

**A COMPARATIVE STUDY OF HYPO-OSMOLAR AND
STANDARD ORS SOLUTIONS IN TREATING CHILDREN
WITH PERSISTENT DIARRHOEA ADMITTED TO
MULAGO HOSPITAL.**

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**A Dissertation submitted in partial fulfilment of the requirements for the
award of the academic degree of Master of Medicine in Paediatrics and
Child Health of Makerere University**

2003

DEDICATION

I wish to dedicate this work to my wife, Rose, who endured my long hours away from home and my children Mercy and Victor who missed a lot of playtime while I was at work.

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DECLARATION

I declare, to the best of my knowledge, that this dissertation has not been submitted for a degree in any University or institution of higher learning or for any publication either in part or in full. All work is original unless otherwise acknowledged.

..... 25/7/2003

Date

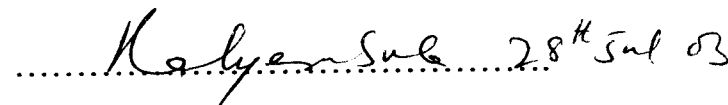
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ACKNOWLEDGEMENTS

To compile a monograph of this nature requires a dedicated team and I am truly indebted to those who gave this project so many undivided hours of attention.

I thank the Almighty God through Jesus Christ my Lord for bringing me this far and enabling me to put this work together.

My main gratitude goes to my supervisors *Dr. G.W. Zirembuzi* and *Dr. I. Kalyesubula* who encouraged and guided me during the project/protocol formulation and thesis writing. I am very grateful for their intelligent, comprehensive, and patient supervision to improve my work.

For the patient follow up, I thank the nurses and staff of C.S.T.U of Mulago Hospital for their consistency.

I thank the Department of Paediatrics and Child Health, and the Faculty of Medicine, Makerere University *that gave me the opportunity to do this study*

I thank *Asoc. Prof J.K.Tumwine and Dr. Addy Kekitiinwa* for coordination of the postgraduate course and all my fellow postgraduate students who contributed to the enrichment of my work.

I thank the Ministry of Health of Uganda for paying my school dues.

I thank the Nuffield foundation for its financial support.

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LIST OF ABBREVIATIONS

WHO	World Health Organisation
UNICEF	United Nations Children's Fund
ORS	Oral rehydration salts
<i>G-ORS</i>	<i>Glucose-based ORS</i>
C.S.T.U.	Child Survival Training Unit.
Na	Sodium
K	Potassium
Mg	Magnesium
KCl	Potassium chloride
ORT	Oral Rehydration Therapy
ACU	Acute Care Unit
IV	Intravenous
ml	millilitre
IMCI	Integrated Management of Childhood Illnesses
IVI	Intravenous infusion
MOH	Ministry of Health

DEFINITION OF TERMS

Diarrhoea: referred to the passage of 3 or more loose or watery stools in a 24-hour period, a loose or watery stool being one that would take the shape of a container.

Acute diarrhoea; referred to diarrhoea that starts suddenly, lasts less than 14 days and involves passage of frequent loose or watery stools.

Some dehydration, referred to a child with diarrhoea and any two of the following signs; irritability or restlessness, sunken eyes, drinks eagerly and skin pinch returns slowly.

Persistent diarrhoea; referred to diarrhoea that begins acutely and lasts at least 14 days.

Severe persistent diarrhoea; referred to persistent diarrhoea with dehydration.

Dehydration; refers to excessive loss of water and electrolytes from the body tissues.

Malnutrition; in this context referred to weight/height <-2 standard deviations (SD) of the National Center for Health Statistics (NCHS) reference value.

Hypoglycaemia; was defined as blood glucose less than 40 mg/dl or 2.2 mmol/l.

Standard ORS is the WHO/UNICEF ORS.

Hypo-osmolar ORS, in this study was obtained by mixing one standard ORS sachet with 1.5 L of clean drinking water.

Diarrhoea Stopping was defined as a 72-hour period without any watery motion.

Treatment failure was defined as developing severe dehydration during the study period or diarrhoea not stopping after 7 days of follow up.

Efficacy; referred to the ability of the ORS solution to produce maximum positive effects on the course of persistent diarrhoea.

ABSTRACT

Background: -

In 1991, the WHO and UNICEF estimated that persistent diarrhoea accounted for 10% of all diarrhoea episodes in the under fives and that it accounts for 30 –50% of the about 2.2 Million diarrhoea-related deaths per year in the under 5 age group. Dehydration is one of the risk factors for mortality in persistent diarrhoea among others. Standard ORS solution, which is the main mode of management of dehydration, has shown no significant effect on the duration of diarrhoea or on the volume of stool output in children with acute diarrhoea but a few studies done on hypo-osmolar ORS solution in persistent diarrhoea have shown some beneficial effects. This study aims to further evaluate the effect of hypo-osmolar ORS solution on the course of persistent diarrhoea in children admitted to Mulago hospital.

Objective: - To compare the effects of hypo-osmolar and standard ORS solutions in treating children with persistent diarrhoea.

Design: - The study was a randomised double blind clinical evaluation.

Study setting: -The study was carried out in diarrhoea treatment ward of Mulago hospital, a national referral and teaching hospital.

Study Population: - The study population was children aged between 6-60 months admitted to Mulago hospital with persistent diarrhoea during the study period.

Methodology: - Children satisfying the inclusion criteria had a history taken and physical examination done. Blood for serum sodium and potassium was obtained on admission, Day 3 and Day 7. The children were randomly assigned to treatment with either standard ORS or hypo-osmolar ORS solution. They were followed up to a maximum of seven days and were assessed for duration of diarrhoea, duration of rehydration, stool frequency, ORS volume intake per child and changes in the electrolyte profiles.

Study Results: - A total of 69 children aged 6 to 60 months were recruited, 35 were assigned to hypo-osmolar ORS and 34 to standard ORS solution. The groups were similar in their baseline characteristics. There was no difference in the mean duration of diarrhoea between the treatment arms ($p = 0.08$) and there was no statistically significant difference in the recovery rates between the two groups ($p=0.12$). The differences in the stool frequency, the duration of rehydration, the serum sodium, the serum potassium and ORS consumption were not statistically significant in the two treatment arms. There was no worsening of the electrolyte status in either treatment arms.

Conclusions: In the treatment of children with persistent diarrhoea, hypo-osmolar ORS is as efficacious as standard ORS solution.

Recommendation: Hypo-osmolar ORS solution can be used interchangeably with standard ORS solution in treating children with persistent diarrhoea. However due to small numbers, a larger study is recommended to further evaluate the impact of hypo-osmolar ORS solution on the course of persistent diarrhoea.

CHAPTER ONE

BACKGROUND AND LITERATURE REVIEW

1.1 Introduction

With improved management of acute episodes of diarrhoea, increased attention is now being given to persistent diarrhoea, its nutritional consequences and associated mortality.^{1, 2, 3} It is known that malnutrition has a strong relationship with increased duration and severity of diarrhoea, reduced intestinal enzyme activity and loss of normal mucosal integrity. The ineffective villous repair or prolonged mucosal injury in children can be a potential cause for persistent diarrhoea.⁴

For the past 25 years, oral rehydration therapy has greatly improved and simplified the treatment of acute diarrhoea.^{5, 6} The oral glucose electrolyte solution recommended by WHO and UNICEF effectively restores and maintains the hydration status of patients with acute diarrhoea.⁷ Standard ORS solution is cheap and widely available. However, standard ORS solution raises the problem of acceptance because the formulation does not reduce the volume, frequency of stools or the duration of the diarrhoea episodes.^{8, 9, 10, 11} The composition of this oral rehydration solution remained a subject of great controversy, especially with regard to the sodium concentration and total osmolarity.^{12, 13} These considerations have prompted efforts to develop an ORS formulation that would reduce the duration of diarrhoea. The American Academies of Paediatrics, Gastroenterology and Nutrition, and the European Society of Paediatrics, Gastroenterology and Nutrition while recognizing the efficacy/safety of standard ORS solution, recommended the use of solutions containing no more than 60 mmol/l of sodium and a total osmolarity between 200-250 mmol/l for prevention of dehydration or for use after dehydration has been corrected.^{12, 13} Recent studies have demonstrated that the stool output and the duration of diarrhoea were reduced in children with diarrhoea who used reduced osmolarity ORS solution compared with children who received the standard ORS solution.^{14, 15, 16, 17} Consequently in May 2002, a meeting of experts jointly organised by UNICEF and WHO agreed to promote a reduced osmolarity ORS formulation with osmolarity of 245 mmol/l, glucose of 75 mmol/l and sodium of 75 mmol/l for the management of dehydration in acute diarrhoea.¹⁸

Hypo-osmolar G- ORS (Glucose-Based ORS) solutions have shown beneficial effects on the course of persistent diarrhoea in children with reduction of the duration of the diarrhoea

episode, the volume of ORS intake and the risk of unscheduled IV infusions.^{19,20} Stopping of the diarrhoea is the primary desire of the parents and caretakers. The reduction of the duration of diarrhoea implies fewer days of hospitalisation, less volume of ORS intake, lesser risk of dehydration, lesser risk of malnutrition and ultimately reduction in economic and social costs, and diarrhoea related deaths.

Hypo-osmolar ORS solution containing Na⁺ 60 mmol/l, K⁺ 14 mmol/l, Cl⁻ 53 mmol/l, citrate 7 mmol/l, and glucose 74 mmol/l, osmolarity 208 mmol/l is obtained by mixing one standard ORS sachet with 1.5 L of clean drinking water. This solution has been found beneficial on the course of persistent diarrhoea.²⁰

1.2 Persistent Diarrhoea Epidemiology

The prevalence of persistent diarrhoea shows a wide variation in the developing countries and it is estimated that 3-30% of acute diarrhoeal episodes become persistent.²¹ WHO puts the average incidence of acute episodes becoming persistent at 10%.²² Several studies in Africa have found different prevalence values; in Kenya 16.5%²³, Ethiopia 5.0%²⁴ and Nigeria 11.7%²⁵. In Papua New Guinea prevalence was 20%.²⁶ Persistent diarrhoea accounts for 30 % of hospital admissions in developing countries and unpublished data reveals that persistent diarrhoea constituted 16% of admissions onto C.S.T.U, a diarrhoea treatment ward, of Mulago hospital in the year 2000.

Age related distribution of persistent diarrhoea shows the largest majority falling below 24 months. In Papua New Guinea the peak age was 12-23 months²⁶, in Kenya less than 12 months²³ and Ethiopian children ranged 7-12 months²⁴. A study in Uganda found a peak age of 5-11 months.²⁷

1.3 Mortality and Morbidity in Persistent Diarrhoea

Among children with diarrhoea, the proportion of persistent diarrhoea is much lower than acute diarrhoea, but death due to persistent diarrhoea accounts for more than half (52%) of the total diarrhoea-related deaths.²⁸ WHO estimates that 15% - 35% of the episodes of persistent diarrhoea result in death.^{22,29} a study in India found that 22.4% of persistent diarrhoea episodes resulted in death,³⁰ while in Pakistan 4% of persistent diarrhoea patients died.³¹ In a Kenyan hospital based study, the mortality was 31.7%.²³

Dehydration is one of the risk factors for mortality, other factors include malnutrition (mainly moderate and severe), over 12 stools /day, indiscriminate use of antibiotics, bacteraemia, septicaemia and stool volume >100g/kg/day.³¹

1.4 Oral Rehydration Therapy Historical background

In the late 1940's Harrison in Baltimore Maryland and Darrow in New Haven Connecticut developed the first oral rehydration solution.³² This ORS solution was designed for the economically disadvantaged populations with cholera. These solutions were less invasive and reduced the need for hospitalisation. Harrison's solution contained (in mmol/l): sodium 62, Potassium 20, Chloride 52, Lactate 30 and glucose 183 (3.3% w/v meaning 3.3 g of glucose dissolved in 100 ml of water). The first field-testing of these solutions was performed initially in rural Bangladesh,³³ and later in India during an episode of cholera affecting war refugees.³⁴ Concern was eventually raised whether a solution designed for rehydration in severe secretory diarrhoea such as cholera would be appropriate for the rehydration of a less severe gastroenteritis.³⁵

In 1975, the WHO and UNICEF agreed to promote a single solution (WHO-ORS) containing (in mmol/l): sodium 90, Potassium 20, Chloride 80, base (bicarbonate) 30, glucose 111 (2.2% w/v).

1.5 Physiological and clinical Basis

In the 1950's and 1960's, researchers delineated in various animal tissues, later human tissue, and in vivo systems the molecular process of co-transport. During this process, the absorption of one sodium ion was linked with that of one glucose molecule at the intestinal brush border.³⁶ It was later demonstrated that other organic molecules such as amino acids, dipeptides, and tripeptides contribute to this co-transport phenomenon and that this remained intact in acute diarrhoea.³⁷ Stools of cholera patients are lower in potassium and higher in sodium concentration than those of patients with rotavirus or Enterotoxigenic E.Coli.³⁸ Yet when the fluid volume loss is high, the threat to the circulation is greatest hence the need for sodium in the replacement solution is increased.

1.6 Clinical Studies on WHO ORS

From the late 1960's to the late 1970's, numerous clinical studies were conducted in developing countries to evaluate the safety and efficacy of various ORS solutions for the treatment of acute diarrhoea.³⁹ A solution with sodium content 90 mmol/l was tested, and shown to be safe and efficacious in treating non-cholera diarrhoea.⁸ On the basis of these studies, the WHO recommended the use of this solution. In the late 1970's, other concerns about standard ORS solution surfaced when rotavirus was identified as an important cause of diarrhoea. Since rotavirus causes a diffuse enteropathy that is sometimes associated with glucose mal-absorption, the appropriateness of standard ORS solution was questioned.^{40, 41} However further researches found this solution to be as good in all children with acute diarrhoea.⁴²

1.7 Clinical studies on Hypo-osmolar G-ORS

In more chronic diarrhoea, sodium losses may be met easily by allowing fluids normally consumed to be taken as desired, but potassium losses may supersede sodium losses in importance hence a solution with higher potassium concentration. Recent studies suggest that the currently recommended formulation of ORS by WHO may not be optimal and those solutions containing lower concentrations of sodium and glucose may be more effective.^{14, 43} Some studies have found patients with blood sodium above the normal level of 150 mmol/l following rehydration with standard ORS solution.⁴⁴ Laboratory work suggests that lower concentration of sodium and glucose enhance a better solute induced water absorption.^{45,42} Other studies have demonstrated that the stool output and the duration of diarrhoea were reduced in children with acute diarrhoea who used reduced osmolarity G-ORS solution compared with children who received the standard ORS solution.^{10, 16, 46} Systematic review of reduced osmolarity G-ORS solution for treating diarrhoea found it to be more effective than standard ORS solution as the first line treatment of children with acute diarrhoea. It reduced the need for unscheduled intravenous infusions, the stool output and vomiting during the rehydration phase.

CHAPTER TWO

PROBLEM STATEMENT AND STUDY OBJECTIVES

2.1 Problem Statement

Persistent diarrhoea accounts for only 10% of the diarrhoea episodes²² but as many as 30-50 % of diarrhoea related deaths in children less than 5 years of age. In Africa the prevalence of persistent diarrhoea is between 5 % and 16.5%.^{23,24} Prolonged duration of a persistent diarrhoea episode often worsens the nutritional status of children which is strongly related to persistent diarrhoea and increases the risk of death.³ Dehydration is prominent among the risk factors for mortality and morbidity in persistent diarrhoea.³¹ Standard ORS has been successful in reducing mortality in acute diarrhoea but it does not reduce the amount of stools and duration of diarrhoea while hypo-osmolar G-ORS solutions has been shown to reduce the duration of diarrhoea, the amount of stools and episodes of vomiting in treatment of both acute and persistent diarrhoea in children.^{19, 47} Unfortunately this treatment regimen known to reduce stool output and promote early recovery in persistent diarrhoea has not been studied in Uganda, and is therefore hardly used. There is therefore lack of awareness of hypo-osmolar ORS solution in treatment of children with persistent diarrhoea in Mulago hospital.

2.2 Justification

Following several studies to evaluate the impact of hypo-osmolar ORS solutions on the course of acute diarrhoea, WHO has formulated hypo-osmolar ORS for rehydration of children with acute diarrhoea. It is therefore important to assess the effect of hypo-osmolar ORS solution on the course of persistent diarrhoea.

The few studies done to evaluate the impact of hypo-osmolar ORS solution on the course of persistent diarrhoea seem to show that it is superior to standard ORS solution. There is therefore need for further research.

No research has been done in Uganda on the impact of hypo-osmolar ORS solution on the course of persistent diarrhoea, a solution that has shown benefits in promoting early recovery of persistent diarrhoea. The efficacy of hypo-osmolar ORS solution in treatment of children with persistent diarrhoea admitted to Mulago hospital is therefore not known. This study

therefore aims to evaluate the efficacy of hypo-osmolar ORS solution compared to standard ORS solution in treating children with persistent diarrhoea admitted to Mulago hospital in order to bridge the knowledge gap on the benefits of hypo-osmolar ORS solution.

2.3 Research Questions

1. What is the effect of hypo-osmolar ORS and standard ORS solutions on the duration of diarrhoea and stool frequency in children with persistent diarrhoea?
2. What is the effect of hypo-osmolar ORS and standard ORS solutions on the time taken to achieve full rehydration and on the electrolyte status of children with persistent diarrhoea?
3. What are the volumes of hypo-osmolar ORS and standard ORS solutions required for the rehydration of children with persistent diarrhoea?

2.4 Hypothesis

Hypo-osmolar ORS solution is as efficacious as standard ORS solution in the treatment of children with persistent diarrhoea.

2.5 OBJECTIVES

2.5.1 General objective:

To compare the efficacy of hypo-osmolar ORS solution with standard ORS solution in the treatment of children with persistent diarrhoea admitted to C.S.T.U of Mulago hospital.

2.5.2 Specific objectives:

1. To compare the effect of hypo-osmolar ORS and standard ORS solutions on the duration of diarrhoea and stool frequency in children with persistent diarrhoea.
2. To compare the effect of hypo-osmolar ORS and standard ORS solutions on the duration of rehydration and electrolyte status of children with persistent diarrhoea.
3. To compare the effect of hypo-osmolar ORS and standard ORS solutions on the volume intake of ORS in the rehydration of children with persistent diarrhoea.

CHAPTER THREE

METHODOLOGY

3.1 Study Design

The study was a randomised double blind clinical evaluation that was carried out on children with persistent diarrhoea and some dehydration who were admitted to C.S.T.U of Mulago hospital.

3.2 Study Setting-

The study was hospital based and it was carried out in C.S.T.U of Mulago hospital, a national referral and teaching hospital. C.S.T.U is a Paediatrics ward that specializes in the management of children with diarrhoeal diseases and is the main centre for IMCI training of Mulago hospital. The site of recruitment was A.C.U, the Paediatrics emergency unit of Mulago hospital. All children with severe medical conditions are first seen in A.C.U, admitted overnight and transferred to one of the main Paediatrics wards the following day if they are not well enough to be discharged. The unit receives children from the assessment centre of Mulago hospital, referrals from health units in and around Kampala City, Wakiso and Mpigi districts which areas are mostly served by Mulago hospital.

3.3 Study Population-

The study population included children aged 6-60 months admitted onto C.S.T.U of Mulago hospital with persistent diarrhoea during the study period.

3.4 Study period

The study took place between September 2002 and February 2003.

3.5 Selection Criteria

3.5.1 Inclusion criteria

1. Children with persistent diarrhoea and dehydration admitted to C.S.T.U of Mulago hospital during the study period.
2. Children aged 6-60 months
3. Children with consent from parents or caregivers

3.5.2 Exclusion criteria

1. Children with obvious severe illnesses such as; severe pneumonia, Meningitis (As defined by WHO).⁴⁸
2. Children who needed intravenous rehydration.
3. Children with grossly visible blood in stool.

3.6 Sampling Procedure

3.6.1 Enrolment and Randomisation

The nurse at the triage of A.C.U of Mulago hospital identified the children with persistent diarrhoea. These children were then re-screened by the principle investigator and included in the study once they met the eligibility criteria. Informed written consent was obtained from parents or caregivers of the children who met the eligibility criteria before inclusion into the study. The enrolment was done by consecutively until the sample size was achieved. The recruited children were immediately transferred to C.S.T.U where they had a clinical history taken, physical examination done and the findings recorded on a standardized questionnaire by the principle investigator. Block randomisation method was used to assign children to receive either of the 2 solutions, according to random numbers generated by a Computer. A statistician grouped the computer-generated numbers into two predetermined blocks with equal numbers of patients. The principle investigator did not know the total number of patients in each block. Each block contained equal numbers of patients. Each number was then assigned a treatment code. The statistician then sealed the number and the treatment code in an opaque envelope.

The sealed envelopes that had the treatment codes were kept in a lockable cupboard on C.S.T.U to which the treatment nurse had a key.

The parent or caregiver picked one envelope and handed it to the treatment nurse who then administered the solution the patient was assigned according to the treatment code found in the envelope. The envelopes were identical in appearance. The code was kept by the statistician and was only broken after analysis of the data was completed.

3.7 Sample Size Estimation

An appropriate sample size calculation for clinical trials was used.⁴⁹

In the formula the following abbreviations are used

n = Sample size

s = Standard deviation (SD)

Z_{β} = is the standard normal value corresponding to the required power of the Study (power of 90% $Z_{\beta} = 1.28$)

Z_{α} = Is the standard normal value corresponding to level of significance ($p \leq 0.05$ $Z_{\alpha} = 1.96$)

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 \times (s_1^2 + s_2^2)}{(M_1 - M_2)^2}$$

M_2 = Mean duration of diarrhoea among the hypo-osmolar ORS group (114.8 hrs)

M_1 = Mean duration of diarrhoea among the standard standard ORS group (145.4 hrs)

s_2 = SD for duration of diarrhoea in hypo-osmolar ORS group(38.3 hrs)

s_1 = SD for duration of diarrhoea in standard ORS group(40.0 hrs)

These values are derived from a similar randomised controlled clinical trial.¹⁸

$$n = \frac{(1.96 + 1.28)^2 \times (38.3^2 + 40.0^2)}{30.6^2}$$
$$= 34$$

This means 34 patients in each group giving a total of 68 patients.

3.8 Data Collection

3.8.1 Study Instrument

A standardized questionnaire written in English was used as the study instrument. The principle investigator administered the questionnaire (appendix B) in the language the parents/caregivers understood well.

3.8.2 Measurements

The variables measured were recorded on a questionnaire. These included clinical history, physical examination, laboratory tests, follow up and treatment outcome.

3.8.2.1 Clinical History

When the parents/caregivers agreed to participate in the study, the principle investigator obtained a full clinical history including patient identification (study serial number, age sex,), whether breast-feeding or not, duration of diarrhoea, frequency of stools in the last 24 hours, consistency of stools, history of vomiting and number of vomiting episodes in the last 24 hours, history of fever, history of abdominal distension, history of antibiotic use, duration of treatment (days), ORS use before admission, history of persistent diarrhoea in last 3 months, number of persistent diarrhoea episodes in last 2 months, measles immunization, history of measles in last 3 months.

3.8.2.2 Clinical Examination

A general physical examination was done with emphasis on the hydration status and anthropometry on all the enrolled children. To minimize observer variation, the principle investigator did all the measurements. The weight was taken using a Salter spring scale manufactured by SALTER England, model 235 6S. The scale was hanged up securely from a beam with the dial at eye level to minimise errors in reading. The scale was adjusted to point to zero with the empty pair of weighing pants in position to account for their extra weight. The child was undressed and placed in the weighing pants. The child was placed on the scale by

hanging the pants on the lower hook making sure the feet are off the ground. The weight was read to the nearest 0.1 kg and recorded.

The length was measured using stadiometer manufactured by Shorr Productions, Irwin J. Shorr, Maryland 20832, USA. The child was laid on the board, the head was put firmly against the fixed head board, and the knees were extended with the feet at right angles to the lower leg with the help of an assistant. The sliding foot piece was moved to obtain firm contact with the heel, and the length read to the nearest millimetre.

Using the midpoint between the acromion and olecranon process, the mid upper arm circumference was measured using a non-stretch fibreglass tape for children above 1 year of age. The information was also recorded on the structured questionnaire. The nutritional status was graded using WHO criteria (appendix E).

3.8.2.3 Laboratory Measurements

Blood: After cleaning the site using a 5% chlorohexidine antiseptic solution, 2 millilitres of blood were drawn from the dorsum of the hand or cubital fossa vein by the principle investigator. Blood was drawn on Day 0, 3, and 7 of the study depending on the patient's length of stay in the study. The sample was centrifuged and stored at temperature of 4 – 8°C till the serum sodium and potassium analysis were tested within and not exceeding 1 week. A Laboratory Technologist in the Mulago hospital Clinical Chemistry Laboratory did the serum electrolyte analysis using an automated flame photometer manufactured by Instrumentation Laboratory, Italy model 09438-04. The results of every sample were crosschecked using human sera controls to ensure accuracy and consistency.

3.8.2.4 Outcome Measures

The major outcome measures of this study were; duration taken to full rehydration, duration of diarrhoea, daily frequency of stools, changes in the electrolyte profiles and ORS volume intake per child.

3.8.3 Assessment of Dehydration

The detection of dehydration was based entirely on signs observed when the child was examined according to WHO guidelines.⁵⁰ The signs that were evaluated in every patient were as follows:

- **Condition and behaviour:** Was the child well or alert, restless or irritable, lethargic or unconscious. It was sometimes difficult to determine whether the child was abnormally lethargic or just sleepy. This was decided by waking up the child.
- **Eyes:** Were the child's eyes: normal or sunken. Whenever we were not sure whether the eyes were normal or more sunken than usual, this was decided by asking the mother/caregiver.
- **Thirst:** The children when offered a drink, were observed whether they:
 - Drank normally, accepted the fluid without particular eagerness, or refused to drink.
 - Drank eagerly, grasped the cup or spoon, or were unhappy when the cup was removed.
 - Were unable to drink or drank poorly, because they were lethargic.
- **Skin pinch.** When the skin of the abdomen was pinched and released, it was assessed whether the fold flattened and disappeared immediately, slowly or very slowly (i.e. taking more than 2 seconds).

3.8.3.1 Determination of the degree of dehydration

The signs that indicated dehydration were organized to determine the degree of severity. Two or more signs in a patient determined the degree of dehydration, according to IMCI classification of children with diarrhoea.⁵⁰

- **Severe Dehydration**

If any **two** of the following signs:

- Lethargic or unconscious.
- Sunken eyes.
- Inability to drink or drinking poorly.
- Skin pinch returns very slowly.

- **Some Dehydration**

If any **two** of the following signs:

- Irritable or restless.
- Sunken eyes.
- Drinks eagerly.
- Skin pinch returns slowly.

- **No Dehydration**

If there is no enough criteria for either severe dehydration or some dehydration, conclude that the patient has no dehydration.

3.8.3.2 Assessment Of Dehydration In Severe Malnutrition

Assessment of hydration status in severely malnourished children was difficult, because a number of the signs normally used are unreliable. The signs therefore used for detecting dehydration included: **dry mouth and tongue**, and **eagerness to drink** (for children with Some Dehydration); or **very dry mouth and tongue**, **cool and moist extremities**, and **weak or absent radial pulse** (for Severe Dehydration).⁵¹

3.8.4 Case Management

Preparation of the solutions:

The ORS solution was prepared by mixing 1 pre-packed coded packet with 3 L of water. The packets were prepared by a pharmacist from the Mulago hospital pharmacy department and sealed in airtight plastic bags and clearly labelled either 'A' or 'B'. For the hypo-osmolar ORS he packed 2 WHO ORS sachets and for standard ORS he packed 3 WHO ORS sachets. An independent nurse not involved in the study kept the packets. This independent nurse was trained by the pharmacist how to mix the solutions. The solutions were prepared according to stipulated instructions (Appendix G).⁵²

Table 1. Composition of the ORS solutions used in the study.

	Standard ORS	Hypo-osmolar ORS
Sodium (mmol/l)	90	60
Potassium (mmol/l)	20	14
Chloride (mmol/l)	80	53
Citrate (mmol/l)	10	7
Glucose (mmol/l)	111	74
Osmolarity (mosmol/l)	311	208

The solutions were mixed daily by an independent nurse and kept in well-labelled identical containers. The containers were clearly labelled either 'A' or 'B' in capital letters. The two solutions were completely identical in appearance to any observer.

Rehydration of the patients:

After assessment and determination of dehydration, the children were assigned solutions in accordance with WHO guidelines⁵³ in which treatment is based on the assessment of dehydration status. The parents or caregivers were counselled not to share the ORS solutions and to follow the treatment protocol as explained by the treatment nurse. The treatment nurse personally gave the rehydration solutions to the parents/caregivers after checking which treatment solution the child is on. The volume of ORS solution was measured at 75 ml/kg to be given over 4 hours with hourly evaluation by the nurse during the rehydration phase. The treatment nurse provided a measured amount of the ORS solution to the mother. The mothers were instructed on how to give the ORS solutions and supervised closely by the treatment nurse. To minimize spilling, the mothers used a spoon to give the ORS solutions. If a patient vomited more than 3 times during the first 4-hour period, a nasogastric tube was used to administer the fluid. If the child achieved rehydration before the end of the 4-hour period, they were switched to the maintenance phase immediately. If the child still had some dehydration by the end of the 4-hour period, the cycle was repeated until there was no dehydration and the time taken to achieve full rehydration recorded. Full rehydration was deemed achieved when there were no enough criteria to diagnose some dehydration. If the child developed signs of

severe dehydration, ORT was terminated, intravenous therapy instituted, patient withdrawn from the study and analysed as a treatment failure.

During the maintenance phase, the ORS solution volume was estimated at 10 ml/kg per diarrhoea motion to cover stool losses till the diarrhoea ceased (defined as a 72 hour period during which no diarrhoea stool was passed). Beyond the prescribed amount of ORS solution, the children were given more of the ORS solution whenever they wanted to drink and the volume recorded. The children were fed as soon as possible after rehydration and in any case not later than 4 hours from initiation of rehydration.⁵⁶ Breastfed infants were allowed to continue breastfeeding throughout the follow up. Children below 6 months were not included in the study because they were more likely to be exclusively breastfed and therefore could not be subjected to the uniform diet. A rice porridge diet of 132.5 g/kg/24 hours divided in 6 feeds/24 hours to provide 110 kcal/kg/24 hours was given to all the children (Appendix D). The rationale for this uniform diet was to avoid the confounding effect of different foods on the outcome of persistent diarrhoea since it is known that nutritional rehabilitation is the mainstay of management of persistent diarrhoea.⁴

The follow up period was 7 days. The patients were followed up till either when they developed severe dehydration, their diarrhoea ceased, when parent/caregiver withdrew consent or after completing 7 days, whichever was earlier. The patients who developed severe pneumonia because they could not drink well and bloody diarrhoea because they needed a different protocol of treatment were withdrawn from the study. All data collected on these children were included in the analysis. Antibiotics were used in one child who had urinary tract infection. Treatment failures were those children who developed signs of severe dehydration while on ORT, and those who had persistence of diarrhoea for longer than 7 days after start of the treatment protocol. All children received Vitamin A treatment unless they had received a dose in the previous 3 months. Zinc was not supplemented because it is not routinely given on C.S.T.U ward of Mulago hospital.

Follow up and recordings:

- a) The volume of ORS intake was recorded every 1 hour in the rehydration phase and then 8 hourly in the maintenance phase till the end of follow up.
- b) Signs of dehydration were monitored and recorded every 1 hour in the rehydration phase and then 8 hourly in the maintenance phase to the end of follow up.
- c) The number of stools was recorded 4 hourly in rehydration phase and 8 hourly in maintenance phase.
- d) The numbers of vomiting episodes were recorded every 8 hours.
- e) Body weights were taken at admission and every 24 hours till end of follow up.
- f) Blood samples were drawn on day 0, 3 and 7, for serum Sodium and Potassium if the children were still in the study.

The treatment nurse did the recordings.

3.9 Data Management

Data was entered using Epi-info 2002 and analysis was done using both Epi-info 2002 and SPSS 10.0/PC by a statistician. Analysis was by 'intention to treat' principle. The code was broken when the analysis was completed. Each of the variables was explored with descriptive statistics, and the distributions of continuous variables were assessed for normality. Baseline variables among the treatment groups were analysed by independent Student t test for normally distributed continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Mann Whitney U test was used for data that was not normally distributed. The proportions of children ceasing from diarrhoea with time were compared using the Kaplan-Meier survival analysis. The duration of diarrhoea, duration of rehydration, and daily stool frequency were compared using the Student t Test. Pearson's χ^2 or Fisher's exact test, when appropriate, was used to determine differences in the proportions of children with cessation of diarrhoea, unscheduled intravenous therapy and treatment failure. The electrolyte changes during the study period were compared using the Paired Sample t test. Data was summarised in form of proportions and frequency tables for categorical variables, means, medians and clustered bar charts for continuous variables. In all cases, $P \leq 0.05$ was considered statistically significant.

3.10 Quality Control

1. The questionnaire was Pre-tested and standardized by the investigator before data collection.
2. The ORS powder was pre-packed by a pharmacist and mixed by an independent nurse not involved in the study ward to ensure complete blinding.
3. Competent treatment nurses trained in IMCI and working on the diarrhoea ward of Mulago hospital were sensitised and given instructions on data collection before the study began.
4. A Competent laboratory technician from the department of clinical chemistry of Mulago hospital main laboratory did the serum analysis for sodium and potassium. The serum was separated within 15 minutes of the specimen collection.

3.11 Ethical Considerations

3.11.1 Institutional Consent

Consent was obtained from the following institutions namely: Makerere University Department of Paediatrics and Child Health, Faculty of Medicine research committee, Mulago hospital administration and Uganda National Council for Science and Technology.

3.11.2 Informed Consent

The study was explained to the parents/caregivers of the children and all the benefits and risks were explained in the language they understood well. Confidentiality was assured to the parents/caregivers. Written consent was voluntarily obtained by signature or thumb on the consent form (Appendix A) indicating acceptance to participate in the study. The parents/caregivers reserved the right to withdraw from the study as and when they wished.

3.12 Dissemination of Results

- The results will be disseminated to the Makerere University, Department of Paediatrics and Child Health.
- Sir Albert Cook Library, Makerere medical school.
- Child Health division, Ministry of Health Uganda.
- The School of Postgraduate Studies Makerere University.

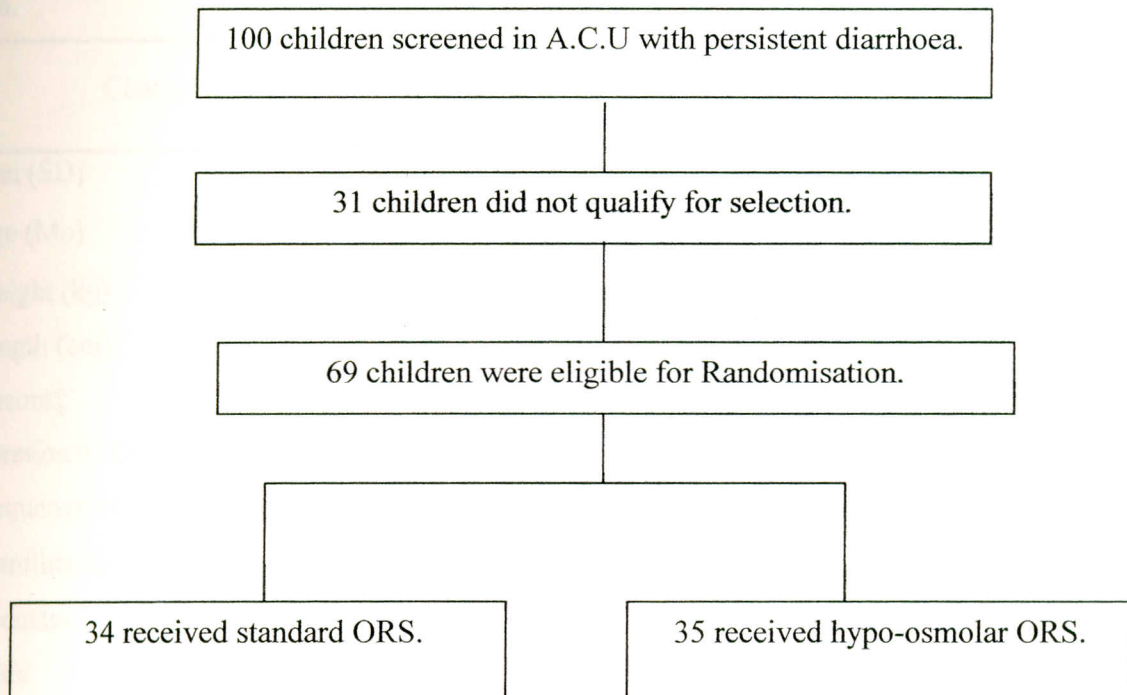
CHAPTER FOUR

4. RESULTS

A total of 100 children with persistent diarrhoea were screened in A.C.U of Mulago hospital during the study period. Sixty-nine children aged 6-36 months met the inclusion criteria and were enrolled in the trial; 34 were randomised to receive standard ORS solution and 35 were randomised to receive hypo-osmolar ORS solution.

Figure 1.

Trial profile of the Randomised controlled evaluation of hypo-osmolar and standard ORS solutions



Four children were withdrawn from the study after enrolment and before day 7 of follow up. They had all been started on standard ORS. Reasons for withdrawal included: the parents of 1 child withdrew consent 24 hours after enrolment; 2 children developed severe pneumonia and were withdrawn 48 hours after enrolment because they were not able to drink well; 1 child developed dysentery after 96 hours and was withdrawn because bloody diarrhoea was an exclusion criteria and the child needed another treatment protocol. All data collected on these children up to the time of withdrawal was included in the analysis and analysed using 'intention to treat' principle.

4.1. Baseline characteristics

The characteristics on admission were similar between the two groups (Table 1). Of the 69 children recruited 22 (31.9%) were female and 47(68.1%) were males. Among the females 11 received standard ORS and 11 received hypo-osmolar ORS while 23 males received standard ORS and 24 received hypo-osmolar ORS. Their ages ranged from 6-36 months with the 52.2% below 11 months, 40.6 % between 12 –23 months, 5.8% between 24-35 months and 1.4 % were above 36 months. There was no statistically significant difference in the age distribution between the two groups (p=0.5, ANOVA).

Table 2. Characteristics on Admission for the 69 children in the Randomised controlled trial.

Characteristic	Standard ORS n=34	Hypo-osmolar ORS n=35	p value
Mean (SD)			
Age (Mo)	13.5 (6.8)	11.6 (4.9)	0.18
Weight (kg)	6.8 (1.6)	6.7 (1.2)	0.69
Length (cm)	71.5 (6.0)	70 (5.2)	0.27
Z score‡	-2.4 (1.08)	-2.2 (1.05)	0.37
Duration of Diarrhoea in days	17.5 (5.8)	20 (7.5)	0.12
Frequency of stools in last 24 hrs.	7 (2)	6 (2)	0.17
Vomiting episodes in previous 24 hrs	2 (3)	2 (2)	0.98
Percentage			
Sex			
F	33.3	31.4	
M	66.7	68.6	1.0 ^a
History of measles in last 3 months	16.7	20.0	0.73*
Measles immunisation	47.1	37.1	0.4 ^a
History of ORS before admission	93.3	91.4	1.0*
Chest crackles	8.8	8.6	1.0*
B/Feeding	96.7	94.3	1.0*
Wasted & stunted	14.7	25.7	0.26 ^a
Severe wasting	23.5	28.6	0.63*

*Fisher's exact test.

^a Pearson's χ^2 test.

‡ weight for length

p < 0.05 considered significant

The mean serum electrolytes were comparable between the two groups. There was no difference in the proportions of children with the various levels of electrolytes except for a statistically significant difference in the children who had both hypokalaemia and hyponatraemia (Table 3).

Table 3. Serum Electrolyte Profile on Admission in the Randomised controlled trial (n=69)

Characteristics	Standard ORS n = 34	Hypo-osmolar ORS n = 35	p value
Mean (SD)			
Serum Sodium	132.4 (6.2)	132.0 (7.2)	0.8
Serum Potassium	3.4 (0.9)	3.2 (0.7)	0.3
Percentage			
Hyponatraemia	32.4	40	
Normal Sodium	67.6	60	0.5
Hypokalaemia	55.5	60.0	
Normal Potassium	38.2	37.1	0.8*
Hyperkalaemia	5.9	2.9	
Both hypokalaemia & hyponatraemia	9.4	31.4	0.027*

*Fisher's exact test.

4.2. OUTCOMES

Overall there was no statistically significant difference in the outcome measures between the two treatment arms as shown in Table 4.

Table 4. Major Outcome Variables for 69 children in the Randomised controlled trial

Variable	Standard ORS	Hypo-osmolar ORS	p value
Mean time to Diarrhoea cessation (Hours)	98.4 ±64.9	87.5±68.1	0.5
No. (%) of children with Diarrhoea cessation by Day 7.	14 (41.2)	21 (60)	0.12 ^a
Median time to full rehydration in hours (range)	7.5 (2-36)	7 (2-55)	0.7‡
No. (%) of children rehydrated in <8hrs.	15(44.1)	17(48.6)	0.7 ^a
Median total Stool Freq. (range)	24 (1 - 82)	16 (2 - 85)	0.8‡
Median total ORS Vol. in ml/kg (range)	280.9 (51-778)	206.3 (52.5-854)	0.8‡
Treatment failure.	13	14	0.8
Treatment Failure with need for IVI	9	11	
Treatment Failure with no need for IVI	4	3	0.67*

^a Pearson's χ^2 test

*Fisher's exact test

‡Mann Whitney U test

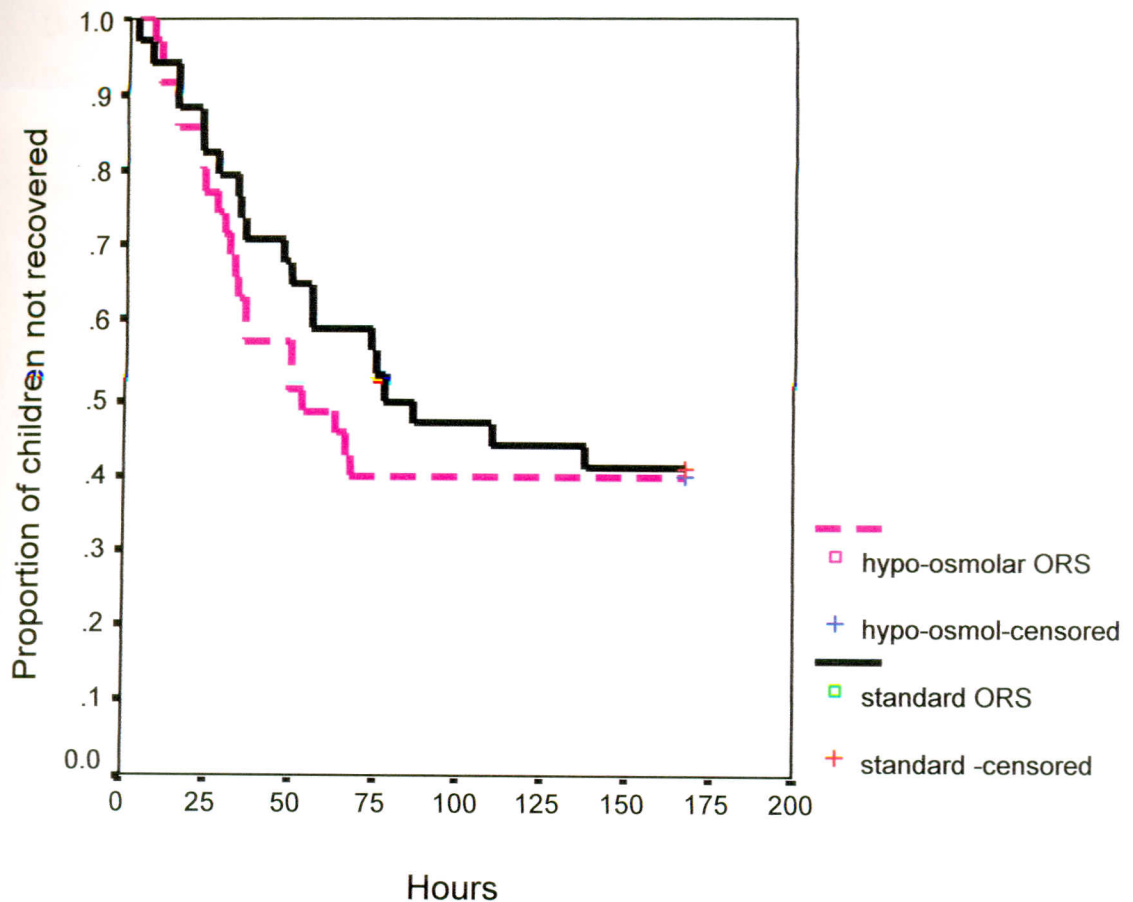
(Significant p<0.05)

Duration of diarrhoea

The mean time to the cessation of diarrhoea was shorter in the children who received hypo-osmolar ORS than in those that received standard ORS (87.5 ± 68.1 hrs Vs 98.4 ± 64.9 hrs), but the difference did not reach statistical significance, ($p = 0.5$, Student t test), (Table 4). There was no statistically significant difference in the numbers of children with cessation of diarrhoea within the seven days of the study period in the two treatment arms (RR 0.6 95%CI 0.4-1.1, $p = 0.12$ Pearson's χ^2 test).

Using the Kaplan-Meier analysis there was no statistical difference between the children who received hypo-osmolar ORS solution and those children who received standard ORS solution ($p=0.7$ log rank test).

Fig 2. Kaplan-Meier curve for the time to the cessation of diarrhoea in children treated with the two ORS solutions.



Stool frequency

The median total number of diarrhoea stools passed during the hospital stay were fewer in children who received hypo-osmolar ORS than in those who received standard ORS solution, but the difference was not statistically significant ($p = 0.8$, Mann Whitney U test). There was a day-to-day variation in the median number of stool frequency with no statistically significant difference throughout the follow up as shown in Table 5.

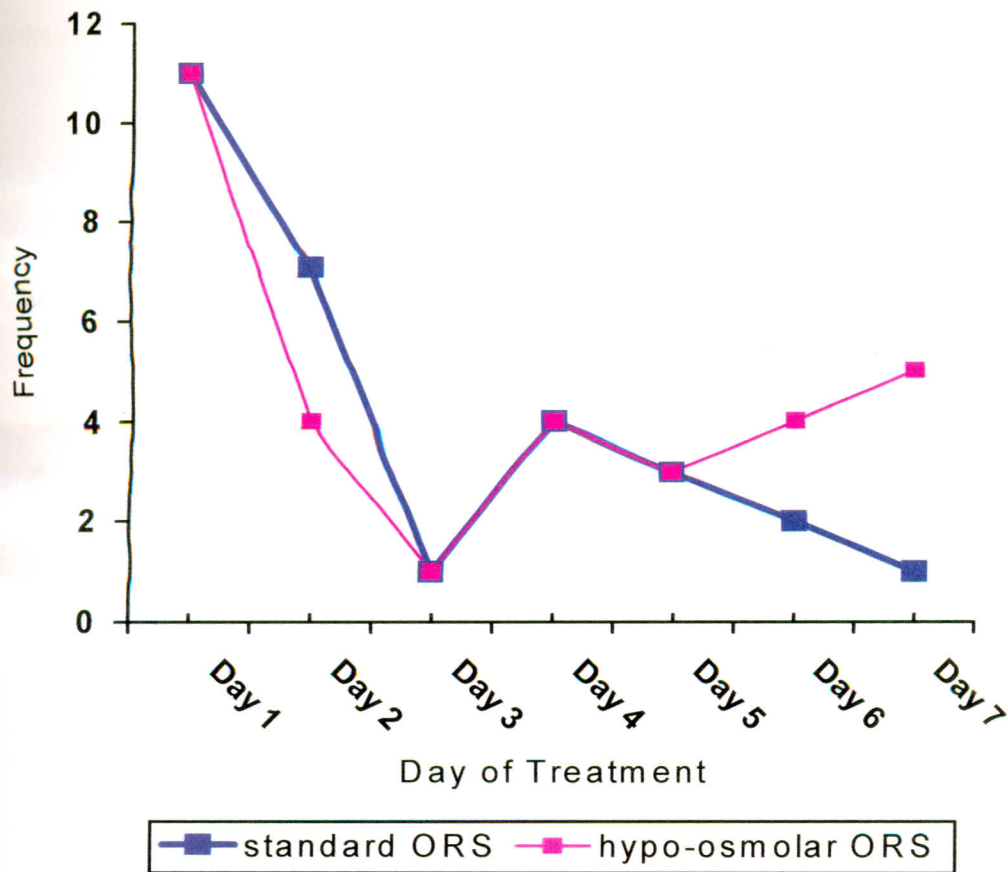
Table 5. The median Stool frequency of children treated with the two ORS solutions

Stool frequency	Standard ORS (Range)	Hypo-osmolar ORS (Range)	p value*
Day 1 n=69	9 (1-32)	9 (2-32)	1.0
Day 2 n=69	5 (0-26)	3 (0-12)	0.15
Day 3 n=60	6 (0-28)	4 (0-17)	1.0
Day 4 n=57	6 (1-14)	9 (0-19)	0.6
Day 5 n=49	6 (0-10)	6 (0-16)	0.7
Day 6 n=25	5 (2-12)	7 (3-19)	0.2
Day 7 n=13	3 (2-4)	9 (5-12)	0.1

*Mann Whitney U test.

There was a similar trend in the stool frequency in both treatment arms Day 4 of follow up as shown in Figure 3. Thereafter a trend of increasing purging rate was noted in the hypo-osmolar ORS treatment arm but a decreasing trend among the standard ORS treatment arm was observed.

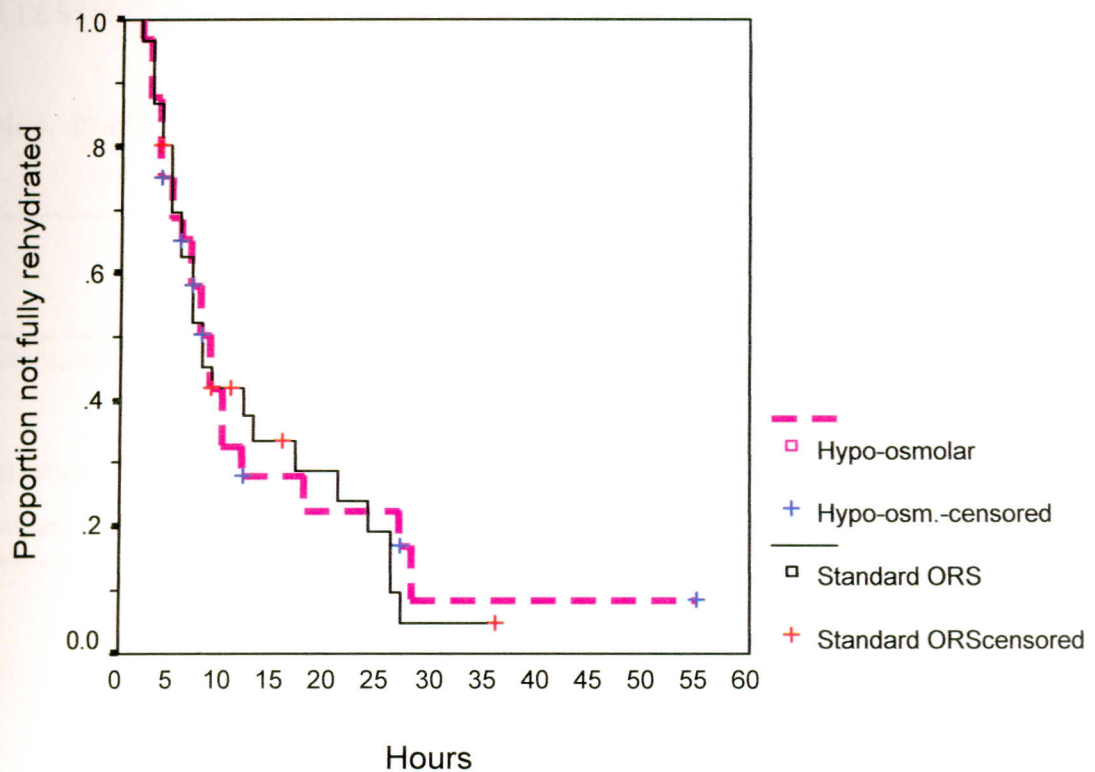
Figure 3. The mean daily stool frequency in the children treated with the two ORS solutions.



Time taken to achieve rehydration

The median duration of rehydration was 7.5 hours (2-36 hours) among children who received standard ORS Vs 7 hours (2-55) among those who received hypo-osmolar ORS solution as shown in Table 3. The difference was not statistically significant ($p = 0.7$, Mann Whitney U test). The difference in the number of children who achieved full rehydration in less than 8 hours was not statistically significant between the two groups (RR 0.9 95% CI 0.6-1.5, $p=0.7$ Pearson's χ^2 test). The Kaplan-Meier survival analysis for the duration of rehydration between the two groups showed no statistically significant difference in proportions of children rehydrated with time, (log rank test $p = 0.79$) as shown in Figure 4.

Fig 4. Kaplan-Meier curve for the time to achieve full rehydration in children treated with the two ORS solutions.



Electrolyte status

The difference in the mean serum sodium and serum potassium concentration on day 3 was not statistically significant between the standard and hypo-osmolar ORS groups as shown in Table 6.

On admission, total of 13 children had both hypokalaemia and hyponatraemia, of these 2 were in the standard ORS arm and 11 in the hypo-osmolar ORS arm [OR 1.83 95% CI 1.26-2.66, $p = 0.015$, Fisher's exact test].

By day 3, three patients still had both hyponatraemia and hypokalaemia (1 in standard ORS vs 2 in hypo-osmolar ORS) (RR=0.5, 95% CI 0.05-5.6, $p=1$, Fisher's exact test), two were treatment failures with need for intravenous infusion (all from the hypo-osmolar ORS treatment arm), two recovered (1 from the hypo-osmolar ORS and 1 from the standard ORS arm), 3 had hyponatraemia and 3 had hypokalaemia. There was no association between having both hyponatraemia and hypokalaemia, and treatment failure by day 3 of treatment, (RR 1.6 95 % CI (0.35-7.34) $p = 0.6$, Fisher' exact test).

Table 6. Profile of electrolytes on Day 3 of treatment in the Randomised controlled

	Standard ORS (mmol/l)	Hypo-osmolar ORS (mmol/l)	p value
Mean serum sodium	133.5±7.6	135±4.9	0.46
Mean serum Potassium	3.6±0.8	3.4±0.6	0.19

When the proportions of children with either hyponatraemia or hypokalaemia on admission and on Day 3 were compared, there was a reduction in the proportions of children with hyponatraemia and hypokalaemia by day 3 in both treatment arms as depicted in Figures 5 and 6.

On day 3 of treatment, a total of 17 children were out of study, 8 in the standard ORS treatment arm (5 had improved Vs 3 who were failures on treatment) and 9 in the hypo-osmolar ORS treatment arm (5 had improved and 4 were failures on treatment).

The difference in the proportions of children with hyponatraemia on day 3 of follow up between the two treatment groups was not statistically significant (RR=2.06, 95 CI 0.35-13, p = 0.6, Fisher's exact test). Similarly the difference in the proportions of children with hypokalaemia on day 3 of follow up between the treatment groups was not statistically significant (RR=0.8, 95%CI 0.8-1.57, p = 0.8, Pearson χ^2 test).

Fig 5. The distribution of hyponatraemia in children treated with the two ORS solutions on Days 1 and 3.

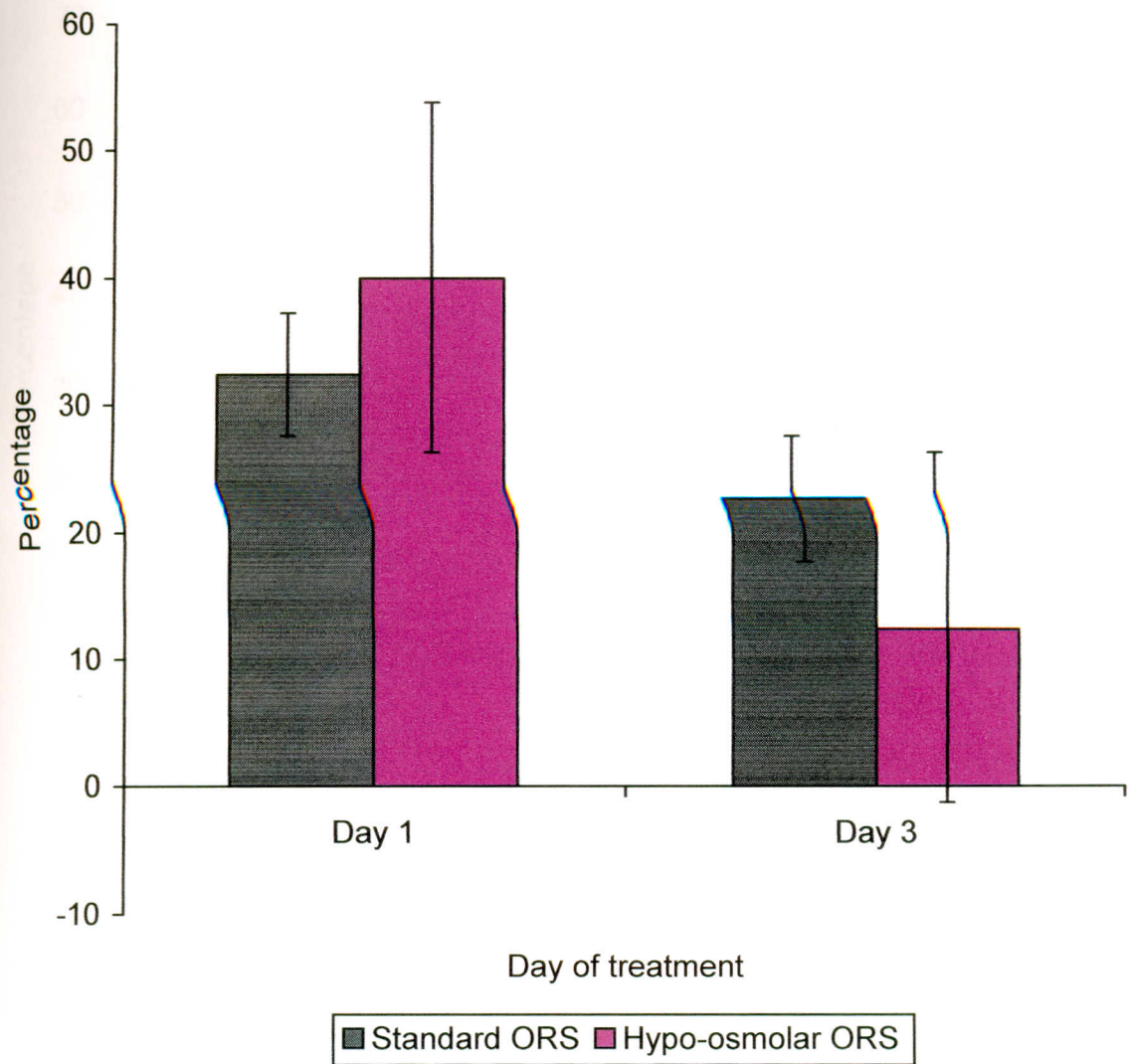
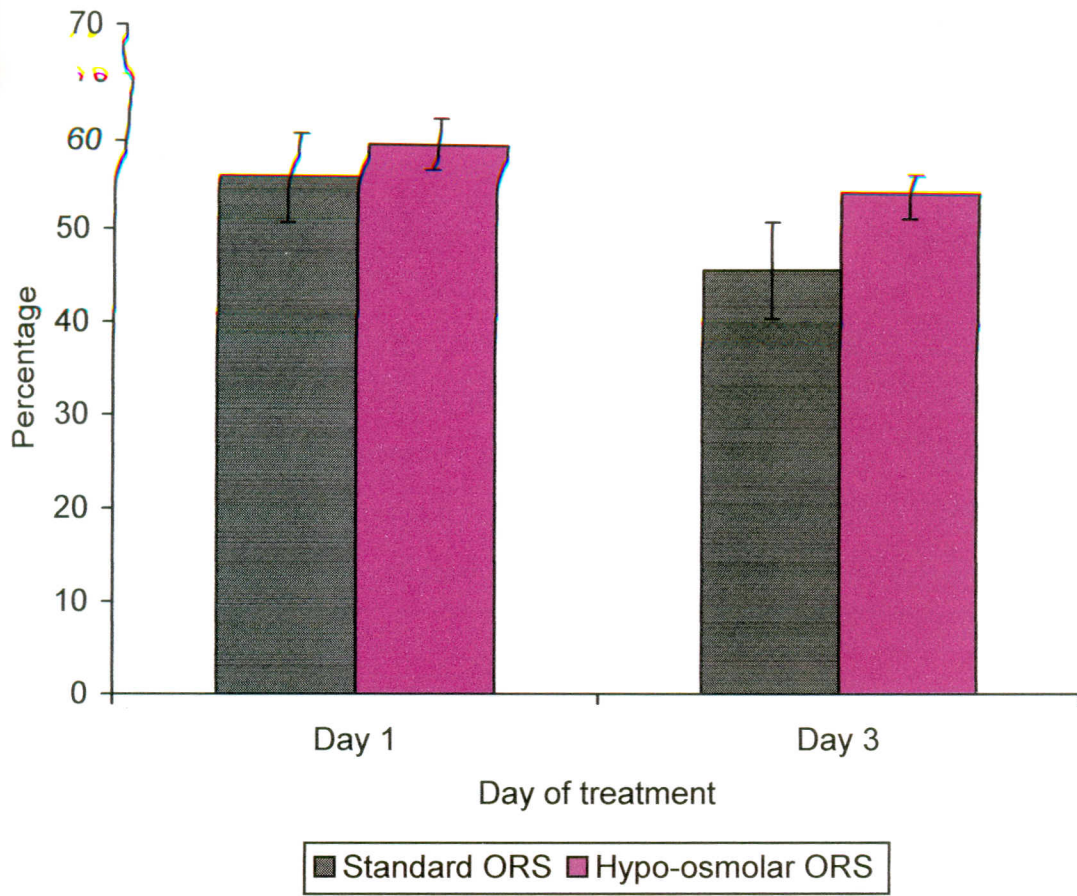


Fig 6. The distribution of hypokalaemia in children treated with the two ORS solution on Days 1 and 3.



The electrolyte levels were compared between those on admission and those on day 3, and there was no worsening in electrolyte profiles by day 3 of follow up as shown in Table 7.

Table 7. Comparison of electrolytes on Admission and on Day 3 of treatment

	Standard ORS			Hypo-osmolar ORS		
	Admission n =35 (%)	Day 3 n =25 (%)	p value+	Admission n =35 (%)	Day 3 n =27 (%)	p value+
Hyponatraemia	11 (32.4)	5 (22.7)	0.34	14 (40)	3 (12.5)	0.5
Normal	23 (67.4)	17 (72.2)	0.95	21 (60)	21(87.5)	0.92
Hypokalaemia	19 (55.9)	10 (45.4)	0.38	21 (60)	13 (54)	0.2
Normal	13 (38.2)	11 (50)	0.5	13 (37.1)	11(45.8)	0.16

+ Paired Sample T test.

There was 9.7 % reduction in the proportion of children with hyponatraemia in the standard ORS solution arm ($p = 0.34$, Paired sample t test) compared to the 27.5 % reduction in the hypo-osmolar ORS arm ($p = 0.5$, Paired sample t test)) on day 3 of treatment.

There was 10.5 % reduction in the proportion of children with hypokalaemia among children treated with standard ORS solution ($p = 0.38$, Paired sample t test) compared to a 6 % reduction in hypo-osmolar treatment arm ($p = 0.2$, Paired sample t test) on day 3 of treatment.

There was an increase in the proportion of children with normal potassium levels from 38.2 % to 50% in the standard ORS solution arm and an increase in the proportions of children with normal potassium levels in the hypo-osmolar ORS arm from 37 % to 45.8%.

Volume of ORS intake

There was no statistically significant difference in the median total ORS consumption in ml/kg per child between the children who received standard ORS and those who received hypo-osmolar ORS solution, $p = 0.8$, Mann Whitney U test, as shown in Table 8.

Table 8. Volume in ml/kg of ORS intake in the Randomised controlled trial

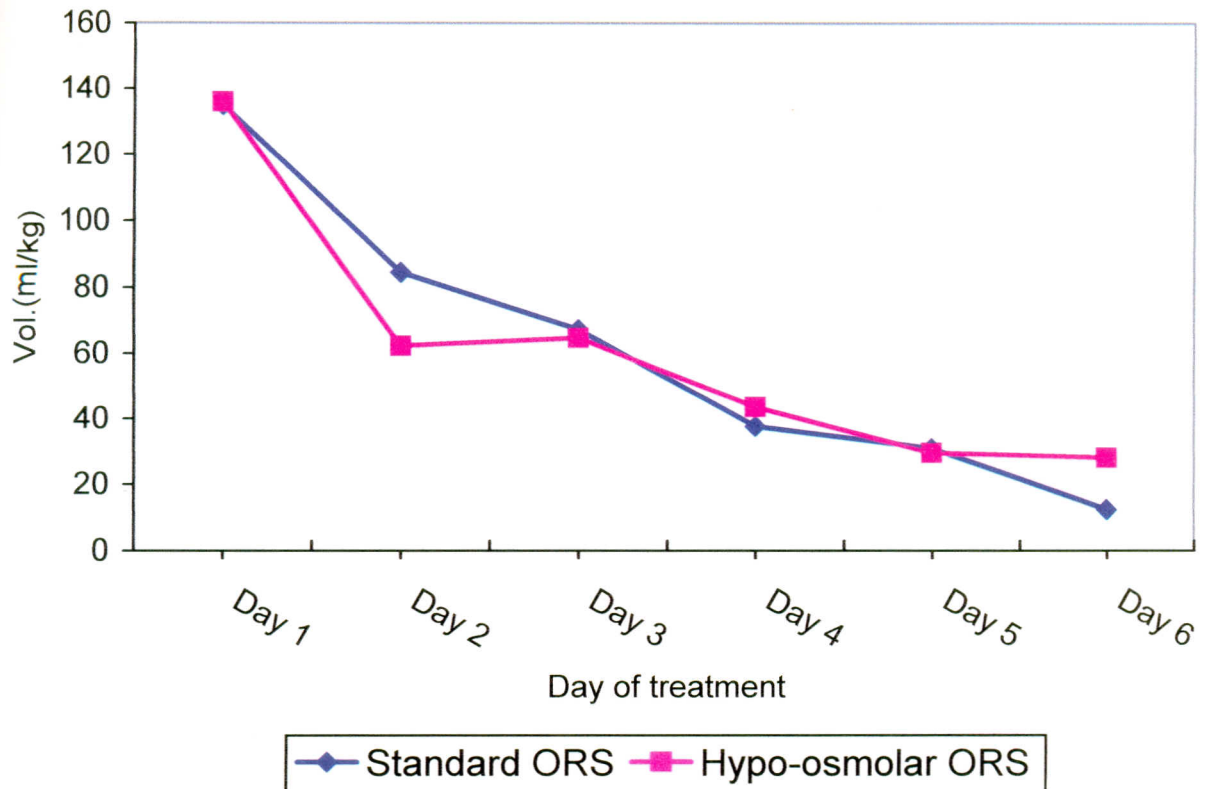
	Standard ORS	Hypo-osmolar ORS	p value*
Day 1 n=69	135 (42-339)	136 (42-348)	0.8
Day 2 n=69	57 (0-256.9)	29 (9.3-145)	0.04
Day 3 n=60	58 (0-164.3)	50 (0-226.8)	0.6
Day 4 n=57	60 (10.2-148)	109.2 (9-180)	0.9
Day 5 n=49	66.6 (46.2-220)	73 (0-143)	0.8
Day 6 n=25	48.3 (24-113)	71 (31.5-95)	0.2
Media total ORS in Litres	1.4 (0.49-6.0)	1.4 (0.32-5.3)	0.7

* *Mann Whitney U test* . All values are medians with ranges in the parentheses

The median total volume of ORS intake in litres during the hospital stay was not different between those children who received standard ORS compared to those who received hypo-osmolar ORS solution, $p = 0.7$, *Mann Whitney U test* .

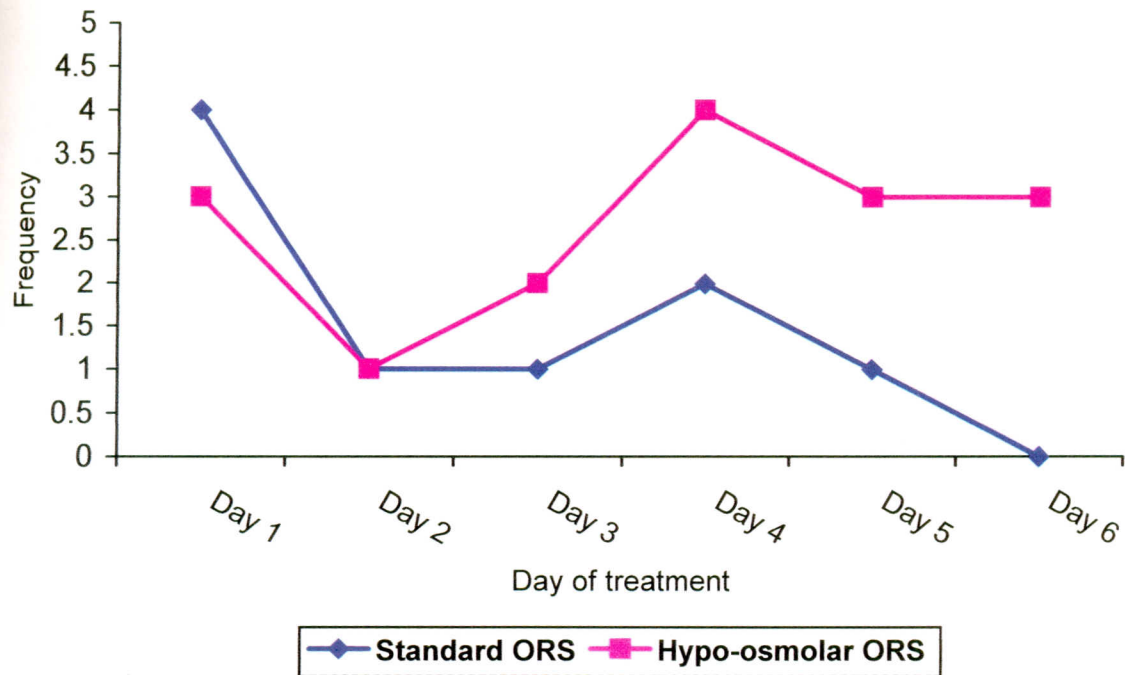
A decreasing trend in the intake volume of ORS was noted in both treatment arms throughout the study as shown in Figure 7.

Fig 7. The mean daily ORS intake in ml/kg in the children treated with the two ORS solutions



There was a day-to-day variation in the frequency of vomiting among the children in either treatment groups with similar trends, as depicted in Figure 8. However, all the differences were not statistically significant. The total median vomiting frequency was smaller in the hypo-osmolar ORS than in the standard ORS treatment arm but the difference was not statistically significant [2 (0-51) vs 3 (0-26), $p = 0.8$, Mann Whitney U test].

Fig 8. Mean daily frequency of vomiting in the children treated with the two ORS solutions



Treatment failure

There were a total of 27 (39.1 % of the study population) treatment failures, 13 (38.2 % of the standard ORS study population) among those that received standard ORS Vs 14 (40 %) in those who received Hypo-osmolar G-ORS solution, ($p = 0.8$ Pearson's χ^2 test). Of the treatment failures, 18 (78.3 % of the treatment failures) received unscheduled IV fluids because they developed severe dehydration. Among the treatment failures who needed IV fluids, 7 had received standard ORS and 11 had received hypo-osmolar ORS, the difference was not statistically significant (RR 0.96, 95% CI 0.13-7.3, $p = 1.0$, Fisher's exact Test).

CHAPTER FIVE

DISCUSSION

This was a randomised double blind clinical evaluation of two types of oral rehydration salt solutions in the rehydration of children with persistent diarrhoea admitted to Mulago hospital. The baseline characteristics did not confound the effects of ORS. All differences were not statistically significant except for the children who had both hyponatraemia and hypokalaemia. The two solutions were indistinguishable in appearance. A minimum sample size of 68 children was required using data from a similar study¹⁹ to detect a 30-hour difference in the duration of diarrhoea with a power of 90%. A total of 69 patients were recruited, 34 to receive standard ORS and 35 hypo-osmolar ORS solution. Data from all 69 children (34 in the standard ORS vs 35 in the hypo-osmolar ORS arm) were analysed.

The Duration of Diarrhoea

In this study the mean duration of diarrhoea was 87.5 hours among those who received hypo-osmolar ORS and 98.4 hours among those who received standard ORS solution but did not reach statistical significance, ($p=0.5$). This contrasts with findings in other clinical trials.^{19, 20} A similar study¹⁹ analysed 70 children aged 3-24 months and found a significantly shorter duration of diarrhoea in the reduced osmolarity treatment arm (114.8 ± 38.3 Vs 145.4 ± 40 ; $p = 0.002$). The differences in the selection of cases with persistent diarrhoea, variations in the standardized diets and differences in the registration of outcomes may explain these differences in the outcomes of the two studies. In the previous studies children with obvious severe malnutrition were excluded hence selecting a less sick population. These are the type of children routinely seen with persistent diarrhoea and so they are key to any study intended to influence diarrhoea treatment. Furthermore, many of the malnourished children might have been suffering from Human immunodeficiency virus infection related diarrhoea. This type of diarrhoea tends to be resistant to the benefits of hypo-osmolar ORS solutions noted in uninfected children.

In previous studies^{19, 20} children who developed severe dehydration were rehydrated by intravenous method then re-introduced to the oral therapy but not dropped, which was not the case in the present study. In the present study all children who developed severe dehydration

were withdrawn from the study and analysed as treatment failures hence they were assigned *the maximum duration of diarrhoea in this study of 168 hours (7 days)*. This reduced the power to detect any meaningful differences in the duration of diarrhoea between the groups.

Diets in the previous studies were devoid of lactose and sucrose. Lactose intolerance has been shown as a common problem in children presenting with persistent diarrhoea⁵⁷ and sucrose increases the gut osmotic potential worsening the diarrhoea. In this study therefore, low lactose rice porridge diet was given to the children to try to reduce the effect of these sugars on the diarrhoeal duration. Besides all the children in the present study began feeding on the enriched rice porridge diet at 4 hours of rehydration irrespective of the hydration status.

The early provision of rice diet most probably is the explanation for the much shorter duration of diarrhoea in the present study compared to that reported in an Indian hospital based study¹⁹. Rice starch broken down into glucose molecules at the epithelial surface with its end products rapidly taken up into cells by sodium co-transport does not cause its accumulation in the intestinal lumen and therefore increased intestinal osmolarity.⁵⁸ Faster absorption of glucose polymers by the intestinal mucosa with kinetic advantages has been proposed.⁵⁸

The difference in the numbers of children with diarrhoea cessation was not statistically significant between the treatment groups. This finding agrees with that of a similar study²⁰ where there was no statistically significant difference in the number of children with cessation of diarrhoea during the study period between those treated with hypo-osmolar ORS and those on the standard ORS solution.

There was no statistically significant difference in the failure rate between the two treatment arms and there was no statistically significant difference in the need for intravenous infusions. A meta-analysis of some studies to evaluate the effect of reduced osmolarity glucose based ORS in acute diarrhoea has reported reduced risk of need for intravenous fluids.⁴²

The 10-hour difference in the duration of diarrhoea in the present study was not statistically significant probably because this study was powered to detect at least a 30- hour difference in the duration of diarrhoea between the two groups. The 10-hour difference is important to the parents (in terms of shorter hospital stay and reducing anxiety), the child and the health

workers in appreciation of the economic and social implications of a faster recovery rate in persistent diarrhoea, especially in the context of poor countries.

The median numbers of stools were similar between the groups. The stool frequencies were reported as medians because the data had a skewed distribution. In this study the Stool frequency was used because of the difficulty in separating stool from urine in our set up, however in a similar study²⁰ where both stool frequency and stool volume were measured, the stool volume and the stool frequency were both significantly lower in the reduced osmolarity ORS treatment arm. The volume of diarrhoea is more appropriate because it reflects absorptive and perfusion properties of the intestinal mucosa. There was a decreasing trend in the stool frequency for the first 3 days in both treatment arms with no significant difference. This is probably the true reflection of the effect of hypo-osmolar ORS especially during the rehydration phase. The trend of stool frequency noted after day 3 is probably because the children vomited much of the hypo-osmolar ORS solution. It is not easy to ascertain to what extent recall bias on the part of the parents affected the number of stools recorded. The small numbers of patients after day 3 could not allow for any definitive conclusions to be drawn on these differences. Besides this study was not powered to detect any differences in the stool frequencies. The difference in the median total stool frequency during the study period was not statistically significant between the two groups, 23 (1 - 82) among those who received standard ORS Vs 16 (2 - 85) in the hypo-osmolar ORS arm, $p = 0.79$, 95% CI. This is similar to previous studies.^{19, 59}

This difference is however of clinical importance because the continuing motions are one of the major sources of anxiety leading mothers to adapt harmful practices in the treatment of diarrhoea. The fewer motions are perhaps related to the hypotonicity of the Hypo-osmolar ORS, which enhances the absorption of electrolytes and water. Moreover the lower glucose concentration allows for more complete absorption of glucose.⁶⁰

Although the difference in the total median stool frequency was not statistically significant in the current study, the median total stool frequency was much less than in the previous studies. This is probably because of the early introduction of the rice diet.

Time taken to achieve Rehydration

The results showed that rehydration could be achieved and hydration status maintained with hypo-osmolar ORS as effectively as standard ORS in the treatment of children with persistent diarrhoea. The median time to full rehydration was shorter, 7 hours (2-55) in those who received hypo-osmolar ORS compared to 8 hours (2-36) among those who received standard ORS solution, but did not reach statistical significance. The previous studies did not report on the duration of rehydration. Most of their patients did not have dehydration and were therefore on fluid therapy to replace ongoing losses only. Comparison by Kaplan-Meier survival analysis showed no significant difference in the proportions of children reaching full rehydration with time. It would be expected that the hypo-osmolar ORS solution would rehydrate faster than standard ORS solution because of the better sodium and water absorption due to the lower osmolarity. The water and solute absorption is a function of the osmotic gap between serum and stool osmolarities. In persistent diarrhoea the osmotic gap is high ($185 \pm 73 \text{ mOsmol/l}$), indicating incomplete absorption of nutrients¹². However also studies in acute diarrhoea have found no difference in the time to full rehydration between children treated with standard ORS and hypo-osmolar ORS solutions.^{61,62}

Electrolyte Status

The findings of this study did not demonstrate any worsening of hyponatraemia or hypokalaemia with either fluid. These findings agree with previous studies.^{19, 20,59} However the hypo-osmolar ORS solution treatment arm had a less improvement in the proportions of children with hypokalaemia by Day 3. The difference was not statistically significant between the treatment groups during the study. This is not surprising because of the low potassium content of the hypo-osmolar ORS solution and there is no documented evidence of enhanced potassium uptake in hypo-osmolar ORS solutions. Besides, there was larger proportion of children with hypokalaemia on admission in the hypo-osmolar ORS treatment arm.

The reduction in the proportion of children with hyponatraemia on day 3 among children who received the hypo-osmolar ORS solution was 4 times that among children who received standard ORS solution. The standard ORS solution has been shown to cause excess excretion

of sodium in stool in children with acute diarrhoea.⁶³ Moreover, the unabsorbed glucose and sodium would increase the osmolarity in the colon, reducing salvation of water hence both increasing and prolonging a diarrhoeal episode. The reduced osmolarity ORS favours enhanced absorption of electrolytes by the solvent drag action and reduces stool sodium loss.⁶⁴ This is the possible explanation for the larger reduction in the proportions of children with hyponatraemia among children treated with reduced osmolarity ORS solution.

Volume of ORS intake

There was no statistically significant difference in the volume of ORS intake. This finding was similar to that found in a Bangladesh study⁵⁹ in which Alanine- and glucose-based hypo-osmolar G-ORS was used and there was no significant difference in the total ORS intake per child but differed from an Indian study¹⁹ in which the ORS intake volume per child was significantly less in the hypo-osmolar ORS arm than in the standard ORS arm.

There was a decreasing trend of volume intake in the two ORS treatment arms throughout the study. A Finland study⁶³ has suggested that probably hypo-osmolar ORS is more palatable than the standard ORS solution hence the children tend to drink larger volumes of it. In the present study similar volumes of ORS were consumed hence palatability is probably not the main factor influencing ORS intake in children with diarrhoea. However, none of the clinical studies of hypotonic ORS has evaluated taste objectively.

The median total volume of ORS intake per child was less in the present study (1.4 L in either arms) compared to the Indian study¹⁹ in which 5.4 Litres per child was taken in the hypo-osmolar arm Vs 7.8 Litres per child in the standard ORS arm. This measured with the fewer number of motions and the shorter duration of diarrhoea in the present study compared to the previous studies.^{19,20}

Limitations of the study

To best measure the impact of hypo-osmolar ORS on the purging rate, other studies^{19, 20} measured the stool output volume and weight. These are better measures of the absorptive capacity of the intestinal mucosa. Where this has been done only males were recruited introducing selection bias into the study. This was not possible in the present study because of the difficulty of separating the stool from the urine especially for female children.

It is known that HIV causes an enteropathy that may contribute to the prolongation diarrhoea. In this study HIV/AIDS was not assessed due to limited financial resources at the disposal of the investigator at the time of the study. Therefore the response of HIV positive children to hypo-osmolar ORS in this study is not known.

There were a large number of treatment failures that were assigned the worst outcomes, which makes it difficult to draw any reasonable conclusions in this study. This scenario was not to the expectation of the investigator. Recruiting more patients and instituting intravenous rehydration therapy for children who developed severe dehydration then continuing with oral rehydration therapy may have limited this. Implementing this alternative was not possible without redesigning the methodology, treatment protocols and extending the time for this research.

To better conclude on the recovery rates, the stool pathogens should have been done. In previous studies^{2,64,66} there has been a high isolation rate of pathogens that was reflected in the high purging rates and dehydration. This was not done in the present study therefore the impact of pathogens on the response to hypo-osmolar ORS is not known in this study. This was mainly because of the limited budget that could not accommodate satisfactory stool analysis.

This can therefore act as a pilot study for a larger study that will take into account the above limitations.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. Children treated with hypo-osmolar ORS had a shorter mean duration of persistent diarrhoea than those treated with standard ORS solution but the difference was not statistically significant.
2. There is no statistically significant difference in the time to full rehydration between the children with persistent diarrhoea who received hypo-osmolar ORS and those who received standard ORS solution.
3. There is no statistically significant difference in the volumes of hypo-osmolar and standard ORS solutions in the rehydration of children with persistent diarrhoea.
4. Both hypo-osmolar ORS and standard ORS solution led to improvement of the electrolyte status of children with persistent diarrhoea.

6.2 Recommendations

1. Hypo-osmolar ORS solution can be used interchangeably with standard ORS solution in the routine treatment of children with persistent diarrhoea.
2. A larger study based on the findings and limitations in this study to further investigate the effect of hypo-osmolar ORS on the course of persistent diarrhoea is recommended.

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APPENDICES

Appendix A

WHO ORS and Hypo-Osmolar ORS Solution Study

Consent Form

Introduction

This study is being conducted in the Department of Paediatrics and Child Health, Makerere Medical School, to evaluate the clinical efficacy of WHO-ORS and hypo-osmolar ORS in the treatment of persistent diarrhoea in children in Mulago hospital. The principle investigator is Dr. Wobudeya Eric. The information will be beneficial in the treatment protocol for persistent diarrhoea in children.

Methods

During this study, the following will be done:

- (i) You will be asked questions about your child's current and past medical history.
- (ii) Your child will receive a complete physical examination.
- (iii) A small amount of blood will be taken from the child thrice, on Day0, 3 &7 if your child will still be in the study, to check for electrolytes.
- (iv) The results will be passed to your doctor for management.
- (v) Your child will be allocated to receive one of the study solutions randomly assigned to him/her. One of the solutions shall be obtained by adding 1 sachet of ORS to 1 L of water and the other to 1.5 L of water.
- (vi) The child will be reviewed regularly by the investigator and his assistants, and receive additional or alternative treatment as his/her condition will warrant.
- (vii) A special diet will be provided for uniformity. Breastfeeding children will continue breastfeeding.

Risks and benefits

The child will experience some pain from the needle prick. Bruising can occur but it is very rare. The amount of blood drawn (2 mls) will be too small to affect your child's health. A sterile technique will be used and any related injuries will be treated appropriately. There might be no immediate benefit to the child. There might be benefit to the child and society later when better management of persistent diarrhoea is established. The treatments and investigations will be done free of charge.

Compensation

No study related injury will be monetarily compensated, however appropriate treatment will be given and referral effected.

The patient's rights

Refusal to participate or withdrawal from this will carry no penalty. Attendants/parents will be entitled to all the information concerning their child during the study. Confidentiality of all the answers and statements shall be maintained.

STATEMENT OF CONSENT

The purpose and nature of this study has been explained to me by I understand that my participation in this study is voluntary and that no consequences will result if I refuse to participate. I am free to withdraw from the study at any time. I have the right to know the results of the laboratory tests.

_____	_____	_____	_____
Child's ID No.	Name	Signature/Finger print of Parent/caretaker.	Date.

_____	_____	_____
Name of investigator or Authorized representative.	Signature.	Date.

Appendix B
Questionnaire

CLINICAL HISTORY.

1. Child's ID No.....			{...}
Age (months):			{...}
Sex	F	1	
	M	2	{...}
2. Breast-feeding	Yes	1	
	No	2	{...}
3. Duration of diarrhoea (Days):.....			
4. Frequency of stools last 24 hours:			
5. Consistency of stools	Loose	1	
	Watery	2	{...}
	Mucoid	3	
6. History of Vomiting	Yes	1	
	No	2	{...}
7. Number of vomiting in last 24 hours:			
8. History of Fever	Yes	1	
	No	2	{...}
9. History of Poor Appetite	Yes	1	
	No	2	{...}
10. History of Abdominal Distension	Yes	1	
	No	2	{...}
11. History of treatment before admission	Yes	1	
	No	2	{...}
12. History of Antibiotic use	Yes	1	
	No	2	{...}
13. Duration of treatment (Weeks) :			
14. ORS use before admission	Yes	1	
	No	2	{...}

15. History of Persistent diarrhoea in last 3 months	Yes	1	
	No	2	{....}
16. Number of persistent diarrhoea episodes in last 2 Months.....			
17. Measles Immunization	Yes	1	
	No	2	{....}
	Unknown	3	
18. History of measles in last 3 months	Yes	1	
	No	2	{....}
19. Two or more Pneumonia episodes in the past 2 Months	Yes	1	
	No	2	{....}

CLINICAL ASSESSMENT

20. General examination			
Temperature..... °C			
Oral thrush (Candidiasis)	Yes	1	
	No	2	{....}
Height/length.....cm			
Weight.....kg			
M.U.A.C.....cm			
21. Respiratory system			
Respiratory rate.Breaths/minute.			
Chest retractions	Yes	1	
	No	2	{....}
Normal Percussion note	Yes	1	
	No	2	{....}
Crepitations	Yes	1	
	No	2	{....}
Rhonchi	Yes	1	
	No	2	{....}
22. Cardiovascular system			
Pulse rate...../minute			
Thready pulse	Yes	1	

	No	2	{....}
Murmurs	Yes	1	
	No	2	
23. Normal Central nervous system	Yes	1	
	No	2	{....}

LABORATORY DATA

24. Serum potassium			
At admission		
At Day 3		
At Day 7		
Serum sodium			
At admission		
At Day 3		
At Day 7		
25. Treatment solution code:	A		
	B		

Appendix C
Patient Progress Chart

Child's ID No..... Admission date..... Hour.....
 Age:.....months Sex.....
 Rehydration start: Date:..... Time:.....
 Fluid Code.....

Time	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	12 th	16 th	20 th	24 th
Amount taken												
Vomit episodes												
No. of stools												
Level of Hydration												
Temperature												
Weight												
Pulse rate												
Character												
Respiratory rate												

Codes:

Level of Hydration: 1. Normal. 2. Some. 3. Severe.

Abdominal Distension: 1. Yes. 2. No

Bowel sounds: 1. Normal. 2. Scanty. 3. Absent. 4. Increased

Character: 1. Normal 2. Thready

Neck floppiness: 1. Yes. 2. No

Appendix D

The Uniform Diet

The diet will provide 83 kcal/100g, 3.7 g lactose/kg body weight/day and 11% of calories as protein.

Whole liquid milk	85 ml
Rice	15 g
Vegetable oil	3.5 g
Cane sugar	3.0 g
Water to make	200 ml

Adapted from WHO/IMCI: Management of the child with a serious infection or severe malnutrition. Pg 53.

Appendix E

Classification Of Malnutrition WHO 2001

Grade of Malnutrition	Weight/Age Gomez	Height/Age Waterlow	Weight/Height Waterlow	Weight/Height in SDS Waterlow
0, normal	>90	>95	>90	> -1 SD
1, mild	75-95	90-95	81-90	1-2 SD
2, moderate	60-74	85-89	71-80	2-3 SD
3, severe	< 60	< 85	< 70	< -3 SD

Adopted from Table 26 of the MANAGEMENT OF THE CHILD WITH A SERIOUS INFECTION OR SEVERE MALNUTRITION of WHO 2001.

N.B: presence of oedema is graded as Severe Malnutrition.

Appendix F
Assessment For Dehydration

<p>Two of the following signs:</p> <ul style="list-style-type: none"> • Lethargy or unconscious • Sunken eyes • Not able to drink or drinking Poorly • Skin pinch goes back very slowly. 	<p>SEVERE DEHYDRATION</p>
<p>Two of the following signs:</p> <ul style="list-style-type: none"> • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly. 	<p>SOME DEHYDRATION</p>
<p>Not enough signs to classify as some or severe dehydration.</p>	<p>NO DEHYDRATION</p>

Assessment of dehydration in severe malnutrition

Signs that remain useful for detecting dehydration in severely malnourished children include: **dry mouth and tongue**, and **eagerness to drink** (for children with Some Dehydration); or **very dry mouth and tongue, cool and moist extremities, and weak or absent radial pulse** (for Severe Dehydration).

Appendix G

The instructions to the nurse for the preparation of the treatment solutions.

1. Wash your hands with soap and water.
2. Pick 1 pre-packed sachet. Ascertain that it is well sealed and is not wet.
3. Take note of the code label and identify the container with the corresponding label.
4. Measure 3 Litres of clean drinking water and pour into the labeled container.
5. Cut the sachet open and pour all the powder into the labeled container with the corresponding label. Mix well until the powder is completely dissolved.
6. Repeat the procedure to prepare both solutions labeled 'A' and 'B'.