

## A Prospective Study To Evaluate The Efficacy Of Probiotics In The Management Of Acute Watery Diarrhoea In Children

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### Abstract

**Background:** Diarrhoea is a leading cause of death in children, accounting for 9% of all deaths among children under age 5 worldwide in 2015. Treatment with ORS has reduced significantly the incidence of mortality and morbidity caused by diarrhoea. Probiotics are commonly used in the treatment and prevention of acute diarrhoea. Probiotics are live microbial feeding supplements that beneficially affect the host animal by improving its microbial balance. However, the clinical efficacy of probiotics in the treatment and prevention of acute infectious diarrhoea has not been fully established. **Aim;** The present study aimed to investigate the effects of probiotic consumption to decrease the severity and duration of diarrhoea in children aged 6 months to 5 years.

**-Method.:** The study was conducted among children in age group of 6- 60 months of both genders admitted to hospital with acute diarrhoea. Total 606 (test=300, control=306) were enrolled, baseline hydration status was assessed and children were managed according to the WHO guidelines which included oral rehydration therapy (ORT) with reduced osmolarity ORS, zinc and continued feeding. Severe dehydration with intravenous fluids (ringer lactate). Test group received *Lactobacillus sporogenes* in addition to the standard management of diarrhoea. primary outcome measures like duration of diarrhoea, change in stool consistency were analysed.

**Result:** present study showed that children receiving *Lactobacillus sporogenes* along with ORS and Zinc had significant difference in the change in consistency and duration of hospital stay, while frequency and duration of diarrhoea didn't differ much in both groups.

**Conclusion:** Diarrhoea in most of the developing countries including India is usually self-limiting and does not require active treatment except replacement of fluids and electrolytes for prevention or correction of dehydration. This study confirms that *L. sporogenes* as probiotic in combination with ORS and zinc reduces the time for change in consistency of stools and duration of hospital stay while the frequency of stools and duration of diarrhoea didn't differ significantly.

**Keywords:** diarrhoea, lactobacillus, probiotics, dehydration, zinc.

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### I. Introduction

Globally in the age group of under 5 years, acute diarrhoea is the second leading cause of death (after pneumonia)<sup>1</sup>. Of all child deaths from diarrhoea, 78% occur in the African and South-East Asian regions. In developing countries, diarrhoeal disease accounts for an estimated 17.5–21% of all deaths in children under the age of 5 years, equivalent to 1.5 million deaths per year<sup>2</sup>. In India, the number of deaths due to diarrhoea in under five children is 1,17,285 in 2015.<sup>3</sup> Rotaviruses are the most common cause of infectious diarrhoea in childhood across the world.

Each child under 5 years of age experiences an average of three annual episodes of acute diarrhoea, and both the incidence and the risk of mortality from diarrhoeal diseases are greatest among children in this age group, particularly during infancy – thereafter, rates decline incrementally<sup>1,4</sup>. Other direct consequences of diarrhoea in children include growth faltering<sup>5-9</sup>, malnutrition, and impaired cognitive development in resource-limited countries<sup>10,11</sup>

Nowadays, treatment of diarrhoea in children is limited to either symptomatic or supportive care. These include oral fluid therapy, nutritional therapy for children at home and IV therapy in the hospital. Antibiotic therapy is not useful in 85-90% of cases as etiology is unknown or viral<sup>12</sup>. Probiotics are non-pathogenic live bacteria which grow in the intestines. Probiotics belong to a large group of bacteria living harmlessly in the human intestine and regulate intestinal micro flora<sup>13</sup>. Stillwell and Lilly introduced the term probiotics in 1965.<sup>14</sup>

Probiotics are live microbial feeding supplements that beneficially affect the host animal by improving its microbial balance.<sup>15</sup> Treatment with ORS has reduced significantly the incidence of mortality and morbidity caused by diarrhoea but ORS does not shorten the duration of diarrhoea, does not change the consistency of stools and it does not normalise gastrointestinal flora<sup>16</sup>

Probiotics are useful for maintaining the constancy of the normal intestinal milieu, reducing the effects of gastrointestinal diseases such as antibiotic associated diarrhoea, inflammatory bowel disease, childhood diarrhoea, traveler's diarrhoea, lactose intolerance, H. pylori infection, irritable bowel syndrome and intestinal disease caused by clostridium difficile<sup>17</sup>. Probiotics have also some rare adverse effects and drug interactions<sup>18,19</sup>. Consumption of probiotics in healthy individuals does not increase risk of bacterial infections. The risk even in patients with immunodeficiency is very low<sup>9</sup>. Probiotics may also prevent antibiotic-associated diarrhoea and acute diarrhoea<sup>10</sup>, and even used in treatment of acute diarrhoea<sup>5,11,12</sup>. However, there are some controversial results<sup>13</sup>.

ORT is a cost-effective method of managing acute gastroenteritis and it reduces hospitalization requirements in both developed and developing countries. Oral rehydration salts (ORS), used in ORT, contain specific amounts of important salts that are lost in diarrhoea stool. The new lower-osmolarity ORS (recommended by WHO and UNICEF) has reduced concentrations of sodium and glucose and is associated with less vomiting, less stool output, lesser chance of hypernatremia, and a reduced need for intravenous infusions in comparison with standard ORS. This formulation is recommended irrespective of age and the type of diarrhoea including cholera. The present study aimed to investigate the effects of probiotic consumption to decrease the severity and duration of diarrhoea in children aged 6 months to 5 years.

## **II. Aim Of The Study**

To evaluate the efficacy of probiotics in the management of acute diarrhoea in children with respect to number of episodes of diarrhoea duration diarrhoea, Consistency of stools and duration of hospital stay.

## **III. Materials And Methods**

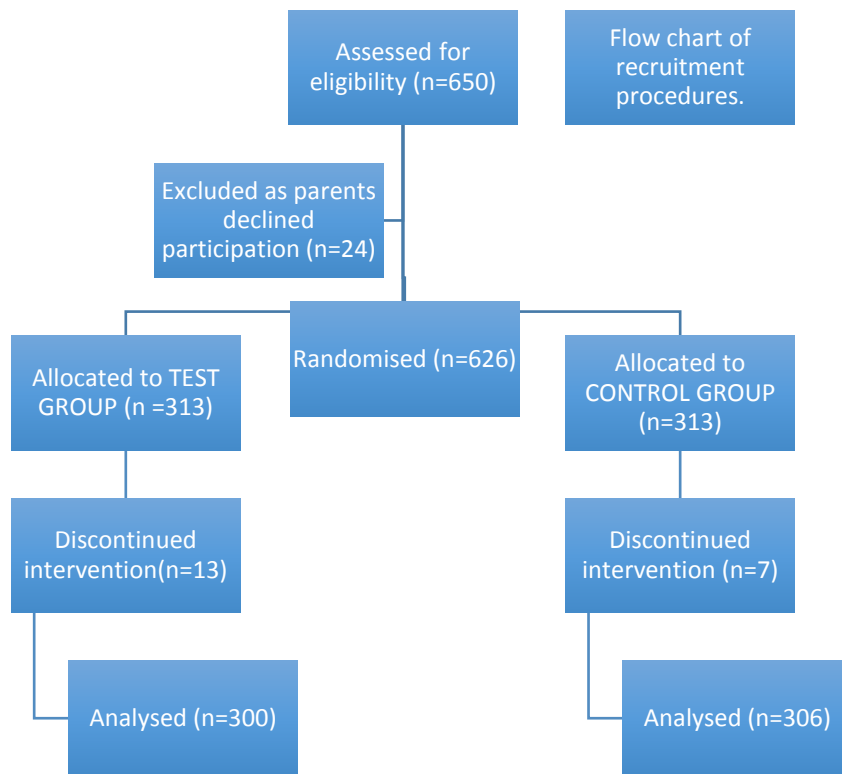
This Study was a Prospective Randomised, double-blind, controlled trial conducted in institute of child health, Niloufer hospital, lakdi-ka-pul, Hyderabad and carried out over a period from July 2015 to September 2016 children in the age group 6 - 60 months of both genders admitted in Niloufer hospital with acute diarrhoea. (3 or more consecutive watery stools during 24h, with duration of no more than 3 days). Children with diarrhoea suspected or diagnosed secondary to other causes like septicaemia, meningitis, malabsorption, motility disorders, on antibiotics, immunodeficiency disorders, malnutrition, dysentery and partially treated diarrhoea outside were excluded from the study

A total of 606 (test=300, control=306) were enrolled in the study. Patients were randomised to receive either probiotic (test group) or no probiotic medication (control group) using block randomization with. Baseline socio-demographic data were recorded and clinical examination was done and hydration status was assessed at the time of enrolment as per WHO guidelines<sup>44</sup>. Study children were managed according to the WHO guidelines which included oral rehydration therapy (ORT) with reduced osmolarity ORS and zinc 20 mg/day for 14 days and continued feeding. Severe dehydration was managed with intravenous fluids (ringer lactate). Intervention group received Lactobacillus sporogenes in addition to the standard management of diarrhoea.

Lactobacillus Sporogenes were administered orally (120 million spores) by dispersing in 15 ml of water two times a day until diarrhoea subsides or 3 days to all the children in test group. All the children in both groups received ORT and oral zinc as recommended by WHO. After correction of initial dehydration, children continued to receive the solution as maintenance therapy matching the stool volume and loss in vomitus until the diarrhoea ceased. However more fluid was given, if the child needed and if there were clinical indications. Children were allowed to continue on breast feeding or animal milk or normal diet as desired. Children did not receive any antibiotic, anti-diarrhoeal, anti-emetic during the study period.

### **3.1 Outcome measures**

Primary outcome measures were duration of diarrhoea [time in hours from enrolment to the last abnormal (loose or liquid) stool] and time to change in stool consistency. Last abnormal stool was defined when the child passed normal stool or no stool for next 24 hrs. Stool consistency was evaluated on a Likert Scale [1-normal (having a hard or firm texture and retaining a definite shape), 2-loose (retaining same general shape in the pan; does not spread all over the pan), 3- semiliquid (lacking any shape of its own; spreads over the pan), and 4-liquid (like water)] and improvement was recorded when there was improvement by at least one score. Secondary outcome measures were duration of vomiting, fever, urine output, adverse effects and the data were recorded.

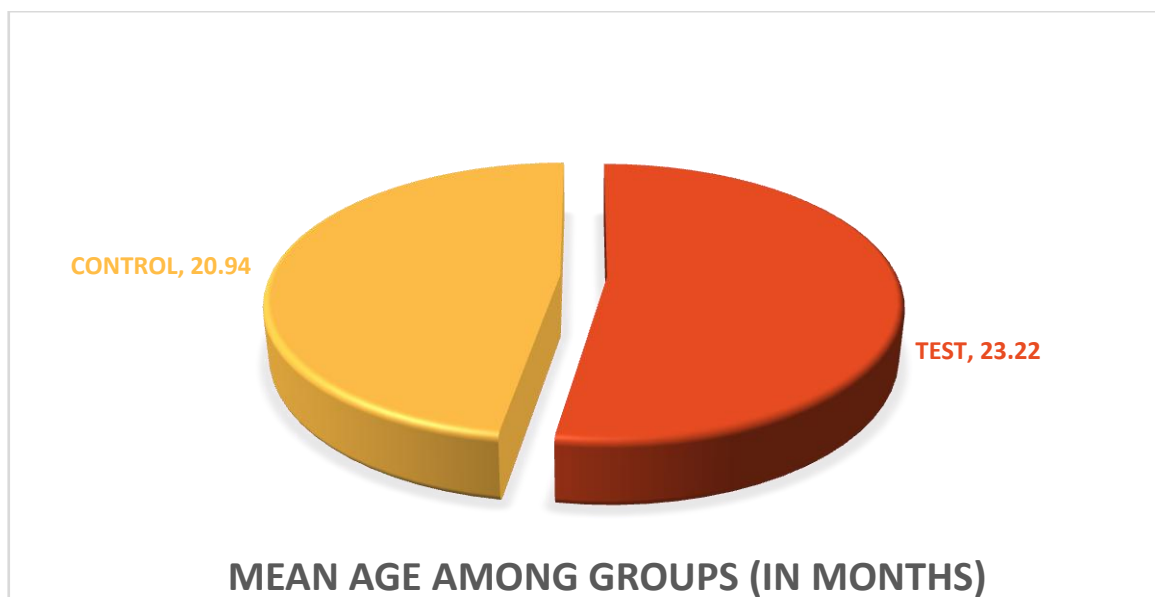


1.Flow chart of recruitment procedures.

#### IV. Results

The data was scrutinised before it was entered into the computer and analysis was done using SPSS windows version 15.0 Mean values, standard deviations and chi square test were done to know the significance of outcome among the study groups .A total of 650 children were identified, out of which 24 didn't want to participate in the study. 626 children were randomised in to two groups, TEST GROUP (n=313) and CONTROL GROUP (n=313) and the study was started. 13 children from test group and 7 children from control group discontinued the study which left the test group with 300 and control group with 306 children.

The children in the study belonged to the age group of 6- 60 months. The mean age of test group is 23.22months, control group is 20.94months and the mean age of total study group is 22.06months.

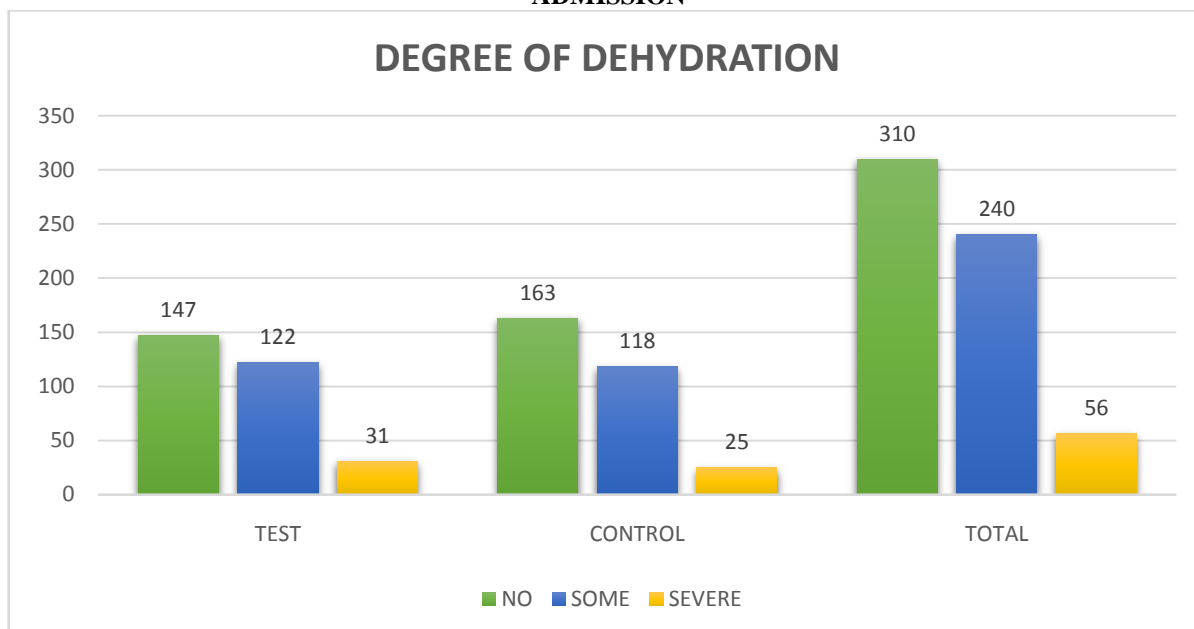


2. chart showing Mean Age among Groups In Month.

Among the studied subjects, 48.3% (n=293) were male and 51.7% (n=313) were female. In the test group, 53% (n=159) were male and 47% (n=141) were female. In the control group, 43.8% (n=134) were male and 56.2% (n=172) were female. P value is 0.05, implies no significant difference between test and control groups with respect to gender.

Of total 603 children, 310 were with no dehydration, 240 had some dehydration and 56 had severe dehydration at the time of admission.

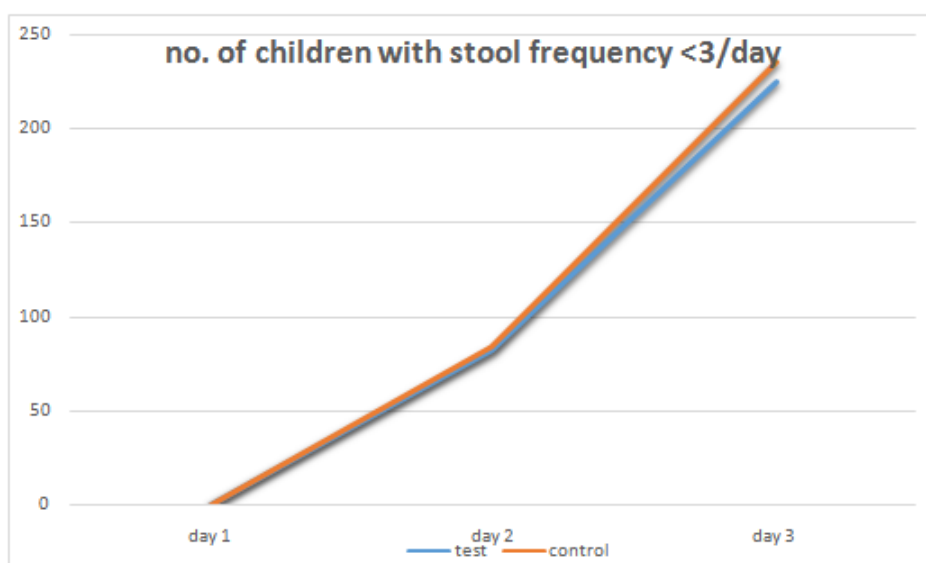
**TABLE 1: DISTRIBUTION OF STUDY SUBJECTS BASED ON DEGREE OF DEHYDRATION AT ADMISSION**



**TABLE 2: COMPARISON OF DURATION OF DIARRHOEA IN STUDY POPULATION (NUMBER OF EPISODES PER DAY)**

Day	Test (<3)	Test (>3)	Control (<3)	Control (>3)	P value
1	0	300	0	303	NS
2	82	218	84	222	0.974
3	225	75	236	70	0.540

NS = not significant



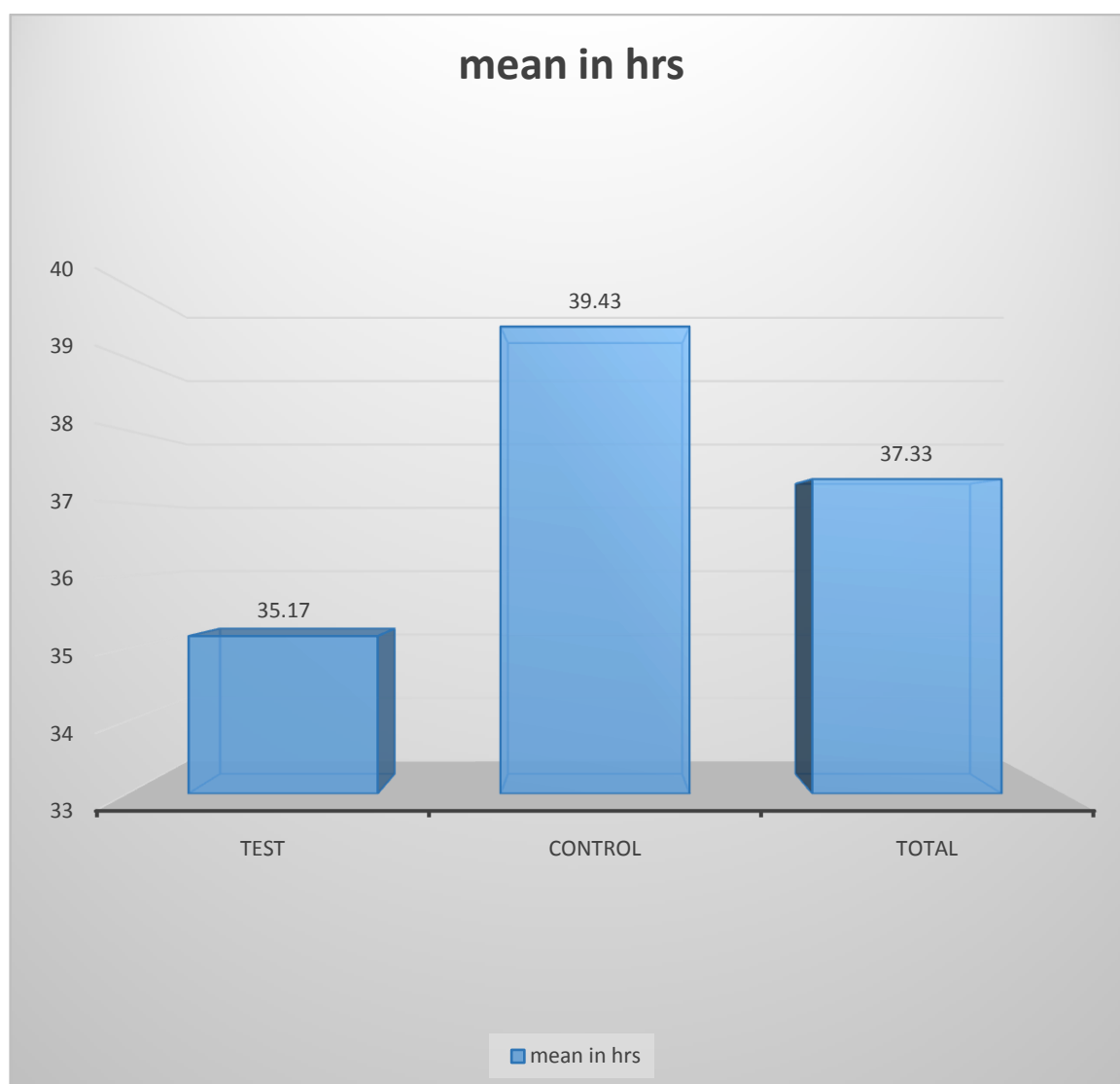
**Chart:3** Stool frequency less than 3 episodes per day.

**TABLE 3: COMPARISON OF CHANGE IN CONSISTENCY OF STOOL IN STUDY GROUPS**

GROUP	Mean( in hrs.)	Std. Deviation
Test (n = 300)	35.17	18.517
Control (n=306)	39.43	17.410
Total (n=606)	37.33	18.075

Groups	Mean difference (in hrs)	Std. error	P
Test & control	4.746	1.448	.001

From the above values, mean duration in hours to normalise the stool consistency from watery to stable, preformed stools in test group is 35.17 hrs while that in control group is 39.43 hrs with a 'p value' of 0.001



**Chart 4: COMPARISON OF DURATION OF VOMITING IN STUDY GROUPS**

Out of total 606, 399 children had vomiting on day 1. 195 out of 300 in test and 204 out of 306 in control groups.

**TABLE 4: COMPARISON OF DURATION OF VOMITING IN STUDY GROUPS**

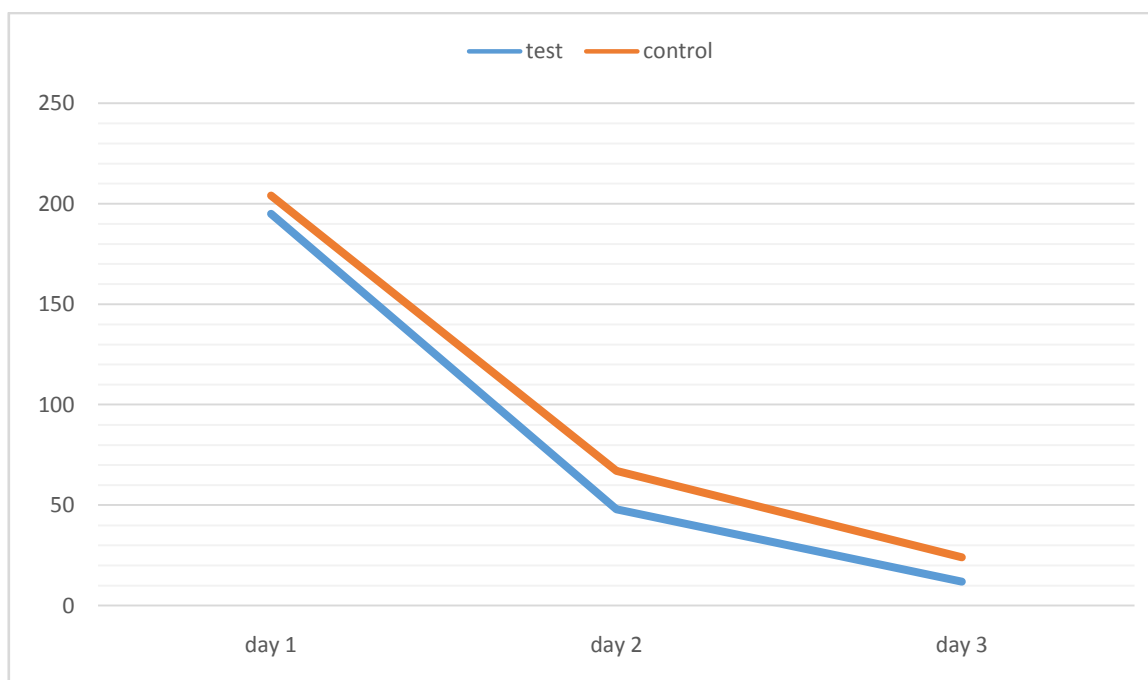
Group	No vomiting	Vomiting on day 1	Vomiting on day 2	Vomiting on day 3
Test	105	195	48	12
Control	102	204	67	24
Total	207	399	115	36

Day	Test (no vomit)	Test (vomiting)	Control (no vomit)	Control (vomiting)	P
1	105	195	102	204	0.665
2	252	48	239	67	0.064
3	288	12	282	24	0.045

Out of total 606, 399 children had vomiting on day 1. 195 out of 300 in test and 204 out of 306 in control groups.

On day 2, out of 195, only 48 had vomiting in test group and out of 204, Only 67 of the control group had vomiting with a p value of 0.064.

On day 3, out of 195, only 12 had vomiting in test group and out of 204, Only 24 of the control group had vomiting with a p value of 0.045.



**Chart 5:** No. of children with vomiting on day1, day2, day3:

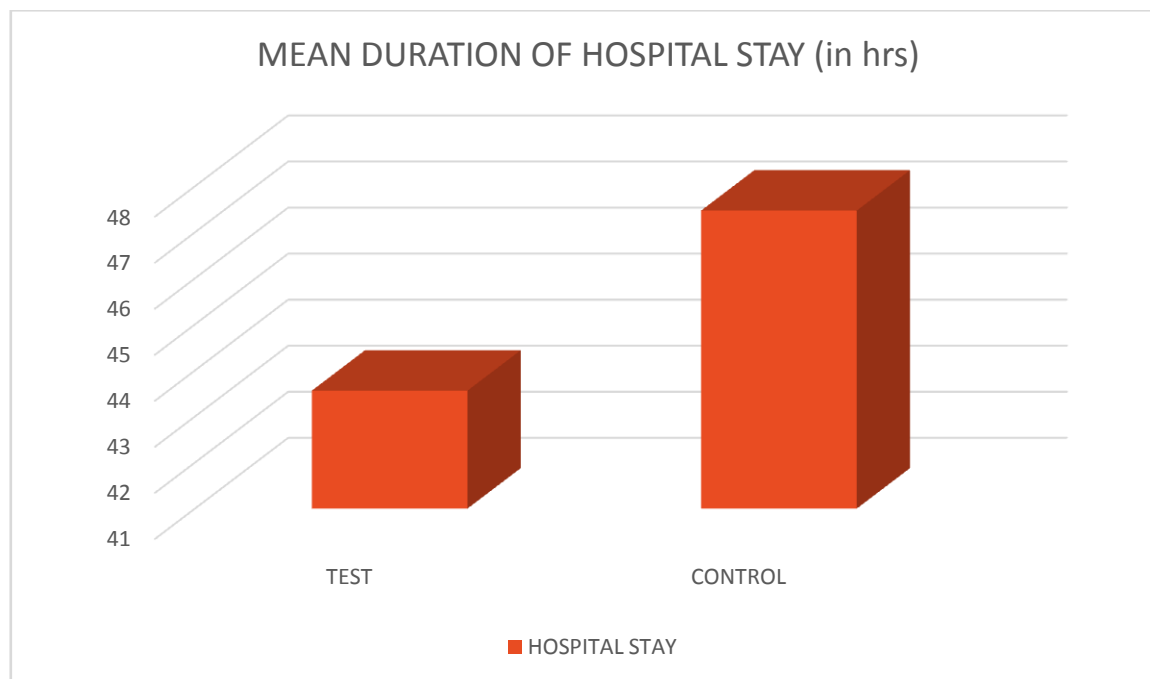
**COMPARISON OF FEVER AMONG THE STUDY GROUPS.**Of the total study subjects, 387 had no complaints of fever.87 of the test group and 132 of control group had fever on day 1.On day 2, only 31 of the test group had episodes of fever and 42 of control group with a p value of 0.200.On day 3, the number of children with fever in both test and control is negligible.

**TABLE 5:COMPARISON OF DURATION OF HOSPITAL STAY AMONG THE STUDY GROUPS**

GROUP	Mean( in hrs.)	Std. Deviation
Test (n = 300)	43.56	18.858
Control (n=306)	47.47	16.729
Total (n=606)	45.54	17.902

Groups	Mean difference (in hrs)	Std. error	P
Test and control	4.329	1.441	.003

From the above values, the mean duration of hospital stay (in hours) in test group is 43.56 and in control group is 47.47 with a 'p value' of 0.003.



**Chart 6: Mean duration Of Hospital Stay in hrs**

## V. Discussion

In industrialized countries, relatively few patients die from diarrhoea, but it continues to be an important cause of morbidity that is associated with substantial health-care costs. ORS and nutritional improvements probably have a greater impact on mortality rates than the incidence of diarrhoea. Prevailing poor living conditions and insignificant improvements in water, sanitation, and personal hygiene, despite some improvement in nutrition, is perhaps important in explaining the lack of impact on the incidence. Interventions such as exclusive breastfeeding (which prevents diarrhoea), continuation of breastfeeding until 24 months of age, and improved complementary feeding (by way of improved nutrition), along with improved sanitation, are expected to affect mortality and morbidity simultaneously. children with diarrhoea in developing countries face dehydration, complications and psychological consequences due to hospitalization.

Zinc deficiency is widespread among children in developing countries. The recommendation for all children with diarrhoea is 20 mg of zinc per day for 14 days. Infants aged 2 months or younger should receive 10 mg per day for 14 days. Supplementation with zinc sulfate in recommended doses reduces the incidence of diarrhoea during the following 3 months, and reduces non-accidental deaths by as many as 50%. It is more important in the management of diarrhoea in malnourished children and persistent diarrhoea. The WHO and UNICEF recommend routine zinc therapy for children with diarrhoea, irrespective of the types.

*Lactobacillus sporogenes* was used in this study to assess the efficacy, which is one of the most commonly prescribed probiotic by paediatricians in India for treatment of diarrhoea in children. The present study showed that children receiving *Lactobacillus sporogenes* along with ORS and Zinc had significant difference in the change in consistency and duration of hospital stay, while frequency and duration of diarrhoea didn't differ much between both the groups. No adverse effects were observed in the study groups during the study period and all the children were discharged.

The probiotic, *Lactobacillus sporogenes* preparation has been marketed in many countries, because it is cheap to produce, easy to prepare, robust to production process and has a long shelf life over wide range of temperatures; it is quite stable in formulation of powder, granules, dry syrup, tablets, capsule, resistant to high moisture and oxygen, and compatible with pharmaceutical ingredients such as vitamins, minerals, amino acids (Vecchi & Drago 2006). Despite these properties, use of this bacterium as probiotic preparation is still debated and based on only three human studies. Two studies reported the data from the same open level studies which showed the reduction of serum cholesterol levels<sup>45,46</sup>. In a more recent study, fructo-oligosaccharide (FOS) in combination with *L. sporogenes* (*B. coagulans*) preparations were evaluated in a multicentre, randomised, double blind study which documented efficacy of these products in combination for prevention of antibiotic associated diarrhoea<sup>47</sup>.

**Ahmadi E et al.**<sup>37</sup> did a meta-analysis and concluded that probiotics exert a positive effect in reducing the duration of acute rotavirus diarrhoea compared with control. Numerous RCTs documented the beneficial effect of probiotic strains to treat diarrhoea in children in developed countries. **Allen SJ et al.**<sup>38</sup> concluded that

probiotics when used alongside rehydration therapy, appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. The most commonly used strains belong to genera *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Escherichia coli* strain Nissle 1917 and the yeast *S. boulardii*<sup>48-51</sup>. ‘Probiotics’ has become the common term to paediatricians and the general public in developed countries.

**FrancaVilla R et al.**<sup>39</sup> concluded with their study that, *L. reuteri* DSM 17938 as an adjunct to rehydration therapy is efficacious in the treatment of acute diarrhoea reducing the frequency, duration and recrudescence rate of the disease. **Roberto Berni Canani et al.**<sup>40</sup> in their study concluded that, “not all commercially available probiotic preparations are effective in children with acute diarrhoea”. Paediatricians should choose bacterial preparations based on effectiveness data. It is based on their Randomised controlled clinical trial in collaboration with family paediatricians over 12 month. **Szajewska H et al.**<sup>42</sup> with their study concluded that the use of LGG is associated with moderate clinical benefits in the treatment of acute diarrhoea in children. These findings should be interpreted with caution due to the important methodological limitations and heterogeneity of most of the studies.

By contrast, a PubMed search on use of probiotics in RCT for the treatment of diarrhoea in Indian children showed a very small number of RCTs, and that very few strains of *Lactobacillus*, *Bifidobacteria* and *Streptococcus* were evaluated as probiotic preparations. **Dutta et al.**<sup>41</sup> in their study concluded that *L. sporogenes* (*B. coagulans*), as an adjunct to ORS, had no therapeutic impact on management of acute dehydrating diarrhoea of diverse etiology including rotavirus associated diarrhoea in children. It was a RCT conducted in India to assess the clinical efficacy of *Lactobacillus sporogenes* (*Bacillus coagulans*), as probiotic preparation, against dehydrating diarrhoea in children.

Dubey et al. (2008)<sup>52</sup> used strains of *L. acidophilus*, *L. casei*, *L. bulgaricus*, *L. plantarum*, *S. thermophilus* in combination for the treatment of rotavirus-associated diarrhoea in children, which showed favourable impact. Another RCT conducted by Narayanappa et al. (2008)<sup>53</sup> showed that Bifilac (Combination of probiotics) was safe and effective in patients with acute viral diarrhoea. Two studies were conducted by the same group of investigators to evaluate the efficacy of *L. rhamnosus* GG strain in acute watery diarrhoea in children; this showed inconsistent effect<sup>54</sup>. No beneficial effect of tyndalised *Lactobacillus acidophilus* was observed in children suffering from acute diarrhoea<sup>55</sup>. Inconsistent results on efficacy of probiotics for the treatment of diarrhoea in these children generated lot of controversy by the Indian experts<sup>56</sup>. The probable explanations are (i) probiotic preparations and doses are not standardised in the Indian context; (ii) data generated in Western countries cannot be extrapolated to Indian setting as breast feeding is very common among Indian children, which may influence probiotic activities due to the presence of significant level of *Bifidobacteria* and *Lactobacillus* as intestinal microflora in breast fed children; (iii) the poor nutritional status of Indian children may have impaired immunity, poor resistance to infection, atrophy of mucosal epithelium which may alter the effects of probiotics; (iv) Indian children have different food habits, which may influence the effects of probiotics; (v) the presence of a wide variety of both helpful and harmful intestinal micro flora may modify the effects of probiotics; (vi) the heat in India may reduce the shelf life of some probiotics; (vii) the 15–20% detection rate of rotavirus as sole etiological agent of diarrhoea in Indian children is lower than in developed countries.

Presently Indian experts feel that although probiotics appear promising in developed countries, there are insufficient data in Indian settings to recommend them for routine therapeutic use for the treatment of diarrhoea<sup>57</sup>. In conclusion, the result of this RCT confirms that *L. sporogenes* (*B. coagulans*) as probiotic in combination with ORS and zinc reduces the time to change in consistency of stools and duration of hospital stay while the frequency of stools and duration of diarrhoea didn’t differ significantly. Before generalizing the results, we must acknowledge the limitations of our study. *L. sporogenes* (*B. coagulans*) is used in this trial knowing that this preparation is commonly prescribed and used in developing countries though the evidences supporting probiotic activity is very sparse.

## VI. Conclusion

Diarrhoea (except cholera and shigellosis) in most of the developing countries including India is usually self-limiting and does not require active treatment except replacement of fluids and electrolytes for prevention or correction of dehydration<sup>57</sup>. However, many probiotic preparations are prescribed by physicians and available over the counter. Some probiotic preparations have proven efficacy in children in developing countries but not all. Probiotic preparations should be selected on the basis of convincing, locally generated efficacy data.

The role of probiotics in the treatment and prevention of infectious diarrhoea continues to be evaluated. The RCTs to date suggest moderate efficacy of *Lactobacillus sporogenes*. On the other hand, as no in-depth diagnostic testing is usually required for managing acute diarrhoea in children, and as rotavirus is a major cause and introduction of rotavirus vaccine in many countries is likely to reduce the burden of the disease (provided it



will be universally available), the significant effect of probiotics in gastroenteritis might become weaker or even disappear. Considering the safety, tolerance and moderate activity of *Lactobacillus sporogenes*, it is worth a try to use this probiotic strain in the treatment of acute diarrhoea in otherwise healthy infants and young children, but this is not a must, as it could reduce the morbidity associated with acute diarrhoea.

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