Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 13 [4] March 2024: 75-81

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Oral Rehydration of Malnourished Children with Diarrhoea and Dehydration: A Systematic Review

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ABSTRACT
We reviewed the substantiation for oral rehydration therapy in children with SAM. Using standard search terms, a systematic review of randomized controlled trials (RCTs) was conducted in December 2022, comparing different oral rehydration solutions (oral) in SAM children with diarrhea and lack of fluids. The author assessed and reviewed various papers. A total of eight RCTs, all published in English and conducted in low-resource settings were identified. These studies evaluated various ORS, including ReSoMal, standard hypo-osmolar WHO ORS, and old WHO ORS. In two trials evaluating ReSoMal, hyponatremia was observed, and severe hyponatremia developed in three children with one experiencing convulsion. Hypo-osmolar ORS was found to have benefits in terms of rehydration, reduction of stool output, and duration of diarrhea. No trials reported over-hydration or deaths. Studies indicate a significant threat of hyponatremia on ReSoMal in Asian children, but very few have been conducted in India, where SAM mortality remains high. Further studies should be conducted in India to assess optimal ORS for SAM children and to produce proof-based, practical guidelines.
Keywords: *Malnutrition; dehydration; rehydration; systematic review; Asia; India; oral rehydration solution.*

Received 24.01.2024 Revised 24.02.2024 Accepted 16.03.2024

INTRODUCTION

According to the World Health Organization (WHO), diarrhea is defined as the passage of three or more loose or watery stools in 24 hours [1]. It is typically a symptom of an infection in the gastrointestinal tract caused by a variety of bacterial, viral, and parasitic organisms. It can last several days and deprive the body of the water and salts required for survival resulting in severe dehydration and death or long-term consequences [2]. There are three main forms of childhood diarrhea, each of which can be fatal and necessitates a unique treatment regimen. Acute watery diarrhea is associated with significant fluid loss and rapid dehydration. Bloody diarrhea, also known as dysentery, is distinguished by visible blood in the stools. It is linked to intestinal damage and nutrient losses in infected people. Persistent diarrhea is an episode of diarrhea with or without blood that lasts at least 14 days [3]. According to the latest report from the World Health Organisation, nearly 8% of children under five are due to diarrhea disease [4]. This indicates an alarming situation worldwide. The latest report of the United Nations International Children's Emergency Fund (UNICEF) revealed that deaths among under-five children are mostly caused by malnourishment (45%), Pneumonia (15%) diarrhea (8%), malaria (5%), and others (9%). Moreover, diarrhea disease is the major cause of malnutrition that contributes to a third major cause of under-5 mortality especially in developing countries. Further, globally 1.7 billion children are affected by diarrhea out of that more than half a million children die every year [5]. Universally, diarrhea remains one of the major health problems. In low- and middle-income countries, diarrhea is still a leading cause of death and health loss among children under the age of five. Evidence from Asian countries showed that early formula feeding increases the risk of childhood diarrhea. Similar evidence from sub-Saharan African countries has indicated that the early introduction of complementary foods and bottle-feeding was associated with the onset of diarrhea among infants and young children. This could be due to the substitution of complementary foods for irreplaceable human milk, as well as contamination of the food and/or the bottle's nipple [1,6]. The National Family Health Survey shows that the prevalence of childhood diarrhea has increased from 9% to 9.2% from 2016 to 2020 in India [7]. According to the latest survey (NFHS-5) conducted by the Ministry, only 60.6% of children under the age of five with diarrhea were given ORS and only 30.5% were given zinc.

This means that there is a lack of awareness among mothers [8,9]. Undernutrition and diarrhea have a bidirectional association. The diarrhoeal disease significantly affects the nutritional status by interfering with the intestinal absorption of nutrients, and, on the other hand, undernutrition might be a predisposing factor to the onset of diarrhoeal diseases by inducing an alteration of the host's immunity. Both pathologies in the same child significantly increase the risk of a child's death [10,11]. However, when children have SAM in addition to diarrhea, the complication of vomiting is presumed to be more fatal. The result of a study conducted by Faruk et al., [17] showed that death was significantly higher in children with diarrhea and severe malnutrition along with vomiting, compared to those without vomiting. The results emphasize the importance of prompt identification and management of SAM children having diarrhea and vomiting using rehydration therapy [18]. Prevention of dehydration is primarily achieved by ensuring that children with diarrhea are provided with more fluids than usual, and/or increased frequency of breastfeeding, during the acute episode. The combination of increased home fluids and the use of Oral Rehydration Salts (ORS) for the treatment of dehydration has proven to be a very powerful intervention for the prevention of childhood deaths from diarrhea [12,13]. Because of this, the Indian Academy of Paediatrics (IAP) Guidelines for the management of severe acute malnutrition have recommended the use of low-osmolarity ORS with added potassium supplements or preparing ReSoMal with low-osmolarity ORS as per WHO recommendation [14, 15].

Table 1: Comparison of formulations of oral rehydration solution (ORS)

	Old WHO ORS	**Standard (hypo-osmolar) WHO ORS**	**ReSoMaL (Rehydration solution for malnutrition)**
Sodium (Mmol/l)	90	75	45
Potassium (Mmol/l)	20	20	40
Chloride (Mmol/l)	80	65	76
Glucose (Mmol/l)	111	75	125
Osmolarity (mOsm/L)	311	245	300

ReSoMal is a Rehydration Solution for Malnutrition. It is a modification of the standard Oral Rehydration Solution (ORS) recommended by WHO. ReSoMal contains less sodium, more sugar, and more potassium than standard ORS and is intended for severely malnourished children with diarrhea [16,17].

To conduct a critical appraisal of available evidence and evaluate the use of different forms of oral rehydration solution (ReSoMal, hypo-osmolar ORS, old WHO ORS) in the treatment of dehydration in children with SAM.

MATERIAL AND METHODS

A search of online literature was performed. There were predetermined criteria, as detailed below for eligibility of studies, data outcomes, and an assessment of the risk of bias and study method quality in each of the identified studies

Selection criteria

Population: Children aged 0 to 5 years with SAM require oral rehydration solution for management of dehydration. We used the WHO definitions for malnutrition (Weight-for-height Z score <-3SD, mid-upper arm circumference (MUAC) 115 mm, 3 loose stools per day), and for dehydration. We excluded studies with chronic or persistent diarrhea lasting ≥ 14 days.

Search methods

Online database search: A comprehensive literature search of the following databases was conducted in December 2022 using the English search terms 'malnutrition' AND 'children' AND 'rehydration' AND 'oral' AND ReSoMaL on the following search engines: PubMed, Medline, Scopus, Cochrane Database of Systematic Review, ClinicalTrials.gov, Google Scholar. Each of the eligible studies was assessed and a manual review of the reference lists was carried out. Additionally, a Google search was performed. The authors screened the results of the literature search for studies that met the inclusion criteria as determined by the PICOS outline.

RESULTS

Selection criteria

The search produced 200 studies; after screening and evaluation, eight studies were identified that investigated oral rehydration solutions in children with SAM complicated by dehydration, incorporating a total of 1114 children.

Out of these studies, one was conducted in Korea, one in Egypt, three of which were conducted at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), and three in India (Hyderabad, New Delhi, and Calcutta). One study included children with and without SAM but reported

independently on outcomes for children with SAM. There was moderate heterogeneity in the population eligibility criteria, sample size, and methods employed by each study, and in their results. Table 2 and Table 3 show the setting, methodology, and features of the included studies and their results.

Table 2: Characteristics of included studies

Author	Location	Study type	Population	Sample size	Comparison group	Conclusion
Memon et al. [20]	Liaquat University Hospital, Hyderabad	RCT	Children aged 6 months to 59 months.	324	ReSoMaL versus low osmolar ORS	ReSoMaL and low osmolar ORS were similarly efficacious in the rehydration of severely malnourished children with diarrhea and dehydration
Kumar et al., [21]	Kalawati Saran Children's Hospital, New Delhi	Open RCT	Children aged 6–59 months	110	Low-osmolarity ORS with added potassium versus modified ReSoMal	Both types of ORS were effective in correcting hypokalaemia and dehydration, but rehydration was achieved in a shorter duration with modified ReSoMal.
Alam et al., [22]	ICDDR, B, Dhaka Hospital, Bangladesh	RCT (double-blind)	Children aged 6 to 36 months	126	Hypo-osmolar ORS with and without additional 15g/L PHGG (partially hydrolyzed guar gum)	PHGG added to ORS substantially reduces the duration of diarrhea. It also enhanced weight gain.
Alam et al., [23]	ICDDR, B, Dhaka Hospital, Bangladesh	RCT (Double-blind)	Children aged 6 to 36 months	130	Modified ORS (ReSoMaL) compared with standard WHO-oral rehydration solution (ORS).	ReSoMaL has a large beneficial effect on potassium status compared with standard ORS.
Dutta et al., [24]	Dr. BC Roy Memorial Hospital, Calcutta	RCT (double-blind)	Children aged 6 to 48 months	64	Hypo-osmolar ORS versus Old WHO ORS	Hypo-osmolar ORS has beneficial effects on the clinical course of dehydrating acute watery diarrhea in severely malnourished (marasmic) children. Furthermore, children did not become hyponatremic after receiving hypo-osmolar ORS.
Kim et al., [25]	Seoul National University Hospital, Seoul, Korea	Meta-analysis	Children aged 6–59 months	20 RCT	Reduced osmolarity ORS with WHO standard ORS	Reduced osmolarity ORS when compared to WHO ORS is associated with smaller stool volume and less vomiting.
Santosam et al., [26]	Abu El Reeche Hospital in Cairo, Egypt	Randomized double-blind clinical trial	Children aged 1 to 24 months	190	Reduced osmolarity oral rehydration solution (ORS) with standard ORS	The reduced osmolarity ORS has beneficial effects on the clinical course of acute diarrhea in children by reducing stool output, and the proportion of children with vomiting

Table 3: Methodology and results of included studies

Author	Methodology	Results
Shahbaz Ahmed Memon [20]	Randomisation, Group A was given ReSoMaL and Group–B was given low Osmolar ORS. Serum electrolytes were sent on admission and then again after 12 hours of giving rehydration solution, and the response was assessed based on laboratory investigations and clinical assessment.	Serum electrolytes were found equal in both groups without significant difference (P-value 0.51). This shows that ReSoMaL and low osmolar ORS were similarly efficacious in the rehydration of severely malnourished children
Kumar et al [21]	Enrolment, randomization (block randomization by computer-generated sequence), then clinical assessment, and blood samples taken. Other treatments as per WHO guidelines. Statistical analysis specified	Time for achieving rehydration was earlier in the ReSoMal group (16.1 vs. 19.6h, p=0.036) Median stool frequency is similar between groups. The frequency of hypokalaemia is similar (ORS vs. ReSoMal, 9.6 vs. 17%, p=0.25). The amount of ORS consumed was lower in ReSoMal (p=0.06)
Nur Haque Alam et al [22]	Eligibility was confirmed and then children were randomized. Children with severe dehydration were first treated with IV fluids and then randomized as soon as they were out of hypovolaemic shock and signs of severe dehydration resolved	The mean duration of diarrhea was significantly shorter in the PHGG group as compared to ORS (p=0.01). Stool weight was reduced in the PHGG group, but not significantly different. The mean time to attain WFL 80% was shorter in the PHGG group (p=0.027) Time to rehydration was not reported. No significant difference in treatment failure (P=0.69)
Nurul Alam et al [22]	Children enrolled and randomized (list provided by WHO Geneva and serially numbered). Clinical history was taken, and blood and stool samples were taken, plus urine and CXR if indicated. WHO standard protocol followed. Children received 10m/Kg/h first 2 hours and then 5ml/Kg/hour over 10–12 hours until the deficit was corrected. On-going stool losses also accounted for.	ReSoMaL corrected hypokalaemia in a greater proportion of children by 24 hours (36% vs 5%, P=.0006) and 48 hours (46% vs 16%, P=.004) compared with WHO-ORS. More children on ReSoMaL than WHO-ORS remained hyponatremia at 48 hours (29% vs 10%, P=.017).
Dutta et al [23]	Eligibility checked, consented, and clinical assessment done. Computer-generated randomization table used for allocation of ORS, held by an independent individual who provided ORS packets. Blood and stool samples were taken. Outcomes not pre-specified	Stool output (52.3v 96.6 g/kg/day), duration of diarrhea (41.5 v 66.4 hours), intake of ORS (111.5v 168.9 ml/kg/day), and fluid intake (214.6v 278.3 ml/kg/day) were significantly less in the hypo-osmolar group than in the standard ORS group. A total of 29 (91%) children in the standard ORS group and 32 (100%) children in the hypo-osmolar group recovered within five days of initiation of therapy.
Y Kim et al [24]	Meta-analysis of randomized controlled trials comparing reduced osmolarity ORS solution with the WHO formulation.	Reduced osmolarity ORS was associated with fewer unscheduled infusions compared with standard WHO ORS (Mantel Haenzel odds ratio 0.61, 95% confidence interval 0.47 to 0.81). Reduced osmolarity ORS when compared to WHO ORS is associated with smaller stool volume and less vomiting.
Alam et al [25]	Serially allotted the study ORS packet (pre-made and ordered by pharmacy according to randomization) – randomization process not specified. Outcomes not pre-specified. If severely dehydrated, they received 50ml/Kg RL in 1 hour before inclusion in the study. Then 75ml/kg ORS over 4 hours. Serial clinical assessments of dehydration.	Shorter duration of rehydration in the hyperosmolar ORS group as compared to WHO ORS, although not significant (10.95 hours vs. 11.72 hours, p=0.32, 95% CI 0.55-0.97) Stool frequency during rehydration was less (4.27 vs. 5.86, p<0.05)

Santosam et al [26]	Randomly assigned to receive either standard ORS (311 mmol/L) or a reduced osmolarity ORS (245 mmol/L). Intake and output were measured every 3 hours.	In the group treated with reduced osmolarity ORS, the mean stool output during the rehydration phase was 36% lower (95% confidence interval, 1%, 100%) than in those treated with WHO ORS. The relative risk of vomiting during the rehydration phase was significantly lower in children treated with reduced osmolarity ORS (relative risk, 2.4; 95% confidence interval, 1.2, 4.8).

Outcomes

Primary outcome

Hyponatraemia: This result was available from four research. Two of these compared old WHO ORS formulations with hypo-osmolar ORS [22,23]. Alam et al. (2000) only stated baseline lab values of 25; however, Dutta et al. (2001) stated no considerable variations in sodium at baseline and recovery [25,23], with sodium values staying within normal limits at recovery for both types of rehydration solutions. ReSoMal with old WHO ORS was compared by two studies [21,25]: the first concluded that 1/64 (2%) in the ORS group had severe hyponatremia (Na≤120mmol/L) in comparison to 3/62 (5%) children taking ReSoMal, with one of these three facing hyponatremia convulsions (serum sodium 108mmol/L). Serum sodium was analogous at the initial stage in both arms (p=0.51) but was less at 24 and 48 hours in the ReSoMal group. Another one [21] contrasted ReSoMal with hypo-osmolar ORS and stated that a large percentage of children in the ReSoMal category developed hyponatremia (15.4% vs. 1.9%, p=0.03).

Secondary outcomes

Mortality: This outcome was reported in two studies [26,18] reported no deaths during the trial periods.

Time to rehydration or recovery: Five of the research stated on time rehydration. One research study (Alam et al. 2009) observed no considerable change in time to rehydration between study groups. Two studies evaluated Old WHO ORS versus hypo-osmolar ORS [22,28] found that there was a faster recovery (passage of 2 consecutive formed stools or no diarrhea for 12 hours) in the group receiving hypo-osmolar ORS compared to old WHO ORS (36 vs. 53 hours, p=0.001). Alam et al. (2000) reported an average time to rehydration (though the method of assessment was not defined) of 10.95 hours in the hypo-osmolar category versus 11.7 hours in the old WHO-ORS category (p=0.32). Dutta et al. (2001) concluded quicker recovery in the hypo-osmolar category. Out of two research comparing WHO ORS (old or hypo-osmolar) with ReSoMal, one study reported a briefer time to rehydration in the ReSoMal category [21] (16.1 hours compared with 19.6 hours in the group taking hypo-osmolar ORS, p=0.036), whilst the Alam et al. (2003) study determined that both categories were uniformly rehydrated by both administrations [22].

Stool output: All the research studies reported on stool output, either by weight measurement of stools or nappies [22,23] or by recording incidence [26,21] Of the two research assessing standards with hypo-osmolar ORS, both concluded that the stool output was significantly less in the group taking hypo-osmolar ORS [25] stated that daily stool frequency was 4.27 compared with 5.86 episodes, p<0.05. Stool frequency was similar between the ReSoMal and hypo-osmolar ORS groups as reported by (25)(21).

CONCLUSIONS

Management of children with SAM and dehydration has limited evidence and does not support the WHO guidelines. There are arguments to support the use of hypoosmolar ORS in children with SAM, but the currently recommended ReSoMal exposes children with SAM to the threat of severe hyponatremia. Further studies should evaluate the use of standard hypo-osmolar ORS and ReSoMaL in children with SAM and assess optimal rates of rehydration to construct research evidence-based guidelines that are designed for the setting in which they will be used. It would be useful for research in India, given that very less of the available proofs relate to this population.

CONFLICT OF INTEREST

The authors declared no conflicts of interest about the work described in the present article.

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CITATION OF THIS ARTICLE

Manisha Rani, Indresh Kumar and Sunil Kumar T. Oral Rehydration of Malnourished Children with Diarrhoea and Dehydration: A Systematic Review. Bull. Env. Pharmacol. Life Sci., Vol 13 [4] March 2024: 75-81