RESEARCH PAPER

Effect of Rehydration With Normal Saline *Versus* Ringer Lactate on Serum Sodium Level of Children With Acute Diarrhea and Severe Dehydration: *A Randomized Controlled Trial*

Md Naseem[1], AP Dubey[1], TK Mishra[2] and Raghvendra Singh[1]

From Departments of [1]Pediatrics and [2]Biochemistry, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India.

Correspondence to: Dr Raghvendra Singh, Associate Professor, Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India. drraghvendrasingh@gmail.com

Received: January 05, 2019; Initial review: June 06, 2019; Accepted: March 20, 2020.

Objective: To demonstrate the equivalence of Normal Saline (NS) and Ringer Lactate (RL) for change in serum sodium levels during correction of severe dehydration in children with acute diarrhea based on World Health Organization (WHO) plan C.

Design: Equivalence randomized control trial.

Setting: Pediatric diarrhea unit of a tertiary care hospital from May, 2016 to April, 2017.

Participants: 72 children of 1-12 years with acute diarrhea and severe dehydration were enrolled. Children with dysentery, severe acute malnutrition, severe anemia, meningitis, and known surgical and systemic diseases were excluded.

Intervention: RL (*n*=36) or NS (*n*=36) were used as per WHO plan C. Blood samples were drawn before intravenous fluid correction and 3 h post-intervention.

Outcome Measures: Mean change in serum sodium level from the baseline between the RL and NS groups.

Results: 70 children (35 in each group) completed the study. The difference in mean serum sodium levels from baseline in RL and NS groups were 1.4 (4.5) mEq/L and 2.1(4.9) mEq/L, respectively (*P*=0.58).

Conclusions: Both RL and NS are equivalent in terms of change in serum sodium from baseline for intravenous rehydration in children with acute diarrhea and severe dehydration.

Keywords: *Acid-base balance, Hyponatremia, Intravenous fluids, pH, Serum potassium.*

Diarrhea is a leading cause of death in children accounting for 9% of all deaths among children under-5 year worldwide in 2015 [1] and an estimated 300,000 children in India each year [2]. Dehydration is associated with deaths in most cases [3] and occurs when fluid losses are not replaced adequately and a deficit of water and electrolytes develops. The total body sodium deficit in diarrheal dehydration in young children is about 70-110 millimoles per liter of water deficit. Potassium and chloride losses are in a similar range [3]. The preferred regime for treatment of children with severe dehydration is rapid intravenous rehydration using World Health Organization (WHO) Plan C. WHO recommends use of Ringer lactate or normal saline in case of non-availability of Ringer lactate, for intravenous rehydration in children under plan C [3].

METHODS

This equivalence randomized control trial was done in the Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi during the period May, 2016 – April, 2017. The study was approved by Institute ethics committee. Children between 1 to 12 years of age with acute diarrhea and severe dehydration were enrolled after taking informed consent from their parents. Acute diarrhea was defined as ≥3 loose stools in previous 24 hour and duration of diarrhea less than 14 days. Severe dehydration was defined as per WHO guidelines [3] with two or more of the following: lethargic or unconscious, drinks poorly or not able to drink, skin pinch goes back very slowly (>2 second) and sunken eyes. Children with dysentery, severe acute malnutrition (WHO criteria), severe anemia (significant palmar pallor), meningitis, seizures, known surgical problems (*e.g.* ileostomy), known systemic disease and hypoglycemia (Blood glucose <54 mg/dL) were excluded. Eligible children were randomly assigned to receive either Ringer lactate or normal saline (***Fig.* 1**). Allocation sequence was computer generated (*www.randomization.com*) and allocation concealment was done through serially numbered opaque sealed envelopes (SNOSE).

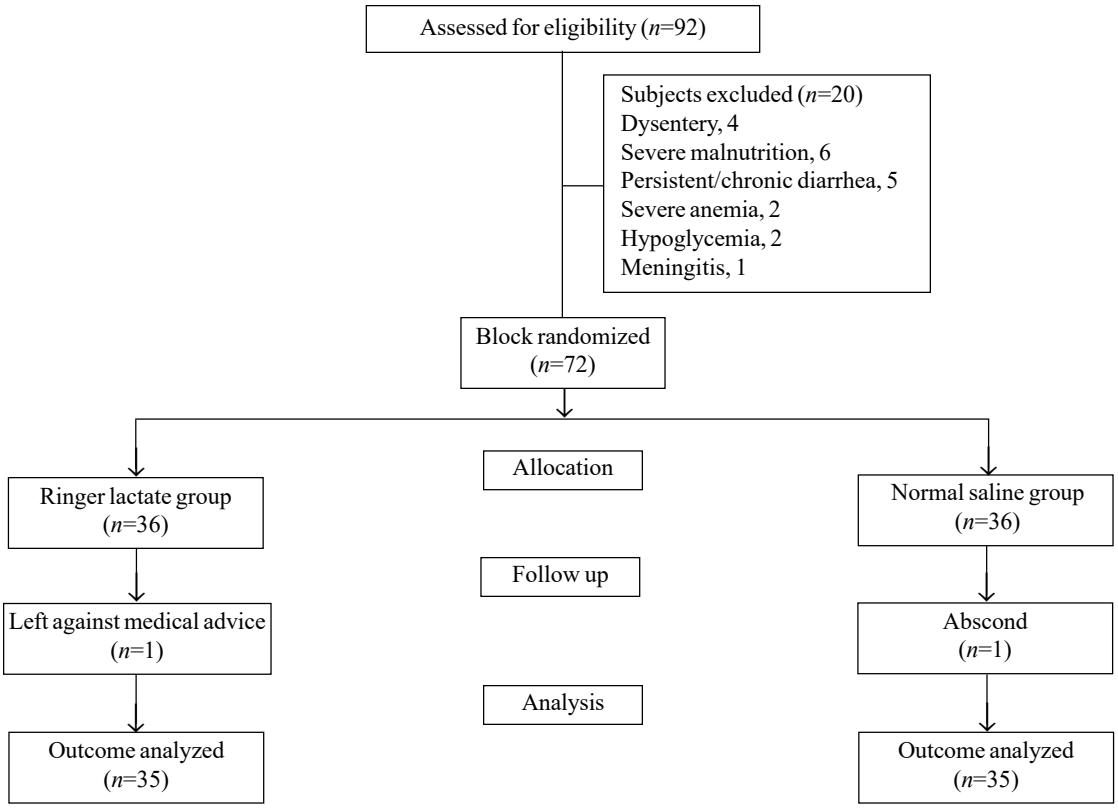

Fig. 1 *Flow diagram of patients*.

Before commencement of rehydration, blood samples were taken for blood gas analysis, kidney function tests and serum electrolytes (sodium and potassium). Hyponatremia was defined at serum sodium <135 mmol/L. Children received Ringer lactate or normal saline according to WHO guidelines in doses of 100 mL/kg over 3 hour and were monitored every 30-60 minutes for vital signs. They were reassessed at the end of 100 mL/kg infusion for clinical signs of dehydration. Caregivers were asked to mark the number of stool purges and the number of vomiting for the correction period. If any child was found in dehydration at the end of first correction, the child was treated according to standard WHO guidelines. At the end of first correction, blood samples were repeated for blood gas, renal function and serum electrolytes. In initial hours ongoing losses were replaced by intravenous fluid solution of 0.45% saline in 5% dextrose and 20 mEq/L potassium chloride at 10 mL/kg per loose stool at hourly intervals. Children also received age appropriate maintenance fluids. All children received oral elemental zinc supplementation at 20 mg/day. Completion of first fluid correction at 3 hour was taken as primary end point and disappearance of all clinical signs of dehydration was taken as endpoint for secondary outcome. Our primary objective was to determine the difference in the change of serum sodium level over baseline in the two groups. We also studied the difference in the change of serum potassium, pH, bicarbonate levels and base deficit at primary end point. The time taken and volume of fluid requirement for complete rehydration in the two groups were compared at secondary end point.

Sample size was calculated to demonstrate equivalence between the two interventions with an equivalence limit not exceeding 3 mEq in serum sodium level with SD of 3, $\alpha = 1\%$ and power of 90. A sample size of 30 children was calculated. Expecting 20% attrition, 36 subjects were enrolled in each group in an age stratified manner in 2:1 ratio for age groups 1-5 years and >5-12 years.

Statistical analyses: Analysis was conducted using IBM SPSS Statistics (version 22.0). The normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of normality. For primary outcome, the two groups were compared for change in serum sodium from baseline. Means of two groups were compared using independent t-test. Mann-Whitney U-test was carried out for statistical analysis of skewed

continuous variables. For comparison of normally time related variables paired t-test was applied. Proportions were compared using Fisher's exact test. All the statistical tests were two-sided and were performed at a significance level of 0.05.

RESULTS

Out of 72 enrolled children, 70 (35 in each group) completed the therapy. One child in each group opted out of the study before the first correction of dehydration. The baseline characteristics of patients are shown in ***Table* I**. Hyponatremia was present at baseline in 26 (74%) in Ringer lactate group and 25 (71%) in normal saline group. No child had symptomatic hyponatremia. Mean (SD) serum sodium values at baseline were comparable (131.3 (4.4) mEq/L in Ringer lactate group and 132.3 (4.8) mEq/L in normal saline group, *P*=0.29). The change in biochemical parameters at primary end point are depicted in ***Table* II**.

After first volume correction (WHO plan C), 23 (65%) children in Ringer lactate group and 17 (49%) children in normal saline group had persistent hyponatremia, one child had symptomatic hypokalemia in the latter group, which responded to standard therapy. A total of 29 (83%) children were completely rehydrated in each group while 6 (17%) had features of some dehydration and required Plan B. No child required subsequent rehydration. Time to rehydration was similar (range 3h-7h) in both groups. The mean (SD) fluid requirement for replacement of ongoing losses was similar in both the groups, 74.29 (35) mL/kg and 76.29 (34.8) mL/kg in Ringer lactate and Normal saline groups, respectively (*P*=0.81).

Table I Baseline Characteristics of Children With Severe Dehydration Receiving Ringer Lactate or Normal Saline for Rehydration

Characteristics	*Ringer Lactate (n=35)*	*Normal Saline (n=35)*
Age (y)	4.3 (2.9)	4.7 (2.9)
Male	16 (46)	17 (49)
Duration of symtoms, d	1.8 (1.6)	1.6 (1.4)
*Sodium, mEq/L	131.3 (4.4)	132.3 (4.0)
*Potassium, mEq/L	3.8 (0.6)	3.5 (0.7)
Blood urea, mg/dL	53 (35.8)	59.6 (28.6)
Creatinine, mg/dL	1.2 (0.7)	1.3 (0.7)
pH	7.26 (0.07)	7.28 (0.08)
Bicarbonate, mEq/L	12.66 (3.33)	12.16 (2.89)
Base deficit, mmol/L	12.58 (3.98)	12.89 (3.66)

**Serum values; data represented as Mean (SD); P >0.05 for all comparisons.*

DISCUSSION

In this study, high rate of hyponatremia was detected in children with acute diarrhea and severe dehydration which persisted after rehydration. The change of serum sodium was similar with use of either Ringer lactate or normal saline for rehydration.

The open label nature of the trial and the non-availability of serum chloride levels and non-utilization of oral rehydration solution for replacement of ongoing losses were the limitations of the study. The study was not powered to detect significant changes in pH, bicarbonate and base excess.

In a similar study by Mahajan, *et al.* [9], the change in serum sodium levels was similar after rapid intravenous rehydration with Ringer lactate or normal saline in children with acute diarrhea. The decline in serum potassium from baseline in both groups was comparable in the present study unlike seen only in normal saline

Table II Change in Biochemical Parameters During Correction of Severe Rehydration

Parameters	*Ringer Lactate (n=35)*			*Normal Saline (n=35)*			*P value**
	Baseline	*After correction*	*Mean (SD) difference*	*Baseline*	*After correction*	*Mean (SD) difference*	
Sodium (mEq/L)	131.3 (4.4)	132.7 (3.5)	1.4 (4.5)	132.3 (4.0)	134.5 (4.5)	2.1 (4.9)	0.58
Potassium (mEq/L)	3.8 (0.6)	3.6 (0.6)	0.2 (0.4)	3.5 (0.7)	3.3 (0.7)	0.2 (0.5)	0.60
Blood urea (mg/dL)	53 (35.8)	42.7 (28.6)	10.3 (18.2)	59.6 (28.6)	40.0 (15.8)	19.6 (21.9)	0.6
Creatinine (mg/dL)	1.2 (0.7)	0.9 (0.5)	0.3 (0.3)	1.3 (0.7)	0.8 (0.3)	0.4 (0.5)	0.42
pH	7.26 (0.07)	7.33 (0.08)	0.07 (0.05)	7.28 (0.08)	7.30 (0.09)	0.02 (0.07)	0.002
Bicarbonate (mEq/L)	12.66 (3.33)	15.92 (4.04)	3.25 (2.14)	12.16 (2.89)	13.19 (2.41)	1.03 (2.66)	<0.001
Base deficit (mmol/L)	12.58 (3.98)	8.85 (4.48)	3.73 (2.48)	12.89 (3.66)	11.67 (3.66)	1.22 (2.80)	<0.001

*All values in mean (SD); *P value for delta difference between both groups.*

WHAT THIS STUDY ADDS?

Ringer lactate and normal saline are equivalent in terms of change in serum sodium from baseline for rapid intravenous rehydration in children with acute diarrhea.

group in the earlier study [9], which was attributed to the composition of normal saline, which does not have potassium as a constituent. The present study had lesser metabolic acidosis in comparison to the previous study [9], which could explain the greater fall in the potassium levels in their study. In the present study, the significant changes in pH, bicarbonate and base deficit in Ringer lactate group as compared to normal saline group can be explained by the conversion of lactate to bicarbonate in the former group. Similar results were observed in an adult study [10], unlike Mahajan, *et al.* [9] where both groups showed comparable change, which was attributed to intravascular volume expansion.

To conclude, normal saline is equivalent to Ringer lactate solution in terms of change of serum sodium and serum potassium from baseline for initial rapid intravenous rehydration in children with acute diarrhea and severe dehydration. Rehydration with normal saline does not cause hypernatremia. Although, quicker resolution of metabolic acidosis occurs with Ringer lactate solution, its clinical significance may need to be studied further.

Ethical Clearance: Institutional Ethics Committee for Human Research, Maulana Azad Medical College; No. 11/IEC/MAMC/2015/317.
Contributors credit: MN,APD,RS: involved in execution of the study, data analysis and writing the manuscript; TKM: contributed in execution of the study, data analysis and writing the manuscript.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Diarrhoea remains a leading killer of young children, despite the availability of a simple treatment solution. UNICEF 2017. Available from: *https://data.unicef.org/topic/child-health/diarrhoeal-disease/#.* Accessed April 15, 2017.
2. Lakshminarayanan S, Jayalakshmy R. Diarrheal diseases among children in India: Current scenario and future perspectives. J Nat Sc Biol Med. 2015;6:24-8.
3. Bhan MK, Mahalanabis D, Pierce NF, Rollins N, Sack D, Santoshum M. The treatment of diarrhoea: A manual for physicians and other senior health workers. 4th rev. Geneva: World Health Organization; 2005.
4. World Health Organization. Cholera annual report 2006: Weekly epidemiological record. World Health Organ 2007;82:273-84.
5. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. Normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond). 2003;104:17-24.
6. Cho YS, Lim H, Kim SH. Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. Emerg Med J. 2007;24:276-80.
7. Hadimioglu N, Saadawy I, Saglam T, Ertug Z, Dinckan A. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg. 2008;107:264-9.
8. O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brintjens TE, Mercer JS, *et al*. A randomized, double blind comparison of lactated ringer's solution and 0.9% saline during renal transplantation. Anesth Analg. 2005; 100:1518-24.
9. Mahajan V, Sajan SS, Sharma A, Kaur J. Ringer's lactate vs normal saline for children with acute diarrhea and severe dehydration: A double blind randomized controlled trial. Indian Pediatr. 2012;49:963-8.
10. Cieza JA, Hinostroza J, Huapaya JA, León CP. Sodium chloride 0.9% versus lactated Ringer in the management of severely dehydrated patients with choleriform diarrhea. J Infect Dev Ctries. 2013;7:528-32.