

UNIVERSITY OF NAIROBI

Department of Paediatrics and Child Health

**EFFECT OF ORAL ONDANSETRON IN CHILDREN
PRESENTING WITH ACUTE DIARRHOEAL ILLNESS
AND VOMITING WITH SOME DEHYDRATION**

By

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DECLARATION

I declare that this proposal is my original work and has not been presented for the award of a degree in any other university.

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DEDICATION

This dissertation is dedicated to my family and friends for their continuous and immense support during the period of the study for my Master's degree of Medicine in Paediatrics and Child Health. Particular thanks go to my parents Mr and Mrs Naeem Shah for their never ending support and encouragement and giving me every opportunity to fulfil my dreams.

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Abbreviations

AAP: American Academy of Pediatrics

CDC: Centers for Disease Control and Prevention

CTZ: Chemoreceptor Trigger Zone

ESPGHaN: European Society for Paediatric Gastroenterology, Hepatology, & Nutrition

ESPID: European Society for Paediatric Infectious Diseases

ETAT+: Emergency Triage, Assessment and Treatment plus Admission

FDA: Food and Drug Administration

GDG: Guideline Development Group

IV: Intravenous

IVT: Intravenous Therapy

KNH: Kenyatta National Hospital

NHS: National Health Services

ORS: Oral Rehydration Salts

ORT: Oral Rehydration Therapy

PEU: Paediatric Emergency Unit

RCT: Randomized Controlled Trial

UNICEF: United Nations Children's Fund

WHO: World Health Organisation

Definition of Terms

ADVERSE EVENT – An adverse event is any untoward medical occurrence in a patient or clinical subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment.

ANTIEMETIC – An antiemetic is a drug that is useful in the suppression of vomiting and nausea.

DIARRHOEA – The WHO definition of Acute Diarrhoea is the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual.

DYSENTERY – Clinical Dysentery refers to infection of the gastrointestinal tract resulting in severe diarrhoea with the presence of blood and mucus in the faeces.

GASTROENTERITIS – Gastroenteritis refers to inflammation of the stomach and intestines, typically resulting from infective causes and associated with vomiting and diarrhoea.

INTRAVENOUS THERAPY – Intravenous therapy (IV therapy) is the infusion of fluids directly into a vein. In this study it refers to the infusion of fluids for rehydration purposes.

VOMITING – The NICE definition of vomiting is the forceful ejection of the stomach contents up to and out of the mouth.

SEVERE ACUTE MALNUTRITION – Severe acute malnutrition is defined in the WHO guidelines as the presence of oedema of both feet or severe wasting.

SEVERE DEHYDRATION – The WHO definition of Severe Dehydration is two or more of lethargy or unconsciousness, sunken eyes, unable to drink or drinks poorly and/or slow skin pinch.

SOME DEHYDRATION – The WHO definition of Some Dehydration is two or more of restlessness, sunken eyes, drinks eagerly and/or slow skin pinch

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Abstract

Background:

Each year, approximately 700,000 deaths occurring worldwide as a result of acute diarrhoeal illness among children under five years of age. Emesis in acute diarrheal illness is both a direct cause of fluid loss and a significant deterrent to Oral Rehydration Therapy (ORT). An effective treatment of emesis can therefore improve successful ORT and this will not only reduce mortality from diarrhoeal illnesses but also reduce requirement for IV rehydration and hospital admissions. Single dose oral ondansetron has been shown to significantly reduce vomiting in children with acute diarrhoeal illness and therefore improve successful ORT and reduce the requirement for IV rehydration and hospital admissions. No local data exists on the use of ondansetron for vomiting in children with acute diarrhoeal illness.

Objectives:

The primary objective was to determine the effect of ondansetron in reducing the rate of ORT failure and therefore hospitalization for intravenous rehydration in children presenting with an acute diarrhoeal illness accompanied by vomiting and some dehydration. The secondary objectives were to compare persistence of vomiting and diarrhoea and the rate of hospital revisits 48 hours after the administration of ondansetron or placebo.

Methods/Design:

This was a prospective randomized double blinded placebo controlled trial. We enrolled children between the ages of 6 and 59 months who presented with an acute diarrhoeal illness accompanied by vomiting and some dehydration at the PEU. Children who fulfilled the criteria for inclusion were enrolled after informed consent was obtained from their parents. They were then randomized to receive either oral ondansetron or placebo in addition to the standard treatment prescribed by the primary clinician. We measured the number of children who failed ORT and thus required admission for IV rehydration and followed up all enrolled patients 48 hours later to measure vomiting and diarrhoea episodes, and number of revisits to a health facility. Baseline characteristics were compared by the chi-square test for proportions and by analysis of variance for continuous variables. Relative risk and 95% confidence intervals are used for categorical data, while means and standard deviations are used for continuous data. The data obtained was analyzed using STATA software according to the intention to treat principle.

Results:

Baseline characteristics for the two groups i.e. ondansetron and placebo groups were found to be similar. The number of children that failed ORT and thus required hospitalization for IV Rehydration was 18.7% less in those who received oral ondansetron compared to placebo i.e. 3.3% Vs. 22%

respectively (i.e. RR 0.17, 95% CI 0.04 - 0.73, P <0.01). Children who received oral ondansetron vs. placebo also had significantly fewer episodes of vomiting i.e. 0.7 vs. 1.4 mean episodes during ORT and 0.27 vs. 0.5 mean episodes at 24 hours of follow up respectively. Proportion of children who had persistent vomiting during the ORT period was significantly higher in the children who received placebo (72.9%) compared to those who received ondansetron (48.3%). There was no significant difference in the number of diarrhoeal episodes between the two groups for up to 48 hours after receiving the drug.

Conclusions:

Single dose oral ondansetron is associated with fewer vomiting episodes during ORT and hence fewer rates of ORT failure in children with vomiting in an acute diarrhoeal illness. Single dose oral ondansetron is not associated with increased episodes of diarrhoea and is a useful therapy in the management of children with vomiting in an acute diarrhoeal illnesses and some dehydration.

Chapter 1 – Background

Acute diarrhoeal illness is a common childhood disease and is among the leading causes of morbidity and mortality worldwide. Each year, an estimated 2.5 billion cases of diarrhoea occur among children under five years of age, and estimates suggest that overall incidence has remained relatively stable over the past two decades.¹

Mortality from diarrhoea has declined over the past two decades from an estimated 2.5 million deaths among children under five to less than a million deaths in 2010,² which parallels downward trends in overall under-five mortality during this period. Despite these declines, diarrhoea remains the second most common cause of death among children under five globally. The toll of deaths due to diarrhoea in this age group is greater than that caused by AIDS, malaria and measles combined.²

Diarrhoeal illnesses disproportionately affect young children in low and middle income countries with over 50% of all cases occurring in Sub-Saharan Africa and South Asia alone. These 2 regions alone account for more than 80% of all the child deaths that occur worldwide due to diarrhoea. However, of note, is that just 15 countries account for almost three quarters of all the diarrhoea related child deaths annually.² Kenya ranks 10th worldwide, with 38,500 deaths annually due to diarrhoea in children under 5 years and is the 2nd highest cause of death (17%) in this age group.³

Though most episodes of childhood diarrhoea are mild, acute cases can lead to significant fluid loss and dehydration, which may result in death or other severe consequences. Thus dehydration that can occur from diarrhoea and/or emesis should be treated vigorously.⁴ Current treatment recommendations given by the WHO, focus on the mitigation of these consequences of acute diarrhoeal illness, specifically dehydration and nutrient losses. The recommended first-line treatment according to this statement is oral rehydration therapy (ORT) with continued feeding, unless certain contraindications exist.⁵ These interventions are proven, affordable and relatively straightforward to implement.

The Oral Rehydration solution is one of the most important medical advances of the 20th century. Since its introduction in the 1970s, use of ORS in oral rehydration therapy has been the cornerstone of treatment programmes to prevent life-threatening dehydration associated with diarrhoea. ORT is a proven safe and cost-effective measure and thus recommended by the Kenya Ministry of Health as first line treatment for acute diarrhoea except in cases of severe dehydration.⁶

With the advent of ORS, the trends in mortality have over time showed a significant decrease, but have since remained stable despite continued efforts.⁷ After the WHO began promoting ORT the diarrhoea related death rate dropped from 3.3 million/year in 1980's, to 2.5 million/year in 1990's and eventually to 1 million/year in 2000's. However, since then the rate of decline has slowed down and in 2010 the diarrhoea related death rates have remained stable at around 700,000/year.⁷

Despite the overwhelming evidence to support the usage of oral rehydration, ORS is still described as an underused simple therapy.⁸ According to the WHO, only 39% of children with diarrhoea in developing countries receive the recommended treatment, and limited trend data suggest that there has been little progress since 2000.⁹ As a continent, Africa has the lowest levels of ORT coverage worldwide at approximately 35%. In Kenya, the situation is almost similar whereby only 39% of children with diarrhoea are actually treated with an ORS solution.³

In the developed world despite high levels of treatment coverage, Intravenous Therapy (IVT) is still often chosen over ORT. Data from Europe, Australia and Canada show that 80 – 94% of hospitalized children with diarrheal illness do not have any signs of dehydration and yet they still receive intravenous therapy.^{10,11,12} The reasons for the underuse of oral rehydration therapy are not fully understood. In a 2002 survey conducted in the USA, patients refusing to drink and vomiting were found to be the two most likely reasons for choosing IVT, with up to 85% of the doctors being more likely to use intravenous therapy when vomiting was the predominant symptom.

Vomiting during an acute diarrheal illness is both distressing for the child and caregiver. In the initial phase of acute diarrhoeal illnesses, vomiting is a typical symptom.¹³ Approximately 70% of all children with an acute gastroenteritis present with vomiting¹⁰, with a similar number reported in a 2007 Kenyan study.¹⁴ Vomiting has also been implicated as a significant predictor of severity of dehydration^{15,16} and is considered as one of the most important factors for failed ORT that leads to intravenous therapy.^{17,18}

Thus, use of an antiemetic drug that could safely suppress vomiting, would be useful in successful oral rehydration. However, current practice recommendations for paediatric acute diarrheal illness do not routinely include pharmacologic treatment for vomiting.¹⁹ However, judging the effectiveness of ORT and the overuse of IVT, any treatment in acute diarrhoea should improve the success or compliance of ORT as the top priority. Safety and cost are also important issues.

Successful ORT always means that children can be managed in the community and reduce the need for hospitalization. It is both more pleasant and comfortable for the children and caregivers.

With the emergence of newer and safer anti-emetics for children, their role is now being reconsidered in acute diarrheal illnesses for ensuring successful ORT. In a 2002 USA study by Kwon et al, it was found that 52% of general paediatricians and 55% of paediatric emergency physicians prescribe antiemetics for paediatric acute gastroenteritis. They found that the most common nonexclusive reason for prescribing antiemetics was to prevent worsening dehydration and need for subsequent IV fluids or admission (72%). This was followed by patient comfort (59%), assurance of oral liquid trial before discharge (35%), and parental concerns/pressures (29%).²⁰ A similar survey carried out by Albano et al²¹ in Italy, found that almost 71% of hospital paediatricians and 96% of the family physicians would use an antiemetic for acute diarrhoeal illness in children. They found that hospital paediatricians were more likely to prescribe antiemetics in order to increase the success rate of ORT (48%), whereas family physicians prescribed them to increase patient comfort or to reduce concerns of parents (46%).²¹

Ondanestron, a relatively new antiemetic, is routinely used for chemotherapy induced nausea and vomiting in paediatric patients and is already well documented. However, recent studies have shown that Ondansetron can also significantly reduce vomiting in acute diarrheal illness and thus improve ORT.²² These studies have further indicated that ondansetron has a relatively good safety profile and is safe to use in children.²² However, none of the studies were carried out in the local or regional setting whereby disease burden remains high and ORT coverage low. This study is thus undertaken to determine the effects of Ondansetron in the management of vomiting in children with acute diarrhoeal illness in order to achieve successful ORT.

Chapter 2 – Literature Review

Antiemetic Therapy

Administration of an antiemetic drug, that could safely suppress vomiting, would be useful in promoting successful oral rehydration. Multiple drugs have been tried to assist oral rehydration, with varying degrees of success and complicating side effects.

The phenothiazines are dopamine antagonists and act centrally by blocking the CTZ. They are used to treat vomiting associated with drugs such as opiates, general anaesthetics, and cytotoxics. Unfortunately, severe dystonic reactions can occur with phenothiazines, especially in children.²³

Metoclopramide acts primarily as a dopamine D2 receptor antagonist and has both central and peripheral actions. It also acts directly on the gastrointestinal tract and it may be more effective than the phenothiazines for vomiting associated with gastro-duodenal disease. As with the phenothiazines, metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. Severe dystonic effects can occur more frequently in the paediatric age and thus its use in children under 16 years old is not recommended.²⁴

Domperidone a D2 receptor antagonist acts directly on the chemoreceptor trigger zone and also accelerates gastric emptying. It has been associated with rare adverse effects such as ventricular arrhythmias (especially with intravenous dosing) and cardiac arrest.²³ Domperidone, however, does not cause any significant extrapyramidal adverse effects because of its poor CNS penetration.

Ondansetron – A New Antiemetic

Ondansetron, is a novel antiemetic that was first synthesized in 1983 and became available for clinical use in 1991.²⁶ It is one of the best known potent serotonin 5-HT₃ receptor-antagonists that blocks receptors at the vagus and sympathetic nerves together with the chemoreceptor trigger zones.²⁵ The efficacy of ondansetron for chemotherapy-induced or postoperative vomiting in the paediatric population is well documented.^{26,27,28} In addition, it has also been shown to have promising effects in patients with vomiting due to migraines, procedural sedation and acetaminophen poisoning.^{29, 30, 31} Moreover, ondansetron is a well tolerated drug that has been shown to be safe for use in children.³² These positive results initiated investigations for their use in vomiting related to acute diarrhoeal illness. A few RCTs regarding its use in paediatric diarrhoeal illnesses have since been published and majority have shown a generally favourable outcome.³⁵⁻³⁸

Ondansetron – Use in Acute Diarrhoeal Illness

In the past, use of antiemetics for children with vomiting in acute diarrhoeal illnesses has generally been avoided by most paediatric guideline panels. The reasons for this being that vomiting in diarrheal illness is self-limiting and antiemetics can have serious side effects.^{11, 33, 34} However, with the recent availability of ondansetron and a proven track record of safe use in children³² it is now being considered in trials for vomiting related to acute diarrheal illness.

The use of ondansetron in acute diarrhoeal illness was first reported in a trial by Cubeddu et al³⁵ in 1997, which used a single IV dose and compared its effect on vomiting with metoclopramide and placebo in the ensuing 24 hours. The effectiveness of ondansetron in halting emesis was found to be significantly better than placebo and metoclopramide. Treatment failures (i.e. more than 2 episodes of vomiting in 90 minutes within 4 hours of drug administration) were less common with ondansetron (17%) than with metoclopramide (42%).

Since then, a number of trials have been conducted for single dose oral ondansetron in acute diarrhoeal illness. In 2002, Ramsook et al,³⁶ conducted a double blinded RCT, of 145 patients between 6 months and 12 years of age who had vomited at least 5 times in the preceding 24 hours (Table 1). The study randomized the patients to oral ondansetron and placebo, followed by oral rehydration. They found that more children in the ondansetron group (86.4%) stopped vomiting in the first few hours after treatment in the emergency department compared with those who received placebo (64.7%). In addition they also found that fewer children treated with oral ondansetron required IVT (8%) or were admitted to hospital (2.7%) compared with those treated with placebo (22.5% and 15.4%, respectively).

In 2006, Freedman et al,³⁷ published a study in which they conducted a trial comparing the effects of oral ondansetron versus placebo in children presenting with gastroenteritis. The children aged 6 months to 10 years were enrolled if they had at least one episode of vomiting in the preceding 4 hours, and mild to moderate dehydration (Table 1). The study found that significantly more children in the ondansetron group (85.9%) stopped vomiting in the first few hours after treatment compared with those who received placebo (65.4%). They also found that fewer of the children receiving ondansetron required IVT (14%) than those treated with placebo (30.8%). There was no difference, however, in the rate of hospitalization between the two groups.

In 2008, Roslund et al³⁸, published a study in which they enrolled children aged 1 to 10 years with acute gastritis or gastroenteritis, mild to moderate dehydration and had failed ORT in the emergency department (Table 1). The study randomized the patients to either receive oral ondansetron or placebo and were restarted on oral rehydration thereafter. The investigators found that 93% of patients who had received ondansetron had fewer episodes of vomiting during a 6 day follow-up, compared with 88% in the placebo group. The study also showed that fewer of the children receiving ondansetron required IVT (18.7%) than those treated with placebo (54.5%). The children who received ondansetron were also less likely to be admitted to hospital (5.9%) compared with those who received placebo (12.7%).

Table 1

Clinical Trials: Use of oral ondansetron for acute diarrhoeal illness with vomiting in children

Source	Size (n)	Age	Inclusion criteria	Results after ondansetron treatment, RR (95% CI)		
				Persistent Vomiting in ED	Receiving IV Fluids	Admission to Hospital
Ramsook et al ³⁶ 2002	145	6 mos to 12 yrs	Acute diarrhoea with recurrent vomiting in the preceding 24 hours	0.38 (0.18–0.80)	0.36 (0.26–0.79)	0.17 (0.04-0.76)
Freedman et al ³⁷ 2006	214	6 mos to 10 yrs	Acute diarrhoea with mild to moderate dehydration and vomiting in past 24 hrs	0.40 (0.26–0.61)	0.46 (0.26–0.79)	0.80 (0.22-2.90)
Roslund et al ³⁸ 2008	106	1 yr to 10 yrs	Acute diarrhoea with failed oral rehydration attempt in ED	0.43 (0.20–0.94)	0.40 (0.20–0.79)	0.46 (0.12-1.79)

ED Emergency Department; IV Intravenous; mos Months; yrs Years

Decamp et al²² published a meta-analysis in 2008 to specifically examine the use of various antiemetic drugs for children with acute gastroenteritis. The investigators reviewed six different studies involving ondansetron: the four studies described above and two other studies that involved the use of IV ondansetron. Five of these studies were based in the USA and one in Venezuela. The combined analysis of the oral and IV ondansetron studies showed that subjects treated with ondansetron were at decreased risk for further emesis in the emergency department, IV fluid administration and hospital admission.²² The most significant adverse event noted from the various studies was an increased risk of diarrhoea up to 48 h after administration of ondansetron. No other adverse events were common across all studies.

In view of these recent studies, Paediatric guideline panels have since reviewed their use of antiemetics in acute diarrhoeal illness. In 2009, the GDG tasked by the UK NHS to review current guidelines in management of gastroenteritis, made the following recommendation on antiemetics: “Although many children vomit during ORT, this is usually not so severe as to prevent oral rehydration. Occasionally, vomiting is frequent and persistent. The availability of an effective antiemetic could therefore be very valuable. The GDG considered that evidence from RCTs indicated that oral ondansetron could increase the success rate with ORT. The GDG was concerned that ondansetron might have adverse effects such as worsening diarrhoea... However, the GDG did consider that further research on the use of ondansetron was needed, focusing particularly on the possible risk of worsened diarrhoea... If ondansetron is shown to be both effective and safe in secondary care then studies should also be undertaken to evaluate its use in primary care.”³⁹

The Canadian Paediatric Society have also since reviewed the role of antiemetics in acute diarrhoeal illnesses, and in 2011 through its Acute Care committee made the following recommendations:

“Oral ondansetron therapy, as a single dose for paediatric gastroenteritis, is effective in reducing the frequency of vomiting and IV fluid administration in infants and children... who present to the Emergency Department with mild to moderate dehydration or who have failed a trial of oral rehydration therapy. The most common side effect of the administration of oral ondansetron in this context is diarrhoea, which is usually self-limited in nature and lasts less than 48h. Further studies are required to address its use and efficacy in the out-of-hospital setting.”⁴⁰

Ondansetron – Pharmacokinetics and Safety Profile

Ondansetron is completely and rapidly absorbed from the gastrointestinal tract after oral administration, with the drug being first detected in plasma 30 minutes after administration of an oral dose. Peak plasma concentration occurs approximately 2 hours post oral intake with a bioavailability of approximately 60%.^{32,41} Hepatic oxidative metabolism accounts for more than 95% of ondansetron clearance, and it does not accumulate with repeated oral administration.

Ondansetron has a half-life of 2 to 6 hours following oral intake and its antiemetic duration of action is variable from 2 to 8 hours with standard dosing.^{32,41} The recommended IV dose of ondansetron is 0.1 to 0.15 mg/kg body weight, up to a maximum of 4 mg.³² The recommended oral dose is 2 mg for children weighing 8 to 15 kg, 4 mg for children weighing 15 to 30 kg and 8 mg for

children weighing over 30 kg up to a maximum of 3 times/day. However, in the case of vomiting related to acute diarrhoeal illness a single dose of oral ondansetron is usually sufficient.⁴⁰

The safety profile of ondansetron is generally favourable, as in the treatment of vomiting during acute diarrhoeal illness, diarrhoea is the most common and only reported side effect.^{35,36,37} However, the diarrhoea associated with this treatment is usually mild and self-limiting. In addition the clinical significance of the increased diarrhoea has not been studied. The increased diarrhoea does not seem to result in increased health care use; the aforementioned studies did not demonstrate a statistically significant increase in return to care in ondansetron-treated patients. No other adverse effect was commonly detected in patients treated with ondansetron.^{35,36,37}

In general, serious adverse events rarely occur with ondansetron use. A large study by Bryson et al,⁴² evaluating ondansetron use for postoperative emesis, found the incidence of adverse events to be similar to that of placebo. Other studies have since shown that it does not cause extra-pyramidal reactions or sedation.⁴³ However, in other trials, including some paediatric patients, documented headache was the most common adverse effect, followed by fatigue and constipation.⁴⁴

Following an FDA notification in 2011, of a possible link between Ondansteron use and arrhythmias, Freedman et al⁴⁵ carried out a thorough in-depth post-marketing analysis and systematic review of published literature. The study investigators did not find any reports of arrhythmia related to the administration of a single oral dose of ondansetron, the most common administration route. They further added that they did not any find evidence to support the use of ECG and electrolyte testing for routine screening of patients without any known risk factors before administering a single oral ondansetron dose.⁴⁵ In 2012, the FDA reviewed its original statement and issued an update linking the risk only to the administration of the drug in high doses intravenously.

Ondansetron – Economic Impact on Acute Diarrhoeal Illness

Acute diarrheal illnesses place a heavy burden on individuals, society and the healthcare system, with long-term consequences on the physical and mental development of children.^{46,47} The use of oral ondanestron for vomiting in acute diarrheal illness has been shown to minimize the need for intravenous therapy and hospitalization.²² The main drawback in the past to the use of ondansetron, has been the cost; however, a generic form of ondansetron has recently become available and cost is no longer an important barrier to its use. The wholesale price of the original drug is at Kshs. 60 and generic at Kshs.10 per 8mg tablet in the Kenyan market.

The direct impact of Ondansetron on the economy was demonstrated by Freedman et al⁴⁸ in a cost analysis study in 2010 in which they evaluated oral ondansetron administration for gastroenteritis from a societal and health care payer's perspective in both the US and Canada.⁴⁸ The study reported that in the US, administration of ondansetron to eligible children would prevent approximately 29,246 IV rehydration and 7,220 hospitalizations annually. The study thus inferred that in the US, routine administration of ondansetron would annually save the society US\$ 65.6 million and health care payers US\$61.1 million. The study also reported that in Canada, administration of ondansetron to eligible children would prevent 4,065 IV insertions and 1,003 hospitalizations annually. Its routine administration would annually save society CDN\$1.72 million and the health care system CDN\$1.18 million. The study thus, concluded that in countries where IV rehydration is often employed, the emergency department administration of oral ondansetron to children with dehydration and vomiting secondary to gastroenteritis results in significant monetary savings compared to a no-ondansetron policy.⁴⁸

The impact of diarrhoeal illnesses on the economy has also been demonstrated in a Kenyan study published by Osano et al⁴⁶, which showed that the overall mean cost for hospitalization of a single patient with rotavirus diarrhoea was US\$ 100. The study concluded that rotavirus gastroenteritis leads to considerable resource utilization in health care setting and the society. Based on the high burden of diarrheal illnesses in the country and the benefit of reduced hospitalization rates and IV rehydration, ondansetron use in acute diarrhoeal illness can reduce overall health care costs.

Chapter 3 – Study Justification & Objectives

Justification of the Study

1. Diarrhoeal illnesses are a leading cause of morbidity and mortality in children worldwide and place a heavy economic burden on individuals, society and healthcare systems.⁴⁶
2. Treatment with oral rehydration therapy and continued feeding are proven, affordable and relatively straightforward options to implement.
3. Vomiting in acute diarrhoeal illness can be a significant deterrent to successful ORT.^{17,18}
4. Recent studies have shown that single dose oral ondansetron can significantly reduce vomiting and therefore improve oral rehydration therapy.²²
5. Various Paediatric societies have reviewed their stand on antiemetic use and some of these societies now recommend that oral ondansetron might have a role in acute diarrhoeal illness but further evaluation was still required.^{39,40}
6. Despite the publication of various studies on the use ondansetron in acute diarrhoeal illness, no local or regional study has been conducted yet.

In light of the above considerations we propose a prospective, randomized, placebo controlled study to determine the effect of Ondansetron in children presenting with vomiting and some dehydration in an acute diarrhoeal illness. It is anticipated that through this study we will be able to determine whether Ondansetron can improve the outcome in children aged 6-59 months with vomiting and some dehydration in an Acute Diarrheal illness.

Objectives of the study

Primary Objective

To determine the effect of oral ondansetron in reducing the rate of failure of Oral Rehydration Therapy (ORT) which in turn reduces the need of hospitalization for IV rehydration in children presenting with an acute diarrhoeal illness accompanied by vomiting and some dehydration.

Secondary Objective

To compare the effects of oral ondansetron and placebo on vomiting and diarrhoea in children with acute diarrhoeal illnesses.

Chapter 4 – Methodology

Introduction

This chapter explains the methodology applied in this study. A description of the study design is presented followed by the criteria used to recruit the subjects into the study. The settings for the study are described and a report of the interventions applied is presented. This includes details of the randomization and blinding procedures. Statistical methods employed in the study and finally the ethical considerations are discussed in this chapter.

Study design

This was a prospective randomized, double-blind, placebo-controlled trial conducted at the Paediatric Emergency Unit (PEU) at Kenyatta National Hospital in Nairobi, Kenya between January 7th and February 20th 2015. We attempted to determine whether the use of oral ondansetron would increase successful ORT in children with acute diarrhoea and some dehydration with vomiting and thus decrease the need for intravenous rehydration therapy and admission.

We hypothesized that patients receiving ondansetron would have a lower proportion of failing ORT compared to placebo due to fewer episodes of vomiting thus requiring fewer hospitalizations for intravenous rehydration. Clients were randomly assigned to either the control arm or intervention arm with a 1:1 ratio. The Kenyatta National Hospital and University of Nairobi Ethics Research and Standards Committee (KNH/UON-ERC) approved the study.

Study Setting

The study was conducted at the Paediatric Emergency Unit (PEU) in Kenyatta National Hospital. The Paediatric Emergency Unit (PEU) is located at clinic 22 on the ground floor of KNH. KNH is the country's largest referral hospital with a total bed capacity of 1800 spread out over 50 wards.

Within the PEU is a Registration office, Triage desk, Pharmacy, Sample collection room, Injection and Dressing room, ORT room, 3 Clinician rooms and an Emergency room. All patients under 12 years of age are seen at the PEU. On average, 100–150 patients are seen daily at the PEU, with majority presenting with an acute illness including acute diarrhoeal illness.

Patients presenting to the PEU are initially registered at the registration desk and move to the triage desk where a triage nurse measures vital signs, obtains presenting complaints and assesses

the urgency of the patient's condition. Patients presenting with non-emergent conditions including acute diarrhoeal illness with some dehydration are referred to the clinician's rooms. The clinician rooms are manned by a Clinical Officer and there are two clinical officers on duty at any one time. Patients once reviewed by the clinical officer are then referred for appropriate management i.e. either to Pharmacy (for prescriptions), Sample Collection Room (for Laboratory investigations), Injection and Dressing room (Injections, wound cleaning and dressing), or to the ORT room (for Oral rehydration and observation). However, any patient presenting with a difficult/complicated condition or worsening of their clinical state during review is referred to the Emergency room by the Clinical Officer. All emergency cases and complicated cases are referred to the Emergency room for review by the Paediatric resident doctor on duty and is responsible for making the final decision of whether to admit the patient or not.

Study Population

The study population was children aged between 6 to 59 months presenting to the PEU.

Case Definition

The study participants were children presenting with a diagnosis of acute diarrhoeal illness with vomiting and some dehydration (Appendix 1 – Table 5).

Inclusion Criteria

1. Age 6 to 59 months;
2. Clinical diagnosis of acute diarrhoea; (Appendix 1 - Table 5)
3. 3 or more episodes of non-bilious, non-bloody vomiting in the preceding 24hrs;
4. Children classified with some dehydration; (Appendix 1 - Table 5)
5. Informed written consent from caregiver.

Exclusion Criteria

1. Treatment with an antiemetic in the previous 24 hours;
2. Clinical diagnosis of dysentery;
3. Underlying chronic illness e.g. Cardiac disease, Liver or Renal failure, malignancy etc.;
4. Severely Malnourished children; (Appendix 1 – Table 5)
5. Known history of hypersensitivity to ondansetron.

Sample size

Estimated sample size using sampsi command in STATA software as shown below:

$$n = \frac{\{u \sqrt{[\pi_1(1 - \pi_1) + \pi_0(1 - \pi_0)]} + v \sqrt{[2\bar{\pi}(1 - \bar{\pi})]}\}^2}{(\pi_0 - \pi_1)^2}$$

n = sample size

Assumption:

u = 0.9, corresponds to power 90%

v = 1.96, corresponds to 5% significance level

Based on the study done by Roslund et al³⁷:

$\pi_1 = 0.216$, corresponds to 21.6% IV fluid therapy in Ondansetron

$\pi_0 = 0.545$, corresponds to 54.5% IV fluid therapy in placebo

Calculated sample size in each arm: 56

Estimated for loss 5%

Final Sample Size in each arm: 60

Total sample Size: 120

Sampling Technique (Randomization and Blinding)

The subjects were randomized into two groups to receive either ondansetron or placebo determined by an allocation list prepared by computer randomization that generated true random numbers using atmospheric noise. The allocation list was sent to an offsite independent study pharmacist that packed the active drug and placebo into tamper proof brown bags. The brown bags were sealed and labelled by the pharmacist according to the allocation sequence provided. The allocation list was then also sealed into a brown envelope and retained by the study pharmacist until the end of the study.

The investigators were blinded to the group assignment until after complete statistical analysis. Both the active drug (ondansetron) and placebo were in the form of dispersible tablets

indistinguishable by taste, odour or appearance. The active drug and placebo were packed in similar sachets with no visible writing on them except for the allocation sequence number assigned. Cachet Pharmaceuticals supplied both the ondansetron tablets and placebo tablets but had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data.

After fulfilling eligibility, patients were sequentially enrolled into the study and received the consecutively assigned brown bags. The allocation of patients was concealed from the principal investigator and research assistants. The researcher had no contact with the pharmacist until the end of the study when the sealed envelope was opened to reveal the allocation sequence.

Procedures

We enrolled a sample of patients with a clinical diagnosis of acute diarrhoeal illness with some dehydration made by the primary clinician (clinical officer) attending to the patient. These children were referred to the ORT room in the PEU for an Oral challenge and observation of oral rehydration with monitoring. The primary clinicians in the study setting use the WHO protocol (Guidelines for The Management of Common Childhood Illnesses) to classify severity of dehydration and treat patients with ORS. This is an important difference in our study from previous studies conducted because of the extent of application in many developing and developed countries, our local policy and its feasibility for outpatient settings.

At the ORT room a research assistant (a registered clinical officer working for the study and trained by the principal investigator) administered an oral challenge to each study participant i.e. ORS Plan B as per standard protocol (Appendix 1 – Figure 5). Patients that failed the oral challenge were then subjected to the inclusion/exclusion criteria by the research assistant and those who satisfied the inclusion criteria were enrolled into the study. Patients were considered to have failed oral challenge if there was vomiting after ORS administration or fluid refusal after three attempts.

Upon enrolment the parent/guardian of the patient was duly informed about the study procedure by the research assistant and written consent obtained from them. The subjects were enrolled in sequential manner to receive an appropriately numbered envelope containing a single oral dose of either ondansetron or placebo unknown to both the patient and research assistant. The similar appearing dispersible ondansetron and placebo tablets used were 4 mg tablets dissolved in water prior to administration. Drug dosing was weight based in which children less than 15 kg received 2 mg (half tablet) and children between 15 to 30 kg received 4 mg (full tablet).

Twenty minutes after administration of the medication, ORT (oral rehydration therapy) was re-initiated and continued based on the amount prescribed earlier by the primary clinician for up to a period of 4 hours. During this period subjects were monitored at half hour intervals in the ORT room to assess hydration status, oral intake and drinking ability. During this period, should there have been any complication or the hydration status worsened, the patients were then referred to the emergency room for review by the paediatric resident doctor on duty.

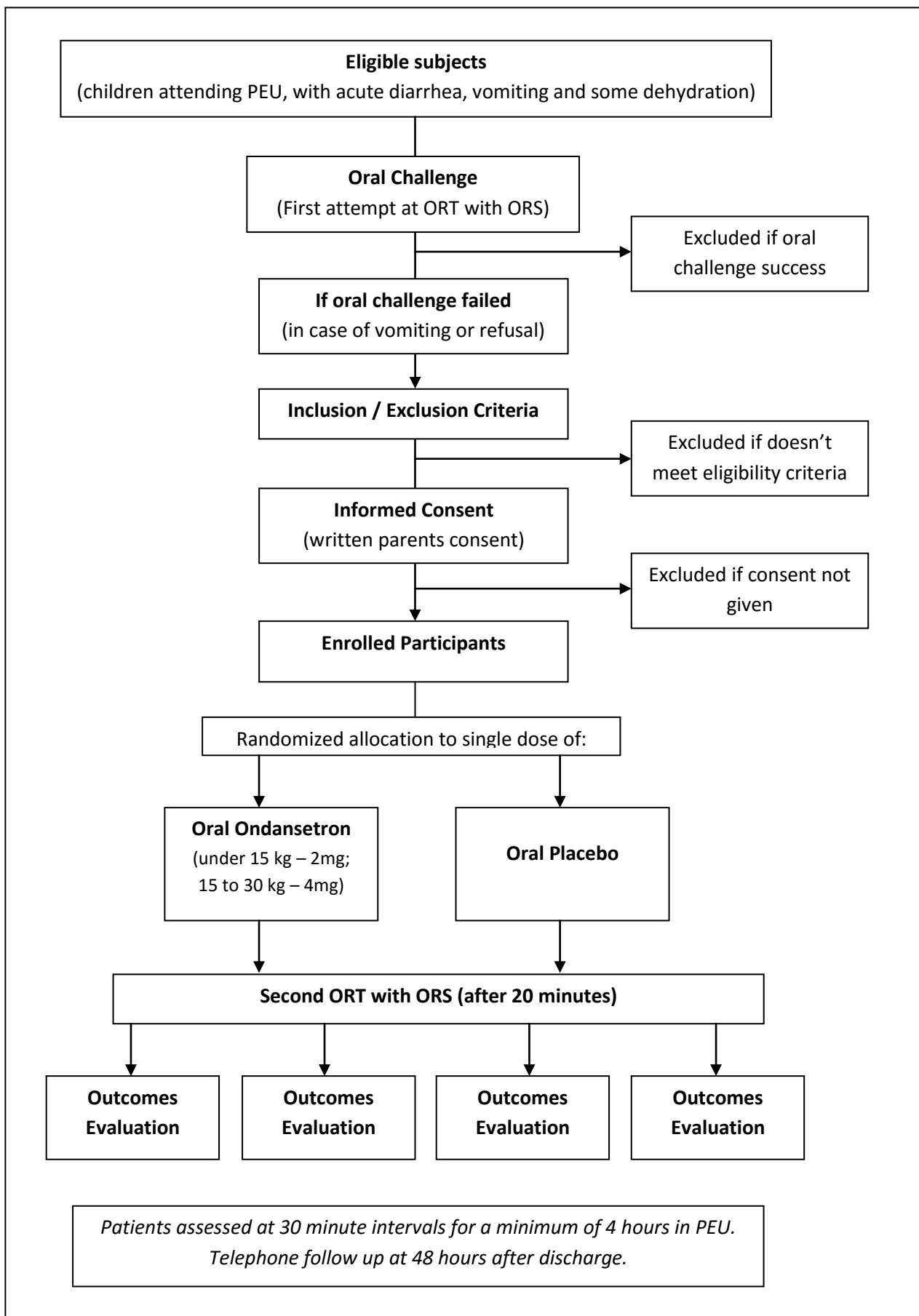
Upon completion of the oral rehydration period subjects were referred back to the primary clinician for re-evaluation and management. Standard of care in this hospital means that patients that tolerated the ORS well and dehydration was found to have resolved, ORT was considered successful and thus discharged home on appropriate treatment i.e. ORS (plan A) and Zinc as per WHO protocol. However, if subjects persisted with some dehydration or further worsened to severe dehydration, ORT was considered unsuccessful. Patients with failed ORT were recommended for hospitalization in order to receive IV fluids for rehydration as per the current standards of treatment in the hospital.

Thereafter Parents/Guardians of all study participants, whether admitted or discharged, received a symptom diary (Appendix 4b) to record episodes of vomiting, diarrhoea or any other adverse event that occurred in the subsequent 48 hours and whether the child was returned to a health facility seeking care for the same illness during that period. A telephone call follow-up was done at the end of the 48 hours, by the principal investigator in order to obtain the information recorded by the parent in the patient symptom diary.

There were two research assistants recruited into the study that assisted with the enrolment, consent, drug administration and observations of the study participants during the period of the study. Both research assistants were certified clinical officers with ETAT+ qualification and received further training relevant to the study from the principal investigator. The two research assistants worked in shifts covering the PEU from 8am to 10pm each day during the period of the study.

A flow chart describing comparison groups and trial procedures is described in Figure 1 below.

Figure 1 – Study Flow Chart



Outcome measures

Primary Outcome

The primary outcome measured was the proportion of patients that failed oral rehydration therapy and hence required admission for intravenous rehydration after administration of ondansetron or placebo.

Secondary Outcomes

The secondary outcomes measured in the two treatment groups were:

1. Number of episodes of emesis up to 48 hours later.
2. Number of episodes of diarrhoea up to 48 hours later.
3. Revisit to a Health Facility up to 48 hours later.

Data Management and Analysis

Data was collected and recorded by the research assistant based in the PEU using data collection forms i.e. Questionnaires and Patient symptom diaries (Appendix 4 – Study Tools). The Data thus obtained was reviewed daily by the primary investigator to identify any errors and omissions before being inputted into STATA software for analysis.

Baseline characteristics of the two groups were compared by the chi-square test for proportion and the analysis of variance for continuous variables. Data obtained was analysed using an intention to treat principle. Descriptive data analysis was done to ascertain proportions and means for categorical and continuous variables, and bi-variate analysis to develop two by two tables. Relative risks and 95% confidence intervals are presented for categorical data while means and standard deviations for continuous data. Chi-square test was used to compare proportions and Student t-test was used to compare means, using a p value of <0.05 for level of significant associations.

Informed consent

Children were recruited in the study only after the purpose of the study was carefully explained to the parent/guardian with the aid of an appended patient information sheet (Appendix 3). Informed verbal and written consent was obtained after giving an opportunity to answer questions and clarifications from the study. Study participants were free to withdraw at anytime from the study.

Confidentiality

Strict confidentiality was maintained throughout the entire study period, held in trust by the investigators, research staff and study institutions. Study participants were identified using serial numbers and no personal identification details recorded. No patient information was released to an unauthorized third party without prior written approval from the ethics committee.

Adverse events

During treatment in the PEU, patients were monitored closely by the research assistants for the development of known adverse effects. The research assistant monitored patients for possible adverse events from enrolment to disposition from PEU. During the interviews parents/guardians were asked for the presence of new symptoms that were of concern or worsening of symptoms that were already present. A significantly increased frequency of diarrhoea from enrolment to 48 hours later was considered an adverse event. However, generalized symptoms related to the underlying illness i.e. fever, vomiting or fatigue were not considered to be adverse events. Review by a data and safety monitoring board would be considered in the event of a serious adverse event.

Source of funding

This study was independently funded by the principal investigator. 'Emitino' the generic tablet form of ondansetron and placebo were both provided at no cost by Cachet Pharmaceuticals India. Currently, 'Emitino' has been registered in Kenya by the Pharmacy and Poisons Board, under the registration identification numbers: H2008/19731/745, and has been approved for administration in children. There is no conflict of interest to report.

Dissemination of results

The findings of the study will be disseminated to the Kenyatta National Hospital. Copies of this dissertation will be made available in the University of Nairobi library and department of Paediatrics and Child Health. The study is also to be published in a peer review journal.

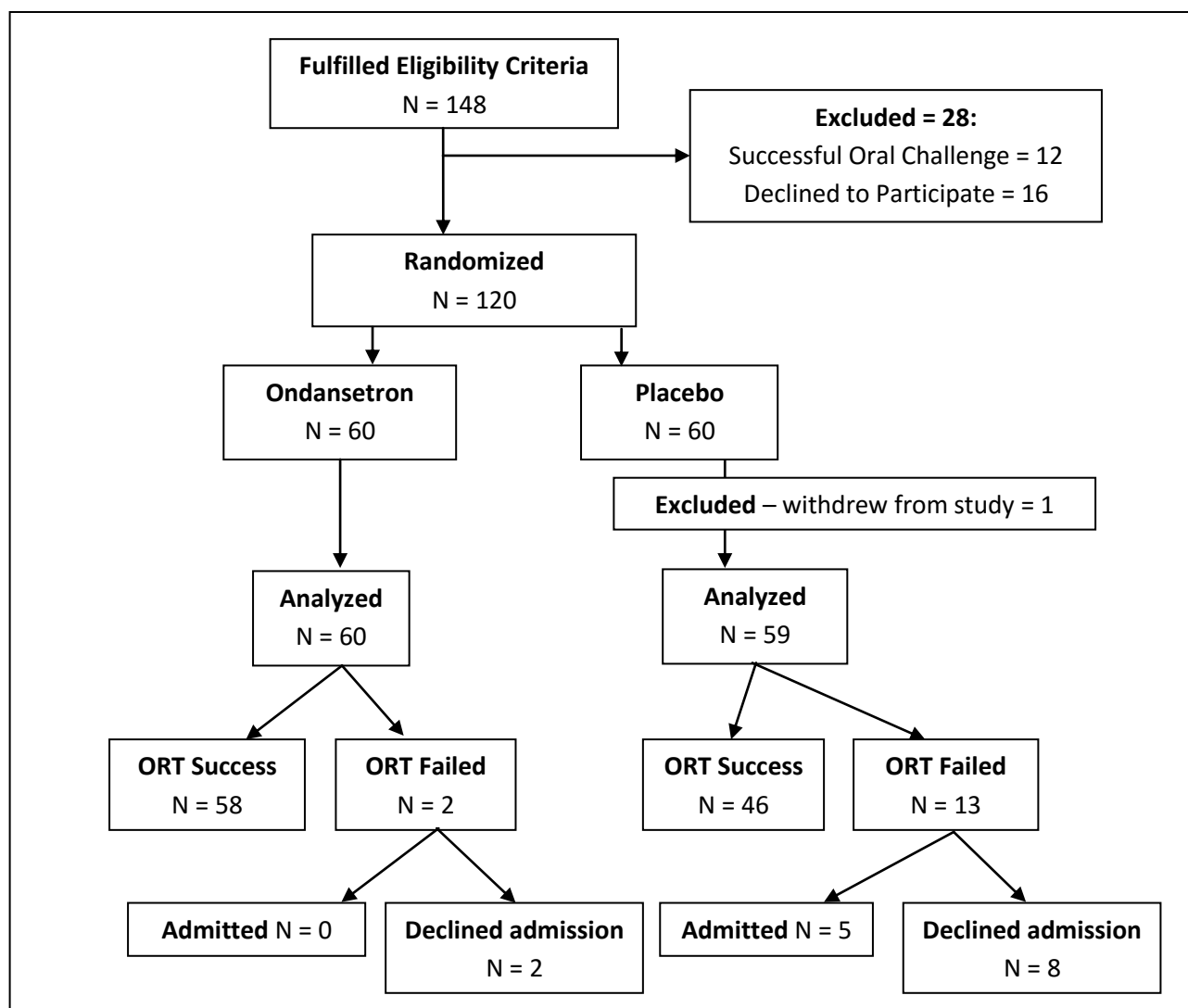
Chapter 5 – Results

A total of 148 children with acute diarrheal illness were screened for the study during the data collection period from the January 7th to February 20th, 2015. These were children aged between 6 months and 5 years who were diagnosed with acute diarrheal illness with some dehydration and had been seen at the Paediatric Emergency Unit.

12 children did not meet the inclusion criteria and parents/guardians of a further 16 chose not to have their children participate after the study was explained to them. A final number of 120 subjects (60 in each arm) were enrolled into the study and randomly assigned to receive either drug or placebo. (See figure 2 below)

Characteristics of Study Participants

Figure 2 – Enrolment and Outcomes



All subjects received the intervention according to their allocations. One of the subjects, from the Placebo arm, was withdrawn as they could not be traced after having received the interventional agent and thus could not be evaluated for outcomes.

The trial ended as planned upon enrolment of the targeted 120 subjects (60 in each arm), with follow up of the final subject done on 22nd February, 2015. Analysis was on an intention to treat basis and included 60 from the drug group and 59 from the placebo group.

Baseline Characteristics of the Enrolled Patients

Table 2 – Table showing Baseline characteristics of the subjects enrolled in the trial*

Characteristic	Ondansetron Group (N=60)	Placebo Group (N=59)
Age – Months		
Mean	18.7 ±13.5	21 ±13.7
Median	14.5	15
Sex		
Male - no. (%)	37 (61.6%)	34 (57.6%)
Female - no. (%)	23 (38.3%)	25 (42.3%)
Weight - Kg.		
Mean	9.45 ±3.4	10.5 ±3.6
Median	8.4	10
<10 Kg. – no.(%)	36 (60.0%)	28 (47.4%)
>10 Kg. – no.(%)	24 (40.0%)	31 (52.5%)
Primary Attending Caregiver		
Mother - no. (%)	54 (90.0%)	51 (86.4%)
Father - no. (%)	4 (6.7%)	6 (10.2%)
Other - no. (%)	2 (3.3%)	2 (3.4%)
Maternal education level		
None – no.(%)	9 (15.0%)	10 (16.9%)
Primary - no. (%)	5 (8.3%)	9 (15.3%)
Secondary - no. (%)	25 (41.7%)	24 (40.7%)
College - no. (%)	19 (31.7%)	13 (22.0%)
University - no. (%)	2 (3.3%)	3 (5.1%)
Vomiting episodes in Preceding 24 hours		
mean vomiting episodes	5.4 ±1.8	5.8 ±2.2
median vomiting episodes	5	6
Diarrhoeal episodes in Preceding 24 hours		
mean diarrhoeal episodes	3.7 ±1.8	3.6 ±1.9
median diarrhoeal episodes	3	3

*Plus-minus values are means ±SD.

The median age of the subjects recruited to the study, was 14.5 months and 15 months for the ondansetron and placebo groups respectively.

There was an overall male predominance in the combined groups, 59.6% as compared with 40.3% of the females. This finding was similar across both groups whereby the male proportion was 61.6% and 57.6% in the ondansetron and placebo groups respectively (Table 2).

There were no significant differences in the baseline characteristics between the two groups. Demographic data, number of emesis episodes and diarrheal episodes prior to enrolment are as depicted in Table 2 above.

Table 3 – Table showing Outcome Measures During PEU Rehydration Therapy*

Outcome	Ondansetron Group(N=60)	Placebo Group(N=59)	RR (95% CI)	P Value
Emesis				
Persistence during ORT – no. (%)	29 (48.3%)	43 (72.9%)	0.66 (0.48 - 0.89)	0.001
Mean no. of episodes	0.73 ±0.97	1.45 ±1.40		0.001
Median no. in those with emesis	1	2		
Failure of ORT - no. (%)	2 (3.3%)	13 (22.0%)	0.15 (0.03 - 0.64)	0.002
Admitted after ORT Failure – no. %	0 (0.0%)	5 (8.5%)	0.08 (0.0 - 1.58)	0.02
Mean no. of Diarrhoeal Episodes	0.6 ±0.66	0.6 ±0.83		0.94
Oral Rehydration fluid consumed – mls	653 ±257	692 ±236		0.29
Length of PEU stay – mins	143 ±34.6	135 ±39.5		0.18

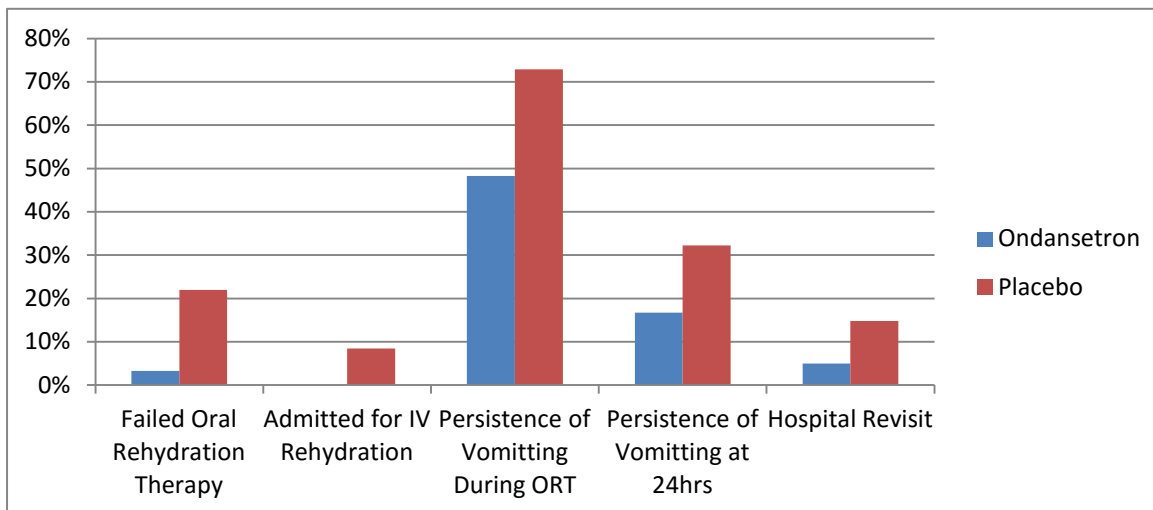
*Plus-minus values are means ±SD.

Proportion of Patients Failing ORT

The primary outcome measure was the proportion of patients failing Oral Rehydration Therapy (ORT) and thus requiring hospitalization for IV rehydration. The proportion of patients failing Oral Rehydration Therapy was higher in the placebo group compared to the ondansetron group i.e. 22% (13 of 59) versus 3.3% (2 of 60), P=0.002 (Table 3 & Figure 3).

Thus the relative risk for failing ORT with ondansetron compared to placebo was 0.15 (95% confidence interval 0.03 to 0.64). Therefore, to prevent 1 child from failing ORT, 5 children had to receive ondansetron (NNT = 5, 95% confidence interval, 3.3 to 13.7).

Figure 3 – Comparison of ORT Failure, Vomiting and Hospital Revisit in Ondansetron versus Placebo

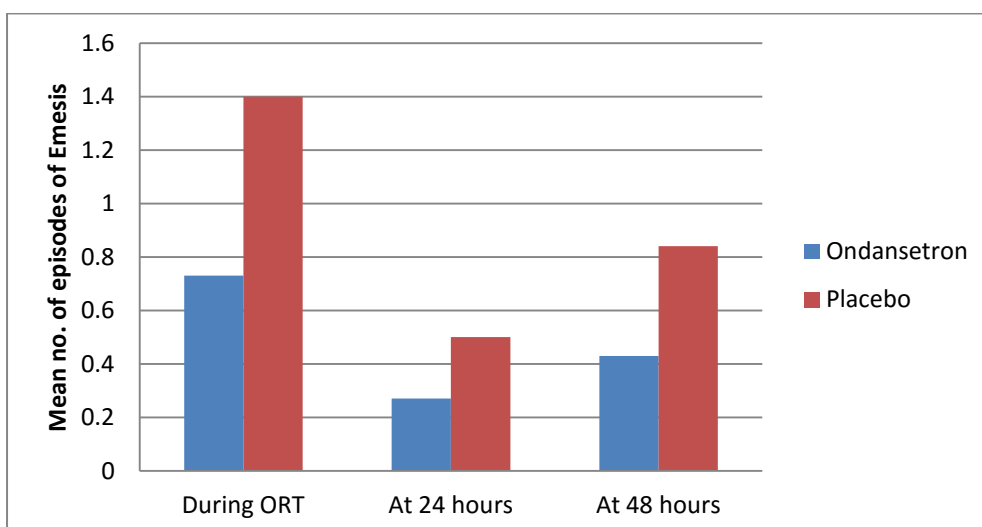


Patients who failed ORT required to be admitted for intravenous fluids as per the standard of care in the hospital. However, the 2 subjects that failed ORT in the ondansetron group both declined admission. In the placebo group, 8 out of the 13 patients that failed ORT also declined admission. As a result, the admissions for IV fluids was 0 in the ondansetron group compared to 5 in the placebo group i.e. 0% vs. 8.5%, $P=0.02$ (Table 3 and Figure 3); which translated into a relative risk of 0.08 (95% confidence interval 0.0 to 1.58).

Emesis during ORT

Patients who received Ondansetron had significantly lower episodes of vomiting and lower likelihood of persistence in vomiting compared to those who received placebo.

Figure 4 – Comparison of Emesis episodes during ORT, at 24 and 48 Hours in Ondansetron vs. Placebo



In the ondansetron group, 29 out of the 60 patients had persistence of vomiting during ORT, as compared to 43 out of 59 patients in the placebo group i.e. 48.3% versus 72.9%, $P=0.001$ (Table 3 & Figure 4). The relative risk for persistence of vomiting with ondansetron versus placebo was 0.66 (95% confidence interval, 0.48 to 0.89). This meant that to prevent vomiting in 1 child, 4 children had to receive ondansetron (NNT = 4, 95% confidence interval, 2.4 to 13.2).

Furthermore, median episodes of vomiting in those who were vomiting during Oral Rehydration Therapy (ORT) was less in the ondansetron group compared to the placebo group i.e. 1 versus 2 respectively. The mean number of episodes of vomiting in all subjects enrolled was 0.73 in the ondansetron group compared to 1.45 in the placebo group, $P=0.001$ (Table 3 and Figure 4).

Other Findings during ORT Period

Overall there was no difference in the two groups with regards to the diarrhoeal episodes during the ORT period. The mean episodes of diarrhoea during ORT was 0.6 (± 0.66) episodes for the ondansetron group versus 0.6 (± 0.83) for the placebo group (Table 3 and Figure 5).

There was also no significant difference between the two groups in either the mean volume of oral-rehydration fluid received or in the mean length of stay in the PEU (Table 3). The mean volume of ORS fluid received by the ondansetron group was 653 ± 257 mls compared to 692 ± 236 mls for the placebo group. The mean length of stay in the PEU in the ondansetron group was 143 ± 34.6 minutes compared to 135 ± 39.5 minutes in the placebo group.

Follow up at 48 Hours

All subjects were followed up at 48 hours via a telephone call regardless of hospitalization. During this call, outcomes on vomiting episodes, diarrhoeal episodes and hospital revisits during the 48 hour period after completion of ORT were obtained and analysed.

Vomiting at 48 Hours

The median number of vomiting episodes at both 24 and 48 hours was found to be zero in both the ondansetron and placebo groups.

However, the mean number of episodes of vomiting was lower in the Ondansetron group compared to the placebo group i.e. at 24 hours, 0.27 episodes in the ondansetron group versus 0.50 episodes in the placebo group, $P=0.11$. At 48 hours, the corresponding numbers were 0.43 in the ondansetron group versus 0.84 in the placebo group, $P=0.04$ (Table 4 and Figure 4).

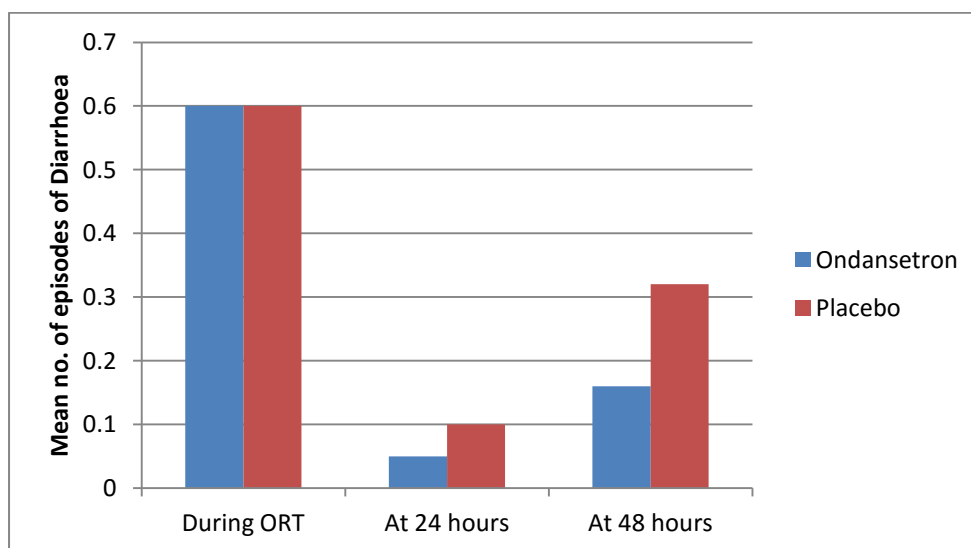
Table 4 – Table showing Caregivers Response on Telephone Follow-up at 48hours*

Outcome	Ondansetron Group	Placebo Group	RR (95% CI)	P Value
ALL SUBJECTS I.E. ADMITTED & DISCHARGED	N=60	N=59		
Emesis Episodes:				
Persistence at 24 hrs - no. (%)	10 (16.7%)	19 (32.2%)	0.51 (0.26 - 1.01)	0.05
Mean episodes at 24 hrs	0.27 ±0.73	0.50 ±0.80		0.11
Median episodes at 24 hrs	0	0		
Mean episodes at 48 hrs	0.43 ±1.04	0.84 ±1.71		0.04
Median episodes at 48 hrs	0	0		
Diarrhoeal Episodes:				
Mean episodes at 24 hrs	0.05 ±0.22	0.10 ±0.55		0.49
Median episodes at 24 hrs	0	0		
Mean episodes at 48 hrs	0.16 ±0.45	0.32 ±1.1		0.34
Median episodes at 48 hrs	0	0		
SUBJECTS NOT ADMITTED	N=60	N=54		
Revisit to a Health facility - no. (%)	3 (5.0%)	8 (14.8%)	0.33 (0.09 - 1.20)	0.11

*Plus-minus values are means ±SD.

Diarrhoea at 48 Hours

Figure 5 – Comparison of Diarrhoeal episodes during ORT, at 24 and 48 Hours in Ondansetron vs. Placebo



There was no significant difference in diarrhoeal episodes between the two groups after administration of the interventional agent up to 48 hours later. The median number of diarrhoea episodes at both 24 and 48 hours was zero in both groups. The mean number of diarrhoea episodes at 24 hours was 0.05 in the ondansetron group and 0.10 in the placebo group, $P=0.49$. The mean number of diarrhoea episodes at 48 hours was 0.16 in the ondansetron group and 0.32 in the placebo group, $P=0.34$ (Table 4 and Figure 5).

Revisit to a Health Facility at 48 Hours

In the subset of patients that were not admitted but discharged from the PEU, the number revisiting a health facility was lower in those who received ondansetron compared to those who received placebo. Of the 60 subjects discharged in the ondansetron group only 3 patients revisited a health facility within the 48 hours after discharge. Whereas, of the 54 subjects discharged in the placebo group, 8 patients revisited a health facility within the 48 hours of discharge. Thus of the discharged patients, hospital revisits in the ondansetron group was 5% compared to 14.8% in the placebo group, $P=0.11$ (Table 4 & Figure 3); Thus patients receiving ondansetron compared to placebo had a Relative Risk of 0.33 (95% confidence interval 0.09 to 1.20) for hospital revisits.

Adverse Events

In both the ondansetron and placebo group, there was no evidence of serious adverse events including headache, vertigo or dermal rash. There were also no significant differences with regards to the number of diarrhoea episodes during both ORT and up to 48 hours after receiving the interventional agent (Figure 4).

Chapter 6 – Discussion, Conclusions and Recommendations

Discussion

This study compared ondansetron to placebo as an adjunct to the management of vomiting in children with an acute diarrhoeal illness and some dehydration. The efficacy of ondansetron as an intravenous antiemetic has been well documented. However, the goal of this study was to determine its effect when given orally and as a single dose. Therefore, the primary focus of the study was to demonstrate if there was any added benefit to the use of single dose oral ondansetron in improving successful oral rehydration in children presenting with vomiting in an acute diarrhoeal illness and some dehydration.

We investigated 119 children, aged from 6 months to 5 years, diagnosed at the PEU with an acute diarrhoeal illness and some dehydration, and referred for ORT in accordance with the World Health Organization (WHO) guidelines. We anticipated that oral ondansetron in our setting would better facilitate oral rehydration and thus preclude the need for hospitalization for intravenous hydration.

In our study we found that with single dose oral ondansetron, patients were less likely to vomit during the ORT period and therefore more likely to have a successful oral rehydration. As a result of this patients who received single dose oral ondansetron were also less likely to be admitted for intravenous hydration than subjects who received placebo. These findings were similar to those described in most other studies done on this subject³⁵⁻³⁸.

In a 2008 study by Roslund et al³⁸ there was a reduction in failure of ORT in patients with acute diarrhoeal illness treated with a single dose of oral ondansetron compared to placebo (21.6% vs. 54.5%). The reduction in ORT failure was similar to that seen in our study in those who received oral ondansetron compared to placebo. The larger proportions of ORT failure seen in the Roslund study could be attributed to the use of the AAP protocol for assessment of dehydration³⁸, unlike the WHO protocol used in our study. The WHO protocol classifies dehydration into two i.e. some and severe dehydration, unlike the AAP dehydration protocol which classifies dehydration into mild, moderate and severe dehydration and is therefore more likely to diagnose dehydration in children.

As seen in our study, a 2006 study by Freedman et al³⁷ also showed that single dose oral ondansetron improves the success of ORT in dehydrated children with an acute diarrhoeal illness.

The Freedman study showed a reduction in the proportion that failed ORT and were therefore treated with intravenous fluids in the ondansetron group compared to placebo (14% vs. 31%)³⁷.

Moreover, in all 3 studies i.e. the Roslund study, Freedman study and our study we found very similar results that support the role of ondansetron as a safe and effective adjunct in ORT for children with acute diarrhoeal illness. All 3 studies demonstrated fewer vomiting episodes and ultimately fewer admissions (4% vs. 5% in the Freedman study, 6% vs. 13% in the Roslund study, and 0% vs. 8.5% in our study)^{37,38}.

A prior study by Ramsook et al³⁶ also examined the role of ondansetron and found a limited benefit in children with an acute diarrhoeal illness. Although there was a modest decrease in number of episodes of emesis in the emergency department and a lower rate of intravenous hydration, the study had several limitations. Subjects in the Ramsook et al³⁶ study were treated if they had a history of vomiting within the preceding 24 hours; because the children were not orally challenged in the emergency department, it is unclear whether they actually needed an antiemetic for successful ORT. In an attempt to avoid this challenge, we only enrolled subjects that failed the oral challenge in the PEU. By ensuring a careful attempt of oral hydration in the PEU, we eliminated those subjects who would have simply tolerated oral rehydration and not required the interventional agent.

Older antiemetics such as metoclopramide and promethazine have also not been widely used, because of their limited success and high rates of serious adverse events in children^{23,24}. Although our study was not designed to detect adverse events, ondansetron was generally well tolerated in our study sample: there were no findings of headache, constipation, fatigue, fever or extrapyramidal reactions. All the subjects in our study remained awake during the ORT period and their ability to drink was not limited because of somnolence.

Although diarrhoea has been reported as an adverse effect of ondansetron in prior studies, we found no significant difference between the ondansetron and placebo groups in the number of diarrhoeal episodes during the PEU stay and up to 48 hours after discharge. In addition, none of the subjects in our study sought further care for increased diarrhoea after discharge. These findings were similar to what was seen in the Roslund study, in which there was no difference detected in the number of diarrheal episodes between the two groups for up to five days after discharge³⁸.

However, the Freedman et al³⁷ study showed a significant increase in diarrhoeal episodes in patients treated with ondansetron during the emergency department stay but the study did not evaluate the diarrhoeal episodes during the follow-up period. Similarly, the Ramsook et al³⁶ study also showed an increase in diarrhoeal episodes in the 48 hours after discharge, however, there was no difference seen during the emergency department stay³⁶. However, this increase could have been attributed to the potential influence of the sorbitol elixir used in the Ramsook study.

Our study is the first of its kind looking at the use of single dose oral ondansetron in an African paediatric population presenting with vomiting in an acute diarrhoeal illness and some dehydration. At a time when interventions to reduce morbidity and mortality from diarrhoea are being studied for inclusion into guidelines for treatment, this study helps further describe the role for ondansetron. It looks at the population hoped to benefit most from the intervention (those with persistent vomiting during oral rehydration therapy) and confirms earlier beliefs that the drug is most beneficial in diarrhoeal illness with some dehydration. This information may therefore help when redesigning guidelines for care on the subject.

Limitations

Although the study had limitations, every attempt was made to minimize their effects on the study outcome. A convenience sample of subjects was enrolled according to the availability of the investigators. The research assistants were available to enrol subjects for about 80 hours per week, typically during the daytime and evening. As a consequence, the study used a convenience sample based entirely on the availability of the investigator.

In addition, some of the patients that met the inclusion criteria were not enrolled even while enrollers were present due to the parents of the patients declining enrolment for various personal reasons. We did not keep track of these failed enrolments despite a research assistant being present and this represents a possible unmeasured source of bias.

The validity of the dehydration determination was another limitation. For each subject, dehydration was graded by the primary clinician in the PEU by selecting each of the appropriate clinical characteristics in Appendix 1 - Table 5. Objective measures were not used to determine the degree of dehydration. The diagnosis and degree of dehydration was determined subjectively by the primary clinician. No attempt was made to quantify the agreement among the primary clinicians on this point, and thus, an inter-rater reliability of dehydration determination could not be analysed.

The variability in the amount of rehydration fluid consumed was also a possible limitation in our study. Although oral rehydration at 75 ml/kg is recommended, some subjects were discharged before receiving the full 75 ml/kg, with instructions to continue the oral rehydration process at home. This was done primarily to avoid crowding in the ORT room and in some cases due to the wishes of the parents. However, patients were only discharged from the ORT room after they demonstrated adequate oral intake and a high likelihood of being able to continue oral rehydration at home. Most subjects tolerated adequate oral hydration at home and did not require a return visit for additional intravenous or oral rehydration.

Finally, our study focused on previously well 6 months to 5 year-old subjects with a diagnosis of acute diarrhoeal illness with some dehydration. Although other studies have included subjects from 1 month to 22 years of age we cannot extrapolate our findings beyond our study sample.

Conclusions

- According to the results mentioned, single dose oral ondansetron is associated with an over 18% reduction in ORT failure in patients with vomiting in an acute diarrhoeal illness.
- Furthermore, single dose oral ondansetron is associated with an 8% lower rate of hospitalization for intravenous rehydration in patients that fail ORT.
- Single dose oral ondansetron decreases vomiting episodes in children with an acute diarrhoeal illness by 24% during the ORT period and by 15% at 24 hours follow up.
- Children who received single dose oral ondansetron for vomiting in an acute diarrhoeal illness had over 9% fewer revisits to a health facility for the same illness, up to 48 hours after discharge.
- Single dose oral Ondansetron did not increase diarrhoeal episodes in children with acute diarrhoeal illness for up to 48 hours after receiving the drug.

Recommendations

- Ondansetron is a safe and effective adjunct to ORS in the oral rehydration process and should be considered in the emergency setting for children with vomiting in an acute diarrhoeal illness and some dehydration.
- Use of single dose oral ondansetron should be considered when preparing guidelines for patients with vomiting in acute diarrhoeal illness.

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Appendix 1 (Figures & Tables)

Figure 6 – Management of Some Dehydration in Acute Diarrhoea

(WHO - Guidelines For The Management Of Common Childhood Illnesses)

Chart 14. Diarrhoea treatment plan B: Treat some dehydration with oral rehydration salts

GIVE THE RECOMMENDED AMOUNT OF ORS IN THE CLINIC OVER 4 H

▶ **Determine amount of ORS to give during first 4 h:**

Age ^a	≤ 4 months	4 to ≤ 12 months	12 months to ≤ 2 years	2 years to ≤ 5 years
Weight	< 6 kg	6–< 10 kg	10–< 12 kg	12–19 kg
	200–400 ml	400–700 ml	700–900 ml	900–1400 ml

^a Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be calculated by multiplying the child's weight (in kg) by 75.

If the child wants more ORS than shown, give more.

▶ **Show the mother how to give ORS solution.**

- Give frequent small sips from a cup.
- If the child vomits, wait 10 min, then continue, but more slowly.
- Continue breastfeeding whenever the child wants.

■ **After 4 h:**

- Reassess the child and classify him or her for dehydration.
- Select the appropriate plan to continue treatment.
- Begin feeding the child in the clinic.

▶ **If the mother must leave before completing treatment:**

- Show her how to prepare ORS solution at home.
- Show her how much ORS to give to finish the 4-h treatment at home.
- Give her enough ORS packets to complete rehydration. Also give her two packets as recommended in plan A.
- Explain the four rules of home treatment:

1. Give extra fluid.
2. Give zinc supplements.
3. Continue feeding.
4. Know when to return to the clinic.

}

See diarrhoea treatment plan A (p. 138) and mother's card (p. 322)

Table 5 – Case Definitions

Children aged 6 months to 5 years presenting with recent onset of vomiting with acute diarrhoea and some dehydration.

DIARRHOEA

WHO definition of Acute Diarrhoea is the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual.

VOMITING

- NICE definition of vomiting is the forceful ejection of the stomach contents up to and out of the mouth.
- Vomiting Episodes separated by no more than two minutes will be counted as a single episode. Non-productive retching, spilling of oral contents, and drooling will not be considered as vomiting.

DEHYDRATION (WHO Classification)

- **Severe Dehydration:** Two or more of the following signs
 - Lethargy or unconsciousness
 - Sunken eyes
 - Unable to drink or drinks poorly
 - Skin pinch goes back very slowly ($\geq 2s$)
- **Some Dehydration:** Two or more of the following signs
 - Restlessness, irritability
 - Sunken eyes
 - Drinks eagerly, thirsty
 - Skin pinch goes back slowly
- **No Dehydration:** Not enough signs to classify as some or severe dehydration

SEVERE ACUTE MALNUTRITION

Severe acute malnutrition is defined in the WHO guidelines as the presence of oedema of both feet or severe wasting i.e. weight-for-height/length $< -3SD$ or midupper arm circumference < 115 mm.

Appendix 2 (Consent)

2a) Consent (English)

Informed Consent Form (ICF) for parents of children between the ages of 6 and 59 months who present to the Paediatric Emergency Unit (PEU) in Kenyatta National Hospital with vomiting and some dehydration due to an acute diarrheal illness and are being requested to participate in research on an antiemetic drug i.e. Ondansetron for the treatment of vomiting in acute diarrhoea.

Principle investigator: Dr. Adeel Ahmad Shah

Institutions: University of Nairobi and Kenyatta National Hospital

Study Title: The effect of ondansetron in children with vomiting and some dehydration in an acute diarrheal illness. A Randomised Double-blinded Placebo controlled trial.

PART I: Information Sheet

I am Dr. Adeel Ahmad Shah a postgraduate student at the University of Nairobi, Department of Paediatrics. I am conducting a study as part of the requirement for the degree of Master of Medicine in Paediatric. The study aims to determine the effect of a new antiemetic (Ondansetron) on children presenting with acute diarrheal illness accompanied by some dehydration and vomiting. The study is based at the Paediatric Emergency Unit in Kenyatta National Hospital.

Diarrheal illnesses are a common and serious problem that affects many children in this country. Though most episodes of diarrhoea in children are mild occasionally it can be severe and lead to significant loss of fluid and dehydration, which can be fatal. Current guidelines approved by the ministry of medical services recommend the use of Oral Rehydration Salts (ORS) and Zinc in the treatment of diarrhoea so as to avoid worsening of dehydration. However, most children with a diarrheal illness commonly present with vomiting which can be very distressing to both the child and caregivers. Despite this, current guidelines do not mention any role of a drug that will assist in reducing vomiting in these children. However, it is known that vomiting makes it difficult for the child who has vomiting and diarrhoea to receive the necessary amount of ORS or any other fluid.

A new drug that helps to stop vomiting called Ondansetron is now available. The drug has been shown to help reduce vomiting episodes in children during diarrheal illnesses and thus reduce the need for fluid drips and admission for the same. Moreover, it allows the child to continue treatment with ORS at home where they are generally more comfortable. The purpose of this study is therefore to test if this drug will be useful in our children.

Children selected for this study will be given a single dose of the drug prior to receiving the treatment prescribed by the clinician seeing them. The drug comes in the form of a tablet that will be dissolved in water and then given to the child. The child will only receive a single dose of this medicine but in-case he/she vomits within 15 minutes of receiving it then they shall receive a repeat dose.

The medicine has already been tested in children with vomiting during diarrheal illness in other parts of the world, and has been found to be useful. Furthermore the drug has also been registered

by the Kenya Pharmacy and Poisons Board and approved for use in both adults and children. However, the medicine is known to have some side effects such as increased diarrhoea, headaches and fatigue. In very rare circumstances and only seen with the injectable form of the drug, arrhythmias (heart beat disturbances) have been reported.

Because we do not know if this medicine will be useful in our setting or if it will be better than the currently available treatment for treating diarrheal illnesses, we need to be able to compare this. Children taking part in this research will therefore be randomly assigned into two groups that will be preselected before-hand.

One group will get the active drug that we are testing, and the other group shall receive a placebo. A placebo or inactive drug looks like the real drug but has no effect on the body and is known as a dummy or pretend medicine. In order to make sure that the research we are undertaking is good and of high quality, it is important that neither the person administering the drug nor the patient are aware of what is being dispensed. This information will be in our records, but it will only be accessed at the end of the research. Once the research is complete we will then compare the two groups and see which of the two has the best results.

If you agree to participate in the study, after your child is discharged from the unit you will be requested to fill a follow up form for the next 48 hours. The nature of the questions in the form will concern episodes of vomiting and diarrhoea, and/or any other drug reaction. After the completion of 48 hours, you will receive a telephone call to confirm the entries made by you in the form.

I would thus like to invite you to participate in this study by allowing your child to receive a potentially active drug and thereafter be monitored during their stay in the unit. I would also like to invite you to participate by providing us with some information regarding your child's experience via a telephone call 48 hours after receiving treatment.

This medicine can, however, have some unwanted effects or effects that we are currently not aware of. Thus, we will follow your child closely and keep track of these unwanted effects or problems. You will be provided with a telephone number that you may call should you notice anything out of the ordinary, or if you are having any concerns or questions related to the study.

By participating in this research it is possible that your child will be at greater risk than he/she would otherwise be. Please note that as a result of taking this drug, there is a possibility that the diarrhoea your child is experiencing may worsen or they may develop headaches or fatigue. While the possibility of this happening is very low, you should still be aware of the possibility. If something unexpected happens and harm does occur as a result of taking this drug, we will provide your child with the care he/she requires for the unwanted effect and we will bear the cost of any investigations and treatment he/she will require including the cost of admission to the general ward if he/she requires.

If your child participates in this research, he/she will have the following benefits: he/she will be followed closely by a nurse/clinical officer during their period of treatment in the Paediatric emergency unit, and they will also be followed up for 48 hours after leaving the unit by me. During this period you may call us with any queries or concerns about the child on the number provided to you. There may be no other obvious benefit for your child but his/her participation is likely to help

us find the answer to this research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit. You will not be with provided any incentive to take part in this research

If you do not wish your child to take part in this research, your child will be provided with the established standard treatment available at the hospital. People who have diarrhoea with some dehydration are given: ORS, Zinc and paracetamol (based on clinician's judgement).

As I seek your participation, I would like to bring to your attention the following ethical considerations which will guide your participation.

1. Participation in this study is purely voluntary.
2. If you choose not to consent, all the services your child receives in this hospital will continue as per the standard of care.
3. You may withdraw from the study at any time and there shall be no consequences with regards to the services your child receives due to your decision to withdraw.
4. After you read through the explanations, please feel free to ask any questions that will allow you to understand the nature of the study.
5. Any information collected from this research including details on your demographic characteristics will be treated as strictly confidential. It will not be shared with or given to anyone except the researchers and hospital ethics board.
6. The knowledge obtained from this study will be made available to the general public and the results published for future scientific purposes.
7. The study protocol has been reviewed by the ethics committee. The protocol can be accessible to you should you choose to know the details.

If you have any questions you may ask them now or later, even after the study has started. You may also ask the assistant who will be present with you throughout the course of treatment during this visit in the PEU.

This proposal has been reviewed and approved by the Ethics, Research and Standards Committee of Kenyatta National Hospital and University of Nairobi {KNH/UON-ERC}, whose task it is to make sure that research participants are protected from harm.

Information on researchers:

Please feel free to contact the following if you have any questions about the study or would like any further information:

Principle investigator:

Dr. Adeel Shah. Telephone number: 0721 485 999

Kenyatta National Hospital and University of Nairobi Ethics Research and Standards Committee (KNH/UON-ERC):

Email: uonknh_erc@uonbi.ac.ke

Website: www.uonbi.ac.ke

Telephone numbers: 020 2726300 (Ext 44355)

PART II: Certificate of Consent

I, the undersigned, as the legal guardian do hereby consent for my child to participate in this study whose nature, purpose and objectives have been fully explained to me. I am aware that participation is voluntary and that there are no consequences to withdrawal from the study. I have been informed that all data provided will be used for the purposes of study only.

Name of Participant (Printed) _____

Name of Parent/Guardian (Printed) _____

Signature of Parent or Guardian _____

Date _____

Statement by the researcher/person obtaining consent

I have accurately read out the information sheet to the parent of the potential participant, and to the best of my ability made sure that the person understands that the following will be done:

1. The child will receive either medicine or placebo
2. The child will be monitored regularly during the period of treatment in the unit
3. The parent will receive a follow up form at discharge to fill over a period of 48 hours
4. The parent will receive a telephone call after 48 hours to obtain the entries made in the follow up form.
5. I confirm that the parent was given an opportunity to ask questions about the study, and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

(A copy of this ICF has been provided to the participant.)

Name of researcher/person obtaining consent (printed) _____

Signature of researcher/person obtaining consent _____

Date _____

2b) Idhini (Kiswahili)

Ukurasa wa maelezo kwa mzazi wa mtoto kati ya umri wa miezi 6 na 56 ambao wamo kwenye sehemu ya kupimia magonjwa ya ghafla (PEU) kwenye Hospitali kuu ya Kitaifa ya Kenyatta wenye kutapika na upungufu kutokana na ugonjwa kali wa Kuhara, wanaombwa kushiriki kwenye uchunguzi juu ya dawa (Antiemetic) ambayo ni (Ondansetron) kwa kutibu kutapika pamoja na kuharisha kwenye nguvu.

Msimamizi Mchunguzi: Daktari Adeel Ahmad Shah.

Mashirika: Chuo Kikuu cha Nairobi na Hospitali Kuu ya Kitaifa ya Kenyatta.

Madhumuni: Uchipukaji, Kupofuka (Placebo) kuzuia juu ya nguvu ya (Ondansetron) kwa watoto wanaotapika na upungufu utokanao na ugonjwa wa Kuharisha kwa nguvu.

Sehemu 1: Ukurasa wa habari.

Mimi Daktari Adeel Ahmad Shah mwanafunzi niliepata Shahada kwenye Chuo Kikuu cha Nairobi, kwenye Kitengo cha (Paediatrics) nachukuwa mafunzo kama sehemu ya mahitaji ya kujipatia Daraja la Ustadi katika (Paediatric). Shabaha ni kuonyesha nguvu ya (Antiemetic) mpya (Ondansetron) juu ya watoto wenye kuharisha kwa nguvu kukifuatana na upungufu na kutapika. Mafunzo yako kwenye (Paediatric) sehemu ya kupimia ya magonjwa ya ghafla kwenye Hospitali Kuu ya Kitaifa ya Kenyatta.

Ugonjwa wa kuhara ni wa kawaida na wenye shida kubwa ambao huathiri watoto wengi katika nchi hii. Ingawaje, mda mwingi wa kuhara kwa watoto kwa mara kwa mara na pole pole inaeza kuwa kali na kupelekea kwenye kukosa maji mwilini na upungufu, ambayo inaeza kuwa mauti. Mongozo wa hivi sasa ulopendekezwa na Wizara ya Madawa na huduma ilishauri matumizi ya (Oral Rehydration Salts-ORS) na madini katika kutibu kuharisha ili kuepuka hali mbaya ya upungufu. Hata hivyo, watoto wengi wenye ugonjwa wa kuhara kawaida huwa wenye kutapika ambapo yaezakuwa dhiki kwa ajili ya wote wawili, yaani mtoto na anayemuangalia. Mbali na hivyo, muongozo wa hivi punde hau elezi kazi yoyote ya dawa yenye kusaidia katika hali ya kutapika kwa watoto hawa. Hata hivyo, inafahamika kwamba kutapika inafanya kuwa ngumu kwa mtoto anayetapika na kuhara kupata madini itakiwayo ya (ORS) au maji yoyote.

Dawa mpya yenye kusaidia kusimamisha kutapika iitwayo (Ondansetron) sasa yapatikana. Hiyo dawa imeonyesha kusaidia upunguzaji wa kutapika katika watoto wenye ugonjwa wa kuhara na pia upunguzaji wa mahitaji ya maji mwilini na uingizaji pia. Zaidi pia, inaruhusu mtoto kuendelea na matibabu ya (ORS) nyumbani ambako kawida hawana shida. Madhumuni ya mafunzo haya, ni kuijaribu dawa hii iwapo itawafaa watoto wetu.

Watoto waliochaguliwa kwa mafunzo haya watapewa kiasi kimoja tu, cha mara moja cha dawa, ikitanguliwa kwa kupata matibabu yaliyoagizwa na Mkufunzi wa matibabu anayewaangalia. Dawa ziko katika hali za kidonge ambayo huyeyushwa kwenye maji, na ndipo kupewa mtoto. Mtoto atapewa pekee kiasi kimoja cha mara moja cha dawa hii, lakini iwapo atatapika ndani ya dakika 15 baada ya kupewa dawa, hivyo atarudiwa tena kupewa kiasi kimoja cha mara moja cha dawa.

Dawa tayari zimejaribiwa kwa watoto wenye kutapika wanapohara katika sehemu zingine za Ulimwengu, na zimeonekana zafaa. Zaidi ya hayo, dawa zimesajiliwa rasmi kwa Halmashauri ya Kenya ya utengenezaji dawa na sumu na kupendekezwa kwa matumizi ya watu wazima na watoto. Hata hivyo, dawa inajulikana ina madhara ya kando kama ongezeko la kuhara, maumivu ya kichwa na uchovu. Kwa uchache, na pia inapatikana katika hali ya shindano, usumbufu wa upigaji moyo pia imeripotiwa.

Kwasababu hatujajuwa iwapo dawa hii itakuwa na manufaa katika msimamo wetu au itakuwa bora kuliko matibabu yaliyoko kwa kutibu magonjwa ya kuharisha, tunahitajika kujibidiisha kulinganisha haya. Watoto wanaochukuwa nafasi kwenye utafiti huu, hivyo basi, watatawanywa makundi mawili ambayo yatakaguliwa mbele yetu.

Kundi moja watapata dawa ifanyayo kazi haraka ambayo tunaijaribu, na lingine litapata (A placebo) au isiyofanya kazi haraka, inaonekana kuwa dawa yenyewe, lakini haina athari kwa mwili kama mfano, au dawa ya kuigiza. Ili kuhakikisha kuwa uchunguzi tunaofanya ni mzuri na wa kiwango cha juu, ni muhimu kuwa eidha yule anayesimamia hiyo dawa, eidha mgonjwa awe na habari ya inavyogawanywa. Habari hii itakuwa katika kumbukumbu zetu, lakini itaidhinishwa tu baada ya uchunguzi. Hapo uchunguzi utakapokamilika, ndiposa, tutalinganisha makundi hayo mawili na kuona nilipi kati ya hayo mawili lenye majibu bora.

Iwapo utakubali kushiriki kwenye mafunzo, baada ya mtoto wako kutolewa kutoka sehemu ya kupimiwa utaombwa kujaza ukurasa wa ufuatiliaji kwa masaa 48 yajayo. Asili ya maswali kwenye ukurasa itahusiana na vipindi vya kutapika na kuhara, na au hali nyengine ya dawa inavyofanya kazi. Baada ya kumalizika masaa 48 utapigiwa simu ili kujua jinsi ulivyojaza huo ukurasa.

Ni matumaini yangu, napenda kuwaalika kushiriki kwenye mafunzo haya kwa kuwaruhusu watoto wenu kupokea dawa yenye kufanya kazi haraka na baadaye waangaliwe vyema wakati wa kukaa kwao kwenye sehemu ya kupimia. Napenda pia kuwaalikeneni ili mshiriki kwa kutuelezea habari zinazohusiana na uzoefu wa mtoto wako kwa njia ya simu baada ya masaa 48 ya kupokea matibabu.

Dawa yaeza, penginepo, kuwa na athari isiyotakikana au athari ambayo kwa mda huu hatuijui, kuihusu. Hivyo tutamfatilia mtoto wako kwa karibu zaidi na kuweka njia maalum wa ufatiliaji wa hizi athari zisizotakikana au shida. Utakabidhiwa nambari yetu ya simu ambayo utatupigia utakapogunduwa kitu chochote nje ile ya kawaida, au iwapo una lolote linalohusu au swali liambatanalo na mafunzo.

Kwa kushiriki kwenye uchunguzi huu yawezekana kuwa mtoto wako atakuwa mwenye bahati kuliko vile angekuwa kwa kutoshiriki. Tafadhali hakikisha kuwa, kwa kuchukuwa dawa kuna uwezekano kuwa, kuhara alikonako mtoto wako huenda kuongezeke au yaeza mpa matokeo ya kuumwa na kichwa au uchovu. Ingawaje uwezekano huu ni wa chini, lakini hata hivyo, lazima uwe mwanagalifu juu ya uwezekano huu. Iwapo chochote kisichotarajiwa kitokee na madhara yatokee kwa kuchukuwa dawa hii, tutampa mtoto wako uangalizi utatikakanao kutokana na athari zisizotakikana na tutagharamia uchunguzi na matibabu yatakayohitajika pamoja na gharama za kiingilio kwa Wadi ya kawida iwapo itahitajika.

Iwapo mtoto wako atashiriki kwenye uchunguzi huu, atapata manufaa yafuatayo:-Ataangaliwa kwa makini na Muuguzi/Mkuu wa utabibu kwenye mda wao wa kutibiwa kwenye sehemu ya kupimia

wagonjwa wa ghafla, na pia kufuatiliwa masaa 48 hata baada ya kutoka kwenye sehemu ya kupimia. Kwenye mda huo pia mnaombwa kutupigia simu kutueleza matokeo yoyote kuhusu mtoto, kutumia nambari ya simu mlopewa. Hakutakuwapo na manufaa yoyote mengine kwa mtoto wako, lakini kushiriki kwake ni kwa kupenda kutusaidia kutafuta majibu la swali la uchunguzi huu. Huenda hakutakuwa na faida yoyote kwa Jamii kwa wakati huu kwa uchunguzi, lakini vizazi vijavyo huenda watafaidika. Hutapewa chochote cha kukushawishi ili kuchukuwa sehemu katika uchunguzi huu.

Iwapo huna nia ya mtoto wako kushiriki kwenye uchunguzi huu, hata hivyo bado mtoto wako atapewa kiwango imara cha matibabu yanayopatikana kwa Hospitali. Watu wenye kuhara na wenye upungufu wanapewa:-ORS,ZINC na Paracetamol(sawa na maamuzi ya Mtabibu).

Kwa ninavyotarajia kushiriki kwenu, napenda kuleta fikara zenu kwa kuangalia maadili yafuatayo ambayo yatawaongoza katika kushiriki kwenu:

1. Kushiriki kwenye mafunzo haya ni kwa kujitolea.
2. Iwapo hutapata idhini, huduma zote watoto wenu watapata kwenye Hospitali hii itaendelea sawa na uangalizi imara.
3. Waezatoka kwenye mafunzo wakati wowote na hakutakuwa na kushurutishwa kutokana na huduma, mtoto wako atapokea sawa na uamuzi wako wa kutoka.
4. Baada ya kusoma maelezo yote, tafadhali jisikie huru kuuliza swali lolote ambalo litakupa uwezo wa kuelewa asili ya mafunzo haya.
5. Habari zozote zitakazokusanywa kwenye uchunguzi huu ikiwemo habari zote za kimwili yatachukuliwa kwa makini kuwa ya kibinafsi. Haitaelezwa au kupewa yeyote isipokuwa Wachunguzi na Kamati ya maadili ya Hospitali pekee.
6. Elimu itakayofundishwa kwenye mafunzo haya yatatawanywa kwa watu wa kawaida na majibu yatachapishwa kwa ajili ya Sayansi ya baadaye.
7. Hati halisi ya mafunzo haya imeangaliwa na Kamati ya Maadili. Hati yaeza chunguzwa kwa ajili yako na kulazimika kujua habari.

Iwapo una maswali au kutaka maelezo zaidi waeza uliza msaidizi wa Mchunguzi ambaye utakuwa naye wakati wowote, wakati wa kipindi cha matibabu kwenye shehemu ya kupimia.

Idhini ya mafunzo haya yametolewa na Hospitali Kuu ya Kitaifa ya Kenyatta na Chuo Kikuu cha Nairobi – Kamati ya Elimu ya maadili (KNH/UON-ERC), ambao walinda wahusika kutokana na madhara ya utafiti kama haya.

Ujumbe kuhusu watafiti:

Tafadhali jihisi huru kuzungumza nasi ikiwa una maswali am unahitaji ujumbe zaidi:

Mtafiti mkuu:

Dr. Adeel Shah. Nambari ya Simu: 0721 485 999

Hospitali Kuu Ya Kenyatta Na Tume Ya Utafiti Ya Chuo Kikuu Cha Nairobi (KNH/UON-ERC):

Barua pepe: uonknh_erc@uonbi.ac.ke

Tavuti: www.uonbi.ac.ke

Nambari za simu: 020 272 6300 (ext 44355)

SEHEMU 2: Cheti cha idhini.

Mimi niliyepewa jukumu kama mlezi natoa idhini ya mtoto wangu ili ashiriki kwenye mafunzo haya, ambayo asili, madhumuni na makusudi yake nimeelezwa kwa ukamilifu. Ninafahamu kuwa, kushiriki ni kwa kujitolea na hakuna jambo lingine ili kutoka kwenye mafunzo. Nimefahamishwa kuwa, mambo ya hakika yote yatakayotolewa yatatumiwa kwa madhumuni ya mafunzo pekee.

Jina la mwenye kushiriki (piga chapa) _____

Jina la Mzazi/ Mlezi (Piga chapa) _____

Sahihi ya Mzazi au Mlezi _____

Tarehe _____

Habari ya anayechunguza/mwenye kupewa idhini.

Kwa usahihi nimemsomea waraka wenye habari kwa mzazi wa mshiriki mhusika, na kwa ubora wa kueleza kwangu nimehakikisha kuwa mtu ameelewa kuwa, yafuatayo yatatekelezwa:-

1. Mtoto atapata dawa au Placebo.
2. Mtoto atachungwa kila mara katika kipindi cha matibabu kwenye sehemu ya kupimiwa.
3. Mzazi atapokea nakala ya ufatiliaji wakati wa kutolewa ili ajaze kwa mda wa masaa 48.
4. Mzazi atapokea simu baada ya masaa 48 ili apewe habari za uingizaji uliofanyika kwenye nakala ya ufatiliaji.
5. Nina imani kuwa mzazi alipewa nafasi ya kuuliza maswali kuhusu mafunzo, na maswali yote yaliyoulizwa na mzazi yalijibiwa sawasawa na kwa sawa ya ubora wa hali yangu, nina imani kuwa, mtu hakulazimishwa katika kutoa idhini, na idhini ilitolewa bila gharama na kwa kujitolea.

(Nakala ya hii Cheti wa Idhini ilikabidhiwa kwa mshiriki).

Jina la Mchunguzi/Mwenye kupewa idhini (piga chapa) _____

Sahihi ya Mchunguzi/Mwenye kupewa idhini _____

Tarehe _____

Appendix 3 – Study Tools

3a) Ondansetron Study – PEU Questionnaire Section I

Study Title: The effect of ondansetron in children with vomiting and some dehydration in an acute diarrheal illness. A Randomised Double-blinded Placebo controlled trial.

This part of the form is to be filled by the interviewer at the point of first contact with the patient presenting at the Paediatric Emergency Unit (PEU) with a diagnosis of acute diarrhoeal illness and some dehydration.

Date: _____

Part 1

Criteria for inclusion into the study:

SECTION 1	TICK (✓ /x)
< 60 months of age	
Acute Diarrhoea (Gastroenteritis) Diagnosis	
Some Dehydration	
At least 3 episodes of vomiting in the previous 24 hours	
No antiemetic use in previous 24 hours	
No blood in stool	
No chronic illnesses or severe PEM	
No history of ondansetron hypersensitivity	
Patient has failed oral challenge i.e. vomited the ORS or fluid refusal after 3 attempts	
Informed Consent Form signed by guardian	

(Only if all the entries above are indicated as a ✓ then patient is eligible for enrollment)

ELIGIBLE		NOT-ELIGIBLE	
-----------------	--	---------------------	--

Signed (interviewer): _____

If patient is eligible then proceed to assign a study code and obtain informed written consent.

Study Code:

3a) Ondansetron Study – PEU Questionnaire Section II

Study Code: _____

Study Title: The effect of ondansetron in children with vomiting and some dehydration in an acute diarrheal illness. A Randomised Double-blinded Placebo controlled trial.

Part 1

This part of the form is to be filled by the interviewer, once the child has been deemed eligible for the study and informed written consent has been obtained

- | | | |
|--|--|--|
| <p>1. Date of enrolment _____</p> <p>2. Patient Surname _____</p> <p>3. Other names _____</p> <p>4. Age(yrs and mo) _____</p> <p>5. Gender (M/F) _____</p> <p>6. Patient weight (Kg) _____</p> <p>7. Area of residence _____</p> <p>8. Guardian name _____</p> | | <p>9. Relationship _____</p> <p>10. Telephone No. _____</p> <p>11. Highest level of education attained by parents: (circle correct option)</p> <p>Mother: None / Primary / Secondary / College / University</p> <p>Father: None / Primary / Secondary / College / University</p> |
|--|--|--|

Part 2

This part of the form is to be completed by the interviewer after the patient has received the interventional drug and oral rehydration has begun i.e. 20 minutes after drug has been given.

- | | |
|--|--|
| 1. Time patient received drug: _____ | 4. No. of emesis in last 24 hours: _____ |
| 2. Time of last emesis: _____ | 5. Amount of ORS prescribed: _____ (mls) |
| 3. No. of stools in last 24 hours: _____ | 6. Time ORS initiated: _____ |

Half Hourly monitoring: (Hour 0 (zero) below indicates time ORS is initiated i.e. as in no. 6 above)

Hr	Time	Hydration status*	ORS amount consumed(ml)	No. of emesis episodes	No. of diarrheal episodes	Drug side effect noted	Drinking ability
0		B	0	0	0	No	-
1							
2							
3							
4							
5							
6							
7							
8							

* Hydration status – A (No Dehydration), B (Some Dehydration), C (Severe dehydration)

** Drinking ability – 1 (Drinking well and tolerating), 2 (Drinking well but not retaining), 3 (Drinking poorly), 4 (Decision to change mode of rehydration), 5 (Treatment completed)

Part 3

This part of the form is to be completed by the interviewer, upon completion of ORT by the patient and has been reviewed by the clinical officer.

1. Time of Review: _____
2. Final Hydration status: _____ (A, B or C as in part 2 above)
3. ORT successful: **Yes or No** (enquire from clinical officer and circle appropriate response)
If No, specify why and measure taken by clinical officer? _____

4. Final Outcome: (circle appropriate response)
 - a. Discharge
 - b. IV Rehydration and discharge
 - c. NG Rehydration and discharge
 - d. Admission
5. If any side effect was noted please describe when, what, where and severity:

3b) Ondansetron Study – Patient Symptom Diary

Study Code: _____

Study Title: The effect of ondansetron in children with vomiting and some dehydration in an acute diarrheal illness. A Randomised Double-blinded Placebo controlled trial.

This part of the form is to be completed by the guardian/parent of the patient after the patient has left the PEU either discharged or home or admitted to the ward.

Relationship of person filling out the form to the patient: _____

Please indicate the number of times your child (patient) had the following:

Day	Date	Number of Vomiting episodes	Number of Diarrhoea episodes
Day 0 (After PEU treatment)			
Day 1 (1 st day after PEU)			
Day 2 (2 nd day after PEU)			

(PEU – Paediatric Emergency Unit at KNH)

1. Did your child get any other medical attention for this illness after discharge?

Yes / No (please circle correct response)

2. If Yes,

a. Where _____

b. When _____

c. Did he/she get fluids intravenously (through a drip)?

Yes / No (please circle correct response)

3. Were you pleased with the medicine you received in the PEU at KNH?

Yes / No (please circle correct response)

4. Would you use this medicine again? **Yes / No** (please circle correct response)

Comment why: _____

5. Development of any new symptoms: _____

6. Any other comments: _____

3c) Ondansetron Study – Investigator Telephone Follow Up Form

Study Title: The effect of ondansetron in children with vomiting and some dehydration in an acute diarrheal illness. A Randomised Double-blinded Placebo controlled trial.

Date of interview: _____ Patient study code: _____

Relationship of interviewee to the patient: _____

Indicate the number of times the patient had the following:

Day	Date	Number of Vomiting episodes	Number of Diarrhoea episodes
Day 0 (After PEU treatment)			
Day 1 (1 st day after PEU)			
Day 2 (2 nd day after PEU)			

1. Did the patient receive any other medical attention for this illness after discharge?

Yes / No (please circle correct response)

2. If Yes,

a. Where _____

b. When _____

c. Did he/she get intravenous fluids? **Yes / No** (circle correct response)

3. Was the parent/guardian pleased with the medicine their child received in PEU?

Yes / No (circle correct response)

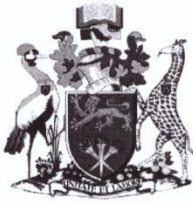
4. Would they use this medicine again? **Yes / No** (circle correct response)

Comment why: _____

5. Did the patient develop any new symptoms: _____

6. Any other comments: _____

Appendix 4 – Ethical Approval



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Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/338

Link: www.uonbi.ac.ke/activities/KNHUoN

10th October 2014

Dr. Adeel Ahmad Shah
Dept. of Paediatrics and Child Health
School of Medicine
University of Nairobi

Dear Dr. Shah

RESEARCH PROPOSAL: EFFECT OF ONDANSETRON IN CHILDREN PRESENTING WITH ACUTE DIARRHOEAL ILLNESS AND VOMITING WITH SOME DEHYDRATION (P424/07/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 10th October 2014 to 9th October 2015.

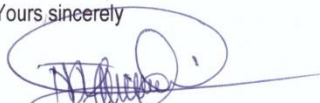
This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
- c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
- g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website www.uonbi.ac.ke/activities/KNHUoN.

Protect to discover

Yours sincerely



PROF.M.L. CHINDIA
SECRETARY, KNH/UON-ERC

- c.c. The Principal, College of Health Sciences, UoN
 The Deputy Director CS, KNH
 The Chair, KNH/UoN-ERC
 The Assistant Director, Health Information, KNH
 The Dean, School of Medicine, UoN
 The Chairman, Dept. of Paediatric & Child Health, UoN
 Supervisors: Prof. Francis E. Onyango, Prof. Dalton Wamalwa, Dr. Ahmed Laving