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Original Article

A Double-Blind, Randomized Control Trial of Rapidly Infused High Strong Ion Difference (SID) Fluid Versus Hartmann's Solution on Acid-Base Status in Sepsis Patients in the Emergency Department

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Background: Balanced fluids are preferred in initial resuscitation of septic patients based on several recent studies. The Stewart's concept on acid-base balance predicts that high strong ion difference (SID) fluid thus will increase the pH level. To date, the impact of high SID fluid in septic patient with metabolic acidosis remains uncertain. We conducted single center, randomized, double-blind trial to compare the effect of high SID fluid vs. Hartmann's solution on acid-base status in selected sepsis patients in the Emergency Department.

Methods: Septic patient with hyperlactatemia and metabolic acidosis were randomized to receive either high SID fluid or Hartmann's solution during initial fluid resuscitation. The primary outcome measures the pH and bicarbonate levels difference pre- and post- resuscitation.

Results: One hundred and sixty-two patients underwent randomization, 81 were assigned each to receive high SID fluid or Hartmann's solution. Both groups had similar baseline characteristics. High SID group received 23.5 mL/kg and the Hartmann's group received 22.7 mL/kg (p = 0.360). High SID fluid increased the mean (± SD) pH by 0.107 (± 0.09) vs. Hartmann's solution by 0.014 (± 0.12), $p \leq$ 0.001. Mean bicarbonate level increased significantly in high SID group compared to Hartmann's (4.30 ± 3.76 vs. 1.25 ± 3.33, $p \leq 0.001$). High SID group had higher post resuscitation lactate clearance than Hartmann's group (25.4 ± 28.3% vs. 12.0 ± 34.1%, p = 0.009). Shorter hospital stay was observed in high SID group 8.04 ± 5.96 days vs. Hartmann's group 12.18 ± 12.41 days (p = 0.048). Both groups showed no difference in incidence of pulmonary oedema, acute kidney injury and mortality.

Conclusions: Initial resuscitation using high SID fluid in selected septic patient improves pH and bicarbonate levels. The high SID group had better post resuscitation lactate clearance and shorter hospital stay.

Key words: *sepsis, balanced fluid, Hartmann's solution, high strong ion difference, resuscitation*

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Introduction

Intravenous administration of isotonic crystalloids is a major component of resuscitation in critically-ill patients in the emergency department. Patients in shock are often given initial crystalloid boluses to maintain haemodynamic stability. In particular, certain shock states, e.g., septic shock, large volume isotonic crystalloid resuscitation in the early stages of up to 30 mL/kg is crucial in improving survival.[1]

Crystalloids administration in shock maintain intra-vascular volume, improve tissue perfusion without resulting in any interstitial edema.[2] Intravenous crystalloids are also a stable medium for administration of drugs and blood products thereby being ideal in maintaining intravenous access. Being isotonic, they do not change the osmolality of the internal milieu much. However, large volume crystalloid administration known to cause hyperchloreamic acidosis.[3,4] This has been attributed in part to the high chloride content, a near-zero strong ion difference (SID) and the dilution effect due to extravascular bicarbonate.[5] Balanced crystalloid solutions, like Hartmann's or Ringer's lactate solutions have lower chloride levels, and a more "balanced" SID difference (of between 24–28), therefore does not cause this hyperchloraemic metabolic acidosis following large volume administration. The selection and administration of resuscitation fluids in septic patients with metabolic acidosis is crucial and must be tailored according to patients' situation without worsening the acidosis unnecessarily.[6]

Stewart pointed out that the whole-body acid-base balance is mainly regulated by the movements of strong ions through cell membranes.[7] He explained that the crystalloid SID, i.e., the net charge difference between the strong cations (mainly Na^+, K^+) and strong anions (mainly Cl^-), is the main factor that determines the impact of an infused solution on acid-base balance in the body. Thus, an infusate like normal saline, with a SID = 0, will result in metabolic acidosis, whereas a more balanced solution like, Hartmann's with a SID = 28, will not directly cause metabolic acidosis. In a study by Omron et al.,[8] solutions with higher SID = 75, resulted in progressive metabolic alkalosis and less progressive metabolic acidosis, i.e., an ability to normalize metabolic acidosis. The traditional saline-based fluid resuscitation strategy, however, fails to link the physicochemical properties of the crystalloid solution or crystalloid SID.[9-11]

The aim of this study, was to determine whether, among patients with severe sepsis and septic shock with severe metabolic acidosis, who needed initial high volume resuscitation, the use of a high SID intravenous solution, i.e., half-normal saline with added 75 mEq/L sodium bicarbonate (resultant SID = 75) as an early fluid choice, when compared to Hartmann's solution (SID = 28), is associated with greater change in arterial blood pH and bicarbonate levels, as well as other outcomes.

Methodology

The high SID in sepsis patients (HiSIDSS) study is an investigator-led double-blinded randomized controlled trial conducted at a tertiary referral center in Malaysia, the study protocol was approved by the Malaysian National Medical Research Registry Ethics Committee (trial number: NMRR-16-2065-33132). There were no financial grants for this study and no conflicts of interest reported.

Adults (age >18 years old) were eligible if they had presumed infection, fulfilled two out of three Sepsis Related Organ Failure assessment (qSOFA) criteria (systolic blood pressure < 90mmHg, altered mental status, respiratory rate > 22), hyperlactatemia (serum lactate > 2 mmol/L) and did not meet any exclusion criteria. Patients who were unable to receive large fluid volume during initial resuscitation were excluded as they were at risk of fluid overload. The exclusion criteria were provided in Fig. 1. All patients provided written consent, or the consent was obtained from the immediate caretaker or family member.

Eligible subjects were assigned in a 1:1 ratio by means of randomization using online randomizer, which was saved and secured in the randomization log. A trained staff member will prepare the study fluids (either high SID fluid, which was prepared by addition of 37.5 mEq/L sodium bicarbonate 8.4% into 500 mL of half saline, or pure Hartmann's solution, all labels removed, volumes similar) according to the randomization log right after a suitable patient is recruited. At the end of preparation, the study fluids will be macroscopically indistinguishable.

All clinicians, patients and investigators were blinded to the study fluids used during resuscitation. All subjects received the appropriate rate of infusion of study fluid based on clinical judgment by the treating physician. Each subject was monitored every 30 minutes for blood pressure, pulse volume and capillary refill time. Blood samples were taken for electrolytes,

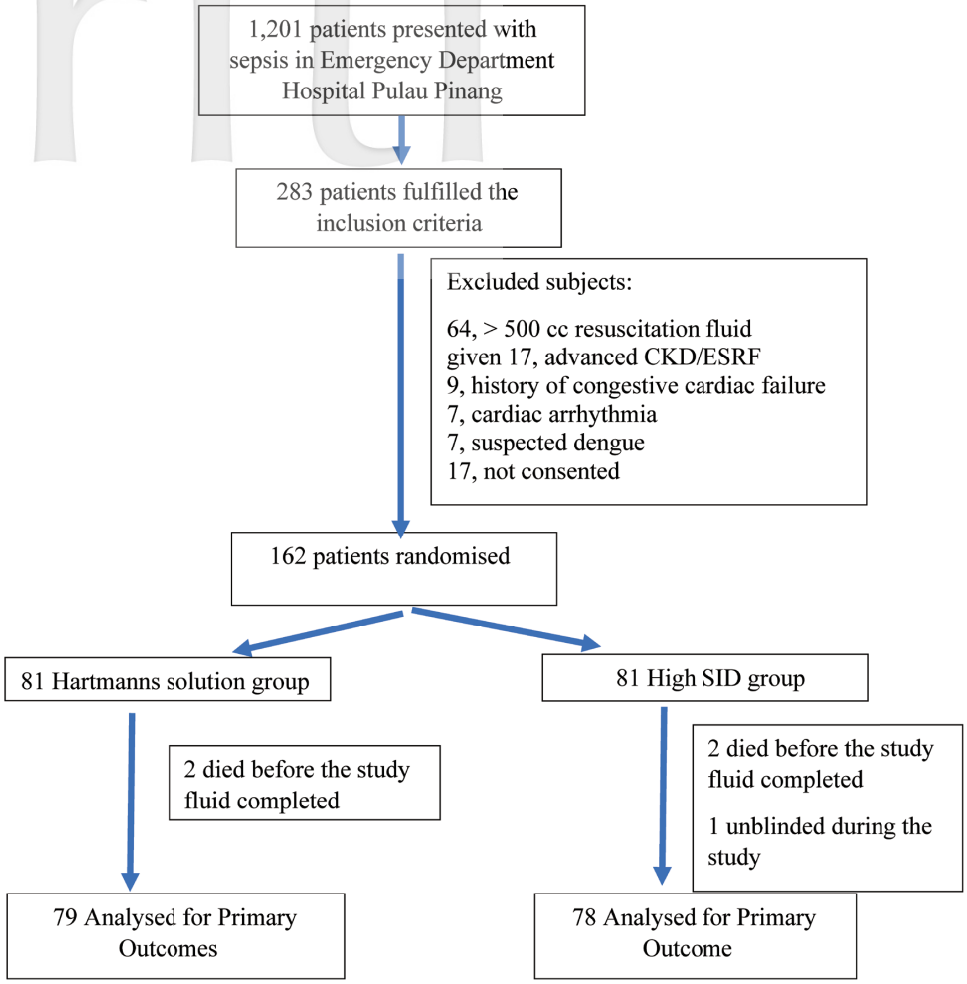

Fig. 1. Flow diagram of patients.
Advanced chronic disease includes stage 4 and 5 chronic kidney disease classification. CKD/ESRF: chronic kidney disease or end stage renal failure; SID: strong ion difference.

urea and creatinine measurement, blood gas with lactate level at baseline before the initiation of study fluid. When 30 mL/kg of study fluid was administered or at two hours (whichever occurs first), another blood gas with lactate level was taken. At the end of two hours of resuscitation or after 30 mL/kg of study fluid was administered, subjects were given the usual resuscitation fluid according to the treating physician's judgement. Subjects are subsequently followed up in the ward for repeat blood investigations within 48 hours and followed up for all-cause mortality in 30 days.

The primary outcome was the change in blood pH and arterial blood bicarbonate levels post administration using the test fluid. Secondary outcomes considered were the change in lactate levels, length of stay, incidence of acute kidney injury (according to Acute Kidney Injury Network [AKIN] criteria) and all-cause 30-day mortality. AKIN defined acute kidney injury as any increment of more than 50% in serum creatinine or more than 26.4 umol/L within 48 hours.[12] Adverse effects and complications were monitored up to 48 hours.

Statistical Analysis

The sample size was calculated based on the following: α value 0.05, power of 0.95 and standard deviation of 0.05.[13] It was powered to detect a 0.03 difference in the post resuscitation blood pH between two study fluids. The calculated sample size was 73 patients each arm with total 146 patients. Considering drop-out rate of 10%, total sample size is 162 (81 patients each arm). The significance level was set at *p*-value less than 0.05.

The mean difference of pre- and post-resuscitation blood pH level, bicarbonate level, difference in lactate level, incidence of acute kidney injury, all-cause mortality at 30 days, length of stay between two groups were analyzed using different test depending on whether the means were normally distributed (independent *t*-test) or non-normally distributed (Mann–Whitney Test). All the data were carefully assessed for skewness and Kurtosis, the sample was assumed not normally distributed if the Kurtosis value is more than 3.29.[14] The normally distributed variables were summarized in mean ± standard deviation. There are few variables are not normally distributed according to the criteria and were represented as median and interquartile range. The categorical data were analysed using chi-square test.

Results

From February 2017 through December 2017, a total of 1,207 patient with presumed sepsis presented to emergency department Hospital Pulau Pinang and were screened for eligibility by the attending physician all the time during the study period. Two hundred and eighty-three patients fulfilled the inclusion criteria. However, 121 of whom were excluded for meeting at least one of the exclusion criteria or refused participation. Eventually we randomized 162 patients (n = 81, each arm). Throughout the study period, there was one unblinding done for a subject who was given the test fluid during resuscitation but subsequently found out to be involved in another international clinical trial. In view of the patient's safety was concerned, unblinding was done. Full clinical report on the patient is available in the Supplement 1. During the commencement of the study fluid there were two from each group died before the completion of fluid resuscitation and were excluded from analysis. Ultimately, we analysed 79 patients from the Hartmann's group and 78 patients from the high SID group (Fig. 1). Twenty-five patients in Hartmann's group and 22 patients in high SID group died before the second sample of blood for renal profile within 48 hours was taken, thus they were excluded from the analysis of blood urea, electrolytes and creatinine level (Hartmann's group = 54 vs. high SID group = 56).

The baseline demographic characteristics were similar in the two groups (Table 1). The initial baseline physiologic variables and blood parameters were also similar. Both groups suffered from similar sources of sepsis (p = 0.654). The Hartmann's group received 22.7 mL/kg fluid during resuscitation whereas the high SID received 23.5 mL/kg fluid (p = 0.360).

The pH changed significantly in high SID group from the initial average pH of 7.229 to 7.336 with the increment of 0.107 (0.094) after resuscitation as compared to Hartmann's group from pH of 7.217 to 7.232 with the increment of 0.014 (0.118). The bicarbonate level in high SID group increased significantly by 4.3 (3.8) mmol/L whereas the Hartmann's group increased by 1.2 (3.3) mmol/L at the end of resuscitation ($p < 0.001$) as shown in Table 2.

The lactate clearance in the high SID group was significantly higher when compared to the Hartmann's group (25 vs. 12%, p = 0.009). There were seven patients in Hartmann's group and six patients in high SID group developed AKI according to AKIN criteria (p = 0.206). Among those who survived till discharge, the Hartmann's group stayed in the hospital significantly longer than high SID group (mean day of stay 12.2 vs. 8.04 days, p = 0.048) (Table 3). Only two patients (one from each group) developed acute pulmonary edema as the result of overzealous fluid during fluid resuscitation. Details on fluid volume and balances are included in Supplement 2–4. The hemodynamical responses in both groups were similar except for high SID group responded better in term of capillary refilling time (p = 0.044).

Serum potassium level (taken within 48 hours) was significantly different between the Hartmann's and high SID groups (4.22 vs. 3.91 mmol/L, p = 0.047). Serum sodium, urea, creatinine on the other hands showed no significant difference between both groups (Table 4).

Discussion

The choice of fluid during resuscitation in sepsis has been hotly debated since the landmark study by Rivers et al. in 2001.[15] The crystalloid remained the choice of fluid in septic patient after several studies such as Saline vs. Albumin Fluid Evaluation (SAFE) study and Colloids vs. Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial failed to prove any beneficial effect of albumin.[16,17] Among the crystalloid, no study has provided any data on high SID fluid in resuscitating a septic patient, considering the potential for a high SID fluid in progressively normalizing metabolic acidosis. Our trial provides evidence on the role of high SID fluid in patient with diagnosis of septic shock. We found that the with the

Table 1. Baseline characteristics of study population[a]

Characteristics	Hartmann's group (n = 79)	High SID group (n = 78)	*p*-value
Age—years	61.3 ± 14.9	64.0 ± 15.9	0.279
Gender—no. (%)			
Male	52 (65.8)	41 (52.6)	
Female	27 (34.2)	37 (47.4)	0.091[b]
Ethnicity—no. (%)			
Malay	31 (39.2)	30 (38.5)	
Chinese	31 (39.2)	34 (45.6)	
India	16 (20.3)	13 (16.7)	
Others	1 (1.3)	1 (1.3)	0.928[b]
Height (cm)	163.7 ± 7.3	160.4 ± 7.2	0.230
Weight (kg)	65 (60–70)	65 (60–70)	0.331
GCS	12 ± 3	12 ± 3	0.614
Premorbid—no. (%)			
Hypertension	48 (60.8)	41 (52.6)	0.300[b]
Diabetes mellitus	47 (59.5)	41 (52.6)	0.382[b]
Ischaemic heart disease	8 (10.1)	2 (2.6)	0.052[b]
Cerebrovascular disease	10 (12.7)	8 (10.3)	0.637[b]
Dyslipidemia	19 (24.0)	20 (25.6)	0.818[b]
Source of sepsis—no. (%)			
Brain	3 (3.8)	3 (3.8)	
Lungs	30 (38.0)	28 (35.9)	
Abdomen	11 (13.9)	14 (17.9)	
Skin	11 (13.9)	9 (11.5)	
Urinary tract	11 (13.9)	6 (7.7)	
Unknown	13 (16.5)	18 (23.1)	0.715[b]
Concurrent DKA—no. (%)			
Yes	16 (20.3)	15 (19.2)	
No	63 (79.7)	63 (80.8)	0.872[b]
Intubated—no. (%)	15 (19.0)	13 (16.7)	0.704[b]
Use of inotropes—no. (%)	23 (29.1)	19 (24.4)	0.510[b]
Fluid received per kilogram (mL/kg)	22.73 ± 5.59	23.62 ± 5.83	0.331
Admission—no. (%)			
General medical ward	58 (73.4)	60 (76.9)	
General surgical ward	8 (10.1)	10 (12.8)	
Intensive units	13 (16.5)	8 (10.3)	0.758[b]
Pre fluid resuscitation			
Systolic blood pressure (mmHg)	94.8 ± 19.3	93.4 ± 17.9	0.641
Diastolic blood pressure (mmHg)	59.3 ± 14.4	57.8 ± 14.0	0.514
Mean arterial pressure (mmHg)	71.1 ± 15.0	69.7 ± 13.7	0.528
Heart rate (beats per minute)	119.4 ± 20.3	115.4 ± 18.5	0.205
Capillary refilling time			
< 2 seconds—no. (%)	68 (86.1)	67 (85.9)	

Table 1. Baseline characteristics of study population (continued)

Characteristics	Hartmann's group (n = 79)	High SID group (n = 78)	*p*-value
> 2 seconds—no. (%)	11 (13.9)	11 (14.1)	0.974[b]
Respiratory rate (breaths per minute)	28 (24–32)	28 (24–30)	0.687
pH	7.217 ± 0.131	7.229 ± 0.115	0.547
PCO_2 (mmHg)	30.7 (23–40.6)	29.7 (22.8–39.7)	0.782
HCO_3 (mEq/L)	14.3 ± 4.7	14.5 ± 4.6	0.792
Base excess (mEq)	-12.5 ± 7.1	-12.9 ± 7.0	0.752
Lactate (mmol/L)	6.4 ± 3.9	6.5 ± 3.7	0.947
Post fluid resuscitation			
Systolic blood pressure (mmHg)	117.2 ± 18.3	118.9 ± 16.4	0.549
Diastolic blood pressure (mmHg)	68.3 ± 13.9	68.8 ± 13.7	0.806
Mean arterial pressure (mmHg)	84.6 ± 13.8	85.5 ± 12.7	0.664
Heart rate (beats per minute)	107.3 ± 19.2	103.1 ± 16.5	0.140
Capillary refilling time			
< 2 seconds—no. (%)	75 (94.9)	78 (100.0)	
> 2 seconds—no. (%)	4 (5.1)	0 (0.0)	0.044[b]
Respiratory rate (breaths per minute)	19.5 ± 10.4	19.3 ± 9.5	0.914
pH	7.232 ± 0.160	7.336 ± 0.125	< 0.001
PCO_2 (mmHg)	36.2 (27.1–41.6)	34.1 (27.7–39.6)	0.321
HCO_3 (mEq/L)	15.6 ± 4.7	18.8 ± 5.7	< 0.001
Base excess (mEq)	-10.38 ± 7.07	-6.18 ± 7.23	< 0.001
Lactate (mmol/L)	5.41 ± 3.55	4.74 ± 3.42	0.229

DKA: diabetic ketoacidosis; GCS: Glasgow Coma Scale; HCO_3: bicarbonate level; PCO_2: partial pressure of arterial or venous carbon dioxide; SID: strong ion difference.
[a]Plus-minus values represents mean ± standard deviation. The non-parametric distributed data were represented as median (interquartile range).
[b]Chi-square test.

Table 2. Primary objectives[a]

Characteristics	Hartmann's group (n = 79)	High SID group (n = 78)	*p*-value
pH difference	+0.014 ± 0.118	+0.107 ± 0.094	< 0.001
HCO_3 difference (mEq/L)	+1.2 ± 3.3	+4.3 ± 3.8	< 0.001

HCO_3: bicarbonate level; SID: strong ion difference.
[a]Plus-minus values represents mean ± standard deviation.

administration of high SID fluid result in greater improvement of blood pH, bicarbonate level and base excess as compared to Hartmann's solution which has the normal SID. The better pH recovery is translated into shorter duration of stay but did not result in better all cause 30-day mortality. Shorter average length of stay is certainly associated with greater cost saving to the health-care service as well as to the community.[18,19] Similar result was observed in a retrospective study as the patient with sodium bicarbonate therapy may ha ve reduced length of stay.[20]

In our study, we included patient who presented to our emergency department that fulfilled at least two out of three qSOFA criteria with lactate more than 2 mmol/L. Unfortunately, the latest surviving sepsis guideline did not have a clear classification for patient diagnosed with sepsis with lactate more than 2 mmol/L but did not require vasopressor support initially. We classified this group of patient into septic shock group in view hyperlactatemia is an objective measures of tissue hypoperfusion.[21] We suggest that in the presence of two or more qSOFA with the presence of hy-

Table 3. Secondary objectives[a]

Characteristics	Hartmann's group (n = 79)	High SID group (n = 78)	*p*-value
Lactate clearance (%)	12.1 ± 34.1	25.4 ± 28.3	0.009
Complication—no. (%)	2 (2.54)	1 (1.28)	0.567[b]
AKI incidence[c]—no. (%)	7 (13)	6 (10.7)	0.206[b]
Creatinine reduction (%)	14.3 ± 44.5	24.7 ± 29.0	0.147
Death			
In hospital death—no. (%)	39 (49.7)	32 (41)	0.302[b]
Cause of death—no. (%)			
Sepsis	37 (46.8)	30 (38.5)	0.462[b]
Cardiac arrest	2 (2.5)	1 (1.3)	0.576[b]
Secondary infection	2 (2.5)	0 (0)	0.267[b]
Multiorgan failure	10 (12.7)	5 (6.3)	0.350[b]
30-day all-cause mortality—no. (%)	42 (53.2)	35 (44.8)	0.299[b]
Length of stay[d]	12.2 ± 12.4	8.0 ± 5.9	0.048

AKI: acute kidney injury; SID: strong ion difference.
[a]Plus-minus values represents mean ± standard deviation.
[b]Chi-square test.
[c]There were 25 subjects in Hartmann's group and 22 subjects in high SID group died before the follow-up blood for renal profiles were taken, thus was excluded from the analysis for AKI incidence. Therefore, there were 54 subjects in Hartmann's group and 56 subjects in high SID group were analysed for AKI incidence.
[d]Total number of 40 subjects in Hartmann's group and 46 subjects in high SID group were analysed for length of stay after excluding those who died during hospital stay.

Table 4. Renal profiles[a]

	Baseline			Within 48 hours post resuscitation		
	Hartmann's solution	High SID	*p*-value	Hartmann's solution	High SID	*p*-value
Sodium (mmol/L)	132.2 ± 9.1	131.3 ± 10.8	0.631	139.3 ± 6.5	138.5 ± 7.0	0.532
Potassium (mmol/L)	4.7 ± 1.2	4.4 ± 1.0	0.085	4.22 (0.9)	3.91 ± 0.7	0.047
Urea (mmol/L)	12.9 (8.3–22.9)	13.4 (8.0–18.5)	0.698	12.1 (7.9–19.0)	11.6 (6.8–18.7)	0.711
Creatinine (μmol/L)	232.1 ± 156.9	239.9 ± 166.5	0.801	199.32 ± 157.1	170.7 ± 130.1	0.298

SID: strong ion difference.
[a]There were 25 subjects in Hartmann's group and 22 subjects in high SID group died before the follow-up blood for renal profiles were taken, thus was excluded from the analysis for acute kidney injury (AKI) incidence. Therefore, there were 54 subjects in Hartmann's group and 56 subjects in high SID group were analysed for AKI incidence. Plus-minus values represents mean ± standard deviation. The non-parametric distributed data were represented as median (interquartile range).

perlactatemia should trigger aggressive resuscitation which involves rapid infusion of fluid in early stabilization of hemodynamical status. This early detection of septic shock will result in lesser use of inotropic support as observed in this study. As a result of that, there were only 25–30% of total study population required inotropic support at the end of resuscitation.

Kiran et al demonstrated metabolic acidosis in critically ill patients especially with sepsis and septic shock was associated with statistically significant mortality up to 70% which is also consistent with the previous study by Jung et al.[22,23] Generally, our septic patients with concurrent metabolic acidosis had higher mortality rate if compared to those in Scadinavian Starch for Severe Sepsis/Septic Shock (6S) Trial (51 vs. 43%).[24] This may be due to local limitation of resources, as most of our patients are admitted to general medical and surgical wards for treatment, not intensive care unit management (only 13% from our patient population benefited from intensive care unit admission).

We observed no significant difference in mortality in between both groups, however our study was not powered to show the statistical difference in mortality. Despite most of our septic patients were treated in general wards, the high SID group had 30-day all-cause mortality almost similar to septic patients who were treated under intensive care in 6S Trial.

It is important to note that in high SID fluid contains 75 IU/L of sodium bicarbonate. Traditionally, sodium bicarbonate administration in sepsis patient is not associated with better mortality based on retrospective study.[20] The latest surviving sepsis guidelines has only weak recommendation against sodium bicarbonate therapy in sepsis based on two randomized control trials which did not result in improvement of hemodynamical status or difference in vasopressor requirement.[25,26] However, these studies were based on infusion of different concentration and different rate of infusion (2 mmol/kg over 15 minutes vs. 1 mmol/kg over 1 hour respectively). Our high SID fluid had a fixed concentration of sodium bicarbonate as mentioned and emphasizes the difference of cation and anion concentration in the fluid to create the higher SID effect. We observed that sodium bicarbonate if it is given together with half saline will be more beneficial as compared to giving a solution with only sodium bicarbonate alone.

Lactate clearance is essential as a prognostic factor for severity of the disease. The high SID group had better improvement in lactate level post resuscitation. This may be a marker of overall improvement in perfusion resulting from the volume infused, but it does not explain why the high SID group performed significantly better. Nonetheless, greater clearance is associated with better survival rate as shown in a Korean study.[27]

The potassium level was significantly lower high SID group vs. Hartmann's group due to the presence of sodium bicarbonate in the high SID fluid. This is an expected outcome of administration of sodium bicarbonate.[28]

Evidence on high SID fluid in terms of acute kidney injury incidence has not been well established. Literature search done by Mark and Hewitt had not found any studies conducted to study the use of sodium bicarbonate in acute kidney injury.[29,30] Our study population did not show any significant difference between the high SID fluid group as compared to Hartmann's group in the occurrence of acute kidney injury. It is interesting to know that the high SID fluid is associated with the reduction of creatinine level by almost 25% within 48 hours. Lowered creatinine level will in turn reduce the use of renal-replacement therapy thus the negative consequences of which can be prevented.[24,31] Chloride-restrictive fluids were proven to better reduction the acute kidney injury incidence as they do not produce hyperchloraemia nor acidosis.[32,33]

Our clinical trial had few limitations. The adverse effects of the fluid administration were solely judged by the treating physician and the study protocol did not specify any treatment algorithm or counter measure if the adverse effect occurred. Whether this would affect the results cannot be assessed. There are about 20% subjects suffered from sepsis with unknown source during the admission. We did not collect the data on the blood culture and sensitivity results which were taken before the commencement of antibiotics and the final diagnosis before discharge. These are needed to ascertain the bias and detect any diagnostic error. The cointervention data such as the use of sodium bicarbonate and the renal-replacement therapy along the course of treatment after the intervention period was not recorded. Due to the intervention was only focused on the early phase of resuscitation to detect the difference of pH and bicarbonate level pre- and post-resuscitation, it is less likely and cointerventions after the intervention period will affect the primary outcomes. Whether the significant change in pH and bicarbonate level was primarily due to high SID or presence of bicarbonate, remained debatable, however, the Stewart principle suggested that SID was responsible to the pH change. Thus, further study using non-bicarbonate buffer is needed to ascertain the issue.

Conclusions

In conclusion, patients with septic shock who received fluid resuscitation with high SID fluid as compared to Hartmann's solution had greater normalization of blood pH and bicarbonate level, better lactate clearance, and had a shorter duration of hospital stay. The high SID fluid is relatively safe to be used in septic shock patient if compared with Hartmann's solution as there is no difference in development of pulmonary edema, incidence of acute kidney injury and 30-day all-cause mortality.

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Supplement 1. Case report

Subject ID: A021
Fluid ID: B021
Patient's initial: SI
Patient's name: Sindamadar Bin Ibrahim
Patient's NRIC: 380713075465

On 22nd March 2017, at approximately 11:30 a.m., Mr. Sindamadar Bin Ibrahim presented to emergency department Hospital Pulau Pinang in shortness of breath and drowsiness, the initial capillary blood sugar was high and the blood gas was acidotic. A diagnosis of diabetic ketoacidosis was made by the treating physician. In view of patient fulfilled the inclusion criteria for my fluid study, investigator team was activated. Informed consent was taken from the son by me.

Test fluid was dispatched to the patient per protocol and infusion started at 12.00 p.m.

Upon examination of the patient's medication, I noticed he has a box of medication which is unlabelled. Further questioning revealed that patient is on antidiabetic drug trial. However, patient's family member did not possess any contact information regarding the drug trial. I managed to call the site principal investigator of the drug trial, Dr. Nor Azizah, at 12:55 p.m. after about an hour of searching the phone number. From the telephone conversion, I was told that the patient is under the clinical drug trial called CARMELINA study and there is no contraindication to start any drugs for patient's current condition.

The patient received all 4 pints of the test fluid which ended at 2:00 p.m. and was subsequently admitted to the medical ward. No immediate and late complications were observed throughout the 48 hours inward follow-up.

On 30th March 2017, Dr. Nor Azizah approached me to ask regarding the test fluid. Her concern is on the possibility of a protocol deviation for her CARMELINA study. As for professional courtesy, I decided to unblind the test fluid which patient had received on that day of presentation (22nd March 2017) to her. After going through the unblinding procedure per protocol, Dr. Nor Azizah was informed about the type of fluid given to the patient via email on 3rd April 2017.

End of report.

By,

Dr. Yeoh Chun Chiat
Principal Investigator
HiSIDSS study
NMRR-16-2065-33132
Date of reporting: 3rd April 2017

Supplement 2. Case report

Subject ID: A020
Fluid ID: B020/1, B020/2, B020/3, B020/4
Patient's initial: YMM
Patient's name: Yee Man Meng
Patient's NRIC: 430911-07-5055
Estimated Weight: 65 kg
Gender: Male
Age: 73 years old

On 21th March 2017, at approximately 12:20 p.m., Mr. Yee Man Meng, underlying chronic obstructive airway disease (COAD), was brought in to the emergency department Hospital Pulau Pinang post syncopal attack at home due to worsening breathlessness associated with productive cough and fever. On presentation, he was febrile, respiratory rate of 36 breaths per minute, hemodynamically stable. The first arterial blood gas showed patient had metabolic acidosis and hyperlactatemia. A diagnosis of sepsis secondary to pneumonia was made. The patient was recruited for our study and consent was taken by principal investigator from the patient.

The patient initially has already received 450 mLs of normal saline (0.9%) before study fluid commencement. He then subsequently received a total of 1950 mL of study fluid over 2 hours despite patient was normotensive. Then he was given another 500 mLs of normal saline. At 3 and ½ hour post fluid resuscitation, he subsequently desaturated to 70% on room air, respiratory rate increased to 40 breaths per minute, developed worsening crepitation over both lungs and needed flow mask oxygen therapy (15 mL/min) to maintain oxygenation. The treating physician immediately reduced rate of fluid infusion and ordered 4 pints (500 mLs each pint) normal saline over 1 day.

In the ward, the patient remained saturated around 88–92% for several days on venturimask oxygen therapy of 6L/60%. He desaturated again at day 4 of admission (24/3/17) due to worsening pneumonia. Antibiotic was subsequently escalated from IV augmentin (amoxicillin/clavulanate) to tazocin (piperacillin/tazobactem) in view of worsening clinical condition with new consolidation visible on chest radiograph. The family members opted for optimal medical therapy and refused for invasive ventilation.

He passed away on day 10 of admission despite optimal medical therapy.

The summary of Input/output chart before detection of acute pulmonary edema as follows:

Date	Time	Input (mL)		Output (mL)	
21/3/17	12:20 p.m.–1:00 p.m.	NS	450		
	1:00 p.m.–3:00 p.m.	Test fluid (B020/1, B020/2, B 020/3, B020/4)	1,950		
	3:00 p.m.–4:00 p.m.	NS	500	Urine	300

Input = 2,900 mL
Output = 300 mL
Fluid balance = +2,600 mL (within 3 hours and 30 minutes)

The patient was given resuscitation fluid overzealously by the treating physician and this had caused the development of pulmonary edema.

Time of death: 8 a.m. 31st March 2017
Cause of death: Sepsis secondary to pneumonia

End of report.

By,

Dr. Yeoh Chun Chiat
Principal Investigator
HiSIDSS study
NMRR-16-2065-33132
Date of reporting: 2nd Apr 2017

Supplement 3. Case report

Subject ID: A047
Fluid ID: B047/1, B047/2, B047/3, B047/4
Patient's initial: PM
Patient's name: Parimala A/P Muthappen
Patient's NRIC: 621114-07-5636
Estimated Weight: 50 kg
Gender: Female
Age: 55 years old

On 4th May 2017, at approximately 9:50 a.m., Mdm. Parimala A/P Muthappen, underlying diabetes mellitus type 2 and hypertension, presented to emergency department Hospital Pulau Pinang in intermittent fever and cough for 2 weeks with productive cough and sudden onset breathlessness for 1 day, patient was tachyponeic, restless and desaturated on room air. Thus, a diagnosis of sepsis secondary to pneumonia was made. The patient was recruited for our study and consent was taken by principal investigator from the patient's daughter.

The patient initially has already received 100mls of normal saline (0.9%) before study fluid commencement.

10:15 a.m.–12:15 p.m.

The patient received all the 1.65 Liters of study fluid (B047/1, B047/2, B047/3, B047/4)

12:15 p.m.

The treating physician continued resuscitating the patient with 500 mL of normal saline (0.9%).

12:27 p.m.–1:00 p.m.

The treating physician noted patient became more tachynaec and confused. Lungs auscultation revealed bilateral mixture of fine and coarse crepitation up to mid zone. A diagnosis of Acute pulmonary edema was made, and patient was intubated.

1:00 p.m.–2:15 a.m. (the next day)

The patient was admitted to ICU. The patient's condition deteriorated further despite of multiple inotrope support and hemodialysis. She did not show signs of improvement of pulmonary edema. The urine output remained poor along the course of treatment.

The summary of Input/output chart before detection of acute pulmonary edema as follows:

Date	Time	Input (mL)		Output (mL)	
4/5/17	9:50 a.m.–10:15 a.m.	NS	100		
		Drug volume	80		
	10:15 a.m.–12:15 p.m.	Test fluid	1,650		
	12:15 p.m.	NS	500		
		Drug volume	50	Urine	400

Input = 2,380 mL
Output = 400 mL
Fluid balance = +1,980 mL (within 2 hours and 20 minutes)

The patient was given resuscitation fluid overzealously by the treating physician and this had caused the development of pulmonary edema.

Time of death: 2:15 a.m. 5th May 2017
Cause of death: Septic shock secondary to severe community acquired pneumonia

End of report.

By,

Dr. Yeoh Chun Chiat
Principal Investigator
HiSIDSS study
NMRR-16-2065-33132
Date of reporting: 6th May 2017

Supplement 4. Case report

Subject ID: A146
Fluid ID: B146/1, B146/2, B146/3, B146/4
Patient's initial: MY
Patient's name: Mohamed Yasim bin ST Sindha Madha
Patient's NRIC: 750102-07-5787
Estimated Weight: 70 kg
Gender: Male
Age: 42 years old

On 17th November 2017, at approximately 6:50 p.m., Mr. Mohamed Yasim bin ST Sindha Madha, underlying diabetes mellitus type 2, presented to emergency department Hospital Pulau Pinang in fever for one week with productive cough and worsening breathlessness, patient was tachyponeic and hemodynamically unstable and diagnosis of septic shock secondary to pneumonia was made. The patient was recruited for our study and consent was taken by principal investigator from the patient.

The patient initially has already received 450mls of normal saline (0.9%) before study fluid commencement.

7:00 p.m.–8:30 p.m.

The patient received all the 2 Liters of study fluid (B146/1, B146/2, B146/3, B146/4).

8:30 p.m.–9:30 p.m.

The treating physician continued resuscitating the patient with 1 liter of normal saline (0.9%).

9:40 p.m.

The patient started to desaturate under high flow mask oxygen therapy (15 L/min) and was given non-invasive ventilation (CPAP mode). His SpO2 achieved 100% during the CPAP deliver.

11:00 p.m.

The treating physician decided to off the CPAP in view of hypotension and subsequently, he was started with Noradrenaline infusion (0.05 mcg/kg/min) before admission to general medical ward.

1:00 a.m. (the next day)

Another 250 cc gelafundine solution was given in view of hypotension despite on inotrope support. He became more tachyneac and drowsy. A diagnosis of acute pulmonary edema was made. He was then intubated and sent to ICU.

1:00 a.m.–10:56 p.m. (the next day)

In the ICU, the patient's condition deteriorated further despite of multiple inotrope support and hemodialysis. He did not show signs of improvement of pulmonary edema. The urine output remained poor along the course of treatment.

The summary of Input/output chart before detection of acute pulmonary edema as follows:

Date	Time		Input (mL)		Output (mL)
17/11/17	6:50 p.m.–6:00 p.m.	NS	450		
	7:00 p.m.–8:30 p.m.	Test fluid (B146/1, B146/2, B 146/3, B146/4)	2,000		
	8:30 p.m.–9:00 p.m.	NS	500		
	9:00 p.m.–12:00 a.m.	NS	500		
18/11/17	1 a.m.	Gelafundin	250	Urine	120
		Drug volume	6		

Input = 3,706 mL
Output = 120 mL
Fluid balance = +3,586 mL (within 6 hours and 10 minutes)

The patient was given resuscitation fluid overzealously by the treating physician and this had caused the development of pulmonary edema.

Time of death: 10:56 p.m. 18th Nov 2017
Cause of death: Septic shock secondary to severe community acquired pneumonia

End of report.

By,

Dr. Yeoh Chun Chiat
Principal Investigator
HiSIDSS study
NMRR-16-2065-33132
Date of reporting: 19th Nov 2017