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A randomized controlled trial: Changes of serum sodium levels in children with diarrhea moderate dehydration receiving rehydration therapy with standard hypotonic solution or balanced solution

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Abstract

***Background*: Hyponatremia is a condition that may cause dangerous clinical manifestations. Diarrhea with dehydration is one of the most common causes for hyponatremia. Intravenous hypotonic fluid is used for children with moderate dehydration and isotonic Ringer lactate is used for severe dehydration in several therapy guidelines for diarrhea.**

***Aims*: To investigate the difference in changes of serum sodium levels between rehydration therapy with standard hypotonic solution and balanced solution for children with diarrhea and dehydration.**

***Design*: Randomized controlled clinical trial.**

***Setting*: Emergency unit in Dr. Soetomo General Hospital, Surabaya, Indonesia.**

***Patients*: Forty children aged between 3 months to 12 years old who were diagnosed with diarrhea with moderate dehydration based on Haroen Noerasid's clinical criteria. Patients were randomly assigned into two groups: standard hypotonic solution therapy group (n=21) and balanced solution therapy group (n=19).**

***Interventions*: Children in the standard therapy group received standard hypotonic solution (Na^+ 50 mEq/L), while the other group received balanced solution (Na^+ 145 mmol/L) as the main fluid during rehydration therapy.**

***Results*: The mean initial serum sodium levels in the standard hypotonic solution and balanced solution group were 141 mmol/L and 141.4 mmol/L, respectively. The difference was found to be not statistically significant. There was a statistically significant difference between the post rehydration mean serum sodium levels of the standard hypotonic (138.3 mmol/L) and balanced solution group (141.7 mmol/L). The mean reduction of serum sodium levels was 2.48 mmol/L in the standard hypotonic solution group and there was a mean increase of 0.37 mmol/L in the balanced solution group. We found clinically a not significant difference of symptoms of hyponatremia in this study. There was no seizure, neurological inpairment in both treatment groups before and after rehydration.**

***Conclusions*: There were difference changes in serum sodium levels post rehydration therapy by using two different solutions. Balanced solution was more stable and a safer choice to protects against hyponatremia.**

Introduction

Hyponatremia may cause dangerous clinical manifestations such as lethargy, muscle weakness, irritability, seizure, coma and even death in some cases. (1) Iatrogenic hyponatremia is a common complication seen in children who received rehydration therapy using hypotonic solutions. The numbers of deaths and significant neurological sequele from hospital-acquired hyponatremia in children receiving hypotonic solution have increased in the past 10 years. (2)

In children, diarrhea with dehydration is one of the most common causes for disturbances of homeostasis in sodium serum. Several guidelines for treatment of patients with diarrhea recommend the use of oral fluid rehydration with low osmolarity (hypotonic) or intravenous sodium chloride (NaCl) 0.45%-0.9% for children with mild to moderate dehydration. (3-5) Several studies have reported the risk of iatrogenic hyponatremia from rehydration therapy using hypotonic fluid. (6-8)

Ringer acetate malate (balanced solution) is an isotonic solution that does not disrupt the acid-bace balance, does not increase metabolic oxygen con-

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sumption or the total energy needs and does not change the serum ion composition. The electrolyte composition of Ringer acetate malate is close to that of human plasma and can be safely used in children for isotonic dehydration. (9) Several studies currently recommend the use of isotonic fluids as a maintenance therapy for pediatric patients. To date, no side effects have been reported with the use of isotonic solutions as maintenance therapy in pediatrics. (10-12) Although different studies have reported that isotonic saline administration may result in an increase in serum sodium levels and/or chloride, they did not show an increase in the risk of hypernatremia. (13-15) Hence, there is no consensus however on the most appropriate electrolyte composition of intravenous (IV) fluids for rehydration, with recommendations ranging from 0.45% to 0.9% saline solutions. (3-5,16)

We designed this randomized, double blind, controlled study to investigate the difference in changes of serum sodium levels between rehydration therapy with standard hypotonic solution and balanced solution for children with diarrhea and dehydration.

Materials and methods

This randomized controlled trial compared the use of two solutions in treating children diagnosed with diarrhea and dehydration. The study has been approved by the institutional review board of Dr. Soetomo Hospital, Surabaya, Indonesia (466/Panke.KKE/XI/2014).

The research population was children with diarrhea and moderate dehydration based on Haroen Noerasid's clinical criteria (**Table 1**), treated in the Dr. Soetomo General Hospital's Emergency Unit aged between 3 months to 12 years old. The exclusion criteria were: (1) incomplete medical data; (2) diarrhea with severe dehydration; (3) patients who were discharged at their own (parents/guardians) request; (4) malnourished patients; and (5) patients with chronic cardiac, endocrine, neurologic, liver or renal diseases. Informed consents were distributed and obtained from willing parents/guardians.

Serum sodium levels were obtained before the subjects were randomly allocated in the different treatment groups. One group was treated with standard hypotonic solution (Ka-En 3B®: Na^+ 50 mEq/L, K^+ 20 mEq/L, Cl^- 50 mEq /L, lactate 20 mEq /L, dextrose 27 g/L; osmolarity 290 mOsm/L; Otsuka, Indonesia) and the other group with balanced solution (Ringerfundin®: Na^+ 145 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^+ 1 mmol/L, Cl^- 127 mmol/L, acetate 24 mmol/L, malate 5 mmol/L; osmolarity 309 mOsm/L; B.Braun, Melsungen, Germany). The measured independent variable was serum sodium levels obtained before and after crystalloid fluid rehydration therapy, the dependent variable was administration of standard hypotonic or balanced solution. The subjects' vital signs and hydration state were constantly monitored during the rehydration therapy. The volume of administered fluid was recorded. The main outcomes were the difference in serum sodium levels after rehydration therapy and the difference of the changes of serum sodium levels after rehydration therapy between the two groups. Randomization was carried out in blocks of four.

Data were analysed using statistic software SPSS version 20.0 (IBM Corporation). Comparisons between baseline and post therapy serum sodium levels in both groups were performed using Kolmogorov-Smirnov test, followed by Mann-Whitney U test. Categorical data were analysed using independent t-test and Chi-square test. Data were presented in graphs and tables.

Results

The trial was performed in December 2014 at Dr. Soetomo General Hospital, Surabaya, Indonesia. Children aged between 3 months and 12 years old with a presumptive diagnosis of diarrhea moderate dehydration were eligible for enrollment in this study (**Figure 1**). Forty-four children were enrolled, one child was withdrawn by the parents before the second blood sample could be taken. Three children were excluded by the researchers because of missing data. Fourty children was obtained successfully at measurement of plasma sodium level both T_0 and T_3. There were more male patients in both treatment groups as shown in **Table 2**.

Thirty-four (85%) of the children experienced vomiting and 31 subjects (77.5%) experienced fever. We found a clinically non significant difference of symptoms of hyponatremia in this study. There was no seizure, neurological impairment in both treatment groups before and after rehydration. There were four patients with hyponatremia during the baseline measurements. One (4.8%) of them was from the standard hypotonic solution group and the other three (15.8%) from the balanced solution group. Four (19.1%) patients in the standard hypotonic solution group were hypernatremic, while there were five (26.3%) hypernatremic patients from the balanced solution group. None of the baseline serum natrium levels differences were found to be statistically significant (p=0.379) as shown in **Table 2**.

Ten of 21 (47.6%) patient treated with hypotonic solution had falls in plasma sodium ≥5 mmol/L (**Figure 2**).

The post-rehydration mean in the balanced solution group showed statistically significant differences of serum sodium levels than in the group treated with hypotonic solution (p=0.001) (**Table 3**).

In the children treated with hypotonic solution the mean sodium levels decreased during the 3 hours of treatment, whereas in the group rehydrated with balanced solution sodium levels slightly increased (**Figure 3**). Differences mean in the changes of serum sodium levels between the two groups was not statistically significant (**Table 3**).

Discussion

Our randomized controlled study showed that there were difference changes in serum sodium levels post rehydration therapy by using two different solutions. There were four children (10%) with hyponatremia before the start of treatment, which can be caused by sodium loss through diarrhea and low salt intake. In this study, there are less patients who experienced hyponatremia before rehydration therapy, most of the patient in normonatremia. After rehydration therapy, we found that 3 patients became hyponatremia in standard hypotonic group and 2 patients became hypernatremia in balanced solution group.

A randomized prospective study conducted by Neville found that there was a higher incidence of hyponatremia in children with diarrhea who received hypotonic solutions compared to those who received isotonic fluids. Half of subjects with normonatremia and 13% of the hyponatremic children who were treated showed a reduction of serum levels by ≥2 mmol/L. (15) Similar to this study, we found that administration of hypotonic solution creates risks for iatrogenic hyponatremia, making isotonic solution a safer choice for rehydration therapy.

There are considerable variations of fluid type recommendations for rehydration therapy. Study conducted by Saba, found that the administration at the appropriate maintenance rate and accompanied by adequate expansion with isotonic fluids, 0.45% saline did not result in a drop in serum sodium during the first 12 hours of fluid therapy in children without severe baseline hyponatremia. (17) This study hypothesized that the patients enrolled in this study were at risk for high ADH secretion, stimulated by either volume depletion (appropriately) or the syndrome of inappropriate ADH secretion (due to pain, medications, pulmonary disease, etc). Because free water excretion is impaired in the presence of ADH, the administration of hypotonic solutions to patients secreting ADH will inevitably lead to a fall in serum sodium levels. (18) Majority of children who received NaCl 0.45% did not experience serum sodium reduction, suggests that most did not have an ongoing stimulus for ADH secretion. Adequate volume repletion with isotonic fluids prior to and during IV maintenance fluid administration likely protected patients against hyponatremia despite hypotonic maintenance fluids. Those who did experience a drop in sodium can be assumed either to have not been adequately volume expanded (and therefore have ongoing physiologic volume-related stimulus for ADH secretion). Children in the 0.9% saline group who experienced a decrease in sodium were very likely to have had inapproriate ADH secretion; unless they developed new onset adrenal insufficiency, hypothyroidsm or renal salt wasting, inappropriate ADH secretion is the only reasonable explanation for a drop in sodium level in this goup. (15,19) The average rate of fluid administration in both treatment groups was only slightly greater than the traditionally recommended maintenance rate. This likely also played a role in the stability in serum sodium levels. Hypotonic fluids prescribed at high rates have been implicated in many of the reported deaths due to iatrogenic hyponatremia. (20)

A systematic review conducted by Choong et al., evaluated the safety profile of hypotonic and isotonic solutions for fluid maintenance therapy in children. They found that hypotonic solutions increase the risk of acute hyponatremia that cause complications with high morbidity. (2) Wilkinson reported 2 cases of seizures out of 26 patients who received hypotonic solution (OR 6.22; 95% CI 0.29-135.8). (21)

There is still an ongoing debate on the most ideal intravenous fluid type for rehydrating patients with diarrhea. Fluid replacement using normal saline (NaCl 0.9%+2.5% dextrose) for gastroenteritis cases is superior compared to hypotonic saline (NaCl 0.45%+2.5% dextrose), because it manages hyponatremia without causing hypernatremia. (15) However, Eisenhut mentioned that administration of isotonic saline may cause hyperchloremic acidosis. (22) There is no single ideal solution for all cases, in terms of rapidity and fluid composition. However, isotonic or near isotonic solutions are most physiologic and therefore is a safer choice for treating acute phase illness or perioperative period. Hyponatremia results from a positive balance of administered sodium-free fluids and the incapability of hypotonic urine secretion caused by the antidiuretic hormone. ADH is secreted in hypovolemic and hypoosmolar condition. In the presence of both conditions, ADH is more responsive to hypovolemia as a stimulus and thus will further worsen the hypoosmolarity condition. (2)

A study conducted by Holliday found that usage of isotonic solutions for maintenance fluid therapy may cause adverse events. Giving isotonic saline for more than 6-12 hours to children with cardiopulmonary or renal disease imposes a hazardous sodium load. (23) Steele et al. reported a case of a female patient who had elective surgery received a post operative infusion for 24 hours of isotonic saline at rates approximating those of maintenance therapy. This led to excess sodium excretion and a decrease in serum sodium; that is, more sodium, but not more water, was excreted than was given. (24) Another study found that patients with relative chronic sodium depletion may promote the development of renal adaptive responses, resulting in more rapid reversal of the natriuresis evident at presentation. Chronic sodium insufficiency will stimulate an adaptive renal response to produce faster natriuresis. Differential suppression of aldosterone activity in the normonatremic versus hyponatremic children during fluid therapy might have contributed if the hyponatremic children were more dehydrated at baseline. However, there were no clinical or biochemical data to support this. (15)

A study conducted by Kocaonglu found that rapid reduction of serum sodium levels in patients with hypernatremic dehydration can lead to cerebral edema, thus necessitate avoiding hypotonic fluid administration. The goal is to reduce sodium levels for 0.5 mEq/L every hour in order to prevent cerebral edema. (25) Hypotonic solution should not be given to children with serum sodium levels lower than 138 mmol/L. A study conducted in the past decade reported an incidence of 30% mortality rate, neurologic disturbances related to cerebral edema or brainstem herniation, as seen in 23 patients who suffered from rapid reduction of serum sodium levels after receiving large doses of hypotonic solution postoperatively. (18)

Administration of bolus intravenous fluid for mild or moderate case of dehydration must performed under a careful and watch continuosly, because it may cause hypertonic urine excretion along with electrolyte free water (EFW), resulting in a reduction of sodium level. (26) One study evaluated the increasing risks of hyponatremia in diarrheal children who were rehydrated using high dose of NaCl 0.9% (60 cc/kg/hour) followed by maintenance dose for 3 hours, experienced a larger mean increase (1.6±2.4 mEq/L vs. 0.9±2.2 mEq/L; p=0.04) and were less likely to experience a sodium decrease of ≥2 mEq/L (8/112 vs. 17/105; p=0.04) than those administered 20 mL/kg. These findings further suggest the necessity for careful monitoring of NaCl administration to prevent hyponatremia. (27) In adult study showed that changes of sodium level for more than 5 mmol/L are correlated with higher mortality. (28) In this study, we found a statistically significant difference of serum sodium levels 3 hours post rehydration between two groups, although clinically not significant.

Conclusions

There were difference changes in serum sodium levels post rehydration therapy using two different solutions. Balanced solution was more stable and a safer choice to protect against hyponatremia.

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Table 1. Assessment of dehydration by Haroen Noerasid's criteria

	Mild (3%-5%)	Moderate (6%-8%)	Severe (>10%)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulse	Normal	Normal or slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased
Skin turgor	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membranes	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits	Deeply sunken orbits
Extremities	Warm, normal capillary refill	Delayed capillary refill	Cool mottled
Mental status	Normal	Normal to listless	Normal to lethargic or comatose
Urine output	Slightly decreased	<1 ml/kg/hr	<<1 ml/kg/hr
Thirst	Slightly increased	Moderate increased	Very thirsty or too lethargic

Table 2. Demographic of subject characteristics and their baseline serum sodium levels

	Standard hypotonic solution (n=21)	Balanced solution (n=19)	p value
Age (month), mean (SD)	15.5 (7.8)	25.8 (23.2)	
Sex Males (%)	13 (61.9%)	11 (57.9%)	
Pre-rehydration sodium status			0.379[a]
• Hyponatremia (≤135 mmol/L)	1 (4.8%)	3 (15.8%)	
• Normonatremia (135-145 mmol/L)	16 (76.2%)	11 (57.9%)	
• Hypernatremia (≥145 mmol/L)	4 (19.1%)	5 (26.3%)	

Legend: [a]=Chi square test.

Table 3. A comparison of mean serum sodium levels before and after rehydration in both treatment groups

	Standard hypotonic solution (n=21)	Balanced solution (n=19)	p value
Pre-rehydration (T_0) (mmol/L), mean (SD)	141 (3.9)	141.4 (6.7)	0.439[a]
Post-rehydration (T_3) (mmol/L), mean (SD)	138.3 (3.2)	141.7 (3.3)	0.001[a]
Differences (mmol/L), mean (SD)	-2.48 (4.9)	0.37 (5.8)	0.101[b]
Total subjects with sodium reduction ≥2 mmol/L 0-3 hours post rehydration	35% (14/21)	20%(8/19)	0.009[c]

Legend: [a]=Mann-Whitney U test; [b]=independent t test; [c]=Kolmogorov-Smirnov test.

Figure 1. Flow diagram of patient selection

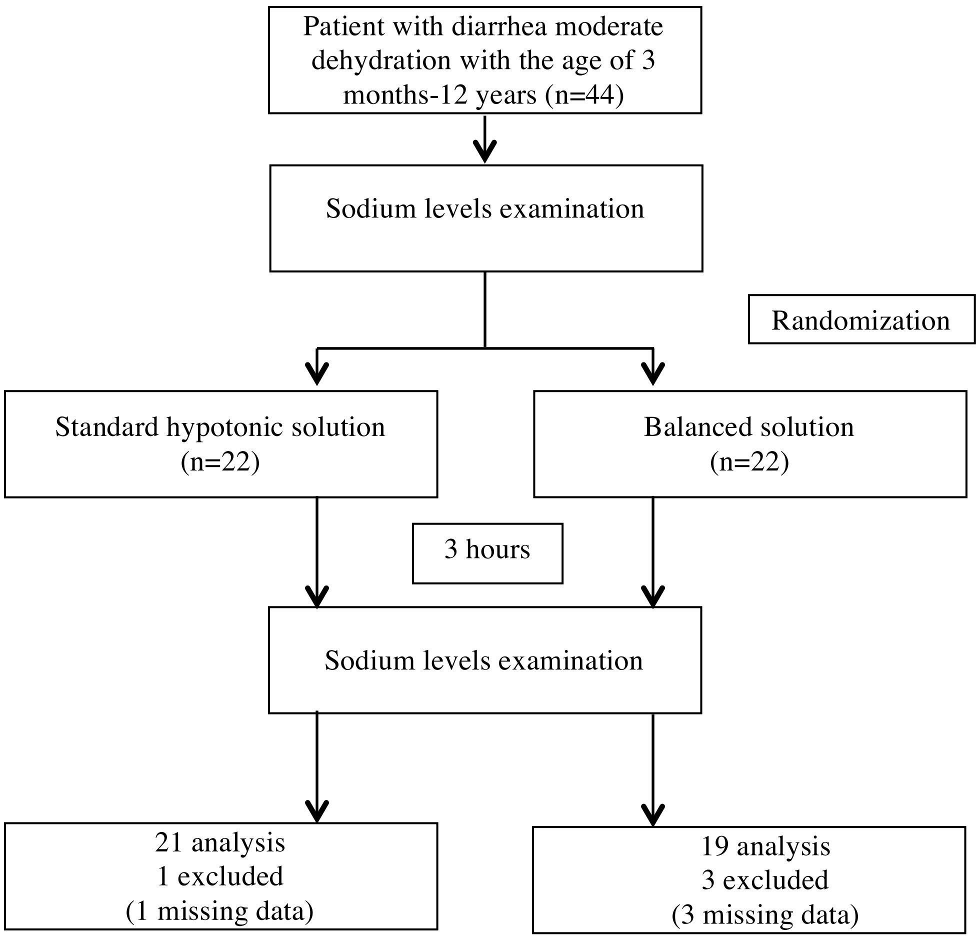
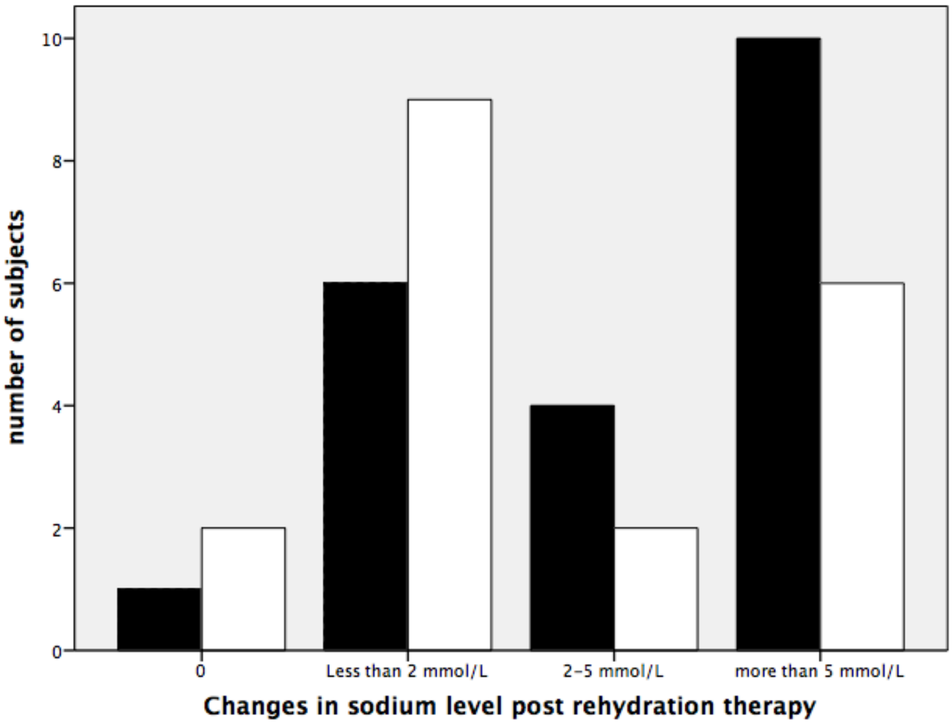
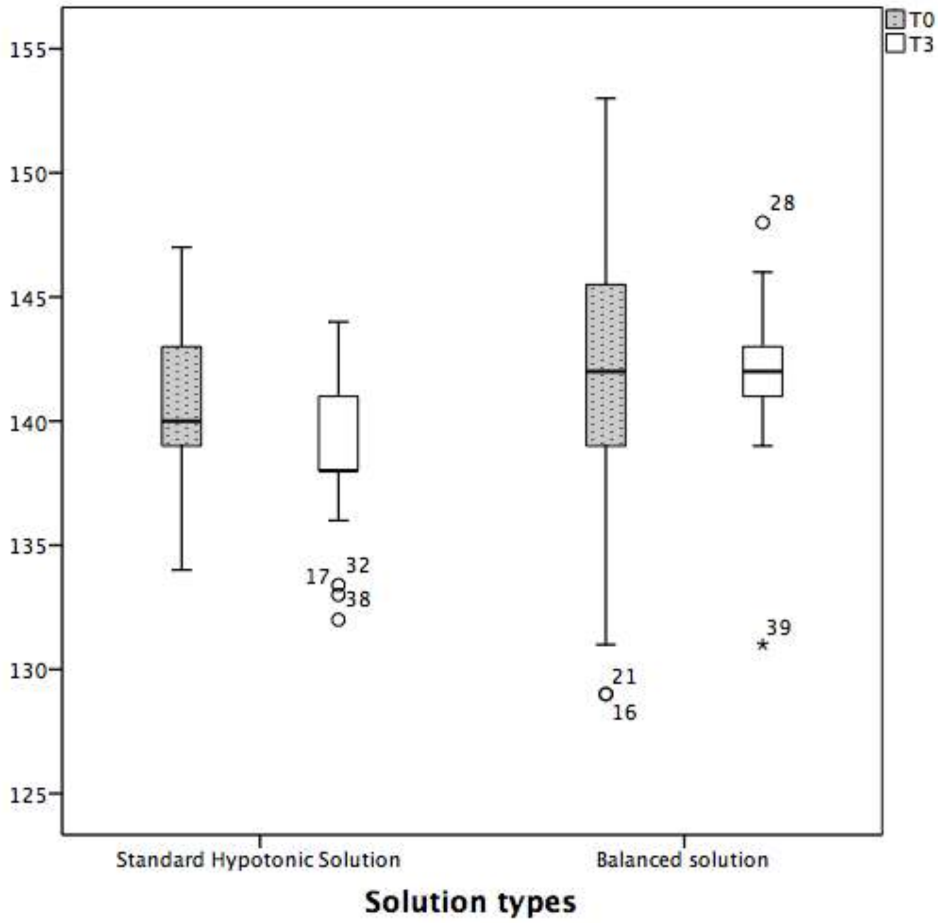


Figure 2. The changes of serum sodium levels three hours post rehydration therapy



Legend: Black=standard hypotonic solution; white=balanced solution. The figure shows that the number of subjects with serum sodium levels changes more than 5 mmol/L with standard hypotonic solution group was 47.6% (10/21) and balanced solution was 31.6% (6/19).

Figure 3. Comparison of sodium levels pre and post rehydration therapy



Legend: Box plots showing the plasma sodium concentration at baseline (black=T_0) and after 3 hours (white=T_3) rehydration of either standard hypotonic solution or balanced solution in all children.

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