

## Comparison Of Clinical Efficacy Of Combined Versus Monotherapy Of Oral Zinc And Probiotic In Pediatric Acute Diarrhoea At Benazir Bhutto Shaheed Teaching Hospital, Abbottabad

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### ABSTRACT:

**Objective:** Evaluation of effectiveness of zinc/ probiotics alone and in combination in children with acute diarrhoea.

**Place of Study:** The study was conducted from May-Dec 2017 at Benazir Bhutto Shaheed Teaching Hospital Abbottabad.

**Methodology:** Single centered, randomized controlled clinical trial was performed in 150 children of either sex (6 months -10 years) with acute diarrhoea having stool frequency of > 5 semi liquid stools per day. Patients were divided into three groups with fifty children in each group on the basis of treatment modality given. Group A received zinc orally (1-2mg/kg/day for five days along ORS and/or IV fluids if required), Group B patients were given one to two sachets of probiotics /day (saccharomyces boulardii) according to age for five days + ORS and /or IV fluid while Group C was administered combination of zinc and probiotics for five days along with ORS and /or IV fluids. Response to treatment was determined on the basis of decrease in frequency of stools i.e. <3 formed stools /day after 72 hours of commencement of treatment. We have also studied the relationship between hygiene and food intake practices with the occurrence of diarrhoea in children.

**Results:** Acute diarrhoea was found to be more prevalent in children with poor hygiene practices and using unboiled water. Among the treatment groups, at the end of 3<sup>rd</sup> day total of forty eight (96%) patients in group C had improved consistency of stools as well as decrease in diarrhoea frequency to less than three formed stools per day while in groups A and B thirty nine (78%) and sixteen (32%) patients respectively showed response to treatment in 72 hours.

**Conclusion:** Combination of zinc + probiotics therapy is more effective in children with acute diarrhoea than either alone. Among the zinc and probiotics therapy, zinc is superior in terms of clinical efficacy than probiotics alone.

**Keywords:** Clinical Efficacy, Zinc, Probiotic, Acute Diarrhoea

### INTRODUCTION:

Diarrhoea associated morbidities are an important health issue worldwide, most common in third world countries. It is postulated that in pediatric population of less than five age group, 21% of the mortality rate is due to unmanaged diarrhoea. This amounts to 2.5 million expiries in less than five age group<sup>1</sup>. Different researches done in the nineteenth century assessed that 4.6 million was the mortality figure in paediatric population from gastroenteritis<sup>2</sup>. Throughout the world, gastroenteritis is one of the significant reasons of death in children, with almost hundreds of million incidents per year and ten to twenty hundred thousand deaths evaluated per annum in children less than five years of age<sup>3</sup>.

Diarrhoea is said to be present when there are three or more unformed stools in a twenty four hour time or one or more

loose stool containing blood. New episode of diarrhoea is labeled if the patient has at least three diarrhoea free days<sup>4</sup>. World Health Organisation incorporated oral rehydration solution (ORS) in the diarrhoea management guidelines thereby decreasing deaths in children by a great proportion<sup>5</sup>. Still acute gastroenteritis poses alarming contribution to paediatric mortality rate inspite of gains with oral rehydration therapy (ORS). Reason for this may be that ORS though improves the hydration status it has no effect on modulation of diarrhoeal episodes and their total extent, so other modalities of treatment to augment the role of ORS have been desired. Many advances have been made in this regard with the inclusion of zinc and probiotics to the paediatric diarrhoea management guidelines<sup>6</sup>. Reduction of diarrhoea associated diseases and subsequent death rates in children has been attributed to two treatment modalities, that is the ORS and zinc supplements<sup>7</sup>. The Centre for Disease Control (CDC) in early nineties gave national guideline, stressing upon the significance of the timely intervention of pediatric gastroenteritis and role of zinc in its management. Since then, many clinical studies have been done for evaluation of zinc and probiotics administration on the duration and extent of diarrhoea<sup>4,6,8</sup>.

Zinc is a fundamental part of nutrition which prevents oxidative damage to the cell. It does not get stored in the body so its deficiency may develop in diarrhoea affected children due to losses from the damaged gut. The effectiveness of zinc therapy in diarrhoea may be due to the

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fact that it increases the overall absorptive capacity as well as more rapid repair of damaged intestine epithelium<sup>9</sup>. It may be used either in tablet form or suspension form, both preparations having the same zinc sulphate monohydrate formulation, but with different efficacy, which was first observed in 2005 after an earthquake in northern areas of Pakistan. After the earthquake a massive number of children developed diarrhoea due to poor hygiene in camps, and zinc was available there in both forms for diarrhoea management. There was the improvement with the treatment of zinc, but there was difference in the efficacy level between zinc tablet and suspension<sup>10</sup>.

Lately, therapeutics of probiotics has been studied in different trials in which the beneficial use in pediatric acute diarrhoea is prominent, so European Society for Pediatric Infectious Diseases has incorporated use of probiotics in the guidelines for management of gastroenteritis in children<sup>11-12</sup>. *Saccharomyces boulardii*, a probiotic is a useful yeast that was initially found in fruits. In the prophylaxis and management of acute paediatric gastroenteritis, *S. boulardii* has shown clinical effectiveness as reported in different clinical studies<sup>11</sup>. The potential therapeutic effect of probiotics may result from their ability to regulate the intestinal microbial homeostasis, disruption of bacterial invasion of intestinal mucosa, immune system modulation, reinforcement of the gut mucosal function and increasing absorptive and nutrient functioning of the intestine<sup>12</sup>.

Studies have been done in Pakistan to investigate the importance of zinc and probiotic administration in acute diarrhoea but no study has compared the clinical efficacy of combination of zinc and probiotics with monotherapy with either in children with acute diarrhoea. Comparison of effects of zinc/ probiotics alone and in combination in paediatric acute diarrhoea (on the basis of decrease in frequency of stools)

#### SUBJECTS AND METHODS:

This single centered, randomized controlled clinical trial was conducted in Abbottabad at Benazir Bhutto Shaheed Teaching Hospital between May, 2017 to December, 2017. Prior approval to carry out the research was taken from the Ethical Committee of the hospital. One hundred and fifty children of either sex, aged between six months to ten years presenting with acute diarrhoea having stool frequency of more than five semi liquid stools per day reporting in OPD as well as admitted children were employed in the study. Permission was sought from the parents/guardians of the children and the children whose parents did not approve were excluded from the study. Other features of exclusion criteria included severely dehydrated children and those requiring ICU, presence of blood in stools, use of antibiotics /probiotics in last four weeks and children likely to move away from the study area during the treatment. Data comprising of duration and frequency of diarrhoea along

with associated symptoms such as vomiting, fever as well as detailed food intake and hygiene practices of both mothers and children was collected on specially designed questionnaire. Patients were then divided by simple randomization based on random numbers into three groups (A, B and C) of fifty patients in each on the basis of treatment modality. Group A: Fifty patients received zinc 1-2mg/kg/day orally five days as per WHO protocol along with ORS and/or IV fluids if req.

Group B: Fifty patients were given 1-2 sachets /day of probiotics according to age (<1 years old - 1 sachet) for five days along with ORS and /or IV fluid if required. The composition of probiotics sachet was: *saccharomyces boulardii*

Group C: Fifty patients were administered a combination of zinc and probiotics in doses mentioned above for five days along with ORS and /or IV fluid as required.

Response to treatment was taken as the decrease in frequency of stools; that is less than three formed stools in a day. Data was analysed using SPSS version 21.0. For comparative analyses chi-square test was used,  $p$  value <0.05 was considered significant. Frequencies of categorical variables evaluated in this study are expressed in percentages.

#### RESULTS:

The study was performed on 150 patients with acute diarrhoea divided randomly into three groups of fifty patients in each. In Group A, in which zinc suspension was given, in the first twenty four hours two patients responded with decrease in diarrhoeal episodes to less than three stools per day as well as improvement in its consistency while maximum therapeutic effect was seen on 3<sup>rd</sup> day where out of total fifty patients thirty nine (78% of group population) children showed response to therapy, only eleven children did not respond and still had more than 5 episodes of watery diarrhoea even after 72 hours of treatment as shown in Figure 1.

In group B, in which only probiotic was given, initially in the first 24 hours no response to therapy was observed. However on the 2<sup>nd</sup> day six patients had decrease in frequency of diarrhoea followed by ten more children recovering in the next 24 hours (32% of group population) as shown below in Figure 1. However thirty four children did not show improvement even after 72 hours of starting the treatment.

In group C where combination of Zinc suspension and probiotic was given, response to therapy was appreciable in first 24 hours where five children recovered from watery diarrhoeal episodes and by the end of third day all fifty patients except for two (96 % of group population) had less than 3 stools per day with semi solid consistency as shown below in Figure 1.

On comparison between Group A and Group B after 72 hours of starting treatment  $p$  value is <0.05 that is considered statistically significant. Also when Group C was compared with Group A and Group B respectively,  $p$  value was < 0.05

which shows that combination therapy is clinically more efficacious in terms of decreasing stool frequency in patients with acute diarrhoea as compared to monotherapy with either.

Amongst the total study population of 150 patients, male patients predominate with a total of 87 (58%) while 63 (42%) were female; giving male to female ratio 1.38:1. Gender wise, there was no significant difference amongst the patients. Moreover, 66 out of 150 (44%) patients were

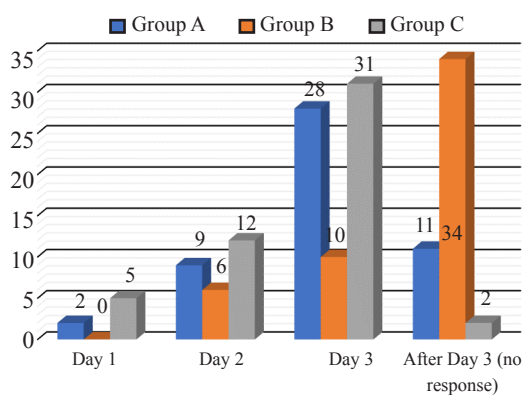


Figure 1: Comparison between Group A, B and C in terms of number of patients showing response to therapy (decrease in frequency, that is less than three formed stools per day) on day 1, 2 and 3

6-12 months old while 84 (56%) patients were between 12 to 120 months old.

Table 1 enlists frequencies of different variables like personal hygiene of mothers and children, sources of food and water accounting for acute diarrhoea. Amongst the variable observed during this study that contribute to acute diarrhoea as tabulated in

Table 1, 123 children (82%) were not using boiled water while 64% and 78% of the mothers were not washing their hands prior to food preparation and feeding respectively. In the children over 12 months of age, only 57% and 29% of the children were in a habit of washing their hands after urination and taking meals respectively. It was also observed that only 32% of the children suffering from acute diarrhoea were consuming home made food items while 68% of the children bought the food from outside.

## DISCUSSION:

In the present study, clinical efficacy of zinc suspension and probiotic monotherapy has been compared with combination therapy in children with acute diarrhoea. It has been shown in this study that by the end of 3<sup>rd</sup> day, nearly all patients in group C who were given combination of zinc suspension and probiotic showed decrease in frequency to less than three stools/day as well as improvement in consistency of stools. In Group A patients who received oral zinc suspension thirty nine patients responded to monotherapy while eleven patients continued passing watery stools even after 72 hours

of starting the therapy. While in Group B patients who were given probiotics alone no significant improvement was seen even after 72 hours of therapy. So according to our findings though oral zinc suspension alone is effective in decreasing frequency and duration of diarrhoea but combination of zinc suspension and probiotics is clinically more effective in pediatric acute diarrhoea.

Our findings regarding effectiveness of oral zinc therapy in acute diarrhoea in children is in accordance with Karamyare *et al*<sup>13</sup> who showed the effectiveness of zinc therapy in acute diarrhoea and fluid deficiency states. They found increase in serum zinc level after zinc treatment in diarrhoeal children. Similar findings have been reported in other studies<sup>14-17</sup>. Further, Habib *et al*<sup>10</sup> showed that zinc decreases the diarrhoeal episodes with faster recovery rates in any available preparation, however better results have been seen with suspension form in terms of patients' compliance. While this was in discordance with the study by Patel *et al*<sup>18</sup>, who found that the total extent of diarrhoea was not different in placebo and zinc groups; the main duration in the zinc group was 4.34 days and that in the placebo group (which received ORS only) was 4.48 days. Also Singh K *et al* in their study concluded that oral zinc therapy has no appreciable outcome on frequency and duration of childhood acute diarrhoea<sup>19</sup>.

Zinc is an important constituent of normal diet having pivotal action in the synthesis and repair of cell constituents. Exact mechanism of action of zinc in acute diarrhoeal states is still not known but it has been reported in literature that zinc improves the overall intestinal absorptive capacity as well as induces the synthesis of cytokines involved in mucosal protection and repair. All these mechanisms may account for the beneficial role of zinc supplementation in children with acute diarrhoea<sup>9</sup>. WHO and United Nations Children's Fund have recommended zinc supplementation for the management of diarrhea since 2004; yet, its usage remains scarce.

In our study Group B fifty children with acute diarrhoea were administered probiotics along with ORS. It was found that only sixteen children showed decrease in frequency of stools in 72 hours while thirty four children did not respond in the mentioned time period. So it is concluded in this study that probiotics alone are not effective in reduction of the acute diarrhoea in children. This is in agreement with the findings in other studies which also showed that probiotic supplementation has no role reducing duration of diarrhea or stool frequency in acute infectious diarrhoea in children<sup>20-21</sup>. While in study by Yazar *et al*, it was concluded that probiotics are equally effective as zinc supplementation in reduction of duration and frequency of diarrhoeal episodes in childhood acute infectious diarrhoea<sup>22</sup>. The effectiveness of *S. boulardii* in reducing the duration of diarrhea and improving the consistency of stools in children with acute diarrhea has been established in other studies as well<sup>23-25</sup>.

**CONCLUSION:**

Acute diarrhoea was found to be more prevalent in children with poor hygiene and dietary habits. It was observed that 82% of children presenting with acute diarrhoea were using unboiled water. Regarding treatment modalities, combinations of zinc + probiotics therapy is more effective in children with acute diarrhoea than either alone; while among zinc and probiotics therapy, zinc is superior in terms of clinical efficacy than probiotics alone.

**LIMITATION OF STUDY:**

This study has been conducted on small group of subjects so further studies on larger scale should be conducted so that results can be extrapolated to larger population.

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