RESEARCH PAPER

Ringer's Lactate *vs* Normal Saline for Children with Acute Diarrhea and Severe Dehydration: *A Double Blind Randomized Controlled Trial*

VIDUSHI MAHAJAN, *SHIV SAJAN SAINI, AMIT SHARMA AND #JASBINDER KAUR

*From the Departments of Pediatrics and Biochemistry,# Government Medical College and Hospital,Chandigarh; and *Department of Pediatrics, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Correspondence to: Dr Vidushi Mahajan, Assistant Professor, Department of Pediatrics, Government Medical College and Hospital, Sector 32, Chandigarh, India. vidushimahajan2003@yahoo.co.in*

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Objective: WHO recommends Ringer's lactate (RL) and Normal Saline (NS) for rapid intravenous rehydration in childhood diarrhea and severe dehydration. We compared these two fluids for improvement in pH over baseline during rapid intravenous rehydration in children with acute diarrhea.

Design: Double-blind randomized controlled trial

Setting: Pediatric emergency facilities at a tertiary-care referral hospital.

Intervention: Children with acute diarrhea and severe dehydration received either RL (RL-group) or NS (NS-group), 100 mL/kg over three or six hours. Children were reassessed after three or six hours. Rapid rehydration was repeated if severe dehydration persisted. Blood gas was done at baseline and repeated after signs of severe dehydration disappeared.

Outcome Measures: Primary outcome was change in pH from baseline. Secondary outcomes included changes in serum electrolytes, bicarbonate levels, and base-deficit from baseline; mortality, duration of hospital stay, and fluids requirement.

Results: Twenty two children, 11 each were randomized to the two study groups. At primary end point (disappearance of signs of severe dehydration), the improvement in pH from baseline was not significant in RL-group [from 7.17 (0.11) to 7.28 (0.09)] as compared to NS-group [7.09 (0.11) to 7.21 (0.09)], *P*=0.17 (after adjusting for baseline serum Na/ Cl). Among this limited sample size, children in RL group required less fluids [median 310 *vs* 530 mL/kg, *P*=0.01] and had shorter median hospital stay [38 *vs* 51 hours, *P*=0.03].

Conclusions: There was no difference in improvement in pH over baseline between RL and NS among children with acute diarrhea and severe dehydration.

Key words*: Diarrhea, Intravenous fluid, pH, Severe dehydration*.

Clinical Trial Registration-CTRI/2009/091/001084

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Worldwide, diarrhea is the second most common cause of childhood mortality [1]. Severe dehydration is a leading cause of death in children with acute diarrhea. Rapid intravenous rehydration over 3-6 hours is the standard management of acute diarrhea and severe dehydration in children [1]. It is safe, well tolerated, and is widely recommended [2-4]. WHO recommends Ringer's lactate (RL) and Normal saline (NS) for rapid intravenous rehydration in childhood diarrhea [5].

Resuscitation with NS is associated with metabolic acidosis and hyperchloremia [6-12]. When children with acute diarrhea and severe dehydration were treated with NS infusion, pH decreased despite clinical improvement in dehydration, as compared to a Polyelectrolyte solution [13]. Worsening of acidosis may have profound clinical implications as pH <7.20 may be associated with multi-organ dysfunction [14]. RL may independently improve pH in such cases, as lactate gets converted to bicarbonate *in vivo*.

There are no studies comparing efficacy of RL and NS in children with acute diarrhea [15]. We designed this trial to determine whether rapid intravenous rehydration with RL improves pH as compared to NS in children with acute diarrhea and severe dehydration. In addition, we compared change in serum electrolytes (sodium, potassium, and chloride), serum bicarbonate levels, base deficit; mortality during hospital stay, fluid requirement, duration of hospital stay, and cannula-related complications amongst children receiving the two fluids.

METHODS

This single centre, double blind, randomized controlled trial was conducted from May 2009 to September 2010 in Pediatric emergency facilities at a tertiary-care referral teaching hospital. Ethical approval was obtained from Institute's ethics committee. The data were monitored by an independent investigator not involved in the recruitment or management of the patients and was reviewed periodically.

Children, from one month to 18 years, with acute diarrhea and severe dehydration were eligible. Acute diarrhea was defined as ≥3 liquid stools in previous 24 hours [5]. Severe dehydration was defined as presence of hypotension or any of the two out of four signs-lethargic or unconscious, sunken eyeballs, drinks poorly or not able to drink, skin pinch goes back very slowly (>2 sec) (WHO criteria) [5]. We excluded children with persistent diarrhea (>14 days), clinical signs of severe malnutrition (WHO criteria) [5], known systemic disease (cardiac, endocrine, neurologic, chronic renal failure), lethal malformations, and hypoglycemia (dextrostix value <40 mg/dL). Before randomization written informed consent was obtained from the parents of eligible children .

Eligible children were randomly assigned to receive either RL (RL group) or NS (NS group). Random allocation sequence was computer generated (www.randomizer.org) by an independent pediatrician, not involved in patient management. RL and NS were obtained in identical-looking bottles. The bottles-set (consisting of 10 bottles each of 500 mL= 5000 mL of the study fluids) were serially numbered according to the random sequence. Their labels were replaced by the study labels containing the study name and serial number. As the subsequent eligible child got randomized, the bottles-set with next serial number was used for rehydration. This was administered by staff nurse on duty. The participants, treating physicians and assessors managing the patients were thereby, blinded to the intervention.

We measured baseline arterial blood gas (AVL Compact 3 Blood Gas Analyser, Roche Diagnostics, Mannheim, Germany), serum sodium and potassium (AVL 9120 Na^+K^+ Analyser, AVL Scientific Corporation, Roswell, Georgia, USA), serum chloride (Erba Chem-5 plus, TransAsia Biomedicals Ltd, India), blood urea, and creatinine before commencement of intravenous fluid correction. For rapid intravenous rehydration, the treatment protocol was according to WHO guidelines [5]. Children received either RL (Sodium-130 mmol/L, chloride-109 mmol/L, lactate-28 mmol/L, potassium-4 mmol/L, calcium-1.5 mmol/L) or NS (sodium-154 mEq/L, Chloride-154 mEq/L) in doses of 100 mL/kg over three or six hours. Children <1 year received fluid correction over six hours, and >1 year old over three hours. Children were monitored every 15-30 minutes for vital signs and reassessed at end of 100 mL/kg infusion for clinical signs of dehydration. If any child was found in severe dehydration at the end of first correction, rapid intravenous rehydration (100 mL/kg) was repeated. If there were no features of severe dehydration, the child was treated according to standard WHO guidelines [5]. We repeated arterial blood gas (ABG) and serum electrolytes at primary end point. Children were followed for secondary outcomes till discharge from hospital.

In addition to study fluids, all children received replacement fluids for ongoing losses (watery stools or vomit) and maintenance fluids. We used either reduced-osmolarity WHO oral rehydration solution (ORS) [5] or an intravenous solution of 0.45% saline in 5% dextrose and 2mEq/L Potassium chloride–as replacement fluids depending upon the child's ability to drink. The volume of replacement fluids was calculated by 10 mL/kg of body weight per stool or vomit. The replacement fluids were charted every 2-hourly after assessment of ongoing losses. Children also received age appropriate maintenance fluids throughout the study period [5]. All children received oral zinc supplements (10-20 mg/day) [5].

Resolution of hypotension and disappearance of clinical features of severe dehydration was taken as endpoint for primary outcome. RL-group and NS-group were compared for primary and secondary outcomes. The primary outcome variable was change in pH from baseline. Pre-specified secondary outcome variables were changes in serum bicarbonate levels, base deficit, and serum electrolytes (sodium, potassium, and chloride) from baseline. We also compared the two groups for all cause mortality during hospital stay, duration of hospital stay, volume of fluids required for rehydration, and local complications at cannula site.

Statistical analysis: The sample size calculations were based on the study results of Juca, *et al.* [3]. To pick up a difference in pH of 0.1 with a standard deviation of 0.07, with an a error of 0.05 and power of 90%, we needed 22 children (11 in each group).

Analysis was performed according to intention-to-treat principle. For primary outcome, the two groups were compared for change in pH from baseline, by using repeated measures ANCOVA (analysis of co-variance). Similarly, changes in serum bicarbonate levels, base deficit, serum electrolytes levels from baseline were also compared by repeated measures ANCOVA. For dichotomous outcomes, we used Fisher's Exact test to compare proportions between the two groups. Mann Whitney 'U' test was used for comparing fluid requirements and duration of hospital stay between the two groups. All analysis was performed with SPSS 17.0.

RESULTS

Thirty four children, presenting with acute diarrhea and severe dehydration, were assessed for eligibility. Twelve children were excluded (persistent diarrhea 4, severe malnutrition 3, consent denied 3, hypoglycemia 2) ***(Fig.* 1**). Twenty two children (11 in each group) were

randomly allocated to either RL group or NS group.

The baseline demographic and clinical characteristics of the study groups are presented in ***Table* I**. The two groups were not significantly different for baseline demographic characteristics, acid-base status, renal function tests, and risk of mortality at the baseline (Pediatric index of mortality-2) [19]. *Vibrio cholera* (eltor ogawa serotype) was the predominant etiology of diarrhea (55%). There was one protocol violation during the study period. One patient in RL-group received NS for 3 hours before being recognized. Subsequently, all fluids were as per randomization.

All 22 children received one cycle of rapid intravenous hydration. Four children in RL-group and six children in NS-group had signs of severe dehydration at the end of first rapid intravenous rehydration and required a second cycle of rapid intravenous hydration. No child required third cycle of rapid intravenous rehydration. We compared RL-group and NS-group for change in pH from baseline to primary end point. After adjusting for baseline serum sodium and chloride, the change in pH from baseline was not significant in RL-group (from 7.17 ± 0.11 to 7.28 ± 0.09) as compared to NS-group (7.09 ± 0.11 to 7.21 ± 0.09), (P=0.17) ***(Fig.* 2)**. We also compared the two groups for the time taken to meet the primary end point, which was also not significantly different (log rank test, P= 0.40).

The change in serum bicarbonate from baseline, was significantly higher in RL group than NS group (P=0.02). The change in serum potassium from baseline, was significantly lesser in RL group than NS group (P=0.03). There was no difference in change of base deficit, and serum sodium/ chloride from baseline between RL-group and NS-group (***Table* II**).

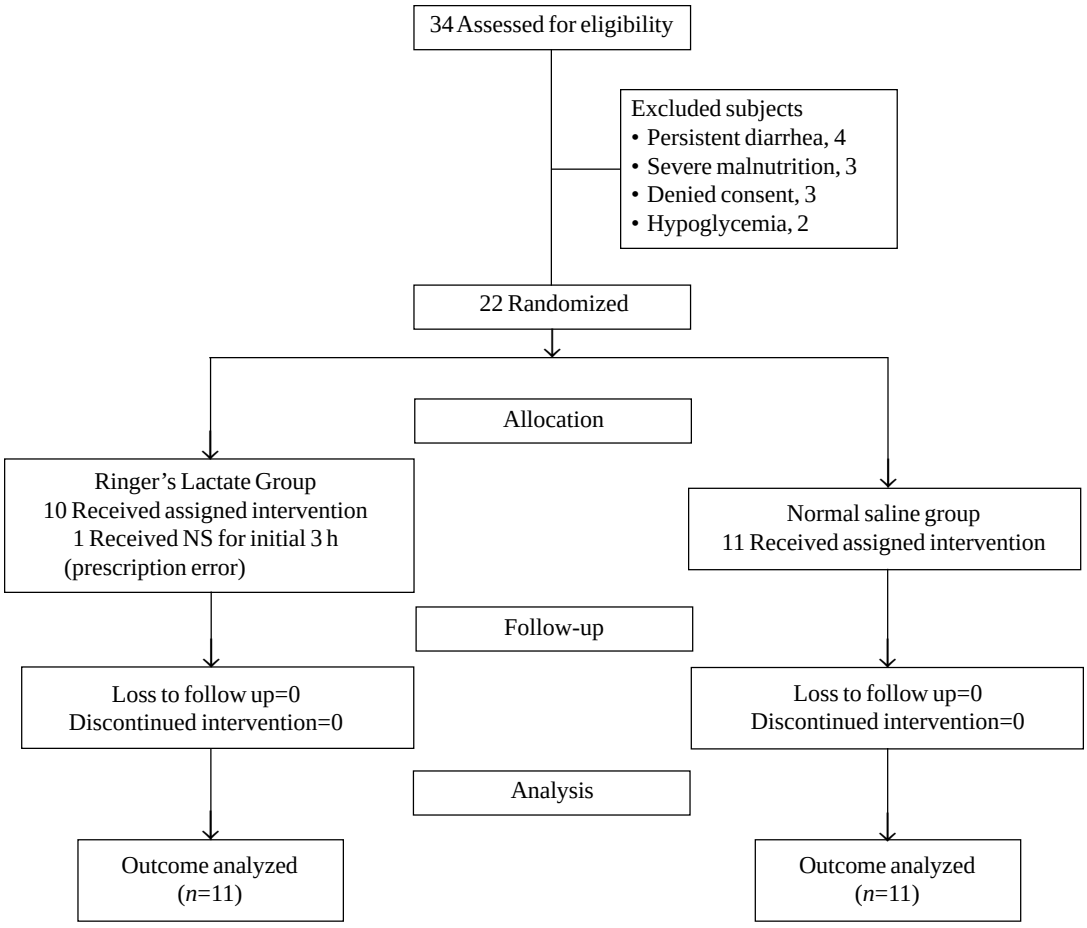

FIG.1 *Flow diagram of patients.*

TABLE I BASELINE CHARACTERISTICS OF STUDY POPULATION

Characteristics	*RL-group (n=11)*	*NS-group (n=11)*
Age (mo)	73 ± 28	58 ± 24
Males (%)	8 (73)	5 (46)
Weight (kg)	15.1 ± 4.6	13.6 ± 5.1
Duration of symptoms (d)	1 (1, 3)	1 (1, 2)
Acid-Base status		
pH	7.17 ± 0.11	7.09 ± 0.11
Serum bicarbonate (mEq/L)	9.4 ± 2.7	8.6 ± 2.8
Base deficit (mMol/L)	17.6 ± 3.7	18.8 ± 5.0
Anion gap	29.4 ± 5.9	23.9 ± 5.3
Sodium (mEq/L)*	138.7 ± 6.0	132.8 ± 6.2
Potassium (mEq/L)	4.6 ± 0.9	4.5 ± 0.9
Chloride (mEq/L)*	101.4 ± 1.1	100.3 ± 1.0
Blood urea (mg/dL)	50 (28, 59)	55 (43, 73)
Serum creatinine (mg/dL)	1.3 ± 0.4	1.7 ± 0.6
Mortality risk at baseline (%)[#]	17.7 ± 9.9	17.3 ± 11.7
Stool culture[$]		
V. cholerae	6 (55)	6 (55)
Normal flora	3	2
E. coli	0	1

*# Pediatric Index of Mortality 2 Score [19]; [$] Stool culture was not available for 4 subjects (2 in each group); *P<0.05.*

The children in RL group required intravenous fluids for significantly shorter duration as compared to NS group (log rank test, *P*=0.005). Median total fluids (including intravenous and ORS) requirement was less in RL-group [310 mL/kg (IQR- 230, 365)] as compared to NS-group [530 mL/kg (IQR- 324, 750)], *P*=0.01. Children in RL group required less *ORS* solution than NS-group [median requirement-60 mL/kg (IQR- 35, 70) *vs* 123 mL/kg (IQR- 69, 233), respectively (*P*=0.01)]. Children in RL group had shorter median hospital stay [38 hours (IQR- 27, 50)] than NS group [51 hours (IQR- 36,71)] (*P*=0.03). There was one death in NS group during study period. Assigned cause of death was septic shock. Two children in NS group, who reached primary end point once, were found to be severely dehydrated again after 4-hours and 24-hours of enrolment, requiring intravenous fluids supplementation. Both children grew *V. cholerae* in stool culture. None of the children in RL group developed features of dehydration once it had been corrected.

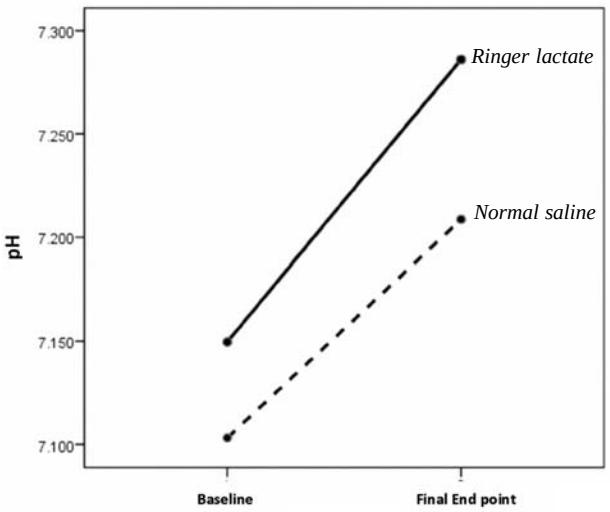

FIG. 2 *Change in pH from the baseline.*

DISCUSSION

In this double blind, randomized, single-centre trial, improvement in pH over baseline in RL-group was not significant as compared to NS-group among children with acute diarrhea and severe dehydration.

Resuscitation with NS has been shown to be associated with metabolic acidosis and hyperchloremia in animal models, healthy adult volunteers, and diseased adult subjects [6,8-11,13]. The low pH can itself potentiate cellular injury [20]. On the contrary, lactate in RL gets converted to bicarbonate ions *in vivo* and can improve pH, in addition to intravascular expansion. We did not find any significant difference in the change in pH

TABLE II EFFECT OF RAPID INTRAVENOUS REHYDRATION ON ACID-BASE STATUS, ELECTROLYTES AND RENAL FUNCTION TESTS

Characteristics	*RL group (n=11)*		*NS group (n=11)*		*P value*
	Baseline	*After correction*	*Baseline*	*After correction*	
Serum bicarbonate (mEq/L)	9.4 ± 2.7	13.4 ± 2.1	8.6 ± 2.8	9.3 ± 2.6	0.03
Base deficit (mMol/L)	17.6 ± 3.7	15.3 ± 6.8	18.8 ± 5.0	15.9 ± 5.7	0.84
Serum sodium (mEq/L)	138.7 ± 6.0	135.0 ± 3.3	132.8 ± 6.2	131.5 ± 9.3	0.05
Serum potassium (mEq/L)	4.6 ± 0.9	3.9 ± 0.6	4.5 ± 0.9	3.6 ± 0.9	0.03
Serum chloride (mEq/L)	101.4 ± 1.1	101.8 ± 1.6	100.3 ± 1.0	101.5 ± 1.4	0.274

WHAT IS ALREADY KNOWN?

- Ringer's Lactate and Normal saline can be used during rapid intravenous rehydration in children with acute diarrhea and severe dehydration.

WHAT THIS STUDY ADDS?

- Among children with severe dehydration receiving rapid intravenous rehydration with intravenous fluids, change in pH over the baseline was not significantly different between Ringer's Lactate and Normal saline group.

over baseline among RL and NS groups. The reason for this difference in observations is the presence of severe volume depletion in children in our study. The improvement in pH in both RL-group and NS-group is likely to be due to intravascular volume expansion. In adult human volunteers and diseased adults, the pH decreased from the baseline after NS infusion but the subjects in those studies were not dehydrated [8, 11]. In the study by Juca, *et al*. [13]; however, the pH in NS group decreased from baseline even in dehydrated children. The children in NS-group in our study did not develop significant hyperchloremia. We observed a significantly greater decline in serum potassium values from baseline in NS-group compared to RL-group at primary end point. The difference could be attributed to the composition of the two fluids as NS does not have potassium as a constituent.

In the study by Juca, *et al*. [13], the primary outcomes (volume of fluids and time to hydration) were not different in two groups. In our study, the fluid requirement was significantly less in RL-group as compared to NS-group. These results should be interpreted with caution as our study aimed to pick differences in pH over baseline and was not powered to answer these outcomes. Unblinded nature of the previous study [13] and difference in the sodium and chloride concentrations of Ringer's Lactate and polyelectrolyte solution could also have contributed for the difference. However, in animal models of hemorrhagic shock, fluid requirement was found to be significantly less in RL-group than NS-group [6]. In the current study, the duration of hospitalization in RL-group was shorter as compared to NS-group. This finding may have financial implications considering the huge burden of disease (median of 3.2 episodes of diarrhea per child-year) [18]. The faster turnover time of beds would be helpful for providing care to more children, especially in the resource-constrained setting. However, these clinical outcomes need to be proven by adequately powered studies. The statistically significant differences obtained in the current study for these outcomes could be due to chance owing to lack of power to measure these outcomes and the differences in the baseline characteristics among two groups.

We used standard WHO guidelines for the management of acute diarrhea [5]. The strengths of our study are the study design, proper blinding, and objective primary outcome. The results met the assumptions drawn during calculating the sample size [16]. However, 55% of our children had cholera. Therefore, our results are valid mainly for cholera-endemic areas. There was no child <1 year of age in the study and hence the results are not applicable to infants. We could not test for rotavirus diarrhea due to non-availability of kits. It remains to be studied whether improvement in pH translates into an impact on hard outcomes like mortality.

In children with acute diarrhea and severe dehydration receiving rapid intravenous rehydration, improvement in pH from the baseline was not significant in RL-group as compared to NS-group.

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Contributors: VM: conceived the idea, was involved in management & data collection, wrote the first draft, interpreted the data and will act as guarantor; SS designed the study, did randomization and blinding, statistically analyzed the data, and critically evaluated the manuscript; AS: helped in management and data collection; JK: supervised the biochemical analysis of samples and edited the manuscript. The final manuscript was approved by all authors.
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