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Wide variability in osmolality of reconstituted powdered oral rehydration salts due to disparity in the method of preparation among Indian consumers

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ABSTRACT

Oral rehydration salts (ORS) powder must be reconstituted accurately with water before consumption to avoid incorrect concentration (recommended osmolality: 245 mOsmol/kg). A consumer behavior study was conducted to understand the process of preparing ORS solution by respondents/caregivers; thereafter, the prepared solutions were tested for osmolarity. Respondents/caregivers (n = 120) from Bengaluru and Pune, who were prescribed ORS from three different brands, either in small (4.2–4.4 g in 200 ml water) or large sachets (21–21.8 g in 1,000 ml water) in the past 3 weeks, were enrolled. The quantity of water and powder, type of water, size of the ORS sachet, and preparation method were recorded. Prepared ORS solutions were tested for osmolality using the United States Pharmacopeia method <785>. Recorded osmolality showed wide variability, ranging from 30 to 1,331 mOsmol/kg. The majority of prepared ORS solutions (52/120, 43%) were >310 mOsmol/kg; 35/120 (29.16%) were in the range of 200–310 mOsmol/kg, and only 17/120 (14.16%) were in the reduced osmolality range of 210–268 mOsmol/kg. The volume of water and quantity of powder used ranged between 100–1,000 ml and 1.38–23 g, respectively. Respondents/caregivers reconstituted the powdered ORS as per their own preferences, regardless of labeled instructions. Reconstitution variations led to a deviation in the resulting osmolality of the ORS solution from the recommended value of 245 mOsmol/kg. Respondents/caregivers should be counseled on the correct method of reconstituting ORS powder and the potential adverse effect of incorrect concentration of ORS, if not prepared as per the labeled instructions.

INTRODUCTION

Diarrheal illnesses are the most common causes of dehydration and can lead to life-threatening complications in both adults and children worldwide, especially in developing countries (Diggins, 2008; Mortality and Causes of Death, 2016; World Health Organization, 2005). Globally, in children <5 years of age, diarrhea is the second leading cause of mortality accounting for ~ 0.7 million deaths annually (Sharma *et al*., 2020). Intravascular volume depletion is the important clinical manifestation of dehydration. Therefore, oral rehydration salts (ORS) solution, as recommended by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), is considered to be the first-line treatment for mild to moderate dehydration in both adults and children (Ahmed *et al*., 2000; Diggins, 2008; World Health Organization, 2019). For more than three decades, ORS has played a pivotal role in the reduction of mortality rate due to diarrheal disease (Gao *et al*., 2013; Sentongo, 2004). It has been estimated that the total diarrheal deaths in children have reduced from >4.6 million in 1980 to 1.3 million in 2008, due to the worldwide distribution of ORS (Santosham *et al*., 2010). In India, diarrheal deaths have declined

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from 2.5 million in 2001 to 1.5 million in 2012 (due to immunization, measures to control diarrheal diseases, and respiratory diseases) (Gandra and Farooqui, 2017). Despite this reduction in the mortality rate, diarrhea remains the third-most common cause of mortality in Indian children <5 years of age, with an estimated 0.3 million deaths every year (Children in India, 2018; Gandra and Farooqui, 2017). Although previously published studies reported less use of ORS in India, an increase of up to 51% was noted in the year 2018 (Children in India, 2018; Kamala *et al*., 1996; Singh *et al*., 1995; Sircar *et al*., 1991).

The WHO and the UNICEF recommended the use of a single standard formula for ORS (WHO-ORS) in 1975 with a total osmolality of 311 mOsmol/l (King *et al*., 2003). However, the acceptance of this formulation is limited as it does not reduce the duration of diarrhea or stool output (World Health Organization, 2019). Also, the slight hyperosmolar nature of the WHO-ORS solution compared with plasma (especially in young children and infants) may risk hypernatremia, or an osmotically driven increase in the stool output (World Health Organization, 2019). The European Society of Paediatric Gastroenterology and Nutrition recommends an ORS with an osmolarity between 200 and 250 mOsm/l, containing 60 mmol/l of sodium, for children in developed countries. The American Academy of Pediatrics (1996) suggests that an ORS containing 45–50 mmol/l of sodium can be used both for maintenance and rehydration in otherwise healthy children who are mildly or moderately dehydrated (American Academy of Pediatrics, 1996; Leung *et al*., 2006).

During the last few decades, various trials have been conducted to develop "improved" ORS by using approaches, such as adding sodium co-transporters like different amino acids or complex carbohydrates (Mahalanabis and Patra, 1983), or reducing the osmolality of the ORS solution (reducing the salt and glucose concentration) to overcome the adverse effects of hypertonicity on the net fluid absorption (World Health Organization, 2019). Another approach was to add glucose polymers, such as whole rice, wheat, sorghum, and maize. This polymer-based ORS aimed to slowly release glucose into the gut and improve salt and water absorption. However, there was insufficient evidence to show that polymer-based ORS was better than the sugar-salt ORS (≤270 mOsmol/l) (Gregorio *et al*., 2016). Notably, ORS solution with reduced osmolality (210-268 mOsmol/l) was found to be associated with a significantly reduced vomiting incidence (about 30%) and a reduced stool output (about 20%). This resulted in a lesser need of supplemental intravenous infusion (about 35%) in comparison with the standard WHO ORS in children with noncholera diarrhea (Hahn *et al*., 2001). In 2001, based on these findings and other studies, the WHO and the UNICEF recommended an ORS solution with reduced osmolality of 245 mOsmol/l, containing 75 mmol/l of sodium and glucose each, in the treatment of diarrhea, regardless of etiology and in all age groups (Sollanek *et al*., 2019; World Health Organization, 2006).

Although, there has been an increase in the usage of ORS in the South Asia region, unfortunately, it is evident that most caregivers still lack correct knowledge about preparation of ORS solutions (Abolurin *et al*., 2017; Osonwa Kalu *et al*., 2016; Victora *et al*., 2000). In most developing countries, ORS is available in the powder form in sachets, and must be reconstituted before consumption with a prescribed amount of water to attain the required osmolality (National Health Portal, 2015; Santosham and Greenough, 1991). Health professionals have now recognized that not only the use, but also the correct method of preparation/reconstitution and storage of solutions from ORS powders, is important for maximum efficacy and safety during diarrheal treatment (Abolurin *et al*., 2017; Ahmed *et al*., 2000; Sollanek *et al*., 2019). A highly concentrated ORS solution will surpass the threshold of the intestinal absorptive capacity, resulting in excess water loss. This leads to hypernatremia and dehydration, ensuing poor outcomes including mortality (Anand *et al*., 2017; Santosham and Greenough, 1991). On the contrary, ORS solution which is excessively dilute (with low sodium concentration), may cause rapid dilution of serum sodium concentration, and can lead to convulsions and water intoxication (Santosham and Greenough, 1991). Thus, it is crucial to ensure that, the prepared ORS solutions do not exceed the total osmolality of plasma, and also match the volume and composition to the loss sustained by the person with diarrhea (Santosham and Greenough, 1991; Rishi *et al*., 2003).

The current consumer behavior study was conducted to understand the common practices of preparing ORS solutions from powder ORS products by responders/caregivers, and thereafter, testing the osmolality of solutions in certified laboratories.

MATERIALS AND METHODS

This study was conducted among respondents/caregivers in two metro cities, Bengaluru and Pune, in India. To qualify for entry into the study, the participants had to be adults, or the mother of a child (aged 3–12 years), who had suffered from any illness for which the electrolyte/ORS powder was prescribed in the past 3 weeks; patients were not in active illness during the time of the interview. Respondents/caregivers were observed in-house while preparing the ORS solution, followed by a short face-to-face quantitative interview which was conducted by trained professionals.

A trained observer noted down the key points, such as quantity of water used, quantity of ORS powder used, type of water used, size of the ORS powder sachet, and the method employed by the respondents/caregivers in preparing the electrolyte solution. After ORS preparation, a short interview was conducted with the respondents/caregivers using a fixed questionnaire.

For both centers, the use of three different ORS brands in two different pack sizes, i.e., small sachet (4.2–4.4 g) and large sachet (21–21.8 g) were reported. A large sachet required powder contents to be dissolved completely in 1,000 ml of water, while a small sachet required 200 ml of water to achieve the recommended osmolality of 245 mOsmol/l, as per pack instructions. The composition of all the three ORS brand powders was noted to be as per the WHO-ORS recommendation (Table 1).

Table 1. Composition of the ORS powder.

Ingredients	Concentration (mmol/l)
Sodium	75
Potassium	20
Chloride	65
Citrate	10
Glucose, anhydrous	75
Total osmolarity	245 mOsmol/l

Data collection

The observations on the method of ORS preparation and the subsequent interview were carried out at the respondents/caregiver's home. The respondents/caregivers were asked to prepare the ORS powder as per their usual practice. Respondents/caregivers were given fresh packets/sachets of ORS powder, as per their previous prescriptions, and the steps of the reconstitution were recorded. Respondents/caregivers were free to choose the utensils and/or containers for measuring and collecting the ORS powder and water. Based on their usual practice, respondents/caregivers were instructed to take ORS powder as much required, or used regularly. Before reconstitution, the dry ORS powder was measured using a high accuracy balance. Following this, the ORS powder was required to be dissolved, taking water from the usual source (e.g., tap, filtered, or boiled water). The water quantity before reconstitution was measured using a calibrated measuring cylinder. The prepared ORS solutions were collected in airtight containers and tested at laboratories, accredited by the National Accreditation Board for Testing and Calibration Laboratories. The osmolality of the ORS solutions was recorded within 24 hours of the ORS solution preparation using the United States Pharmacopeia method <785>. Samples of water were also collected from the source used by the participants for water hardness testing. A total dissolved solids (TDS) meter was used in a testing lab for this analysis.

RESULTS

Demographics

Out of the 120 respondents/caregivers enrolled in the study, $n = 60$ were mothers of 3–12-year-old children and $n = 60$ were adults (>18 years) (Fig. 1). Of the respondents/caregivers, the majority were women (102/120). As per the interview, respondents/caregivers reported tiredness (85.0%), followed by diarrhea (63.0%), as the health conditions for which the electrolyte was mainly prescribed.

Osmolality of the reconstituted electrolyte solution from powdered ORS products

Overall, the electrolyte solution, reconstituted by respondents/caregivers, had a mean ± SD osmolality of 316.42 ± 185.43 mOsmol/kg. A total of 52/120 (43.3%) respondents/caregivers prepared a high osmolality electrolyte solution of >310 mOsmol/kg; only 35/120 (29.16%) of respondents/caregivers prepared an electrolyte solution, which was in range of 200-310 mOsmol/kg (as per the WHO and the UNICEF published criteria for ORS) (World Health Organization, 2006). None of the prepared electrolyte solutions resulted in the recommended osmolality of 245 mOsmol/kg. Few [17/120 (14.16%)] respondents/caregivers prepared an electrolyte solution, resulting in the reduced osmolality range of 210-268 mOsmol/kg for ORS (Fig. 2). For this, increased clinical benefit was observed versus higher osmolarity. Osmolality of the electrolyte solution obtained from Bengaluru ranged between 30 and 490 mOsmol/kg; likewise, the solution from Pune had the osmolality ranging between 80 and 1,331 mOsmol/kg.

Overall, 102/120 (85.0%) of the respondents/caregivers were prescribed a large sachet of the ORS powder. Of the 18/120 (15.0%) solutions prepared by respondents/caregivers who were prescribed a small sachet of the electrolyte, 4 (22.2%) were in the range of 200-310 mOsmol/kg, 3 (16.7%) were in the reduced osmolality range of 210–268 mOsmol/kg, and none of the prepared electrolyte solutions had osmolality >310 mOsmol/kg. The overall mean (SD) TDS of water was found to be 92.12 (79.69) mg/l, ranging between 0.13 and 378 mg/l. The overall tested and theoretically calculated osmolalities (i.e., based on premeasured ORS powder and water) were found to be in the range of 30–1,331 mOsmol/l and 125–1,621 mmol/l, respectively.

Compliance

To pack instructions

Majority (90%) of the respondents/caregivers used a glass jar to reconstitute the solution from the ORS powder. The quantity of water used for the large and small sachets ranged between 100–1,000 ml and 150–500 ml, respectively. The mean (SD) quantities of water used for the large and small sachets were 242.37 (133.53) ml and 245.17 (79.41) ml, respectively. The mean (SD) quantities of powder used for the large and small sachets were 8.7 (5.51) g and 8.4 (5.78) g, respectively. Overall, only 11% of the respondents/caregivers completely utilized the ORS powder from the sachet in preparing the solution.

As reported by the respondents/caregivers during the interview, majority (64%) of the respondents consumed the electrolyte solution in one go. The respondents who reported to consume the electrolyte solution in portions (36%), stored the

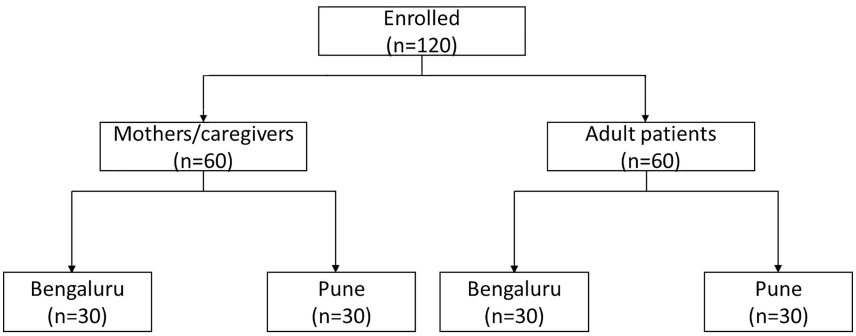

Figure 1. Study flow diagram of respondents/caregivers' enrollment.

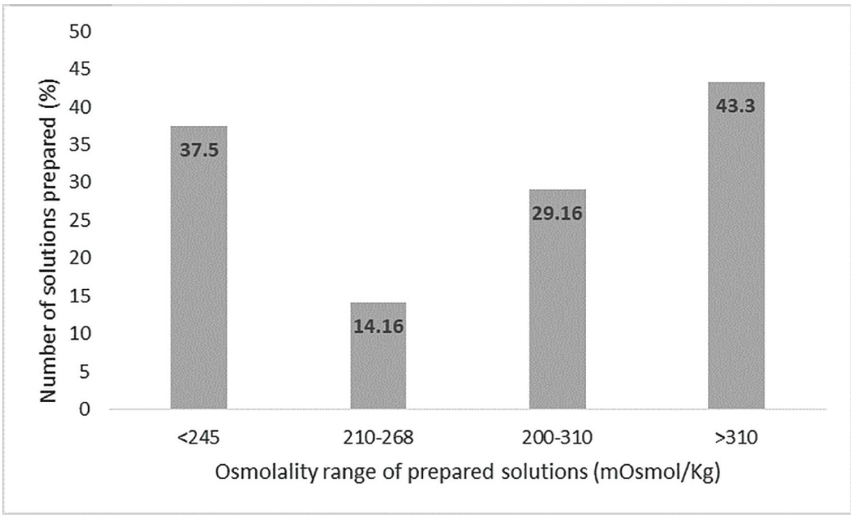

Figure 2. Osmolality of the reconstituted electrolyte solution.

leftover solution in the glass/plastic bottle/vessel used to prepare the solution. The leftover solutions were either stored inside the refrigerator (21%), or at room temperature (79%), until full consumption.

To prescription instructions

The electrolyte solution was prescribed by doctors, to the respondents/caregivers, for consumption in mean (SD) of 3.3 (1.5) days; it was consumed by the respondents/caregivers in mean (SD) of 3.2 (1.44) days, as per the interview.

DISCUSSION

ORS solution is a safe and effective therapy in the treatment of dehydration caused by diarrhea (Rishi *et al*., 2003; World Health Organization, 2019). As evidenced by nonclinical and clinical studies, osmolarity is a critically important factor for the net intestinal absorption of an electrolyte solution (Santosham *et al*., 1997). In place of the previously recommended ORS solution with a total osmolarity of 311 mOsm/l, ORS solution having a lowered osmolarity of 245 mOsm/l, containing 75 mEq/l of sodium and 75 mmol/l of glucose, is the ORS formulation officially recommended by the WHO and the UNICEF. This is because of its improved effectiveness (decreased need for IV therapy, reduced stool output, and reduced vomiting), especially for children with acute, noncholera diarrhea (World Health Organization, 2004, 2005). However, it has been noted in several studies that very few respondents/caregivers using ORS, especially mothers, were aware of the correct method to prepare an electrolyte solution (Abolurin *et al*., 2017; Osonwa Kalu *et al*., 2016; Rishi *et al*., 2003; Victora *et al*., 2000). The current consumer behavior study was, therefore, conducted to understand the common practices of preparing electrolyte solutions by Indian users of ORS, and to ascertain the resulting osmolality of the prepared solutions. About 29% of the prepared reconstituted electrolyte solutions were within an osmolality range of 200-310 mOsmol/kg. Majority (~43%) of the prepared electrolyte solutions resulted in osmolality scores above the recommended range (>310 mOsmol/kg); the results obtained were consistent with previously published studies (Abolurin *et al*., 2017; Bhatia *et al*., 1999; Osonwa Kalu *et al*., 2016).

Not surprisingly, none of the prepared electrolyte solutions resulted in the recommended osmolality of 245 mOsm/l. However, more importantly, only 14.16% measured within the reduced osmolality range of 210-268 mOsmol/kg for ORS, which is known to give additional benefits of reduced vomiting incidence (about 30%), reduced stool output (about 20%), and decreased need of supplemental intravenous infusion (about 35%) versus previous standard WHO ORS (200-311 mOsm/L) in children with noncholera diarrhea (Hahn *et al*., 2001).

The maximum osmolality of the electrolyte solutions reconstituted by respondents from Bengaluru (481 mOsmol/kg) and Pune (1331 mOsmol/kg) showed wide variations. A majority of the respondents/caregivers in this study were prescribed the large sachet of the ORS powder. Of these, majority of the prepared solutions were either high (>310 mOsmol/kg) or low (<245 mOsmol/kg) osmolality. On the contrary, among respondents/caregivers who were prescribed small sachets, majority of the prepared electrolyte solutions were <245 mOsmol/kg. This may be due to the wide variability observed in the amount of water used for reconstitution of the ORS powder in large and small sachets, required to attain the recommended osmolality of 245 mOsmol/Kg. These results are consistent with previous studies that explained confusion between two different sizes of electrolyte packets, leading to hypernatremic dehydration or even death (Kadam *et al*., 2013; Quereshi *et al*., 2010). Both large and small sachets tend to be reconstituted similarly. A very recent case study also depicted that hyperosmolar ORS solutions (>310 mOsmol/Kg) may result in electrolyte imbalance and intestinal mucosal damage or irritation, leading to gastrointestinal bleeding (Chung *et al*., 2020). Thus, it is clear that incorrect preparation of the ORS solution may lead to lack of efficacy, hypernatremia, and possibly, worsening of the diarrheal condition (Anand *et al*., 2017; Chung *et al*., 2020; Kadam *et al*., 2013; Quereshi *et al*., 2010). The source water (e.g., tap, filtered, or boiled) used to prepare

the ORS solution was tested with a resultant mean osmolality of 4.2 ± 2.21 mOsmol/kg. This can be considered to have minimal impact on the osmolality of the electrolyte solutions prepared in this study.

It was also observed that some respondents/caregivers did not carefully follow the labeled instructions, or may not have understood them clearly. Some employed a practice that may be considered ill-advised, i.e., tasting the prepared solution and adjusting it, either by adding ORS powder or water, based on personal taste preferences. This contributed to the deviation from the expected osmolality of the reconstituted electrolyte solutions. Previously published studies showed that caregivers who were given a demonstration of the electrolyte solution preparation were better able to prepare the solution correctly (Ahmed *et al*., 2000; Chowdhury *et al*., 1988; Gandra and Farooqui, 2017). Therefore, to prevent mixing errors, it is recommended that respondents/caregivers be counseled on the method of preparation of electrolyte solutions and the potential adverse effects of ORS, if not prepared as per labeled directions (Anand *et al*., 2017). They should be encouraged to utilize the complete dose of ORS to improve patient health. Also, these instructions should be introduced into routine health counseling sessions given to mothers at antenatal and immunization clinics, and over the mass media, if possible (Abolurin *et al*., 2017; Osonwa Kalu *et al*., 2016). With regard to the storage format, it is widely recognized that oral rehydration powders are easy to store, less expensive, and have a longer shelf-life than ORS solutions; however, they must be mixed accurately to ensure the correct glucose and electrolyte concentrations (Leung and Robson, 1989). As demonstrated in this study, the inaccurate calculation of the volume of water for dilution and the amount of powder used can result in an erroneous concentration of electrolytes. Also, most common households will not have containers to accurately measure the water for dissolving the ORS powder. This contributes to inaccuracy. For this reason, the Nutrition and Gastroenterology Committee recommends a premixed ORS over a powdered or homemade one (Leung *et al*., 2006). The issue of leftover liquid may be addressed by offering smaller ORS sachets. Similar to recommendations in other studies, the use of unique product presentations, such as premixed or ready-to-drink formulations, may also help address administration and dosing challenges (Digre *et al*., 2016).

The main strength of this consumer behavior study is that it identified many modifiable risk factors that may impact the osmolality of electrolyte solutions. However, the study has certain limitations, such as a small sample size. Further studies with larger sample sizes are required in this region. As the main objective of this consumer behavior study was to analyze common practices of ORS preparation and the resultant deviation from the ideal ORS osmolality, there was no recording of any clinical signs and symptoms of respondents administered with the ORS solution". Moreover, various aspects of the respondents'/caregivers' knowledge of diarrhea (e.g., awareness of the quantity of ORS to be taken or given to their child and hygienic practices) and other related factors (e.g., socioeconomic class of the study participants) were not included in the study. This study focused mainly on the resultant osmolarity of the ORS solution, after the respondents/caregivers reconstituted the powdered ORS.

The current study, therefore, recommends to counsel respondents/caregivers on the correct method of reconstituting the ORS powder before consumption and potential adverse effects of the incorrect concentration of ORS, if not prepared as per labeled instructions. Respondents/caregivers should be encouraged to use the complete dose of ORS to improve patient's health. The study also recommends the use of ready-to-drink ORS if possible.

CONCLUSION

This study demonstrated that respondents/caregivers reconstituted electrolyte solutions using the powdered ORS as per their own preferences, regardless of the instructions on the sachet. Variabilities in the methods of reconstitution resulted in the osmolality of the electrolyte solution to deviate widely from the recommended value of 245 mOsmol/kg. Osmolality was expectedly impacted by the quantity of the powder ORS and the water used, whereas TDS/hardness of water had little to no impact on the osmolality of the electrolyte solution.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the development, review, and final approval of this manuscript. MR, CS, and CT contributed to the concept, design, and data interpretation of this manuscript. MR and CS contributed to data acquisition. MR conducted statistical analysis; CS participated in supervision. All authors had access to the study data, provided guidance and inputs on the manuscript; agreed to submit this manuscript in the current journal; provided final approval of the version to be published; and also agreed to be accountable for all aspects of the work. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria and all those who fulfilled those criteria are listed as authors.

CONFLICT OF INTEREST

MR, CS, CT, PT, and AC are employees of Johnson and Johnson group of companies (Consumer Health Division), who have food products under the category "electrolyte drinks" but no product under the ORS/solutions category.

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ETHICAL APPROVAL

Ethical approval was not required as this is a noninterventional, retrospective, observational study.

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