fluid overload that secondary from more fluid resuscitation was associated with the development of acute kidney injury. (10,20-22) Moreover, fluid overload could lead to more inflammation, release of anti-diuretic hormone and capillary leak. (7) The use of RLS tended to improve percentage of fluid overload. There was also a trend of using less inotropic drugs indicated by less inotropic score in RLS group. This might result in improving of myocardium activity secondary from improving acid base status and less fluid overload. There was no significant difference regarding the number of day on mechanical ventilator (MV) and day in PICU between two groups. However, our current septic shock mortality was significant lower compared to previous study (11.4% vs 19.1%, $p < 0.01$). (23) Our study had some limitations such as small sample size and not a randomized trial.

In summary, the use of balanced salt solution for resuscitation decreased metabolic acidosis and tended to decrease fluid intake and fluid accumulation. Furthermore, type of fluids, fluid balance may have an effect on morbidity and mortality. The less fluid resuscitation and higher positive fluid balance tended to increase mortality in pediatric septic shock.

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Table 1. Baseline clinical characteristics

Data	Mean±SD (n=35)
Age (month)	50.35±58.99
Sex (male:female)	21:14
BW (kg)	17.27±14.89
Height (m)	0.92±0.36
BMI (kg/m ²)	17.9±5.2
PELOD score	8.75±8.86
PRISM III score	8.75±4.64
SOFA score	8.30±2.64
MAP initial (mmHg)	65.35±19.98
Mechanical ventilator support (n, %)	16 (45.71%)
Renal replacement therapy (n, %)	3 (8.3%)
Diagnosis	
- Pneumonia	18 (51.42%)
- Bacteremia	1 (2.86%)
- Diarrhea	1 (2.86%)
- Skin infection	5 (14.29%)
- Urinary tract infection	4 (11.43%)
- Others	2 (5.71%)
- No underlying disease	4 (11.43%)

Legend: BW=body weight; BMI=body mass index; PELOD=pediatric logistic organ dysfunction; PRISM III=pediatric risk of mortality III; SOFA=sequential organ failure assessment; MAP=mean arterial blood pressure; SD=standard deviation.

Table 2. Baseline clinical characteristics comparison between 0.9% NSS and RLS

Data	NSS group (n=20) (mean±SD)	RLS group (n=15) (mean±SD)	p-value
Age (month)	50.35±58.99	76.60±57.84	0.19
Sex (male:female)	12:8	9:6	0.45
BW (kg)	17.27±14.89	24.28±17.67	0.21
Height (m)	0.92±0.36	1.07±0.39	0.23
BMI (kg/m ²)	17.90±4.73	17.83±5.96	0.97
PELOD score	8.75±8.86	8.20±8.44	0.85
PRISM III score	8.75±4.64	5.40±4.64	0.02
SOFA score	8.30±2.64	6.67±2.02	0.05
MAP initial (mmHg)	65.30±19.98	66±21.88	0.95

Legend: BW=body weight; BMI=body mass index; PELOD=pediatric logistic organ dysfunction; PRISM III=pediatric risk of mortality III; SOFA=sequential organ failure assessment; MAP=mean arterial blood pressure; NSS=0.9% normal saline solution; RLS= Ringer lactate solution; SD=standard deviation.

Table 3. Microorganism identified in this study

Pathogen identification	n (35)
Tracheal secretion culture positive	4 (11.43%)
Hemoculture	
- Klebsiella pneumoniae	2 (5.71%)
- Candida spp.	2 (5.71%)
- Escherichia coli	2 (5.71%)
- Pseudomonas aeruginosa	1 (2.86%)
- Staphylococcus aureus	1 (2.86%)
Stool culture positive	5 (14.29%)
Urine culture positive	1 (2.86%)
Culture negative	17 (48.57%)

Table 4. Clinical parameters comparison between 0.9% NSS and balanced fluid (RLS)

Parameters	0.9% NSS (mean±SD)	RLS (mean±SD)	p-value
CVP 6 hrs (mmHg)	9.07±3.41	9.15±3.10	0.94
CVP 24 hrs (mmHg)	10.13±3.32	9.86±3.21	0.82
MAP 6 hrs (mmHg)	72.95±13.16	75.87±10.87	0.49
MAP 24 hrs (mmHg)	77.20±10.96	80.27±12.24	0.44
ScvO ₂ 6 hrs (%)	76.74±11.07	78.14±8.55	0.74
ScvO ₂ 24 hrs (%)	75.02±9.76	79.55±7.00	0.22
Base excess 6 hrs	-3.65±4.14	2.46±4.07	<0.001
Base excess 24 hrs	-1.18±3.95	3.36±3.20	0.002
Fluid intake in 1 hr (ml/kg)	34.85±13.26	29.46±9.54	0.23
Fluid intake in 6 hrs (ml/kg)	91.83±33.93	66.73±25.03	0.02
Fluid intake in 24 hrs (ml/kg)	171.32±49.49	132.62±42.90	0.02
Fluid intake in 48 hrs (ml/kg)	311.90±116.78	245.63±73.17	0.06
Urine output in 1 hr (ml/kg)	5.06±7.91	3.19±4.76	0.44
Urine output in 6 hrs (ml/kg)	43.68±26.58	39.08±34.34	0.67
Urine output in 24 hrs (ml/kg)	163.66±171.80	98.66±46.52	0.16
Urine output in 48 hrs (ml/kg)	249.37±108.01	196.22±66.13	0.1
Fluid overload in 24 hrs (%)	4.77±3.34	3.77±3.00	0.37
Fluid overload in 48 hrs (%)	6.03(±4.12)	4.12±4.11	0.24
Inotropic score	23.70±17.36	15.47±9.04	0.1
Ventilator support (n, %)	10 (50%)	6 (40%)	0.4
Mechanical ventilator free day	16.80±10.62	18.17±8.61	0.8
Renal replacement therapy (n, %)	3 (15%)	0	-
PICU LOS (days)	6.55±8.39	6.00±7.18	0.8
Mortality (n, %)	3 (8.57%)	1 (2.86%)	0.4

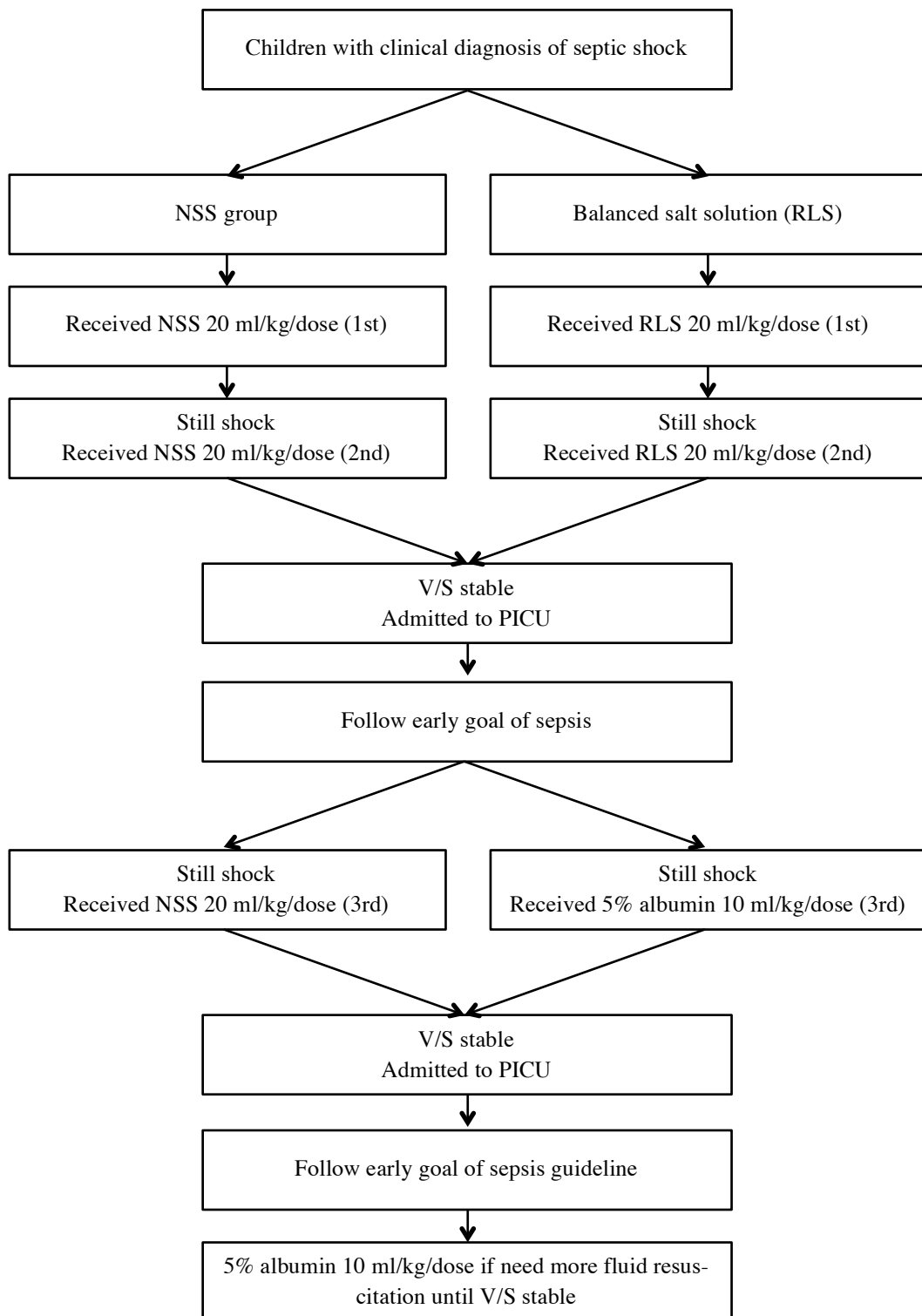
Legend: CVP=central venous pressure; MAP=mean arterial blood pressure; ScvO₂=superior cava vein oxygen saturation; PICU=pediatric intensive care unit; LOS=length of stay; NSS=0.9% normal saline solution; RLS= Ringer lactate solution; SD=standard deviation.

Table 5. Percentage fluid overload and mortality comparison between historical control and current study

	Historical control (mean±SD)	Current study (mean±SD)	p-value
Fluid overload (overall) (%)	5.36±4.04	1.87±13.01	0.08
Fluid overload (mortality) (%)	8.38±3.83	3.89±3.68	0.75
Mortality (%)	19.1	11.4	<0.001

Legend: SD=standard deviation.

Figure 1. Diagram for fluids resuscitation protocol for this study



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