Original Article

Change in Serum Chloride Level after Loading Dose of Sterofundin Solution Compared with Normal Saline Solution

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Objective: To evaluate serum chloride level after loading dose of sterofundin solution given to healthy volunteers in the resuscitation manner compared with normal saline solution.

Materials and Methods: Ten healthy volunteers were randomly assigned to receive normal saline or sterofundin for the first solution in dose of 30 mL/kg (maximum 2 liters) over one hour. After washout period of at least one week, crossover studies were performed in the same participants with another remaining solution (10 participants for each solution, total n = 20). For each solution loading, blood was collected at baseline (T0), at 60 minutes (T1), 120 minutes (T2), and 240 minutes (T4) from baseline. Time to first void after initiation of fluid and urine volume were also recorded. Primary outcome was change in serum chloride level.

Results: With sterofundin loading, delta chloride level change from baseline at T1, T2, and T4 were 2.33±1.41, 0.78±0.83, and 0.89±1.17, respectively, which were significantly lower than delta change after normal saline loading (4.2±1.03, 3.3±1.16, and 2.4±1.58, $p = 0.021$). The decrease in SID was lesser ($p = 0.017$), time to first void was significantly shorter ($p = 0.008$), with larger but not statistically significant urine volume ($p = 0.068$).

Conclusion: Sterofundin solution loading slightly increased serum chloride level, but delta change from baseline was significantly lower as compared with normal saline solution.

Keywords: Chloride, Fluid, Normal saline, Osmolality, pH, Resuscitation, SID, Sterofundin, Urine

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Normal saline solution is the most common intravenous fluid used in clinical practice[1] due to its advantage of isotonicity and no additional cation. However, this type of fluid is not without concern as solution contains high chloride level (154 mEq/L) and strong ion difference [SID] of zero. Apart from its well-known side effect of hyperchloremic metabolic acidosis, many studies could demonstrate another adverse effects from increased serum chloride level, for example, renal artery vasoconstriction, decreased renal cortical blood flow[2], and increased incidences of acute kidney injury and renal replacement therapy in critically ill[3] and septic patients[4].

Sterofundin is a new balanced-salt solution designed to reduce these complications by decreasing solution's chloride level while maintaining isotonic property and make the solution's SID equal to 21, which is close to the ideal solution's SID of 24[5], which means the new fluid should not alter plasma acid-base status. However, solution's chloride level of 127 mEq/L is still high, which might cause hyperchloremic state after infusion (compositions of both solutions were shown in Table 1). Therefore, we conducted the present prospective trial to determine how serum chloride and other plasma compositions will be changed after receiving a loading dose of sterofundin compared with normal saline solution.

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Materials and Methods

Study design

The present study was designed as randomized, open-labeled, cross-over clinical trial. The study protocol was approved by the Ethic Committee of Ramathibodi Hospital, Mahidol University.

Study participants

Healthy volunteer was defined as adult (age 18 or older) without any underlying disease (by history taking, physical examination, and review of medical record), left ventricular ejection fraction of at least 0.5 (echocardiography performed by intensivist in the morning of intervention day), and no current medication

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Table 1. Characteristics of two solutions

Composition	NSS	Sterofundin
Na^+	154	145
K^+	-	4
Ca^{2+}	-	2.5
Mg^{2+}	-	1
Cl^-	154	127
Acetate	-	24
Maleate	-	5
Real osmolality	286	290
SID	0	21

NSS = normal saline solution; SID = strong ion difference

usage. Exclusion criteria were pregnancy or lactation, body mass index [BMI] of less than 18 or more than 25, and fever presented in the past two weeks. After explaining the study protocol, written informed consent form was signed by all participants. Protocol of the present study was registered on http://clinicaltrials.gov and was coded as NCT02950974.

Study protocol

Participants were asked to have nothing by mouth [NPO] a night before intervention day and during intervention time. In the morning after voiding, either sterofundin or normal saline solution randomized by computer to be the first fluid was given to participants in dose of 30 mL/kg (maximum dose of 2 liters) over one hour. Venous blood was drawn four times, first was at baseline before starting fluid infusion (T0), then at 60 minutes (T1), 120 minutes (T2), and 240 minutes (T4). Time required from baseline until first void, and urine volume was also recorded. After washout period of at least one week, cross-over study was performed similarly with the other fluid.

Data collection

Basic information (sex, age, body weight, height, NPO time) of volunteers were recorded. Vital signs were measured every time before blood samplings were drawn. Blood was sent to test for level of sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate, albumin, lactate, pH, and osmolality. Blood chemistry was measured by Dimension RxL MAX (Siemens Healthcare Diagnostics Inc., Newark, DE 19714, USA), blood gas and lactate level was measured by amperometry technique (Stat Profile Critical Care Xpress analyzer, Nova Biomedical, 200 Prospect Street, Waltham, MA 02454-9141 USA), and serum osmolality was measured by freezing-point method (Advanced 3320 Osmometer, Advanced instrument, Two Technology Way, Norwood, MA 02062). Time to first void was defined as time since initiation of fluid infusion until the participants need to void on their own requirement. Urine volume was measured and recorded both before and after fluid infusion for data analysis.

Any acute complications, if presented, were recorded and treated accordingly by attending intensivist.

Study outcomes

Primary outcome: The primary outcome was change in serum chloride level.

Secondary outcomes: The secondary outcomes were change in serum pH, osmolality, and SID level and time to first void after initiation of fluid. SID was calculated from: $SID = [Na^+ + K^+ + Ca^{2+} + Mg^{2+}] - [Cl^- + lactate]$; (all parameters were expressed in mmol/L)

Statistical analysis

The present trial was the pilot study, so the sample size was planned to be calculated from the result of chloride level after initial ten cohorts were finished. After collecting data from pilot populations of 10 volunteers, we found that delta change of serum chloride level differed at least 2 mEq/L between each solution group. When using this different value for calculating cohort number, the final number of population needed is seven in each solution group. For study power of ninety percent with thirty percent dropout rate and five percent alpha error, we decided to use 10 in each solution group for our final cohort number in the present study.

Data analysis were done by statistician blinded from the intervention after all interventions were completed.

Continuous data with normal distribution were expressed in mean ± SD, comparing difference by paired t-test or repeated ANOVA test. Categorical data were expressed in number and percent, comparing difference by Chi-square test. Defined statistically significance when *p*-value was less than 0.05. All data were analyzed by SPSS software v.18.0.

Results

Participants consisted of five men and five women, average age was 29.6±2.63 years and average BMI was 21.99±2.2. There was no difference in any baseline parameters between each group as shown in Table 2. Final participant number in sterofundin group was nine due to one dropped-out female volunteer because of severe muscle pain.

Table 2. Volunteer's characteristics before study fluid infusion

	Before normal saline (n = 10)	Before sterofundin (n = 9)	*p*-value
Sex: male/female, n	5/5	5/4	>0.999
Age (year)	29.60±2.63	29.67±2.78	0.958
Body weight (kg)	58.80±9.44	60.11±8.99	0.761
Height (cm)	163.10±7.52	164.00±7.38	0.796
BMI ($kg•m^{-2}$)	21.99±2.20	22.26±2.15	0.791
EF (%)	68.17±7.94	68.17±7.94	>0.999
NPO Gap (minute)	608.50±110.33	615.56±121.64	0.896
Na^+	135.00±3.27	135.89±2.85	0.538
Cl^-	102.30±1.42	101.89±2.15	0.625
Ca^{2+}	2.33±0.07	2.29±0.10	0.342
Mg^{2+}	0.87±0.06	0.87±0.07	0.891
HCO_3^-	25.28±1.56	24.53±2.05	0.380
Albumin	42.38±2.02	41.92±2.89	0.691
Serum osmolality	287.00±2.45	285.89±4.11	0.478

BMI = body mass index; EF = ejection fraction; NPO = nothing by mouth
Data presented as number or mean ± SD

After normal saline infusion, the increase in serum chloride level from baseline at T1, T2, and T4 were 4.2±1.03, 3.3±1.16, and 2.4±1.58, respectively, which were significantly higher than delta change after sterofundin loading (2.33±1.41, 0.78±0.83, and 0.89±1.17, $p = 0.021$) (Table 3).

There also was statistically significant difference in plasma SID value after infusion of each fluid, which SID was lower following normal saline infusion (39.41±2.56, 37.69±2.90, 38.12±3.14, 38.25±2.55 versus 40.93±2.03, 40.63±1.58, 41.64±2.00, 41.47±2.09, $p = 0.017$) (Table 3). All other parameters included in SID calculation are shown in Table 3.

In part of serum pH and osmolality, there was no difference detected as shown in Table 3.

Time to first void was significantly longer after normal saline loading as compared with sterofundin loading (142.5±74.69 minutes versus 80.56±37.12 minutes, $p = 0.008$) (Figure 1) with less urine volume but it did not reach statistically significance ($p = 0.068$) (Figure 1).

There were two reports of pain after sterofundin infusion versus none after normal saline infusion. Pain was described as muscle pain in participants' arm and forearm both ipsilateral and contralateral to infusion site. No redness, swelling, or warmth was detected. Pain was so severe (numeric rating scale of 8/10) causing one of the female volunteer to be dropped-out as mentioned above. Around five to ten minutes after stopping infusion, pain disappeared. Another male volunteer who also experienced pain gave numeric rating scale of 5/10, but this participant insisted that he could stand the pain and finally got through the intervention. There was no other complication detected.

Discussion

After loading dose of sterofundin was given to healthy volunteers in the resuscitation manner, serum

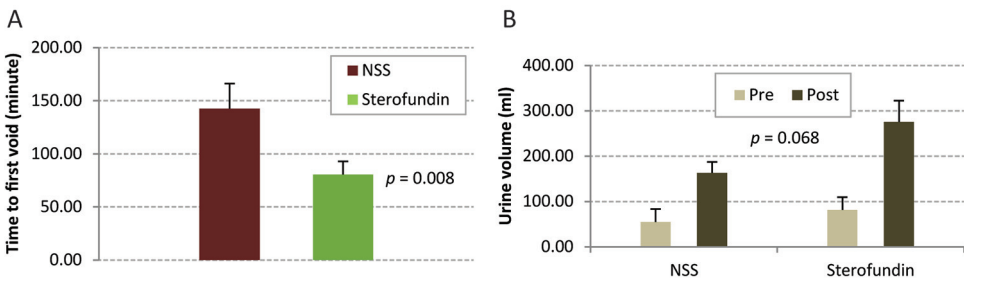

Figure 1. Time to first void and urine volume after infusion of normal saline solution and sterofundin.

Table 3. Changes in serum composition

	NSS	Δ†	Sterofundin	Δ†	*p*-value
Serum chloride level					0.021*
T0	102.30±1.42		101.89±2.15		
T1	106.50±1.51	4.20±1.03	104.22±2.11	2.33±1.41	
T2	105.60±1.17	3.30±1.16	102.67±2.06	0.78±0.83	
T4	104.70±1.7	2.40±1.58	102.78±1.86	0.89±1.17	
SID					0.017*
T0	39.41±2.56		40.93±2.03		
T1	37.69±2.90	-1.01±2.15	40.63±1.58	-1.68±1.65	
T2	38.12±3.14	-0.51±1.47	41.64±2.00	-0.39±1.87	
T4	38.25±2.55	-0.53±1.17	41.47±2.09	-0.38±1.51	
Na					0.593
T0	135.00±3.27		135.89±2.85		
T1	137.50±3.60		137.78±2.64		
T2	137.00±3.06		137.33±2.78		
T4	136.30±2.50		137.67±3.12		
K					0.638
T0	4.59±0.28		4.71±0.25		
T1	4.44±0.41		4.43±0.29		
T2	4.26±0.29		4.32±0.33		
T4	4.01±0.23		4.03±0.37		
Ca					<0.001*
T0	2.33±0.07		2.29±0.10		
T1	2.03±0.08	-0.30±0.06	2.35±0.07	0.06±0.05	
T2	2.11±0.07	-0.22±0.05	2.34±0.11	0.05±0.03	
T4	2.16±0.06	-0.17±0.05	2.30±0.12	0.01±0.05	
Mg					0.008*
T0	0.87±0.06		0.87±0.07		
T1	0.70±0.17	-0.17±0.19	0.86±0.05	0.00±0.04	
T2	0.78±0.06	-0.09±0.03	0.86±0.06	0.00±0.03	
T4	0.81±0.05	-0.07±0.03	0.85±0.06	-0.02±0.04	
Lactate					0.455
T0	1.08±0.44		0.93±0.46		
T1	0.48±0.27		0.57±0.38		
T2	0.42±0.16		0.54±0.25		
T4	0.32±0.12		0.60±0.42		
pH					0.094
T0	7.36±0.02		7.37±0.03		
T1	7.31±0.04		7.35±0.04		
T2	7.34±0.04		7.37±0.04		
T4	7.34±0.03		7.37±0.05		
A_{tot}					0.127
T0	636.77±10.46		695.31±34.41		
T1	558.62±13.09		607.56±43.68		
T2	574.10±10.55		649.91±41.04		
T4	587.45±12.84		662.50±38.51		
Serum osmolality					0.982
T0	287.00±2.45		285.89±4.11		
T1	287.40±2.99		287.56±3.64		
T2	287.10±2.51		287.00±3.94		
T4	286.60±2.95		287.78±3.19		

A_{tot} = non-volatile weak acid; NSS = normal saline solution; SID = strong ion difference

* *p*-value <0.05

chloride level still increased from baseline, but delta change was significantly lower, SID level was maintained near baseline and significantly higher, while there was no difference in aspect of serum pH and osmolality when compared to changes caused by normal saline solution loading.

Chloride change found in our study was similar to a previous trial performed in children populations

undergoing general anesthesia, which compared sterofundin with normal saline solution for intra-operative maintenance fluid[6]. In that trial, they also noticed that the risk of hyperchloremia was increased if infused volume was greater than 46.7 mL/kg, which is quite common amount used in resuscitating adult patients with shock. Our study is the first trial comparing change in serum chloride level after loading dose of either sterofundin or normal saline solution in adult populations. We chose to perform the intervention in adult healthy volunteers because we need to control all confounding factors that can affect the plasma compositions, such as underlying disease of liver or kidney.

As shown in animal study, that intra-renal infusion of chloride-containing solutions led to decreased renal blood flow and glomerular filtration rate [GFR][7]. The same result was shown in other human study that concluded that hyperchloremic metabolic acidosis has a detrimental effect of decreased renal artery blood flow velocity and renal cortical tissue perfusion[2]. Therefore, lower level of rising serum chloride may be the cause of shorter time to first void and a trend toward larger urine volume after sterofundin infusion found in our study.

According to Stewart's approach to acid-base status, we found that after sterofundin loading, SID was maintained around baseline level and significantly higher when compared to normal saline solution loading while there was no difference in level of non-volatile weak acid [A_{tot}] after both fluid infusion. Combining these two results, pH level should be statistically significant different between two solutions. Surprisingly, there was just a trend toward lower serum pH after normal saline solution loading. This may be due to smaller than required of sample size to reach statistical significance (required n = 13) for this aspect. Another explanation may be the difference in each volunteer's $PaCO_2$, which is the last factor in regulating acid-base status by Stewart's approach that was not measured in our study.

Slightly hypotonicity is one of major disadvantage of older balanced-salt solution. We found that serum osmolality was nicely maintained after sterofundin infusion and not different when compared to normal saline solution.

In the manufacturer's leaflet, pain is mentioned as one of the adverse effects of sterofundin and has characteristics of irritation, local reaction, or phlebitis. Two of the volunteers in the present study experienced pain while receiving sterofundin. However, the characteristics suggested more of muscle pain. After review of all available sources, unfortunately, the data about muscle pain as an adverse effect of sterofundin was not found. We suggest sterofundin should be administered with caution and vigilance.

There were some limitations in the present study. First, the results of the study were derived from healthy volunteers, which could be different from critically ill patients. This means further studies about sterofundin loading in critical patients are needed. Second, as serum chloride was significantly increased in normal saline loading group, the relation of hyperchloremia affecting renal blood flow and kidney function were not monitored in our study. Finally, the amount of fluid in the present study (30 mL/kg maximum two liters over period of one hour) does not represent the real-world practice. For instance, in septic shock, the average fluid resuscitation was up to five liters in six hours[8]. This meant serum chloride change might be more in real patients.

In conclusion, sterofundin solution given in the resuscitation manner to healthy volunteers results in slightly increased serum chloride level but delta change from baseline was significantly lower as compared with normal saline solution loading.

What is already known on this topic?

Excessive normal saline solution loading results in hyperchloremic state. Sterofundin is a new balanced-salt solution designed to reduce this complication by reducing chloride level. However, its chloride level is still higher than normal plasma chloride level.

What this study adds?

Rising in chloride level can be seen after receiving sterofundin solution loading. However, the magnitude of plasma chloride rising is less than after normal saline solution loading.

Acknowledgement

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Potential conflicts of interest

The authors declare no conflict of interest.

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