Analysis of impact of ors with zinc & probiotics supplements in curing acute diarrhoea

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ABSTRACT

Information about diarrheal diseases, their determinants in India, and prevention and control strategies must be reviewed in light of recent developments to ensure better planning and organization of public health services. In childhood, especially in developing countries, diarrhoea is most frequent. This research analyses the usage of ORS and measuring agents in diarrhoea management and care. To test the effectiveness of application of Zinc plus Saccharomyces boulardii (as probiotic) to WHO-ORS as well as to equate these results with WHO-ORS only. Currently, probiotics, in particular, in severe bacterial diarrhoea, are used in various preventive and treatment areas. In this analysis the regulation of vomiting between the three groups was not substantially different (p>0.05). In the ORS+Probiotic Group and ORS+Zinc Group, the patients were shown to be completely hydrated slightly earlier than the ORS group (p < 0.0001). But for the first day, ORS+Zinc Group and ORS+Probiotic Group greatly maintained the lack of stool frequency in contrast with the ORS Group patients. The incidence of losing stool in patients from Probiotic Group were also found to control considerably more quickly. Furthermore, in patients from Probiotic group, the mean length of diarrhoea was fewer. In our research, in the first 48 hours of care, children who were probiotic-present were more vulnerable to diarrhoea with stronger outcomes between 72 and 96 hours, and to increase continuity as well as shortening stays.

INTRODUCTION

Background

The state of at least 3 loose or liquid bowels per day is diarrhea, also classified as diarrhoea (Bhan, 2013). The exhaustion also continues for many days owing to fluid depletion. Signs of dehydration typically arise when the skin becomes normally stretchy as well as irritated (Million Death Study Collaborators, 2010). It will lead in lower urination, skin color loss, faster pulse, and reduced reactivity as it gets extreme. Non-watery but loose stools can be common for infants (WHO, 2013). India has achieved significant advances in minimizing mortalities of children below 5 years in age, from 2.5 million of 2001 to 1.5 million in 2012. India's annual childhood mortality rates have also significantly reduced. The launch and demise of a variety of popular services, including an extended immunization system, diarrhoea prevention and severe respiratory conditions, are responsible for this significant fall. While the mortality rates have declined for children under the age of 5, the equitable mortality rates from severe diarrhoea is still strong (Million Death Study Collaborators, 2010). Diarrhea, which constitutes 13% of child deaths in this age range, is the third highest infant mortality factor in children. In India...
each year over 300,000 children die due to diarrheal implications (B and D, 2013).

Diarrhoea is classified into 3 divisions: severe, watery diarrhoea (often termed dysentery), chronic and messy diarrhoea. Dysentery accounts for 20 percent of deaths from diarrhoea within such forms of diarrhea (Sapone et al., 2012; DuPont, 2014). The usage of oral rehydration (ORS) solutions with decreased osmolality as well as, where applicable, intravenous fluids and zinc supplements are main considerations suggested by the World Health Organisation for the battle against acute gastroenteritis. The severity of diarrhoea during diagnosis has been found to be reduced by timely treatments. Moreover, ORS consumption reduces death and damage caused by diarrhoea but has no influence on the duration and severity of the disease (Lotfi et al., 2015; Boirivant and Strober, 2007). Numerous reports have demonstrated that probiotics are widely used as an alternative remedy for severe diarrhoea.

The probiotics has been identified by the WHO as live microorganisms beneficial to health if ingested in reasonable quantities. Furthermore, Probiotics were used in many areas, particularly acute infectious diarrhoea, for its control and treatment. The antibiotics recommended are treated on the basis of the target pathogen (Boirivant and Strober, 2007; Sharif et al., 2016; Allen, 2011). In recent times, probiotics have also been suggested to reduce bacterial diarrhoea care period and frequency. Whilst most probiotic trials concentrate on acute watery diarrhoea, some reports on dysentery (Allen, 2011) endorse the efficacy of Lactobacillus and Saccharomyces to manage acute diarrhoea and dysentery.

This research has therefore been undertaken in our tertiary core, to determine the efficiency and to only equate such potency outcomes with WHO-ORS in addition to zinc including saccharomyces boulardii (as probiotics).

Research Objectives

To test the effectiveness of application of Zinc plus Saccharomyces boulardii (as probiotic) to WHO-ORS as well as to equate these results with WHO-ORS only.

Literature Review

According to Yazar et al. reports, the impact of symbiotic preparation on children’s length of diarrhoea in relation to zinc suspension were examined in 2016 in a randomized, regulated clinical trial of children with acute infectious diarrhoea (Yazar et al., 2016). The authors observed that diarrhoea durations were greatly decreased in the Symbiotic and Zinc classes, as compared to 114.3 ± 30.9 hours in the control community (p < 0.001; 86.4 ± 30.8) hours vs 114.3 ± 30.9 hour in comparison to 114.3 ± 30.001 hours). The length of diarrhoea between symbiotic as well as zinc classes was not substantially different (p > 0.05). The percentage of children with diarrhoea in the zinc group following 72 and 96 hours were smaller than those in the synergistic probiotic groups (p < .05). The authors conclude that zinc or symbiotic preparations reduce diarrhoea after 72 hours and 96 hours, with better clinical results, both of which can be used in children with acute diarrhea.

(Abraham et al., 2016) have only contrasted in a forward-looking comparative analysis in 2016 the efficacy of zinc-probiotic combination therapy and probiotics therapy and assessed the awareness, actions as well as behaviours (CAP) of mothers of the children affected and their impact and guidance on diarrhoea therapy. The authors found in group 1, 54.6% of patients were male and in group 2, 58.6% were female. The mean age of children affected was 5.14 ± 3.53. The majority of patients in both groups came from outpatient facilities. In group 1, the majority of patients were in the lower economic class with 49.3%, followed by 30.7% in the lower middle class. In group 2, 34.6% of patients came from the lower middle class as well as 28% from the upper-middle class. The authors conclude that low socioeconomic life is a risk factor for diarrhoea. The combination of zinc and probiotic therapy is more effective in treating acute diarrhea and vomiting in children than probiotic therapy or ORS alone.

In a randomised double-clinical trial in 2017, Hesaraki M et al. (Hesaraki, 2017) investigated Kidilact’s impact on diagnosis of children with severe diarrhoea. After 3 days in the experimental sample, the investigators observed that heart rate, body temperature as well as intestinal capacity decreased substantially (p<0.05). Furthermore, weight gain in the intervention community demonstrated an growing increase, which was not significantly separate from the test group (p < 0.05). The authors conclude that the use of Kidilact in the treatment of acute viral diarrhoea in children can play a key role in early recovery, reduce disease severity, and increase life expectancy in these patients.

TREATMENT OF DIARRHOEA

Osmotic Diarrhoea

The involvement of the intestinal lumen of solvents not properly absorbed allows water and electrolytes to pass from plasma to the intestine. Magnesium, phosphate or citrate may be the remedy.
But, in infants, accumulation of carbohydrates is the most popular cause of OSD. Carbohydrates such as lactose, sucrose, isomaltose, glucose and galactose can be present in large amounts in the intestine due to innate or acquired enzymes or transportation defects. Loss of diarrhea during fasting or when removing the affected solute is characteristic of osmotic diarrhea. There is an osmotic gap in the stool (without salt molality - stool (Na + K) x 2 => 50 mOsm). Tables 1, 2, 3 and 4 follows.

**Secretory Diarrhoea**

The secretion of active electrolytes with associated water may trigger this kind of diarrhoea. Dirt may be plasma isotonic and may affect the intestine or even outside. Large amounts of secretions may be ubiquitous or marked. Hormones (vasoactive intestinal polypeptides--VIP), bacterial poisons (E coli, cholera), and medicines can instigate increased intestinal secretions. These compounds, as well as bile acids, the adenyl cyclase and prostaglandins induces a rise in cyclic AMP in the mucosal lining as well as increase in secretions. Secretory diarrhea is usually large in volume, persists during fasting, and has an isotonic electrolyte composition.

**ORS**

An easy cost-effective and life-saving treatment for dehydration protection in diarrhoeal children; oral rehydration solution (ORS) is a cure for dehydration or excess water loss. Once the ORS has reached in the gastrointestinal tract/small intestine the combination of sodium with glucose is distributed through the intestinal lining, as well as the water retention in the intestines is facilitated back to the body by sodium that is now at elevated rates in the digestive tract.

**Zinc**

The general safety, growth and production of zinc is important. This also makes the immune system work appropriately. Zinc insufficiency is predominant within the developing world, but it is commonly present in protein-rich foods along with other food products, and has also been linked with higher outbreak levels of diarrhoea as well as the mortalities from such conditions.

Zinc status can not be assessed consistently. The plasma zinc levels typically vary from 80 to 120 g / l or 12–18 mol / l. Though, circulated amounts of Zinc are insufficient, there are many factors that render this calculation ineffective for low circulated zinc rates. Leukocyte zinc levels have lately been found to have become a good predictor of a zinc deficit, but this test can not be achieved easily. 58 At present, many scientific criteria are used to determine zinc status and specifications in the best possible way.

**Saccharomyces Boulardii as a Probiotic**

An increase in the number of potential health benefits is associated with probiotic treatment. However, only a limited number have been confirmed in randomized and well-designed randomized controlled trials (RCTs), and even fewer in the pediatric population. S. boulardii is a live yeast that is often used as a probiotic and is often marketed as a food supplement (Billoo et al., 2006). Several specific host mechanisms of action and pathogenic microorganisms have been identified, including regulation of intestinal microbial homeostasis, impaired pathogenic ability to colonize and infect mucous membranes, modulation of local and systemic immune responses, and stabilization of the gastrointestinal tract. Practice and intestinal stabilization of enzyme activity, which supports absorption and nutrition (G et al., 2014).

**Mechanism of action of Saccharomyces boulardii**

**Luminal effect**

**Antimicrobial activity**

1. Inhibition of bacterial and parasitic growth
2. Reduction of intestinal pathogen translocation
3. Neutralization of bacterial virulence factors
4. Suppression of host cell adhesion which interferes with bacterial colonization

**Antitoxin effect**

1. Inhibition of toxin receptor binding site
2. Stimulation of antibody production against Clostridium difficile A.
3. Direct proteinolysis of pathogenic toxins / enzyme protein secretions

**S. boulardii effects on adaptive immunity**

1. Increase the systemic immune response and serum IgG levels to the toxins Clostridium difficile A and B.
2. Increase the mucosal immune response and the level of IgA secretion in the intestine
3. Inhibits the activation of T cells induced by dendritic cells.
4. Stimulate regulatory T cells.
5. Contribute to previous IFN-γ and IL-12 production
6. Change the lymphocyte migration in the inflammatory bowel disease model
| Table 1: Distribution of patients according to Age |
|-----------------------------------------------|
| **Age (months)** | **ORS Group** | **ORS+Zinc Group** | **ORS+Probiotic Group** |
| **Values** | **N** | **%** | **N** | **%** | **N** | **%** |
| 6-12 | 6 | 12% | 7 | 14% | 6 | 12% |
| 13-24 | 8 | 16% | 8 | 16% | 9 | 18% |
| 25-36 | 13 | 26% | 14 | 28% | 15 | 30% |
| 37-48 | 12 | 24% | 11 | 22% | 11 | 22% |
| 49-60 | 11 | 22% | 10 | 20% | 9 | 18% |
| **Total** | 50 | 100% | 50 | 100% | 50 | 100% |
| **Mean±SD** | 34.2±15.9 | 33.3±15.7 | 32.9±15.5 |
| **p Value** | P=0.9141 (ANOVA) |

| Table 2: Status of Vomiting of in-patients |
|------------------------------------------|
| **Vomiting** | **ORS Group** | **ORS + Zinc Group** | **ORS + Probiotic Group** | **Chi square** | **p value** |
| **N** | **%** | **N** | **%** | **N** | **%** | **%** | **%** |
| Day1 | Present | 18 | 36% | 15 | 30% | 14 | 28% | 0.80 | 0.66 |
| Absent | 32 | 64% | 35 | 70% | 36 | 72% | - | - |
| Day2 | Present | 16 | 32% | 12 | 24% | 10 | 20% | 1.97 | 0.377 |
| Absent | 34 | 68% | 38 | 76% | 40 | 80% | - | - |
| Day3 | Present | 8 | 16% | 8 | 16% | 5 | 10% | 0.99 | 0.60 |
| Absent | 42 | 84% | 42 | 84% | 45 | 90% | - | - |
| Day4* | Present | 0 | - | 2 | 4% | 3 | 7% | - | - |
| Absent | 49 | 98% | 46 | 96% | 41 | 82% | - | - |
| Day5* | Present | 0 | - | 0 | - | 0 | - | - | - |
| Absent | 47 | 94% | 45 | 90% | 38 | 76% | - | - |

| Table 3: Status of dehydration of in-patients |
|---------------------------------------------|
| **Dehydration** | **ORS Group** | **ORS+Zinc Group** | **ORS+Probiotic Group** | **p Value** |
| **N** | **%** | **N** | **%** | **N** | **%** | **%** |
| Day1 | Present | 40 | 80% | 39 | 78% | 42 | 84% | p<0.0001 |
| Absent | 10 | 20% | 11 | 22% | 8 | 16% | (Chi-Square value - 43.027) |
| Day2 | Present | 18 | 36% | 12 | 24% | 4 | 8% | - |
| Absent | 32 | 64% | 38 | 76% | 46 | 92% | - |
| Day3 | Present | 10 | 20% | 0 | - | 0 | - | - |
| Absent | 40 | 80% | 50 | 100% | 50 | 100% | - |
| Day4* | Present | 0 | - | 0 | - | 0 | - | - |
| Absent | 49 | 98% | 48 | 96% | 44 | 88% | - |
| Day5* | Present | 0 | - | 0 | - | 0 | - | - |
| Absent | 47 | 94% | 45 | 90% | 38 | 76% | - | - |
**Table 4: Total cases after 5th day of study**

| Status of cases | Day | ORS | ORS+Zinc | ORS+Probiotic |
|-----------------|-----|-----|----------|--------------|
| Discharged      | 3   | 1   | 2        | 6            |
|                 | 4   | 2   | 3        | 6            |
|                 | 5   | 6   | 9        | 13           |
| Under observation after 5th day | 41  | 36  | 25       |

7. Change lymphocyte adhesion to endothelial cells, increase motility and cell adhesion.

Clinical efficacy of *Saccharomyces boulardii* in acute and chronic diseases,

Persistent diarrhoea Antibiotic-associated diarrhoea Enteral nutrition-related diarrhoea Acute diarrhoea Human Immunodeficiency virus related diarrhoea Helicobacter Pylori Infection Clostridium difficile infection Traveler’s diarrhoea Chron’s disease Ulcerative colitis Inflammatory bowel disease Parasitic infection

**Diarrhoeal Management**

Routine management of acute diarrhoea should be based on clinical features. Microbiological examination is not helpful in most cases and should be reserved for persistent diarrhoea for which antibiotic treatment is potentially useful. However, compliance with the guidelines is far from optimal, and generally inappropriate medical interventions for acute gastroenteritis may increase the costs while prolonging the duration of the disease (Htwe et al., 2008; Ahmadi et al., 2015).

The ORS is recommended as a firstline treatment for acute diarrhoea and should be initiated as soon as possible after the onset of symptoms. Oral rehydration solution is commonly used worldwide, also if the composition of the ORS is not yet standardized and different sodium concentrations are routinely used in different countries. So far, most trials have been conducted using the WHO standard ORS (90 mmol/liter Na+) or the “reduced osmolarity ORS” (75 mmol/liter Na+) in children in developing regions. Large systematic reviews showed that the so-called “reduced osmolarity ORS” was associated with fewer unscheduled intravenous fluid infusions, lower stool volume and less vomiting than the WHO standard ORS (B and D, 2013; Sapone et al., 2012; DuPont, 2014).

**MATERIALS AND METHODS**

The hospital based observational comparative study was undertaken to evaluate the efficacy of addition of Zinc and *Saccharomyces boulardii* (as probiotic supplement) to WHO-ORS and compare those effects with WHO-ORS alone in treating children with acute watery diarrhoea. 150 patients were divided into the following three groups of 50 patients,

**ORS Group**

Patients received WHO-ORS only

**ORS+Zinc Group**

Patients received WHO-ORS with Zinc

**ORS+Probiotic Group**

Patients received WHO-ORS and *S.Boulardii*

**Source of data**

Paediatric patients attending Krishna Institute of medical sciences deemed university, Karad for treatment of acute diarrhoea.

**Study duration**

18 months

**Study design**

The hospital based observational comparative study

**Sample size**

150 patients

150 (Group A with 50 controls + 100 cases divided into group B and group C) Trial size was computed by the use of given equation,

\[ n = \left( \frac{Z^2 \cdot p \cdot (1 - p)}{d^2} \right) \]

where: \( Z \) = table value of alpha error from Standard Normal Distribution table (0.95).

Power (p) = 80%

Precision error of estimation (d)= 0.55

\[ n = \left[ 0.95 \times 0.95 \times 0.8 \times (0.2) \right] / 0.55 \times 0.55 = 47.7 \]

**Methodology**

The subjects were divided into THREE groups, the first group i.e. Group A received WHO-ORS only, the second group i.e. Group B received WHO-ORS with Zinc and the third group i.e. Group C received WHO-ORS, *S.Boulardii*. Their effects were compared based on the outcome measures (Allen, 2011; Yazar et al., 2016).

**Outcome Measures**
1. Status of vomiting
2. Status of dehydration
3. Status of stool frequency
4. Status of stool consistency
5. Comparision of mean duration of diarrhoea
6. Comparision of mean duration of hospital stay

The following investigations were done,
1. Stool routine and reducing substance
2. Serum sodium, potassium
3. CBC

Clinical Examination
A thorough clinical examination was done for all children including weight, temperature, pulse rate, and respiratory rate. Status of vomiting, dehydration, stool frequency, stool consistency, and mean duration of diarrhoea with mean duration of hospital stay was studied and compared in all the three groups. Those who were well hydrated, improved consistency and had well formed stools were discharged accordingly and were not included in the study thereafter.

Statistical Analysis
The mean and standard deviation are used to display the quantitative statistics. The relation between the trial groups is carried out using the unpaired t scale, as per rationality scale findings. Supporting the frequency as well as the percentage table, output qualitative statistical data is exhibited. For the sample validation and outputs, student’s ‘t’ test and Chi-Square ‘p’ tests have been used to determine the relationship between the research classes p<0.05 is deemed to be relevant.

RESULT OUTCOMES

Distribution of patients according to Age (months)
Age distribution was done according to the months. The ORS group had 12% of patients in the age group from 6 to 12 months, while 16% and 26% were in the age group from 13 to 24 months as well as 25 to 36 months, respectively. 24% and 22% of patients were in the 37-48 as well as 49-60 months age groups. The mean age of the patients was 34.2 ± 15.9 months. The ORS + zinc group had 14% of patients in the 6-12-month age group, while 16% and 28% were in the 13-24 month and 25-36-month age groups respectively. 22% and 20% of patients are in the 37-48 and 49-60-month age groups. The mean age of the patients was 33.3 ± 15.7 months. The ORS + Probiotic had 12% of patients in the 6 to 12-month age group, while 18% and 30% were in the 13 to 24 month and 25 to 36 month age groups respectively. 22% and 18% of patients were in the 37-48 as well as 49-60-month age groups, respectively. The mean age of the patients was 32.9 ± 15.5 months. Age distribution in groups is proportional according to ANOVA and not statistically significant (p>0.05).

Status of Vomiting of in-patients
Overall association between vomiting in ORS Group, ORS+Zinc Group and ORS+Probiotic Group. On Day 1, vomiting was present in 36% patients in ORS Group and in 30% and 28% patients of ORS+Zinc Group and ORS+Probiotic Group respectively. There was no vomiting present in all patients of ORS Group by Day 4 while vomiting was present in 2 patients of ORS+Zinc Group and 3 patients of ORS+Probiotic Group for which they were given antiemetic after which it resolved. There was no significant difference in controlling the vomiting between the three groups (p>0.05).

Status of Dehydration of in-patients
On Day 1, moderate dehydration was present in 80% patients in ORS Group and in 78% and 84% patients of ORS+Zinc Group and ORS+Probiotic Group respectively. There was no dehydration in all patients of ORS Group by Day 4 while all patients of ORS+Zinc Group and ORS+Probiotic Group were fully hydrated by Day 3. It was observed that patients were fully hydrated significantly faster in ORS+Probiotic Group and ORS+zinc group as compared to ORS Group (p<0.0001).

Number of cases after day 5 of study
On day 5, 50% of patients in ORS+Probiotic group, 28% from ORS+Zinc and 18% from ORS+Zinc were well hydrated with reduced frequency and improved consistency of stool, hence they were discharged. As the present study was planned for 5 days observation period, hence those cases which did not show all round improvement were observed and were under treatment in ward.

CONCLUSIONS
The application of zinc or probiotics (Saccharomyces Boulardii) reduces the severity of diarrhoea with aqueous diarrhoea that is not contagious severe. In our research, in the first 48 hours of care, children who were probiotic-present were more vulnerable
to diarrhoea with stronger outcomes between 72 and 96 hours, and to increase continuity as well as shortening stays. Children undergo diarrheal treatments and handle S. boulardii well without any side effect as clinical trial records have reported. WHO suggest zinc and pro-biotics should propose minimizing hospitalization, improving stuff quality and decreasing occurrence of severe non-communicable diarrhoea (Saccharomyces boulardii).

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Conflict of Interest

I hereby declare that there is no conflict of interest related to this manuscript.

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