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EFFICACY OF NITAZOXANIDE AND PROBIOTICS IN CHILDREN PRESENTING WITH ACUTE WATERY DIARRHEA PRESENTING AT TERTIARY CARE HOSPITAL, KARACHI

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Abstract:

Objective: *To compare the efficacy of nitazoxanide and probiotics in children presenting with acute watery diarrhea presenting at Tertiary Care Hospital, Karachi.*

Material and Methods: *The study design was randomized control trial. Study was conducted at Department of Pediatrics, Ziauddin University Hospital, Karachi. The duration of this study was Six months after approval from 02 December 2019 to 02 June 2020. Data was prospectively collected from patients after taking a verbal consent. 160 patients who met the diagnostic criteria were included. Brief history was taken and demographic information was entered in the Performa. Quantitative data was presented as simple descriptive statistics giving mean and standard deviation and qualitative variables was presented as frequency and percentages. Effect modifiers were controlled through stratification. Post stratification chi square test was applied taking p-value of ≤0.05 as significant.*

Results: *A total of 160 patients were included in this study. Out of 80 patients in the nitazoxanide group mean age, duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 24.21±4.24 months, 5.87±1.78 days, 8±2.54 days, 130.6±10.21 cm, 27.7±2.25 kg and 4.7±0.89 respectively. Whereas, out of 80 patients in the probiotics group minimum age, duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 26.48±4.24 months, 6.41±1.14 days, 8±1.89 days, 121.9±7.47 cm, 29.2±3.41 kg and 5.1±0.58 respectively. Efficacy in the nitazoxanide group was 67 (83.8%) compared with 58 (72.5%) in the probiotic group.*

Conclusion: *Treatment with nitazoxanide and probiotics is effective in the management of children with acute watery diarrhea. Small differences in favor of nitazoxanide were found in comparison with probiotics. Nitazoxanide is an important treatment option for acute watery diarrhea.*

Key Words: *Acute Watery Diarrhea, Nitazoxanide, Probiotics And Efficacy.*

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INTRODUCTION:

Acute gastroenteritis (AGE) is a common illness that occurs worldwide. It has been defined by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24 hours), with or without fever or vomiting. Childhood diarrhea is also associated with impaired growth and cognitive development. In developing countries, 15% of the 10.5 million children died per year because of acute gastroenteritis. Pakistan stands 5th by scoring 10.8% among fifteen developing countries that accounts for a total of 73% of diarrheal deaths occurring globally in children under 5 years of age, making it the chief cause of death in Pakistan. The aim of treatment is to prevent or reverse dehydration, shorten the duration of the illness (important for preventing progression to persistent diarrhea, which is associated with adverse outcomes such as malnutrition), and reduce the period during which a person is infectious. [5] The standard recommended treatment is based on diet and rehydration therapy. In 1980, a new thiazolide antimicrobial was introduced named nitazoxanide. At first, it was thought to be an anti-parasitic agent effective against helmithic and protozoan infections. In 2002, USA food and drug administration (FDA) recommended the use of nitazoxanide in pediatrics age group. Then first clinical trial was performed in 2006 in patients with acute rota virus diarrhea emphasizing on the fact that tizoxanide , an active metabolite of nitazoxanide has a cytoprotective effect in cells infected by rotavirus. It also shows activity against facultative and obligate gram positive and negative anaerobes by inhibiting pyruvate-ferrexodinoxidoreductase (PFOR) enzyme dependent electron transfer reaction it inhibits anaerobic energy metabolism essential for their growth. In another randomized control trial done in India in 2016, nitazoxanide was given orally twice daily for 3 days to the patient with acute rotavirus diarrhea, the median duration of diarrhea 54 vs.80 hours, 95% CI:-26 and hospitalization 68 vs 90 hours 95%CI was significantly shorter in patient receiving nitazoxanide.

Probiotics have been defined as microorganisms that exert beneficial effects on human health when they colonize the bowel. They have been demonstrated to be efficacious for the treatment of diarrhea of suspected viral origin as well as for antibiotic-associated diarrhea by reducing the duration of the diarrhea and, additionally, as demonstrated in recent systematic reviews, reducing stool frequency. Although less well-demonstrated, some randomized clinical trials suggest that probiotics could also be effective for the prevention of nosocomial infections. Over the past few years, an abundance of probiotic-based products has appeared. Because probiotics are live microorganisms, the mere characterization of the strains contained in the product, independent of the evidence available of such strains, is insufficient to claim a beneficial effect. Pilot study conducted at our hospital on 50 children showed efficacy of 92% in the nitazoxanide group and 78% in the group.

METHODS AND MATERIALS:

The study design was randomized control trial. Study was conducted at Department of Pediatrics, Ziauddin University Hospital, Karachi. The duration of this study was Six months after approval from 02 December 2019 to 02 June 2020. The sample size was calculated by using the WHO software where, Alpha=5%, Power of the test 1-beta=80, taking efficacy from pilot study. Anticipated population proportion N= Nitazoxanide group (92%)% and Anticipated population proportion P= Probiotics (78%)%. Thus calculated sample size was n=160 i.e 80 patients in each group. Non-probability consecutive sampling. This study was conducted after approval from College of Physicians and Surgeons Pakistan. Consenting cases as defined in operational definition and meeting inclusion criteria were enrolled in the study from the Department of Pediatrics, Ziauddin University Hospital, Karachi. Informed consent was obtained from all the patient's parents for assigning them to sample and using their data in research. Brief history about demographic information and duration of diarrhea was taken from the patient parents. Patients were randomly allocated using sealed opaque envelop bearing N= Nitazoxanide and P= Probiotics. Patients in group N received nitazoxanide (<1 year old: 7.5mg/kg/dose, 1 to 3 years: 100mg/dose, ≥ 4 years 200mg/dose twice daily for a period of 3 days) and group P received probiotics (one sachet per day for a period of 3 days). Patients in each group were assessed on Day 4 for the variables of Modified Vesikari score **(**ANNEXURE**)** by the researcher under the supervision of her supervisor and patients having Modified Vesikari score serum ≤7 was used to label efficacy in either group. The findings of quantitative variables (age, Modified Vesikari score, height, weight, length of hospital stay and duration of diarrhea) and quantitative variable (gender, family monthly income status, educational status of mother, history of breast feeding, history of hospitalization for diarrhea and efficacy) will be entered in performa attached as annexure. Data was analyzed on SPSS Version 16. Mean and standard deviations for the quantitative

variables like age, Modified Vesikari score, height, weight, length of hospital stay and duration of diarrhea was calculated. Frequencies and percentages for the qualitative variables like gender, degree of dehydration, family monthly income status, educational status of mother, history of breast feeding, history of hospitalization for diarrhea and efficacy was calculated. Chi-square was used to compare two groups for efficacy. Effect modifiers was controlled through stratification of age, gender, degree of dehydration, family monthly income status, educational status of mother, history of breast feeding, history of hospitalization for diarrhea and duration of diarrhea to see the effect of these on the outcomes variable i.e efficacy. Post stratification chi-square test was applied and p-value of ≤ 0.05 was considered significant.

RESULT:

A total of 160 patients who presented at Department of Pediatrics, Ziauddin University Hospital, Karachi who met the inclusion and exclusion criteria were included in this study. Out of 80 patients in the nitazoxanide group minimum age of the patient was 20 while maximum age of the patients was 60 months. Mean age in our study was 24.21 months with the standard deviation of ±4.24. Whereas, mean duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 5.87±1.78 days, 8±2.54 days, 130.6±10.21 cm, 27.7±2.25 kg and 4.7±0.89 respectively. Similarly, out of 80 patients in the probiotics group minimum age of the patient was 20 while maximum age of the patients was 60 months. Mean age in our study was 26.48 months with the standard deviation of ±4.24. Whereas, mean duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 6.41±1.14 days, 8±1.89 days, 121.9±7.47 cm, 29.2±3.41 kg and 5.1±0.58 respectively. As shown in Table 1. Frequency distribution of efficacy showed that out of 80 patients in the nitazoxanide group, 67 (83.8%) and 13 (16.2%) achieved and did not achieve efficacy respectively. Whereas out of 80 patients in the probiotic group, 58 (72.5%) and 22 (27.5%) achieved and did not achieve efficacy respectively. As presented in Figure 1.

Frequency distribution of age showed that out of 80 patients in the nitazoxanide group, 52 (65%) and 28 (35%) were in age group 3-30 months and 31-60 months respectively. Whereas out of 80 patients in the probiotic group, 51 (63.8%) and 29 (36.2%) were in age group 3-30 months and 31-60 months respectively. As presented in Figure 2. Frequency distribution of gender showed that out of 80 patients in the nitazoxanide group, 51 (63.8%) and 29 (36.2%) were male and female respectively. Whereas out of 80 patients in the probiotic group, 50 (62.5%) and 30 (37.5%) were male and female respectively. As presented in Figure 3. Frequency distribution of duration of diarrhea showed that out of 80 patients in the nitazoxanide group, 48 (60%) and 32 (40%) had diarrhea < 3 and > 3 days respectively. Whereas out of 80 patients in the probiotic group, 40 (50%) and 40 (50%) had diarrhea < 3 and > 3 days respectively. As presented in Figure 4. Frequency distribution of degree of dehydration showed that out of 80 patients in the nitazoxanide group, 03 (3.8%), 51 (63.8%) and 26 (32.5%) had mild, moderate and severe dehydration respectively. Whereas out of 80 patients in the probiotic group, 06 (7.5%), 59 (73.8%) and 15 (18.8%) had mild, moderate and severe dehydration respectively. As presented in Figure 5.

Stratification for efficacy with respect to efficacy in nitazoxanide and probiotics group showed that 67 (83.8%) and 58 (72.5%) had efficacy respectively. P-value was 0.08. As presented in Table 2. Stratification for age with respect to efficacy in nitazoxanide and probiotics group showed that 44 (84.6%) and 36 (70.6%) had efficacy in age group 3-30 months respectively. P-value was 0.08. Whereas age with respect to efficacy in nitazoxanide and probiotics group showed that 23 (82.1%) and 22 (75.9%) had efficacy in age group 31-60 months respectively. P-value was 0.56. As presented in Table 3. Stratification for gender with respect to efficacy in nitazoxanide and probiotics group showed that 42 (82.4%) and 35 (70%) had efficacy in male group respectively. P-value was 0.14. Whereas gender with respect to efficacy in nitazoxanide and probiotics group showed that 25 (86.2%) and 23 (76.7%) had efficacy in female group respectively. P-value was 0.34. As presented in Table 4. Stratification for duration of diarrhea with respect to efficacy in nitazoxanide and probiotics group showed that 46 (95.8%) and 30 (4.2%) had efficacy in < 3 days duration of diarrhea group respectively. P-value was 0.00. Whereas gender with respect to efficacy in nitazoxanide and probiotics group showed that 21 (65.6%) and 28 (70%) had efficacy in > 3 days duration of diarrhea group respectively. P-value was 0.69. As presented in Table 5.

Table-1: Descriptive Statistics Nitazoxanide Group (80) Versus Probiotic Group (80) n=160

Variable	Mean ± Sd	Standard Deviation	Min-Max
Age Nitazoxanide Group (Months)	24.21	±4.24	20-60
Age Probiotics Group (Months)	26.48	±7.41	20-60
Duration Of Diarrhea Nitazoxanide Group (Days)	5.87	±1.78	1-6
Duration Of Diarrhea Probiotics Group (Days)	6.41	±1.14	1-6
Length Of Hospital Stay Nitazoxanide Group (Days)	8	±2.54	4-10
Length Of Hospital Stay Probiotics Group (Days)	8	±1.89	4-10
Height Nitazoxanide Group (Cm)	130.6	±10.21	108-141
Weight Nitazoxanide Group (Kg)	27.7	±2.25	18-48
Height Probiotics Group (Cm)	121.9	±7.47	108-141
Weight Probiotics Group (Kg)	29.2	±3.41	18-48
Vesikari Score Nitazoxanide Group	4.7	±0.89	3-7
Vesikari Score Probiotics Group	5.1	±0.58	3-7

Figure-1: Efficacy Distribution In Nitazoxanide (80) Versus Probiotics (80) Groups n=160

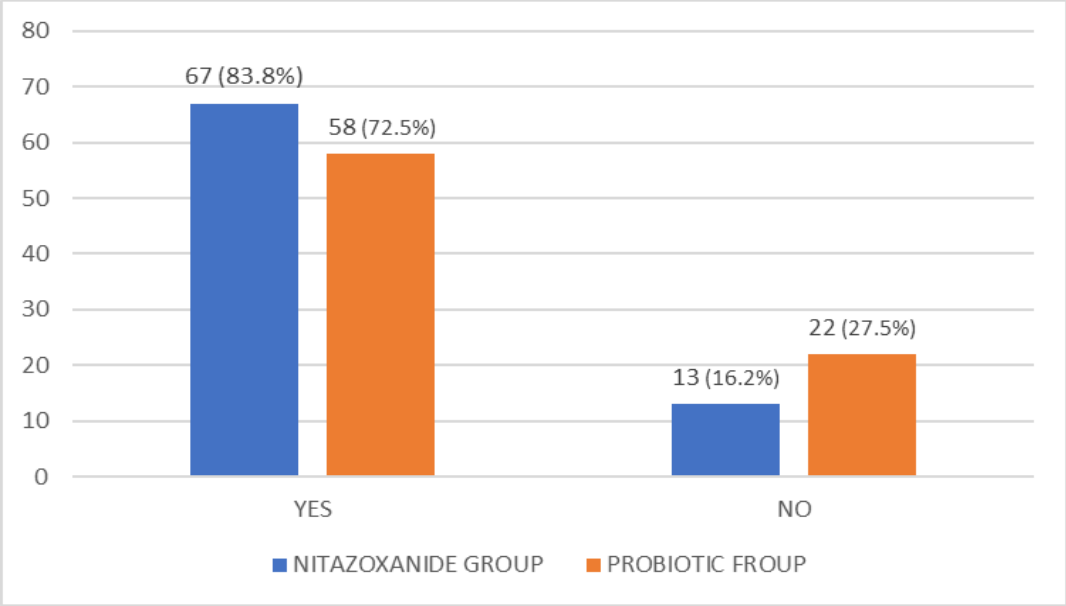

Figure-2: Age Distribution In Nitazoxanide (80) Versus Probiotics (80) Groups n=160

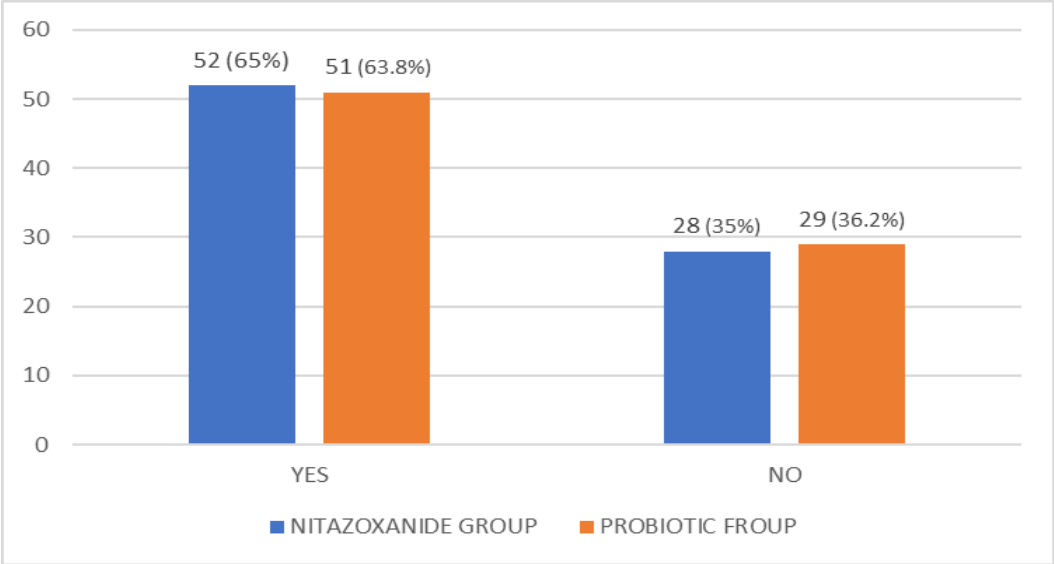

Figure-3: Gender Distribution In Nitazoxanide (80) Versus Probiotics (80) Groups n=160

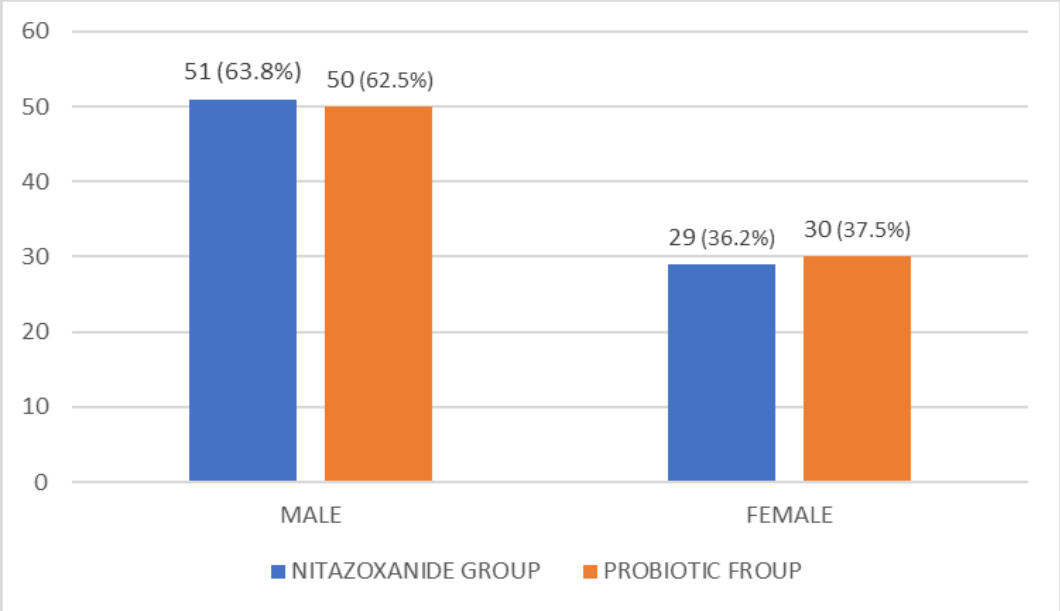

Figure-4: Duration Of Diarrhea In Nitazoxanide (80) Versus Probiotics (80) Groups n=160

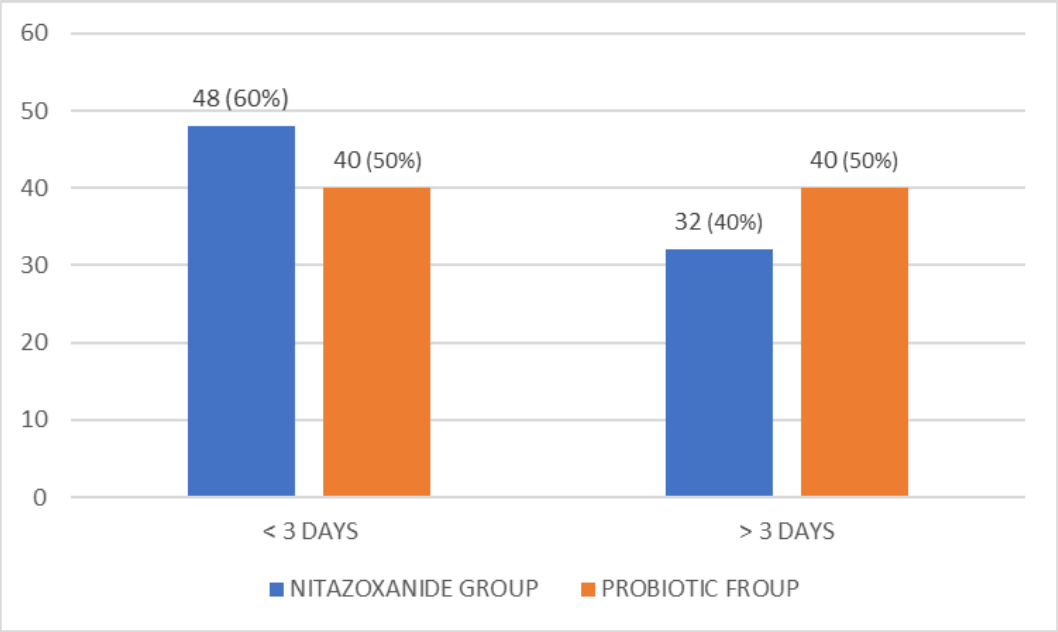

Figure-5 : Degree Of Dehydration Distribution In Nitazoxanide (80) Versus Probiotics (80) Groups n=160

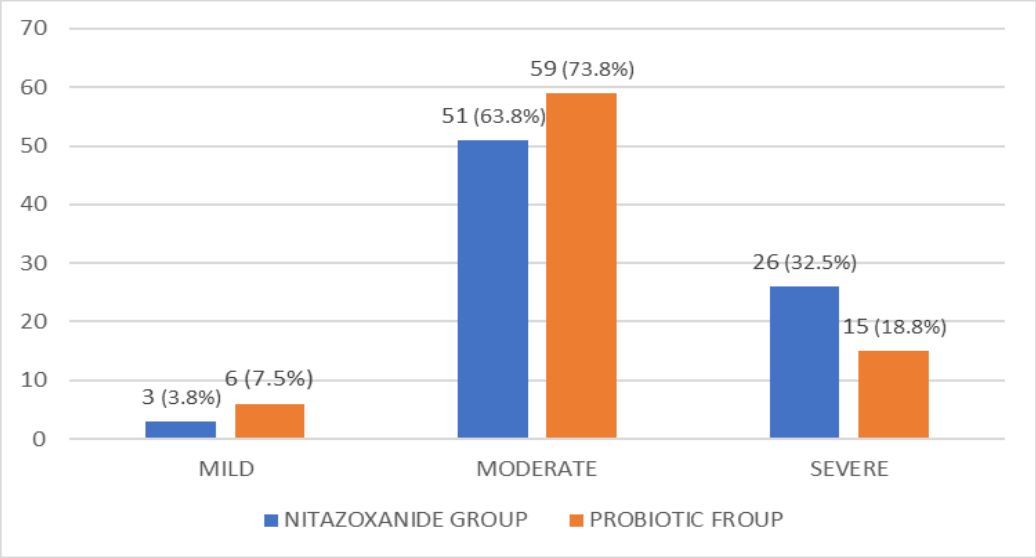

Table-2: Efficacy Of Nitazoxanide (80) Versus Probiotics (80) In Children Presenting With Watery Diarrhea (n=160)

Groups	Efficacy		P-Value
	Yes	No	
Nitazoxanide Group	67 (83.8%)	13 (16.2%)	**0.08**
Probiotics Port	58 (72.5%)	22 (27.5%)	

Table-3: Efficacy Of Nitazoxanide (80) Versus Probiotics (80) In Children Presenting With Watery Diarrhea According To Age (n=160)

Age (Months)	Efficacy Nitazoxanide Group		Efficacy Probiotics Group		P Value
	Yes	No	Yes	No	
3-30	44 (84.6%)	08 (15.4%)	36 (70.6%)	15 (29.4%)	**0.08**
31-60	23 (82.1%)	05 (17.9%)	22 (75.9%)	07 (24.1%)	**0.56**

Table-4 : Efficacy Of Nitazoxanide (80) Versus Probiotics (80) In Children Presenting With Watery Diarrhea According To Gender (n=160)

Gender	Efficacy Nitazoxanide Group		Efficacy Probiotics Group		P Value
	Yes	No	Yes	No	
Male	42 (82.4%)	09 (17.6%)	35 (70%)	15 (30%)	**0.14**
Female	25 (86.2%)	04 (13.8%)	23 (76.7%)	07 (23.3%)	**0.34**

Table-5 : Efficacy Of Nitazoxanide (80) Versus Probiotics (80) In Children Presenting With Watery Diarrhea According To Duration Of Diarrhea (n=160)

Duration Of Diarrhea	Efficacy Nitazoxanide Group		Efficacy Probiotics Group		P Value
	Yes	No	Yes	No	
< 3 Days	46 (95.8%)	02 (4.2%)	30 (75%)	10 (25%)	**0.00**
> 3 Days	21 (65.6%)	11 (34.4%)	28 (70%)	12 (30%)	**0.69**

DISCUSSION:

Acute gastroenteritis, characterized by the onset of diarrhea with or without vomiting, continues to be a major cause of morbidity and mortality in children in mostly resource-constrained nations. Although generally a mild and self-limiting disease, gastroenteritis is one of the most common causes of hospitalization and is associated with a substantial disease burden. Worldwide, up to 40% of children aged less than 5 years with diarrhea are hospitalized with rotavirus. Also, some microorganisms have been found predominantly in resource-constrained nations, including *Shigella* spp, *Vibrio cholerae*, and the protozoan infections. Prevention remains essential, and the rotavirus vaccines have demonstrated good safety and efficacy profiles in large clinical trials. Because dehydration is the major complication associated with gastroenteritis, appropriate fluid management (oral or intravenous) is an effective and safe strategy for rehydration. Continuation of breastfeeding is strongly recommended. New treatments such as antiemetics (ondansetron), some antidiarrheal agents (racecadotril), and chemotherapeutic agents are often proposed, but not yet universally recommended. Probiotics, also known as "food supplement," seem to improve intestinal

microbial balance, reducing the duration and the severity of acute infectious diarrhea. Our study included a total of 160 patients. Out of 80 patients in the nitazoxanide group mean age, duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 24.21±4.24 months, 5.87±1.78 days, 8±2.54 days, 130.6±10.21 cm, 27.7±2.25 kg and 4.7±0.89 respectively. Whereas, out of 80 patients in the probiotics group minimum age, duration of diarrhea, length of hospital stay, height, weight and Vesikari score in our study was 26.48±4.24 months, 6.41±1.14 days, 8±1.89 days, 121.9±7.47 cm, 29.2±3.41 kg and 5.1±0.58 respectively. Efficacy in the nitazoxanide group was 67 (83.8%) compared with 58 (72.5%) in the probiotic group. A study included seventy-five children aged from 28 days to 24 months. The median duration of hospitalization was significantly shorter (p = 0.017) in patients who received nitazoxanide (81 h) and probiotics (72 h) compared to patients who received oral rehydration solution alone (108 h). Similarly, the median duration of diarrhea was significantly reduced (p = 0.009) in children who received nitazoxanide (54 h) and probiotics (48 h) compared to the control group (79 h). Another study showed the median duration (hrs) of diarrhea (54 versus 80; 95% CI: –26 [–13.2 to –38.8]) and hospitalization (68 versus 90; 95% CI: –22 [–12.98 to –31.02]) was significantly shorter in the nitazoxanide group. No significant difference was seen in the median duration (hrs) of fever or vomiting or the proportion of children requiring parenteral rehydration. There was no report of any adverse events. *Conclusions*. Oral nitazoxanide is effective and safe in the management of acute rotavirus diarrhea in Indian children.

Episodes of acute infectious diarrhoea remain a major disease burden throughout the world, especially in developing countries. They are due to infection by many different organisms. Most episodes are self-limiting and usually investigations are not done to identify the infectious agent. The main risk to health is dehydration and management aims to improve and maintain hydration status. However, rehydration fluids do not reduce the stool volume or shorten the episode of diarrhoea. Probiotics are "friendly" bacteria that improve health and are not harmful in themselves. A number of randomized controlled trials have been done to see whether probiotics are beneficial in acute infectious diarrhoea. We have searched for as many of these trials as possible and collected together the data in a systematic way to try to discover whether or not probiotics are beneficial in acute diarrhoea. We identified 63 trials, which included a total of 8014 people - mainly infants and children. Probiotics were not associated with any adverse effects. Nearly all studies reported a shortened duration of diarrhoea and reduced stool frequency in people who received probiotics compared to the controls. Overall, probiotics reduced the duration of diarrhoea by around 25 hours, the risk of diarrhoea lasting four or more days by 59% and resulted in about one fewer diarrhoeal stool on day 2 after the intervention. However, there was very marked variability in the study findings and so these estimates are approximate. We concluded that these results were very encouraging but more research is needed to identify exactly which probiotics should be used for which groups of people, and also to assess the cost effectiveness of this treatment. A meta-analysis undertaken by Van Niel et al was restricted to adequately randomized and blinded studies of several strains of lactobacilli in children. Children who had received recent antibiotics were excluded from the study. Probiotics reduced the duration of diarrhoea by 0.7 days (95% CI 0.3 to 1.2 days, seven studies including 675 children) and diarrhoea frequency on day 2 by 1.6 (95% CI 0.7 to 2.6, three studies including 122 children). The heterogeneity of results among the studies prevented an analysis of the effects of individual strains of lactobacilli.

Three meta-analyses have focused on randomized controlled trials of specific probiotics in acute infectious diarrhoea in children. Szajewska et al analysed trials of *Lactobacillus casei* strain GG where a > 80% follow up was achieved. Trial results published as letters to the editor, abstracts, and proceedings from scientific meetings were not included. *L.casei* GG reduced the duration of diarrhoea by 1.1 days (95% CI 0.3 to 1.9, seven trials, 876 infants) and was particularly effective in rotavirus diarrhoea (duration reduced by 2.1 days, 95% CI 0.6 to 3.6). However, the authors urged caution in the interpretation of the results in view of methodological limitations in the trials and the heterogeneity of the results in the studies. It was identified two trials of *Lactobacillus reuteri* strain ATTCC 55730. This probiotic reduced the duration of diarrhoea by 22 hours (95% CI 6 to 38, 106 participants). In an update of a previous review pooled data from seven randomized controlled trials of *Saccharomyces boulardii* in 944 otherwise healthy children with acute gastroenteritis. The duration of diarrhoea was reduced by 1.08 days (95% CI 0.53 to 1.64) in children who received the yeast compared with the placebo although there was marked heterogeneity in results among the studies. A recent review concluded that the beneficial effects of probiotics in acute infectious diarrhoea were

dependent on the strain of bacteria and the dose (a greater effect with doses $>10^{10}$-10^{11} colony-forming units (CFU)/day). They were significant in watery diarrhoea and viral gastroenteritis but absent in invasive bacterial diarrhoea, and were greater when probiotics were administered early in the illness and were more evident in developed countries.

CONCLUSIONS:

AGE remains a major problem in children and still represents one of the leading causes of illness costs and of deaths. Most cases of AGE in children are viral, self-limited, and need only supportive treatment. Rehydration (oral or intravenous) with an appropriate fluid-and-electrolyte balance, with close attention to nutrition, remains central to therapy: this may turn into an additional benefit in limiting hospitalizations. Treatment with nitazoxanide and probiotics is effective in the management of children with acute watery diarrhea. Small differences in favor of nitazoxanide were found in comparison with probiotics. Nitazoxanide is an important treatment option for acute watery diarrhea. Intestinal infections often require drugs such as antiemetics, antidiarrheal agents, and probiotics that may deeply change the impact, severity, and duration of acute diarrhea. In cases of severe infectious diarrhea with a prolonged course, signs of inflammation, bloody stool, immunosuppression, and comorbidity, and in suspected outbreaks, fecal microbial analysis, should always be performed, and a specific therapy should be considered if indicated to shorten the clinical course, eradicate causative organisms, reduce transmission, and prevent invasive complications. Selection of anti-bacteria's to use in acute bacterial gastroenteritis is based on clinical diagnosis of the likely pathogen and on definitive laboratory results. Based on epidemiological data and after collecting organic materials for etiological diagnosis (often a single fecal sample studied for etiologic agents is the customary way to make an etiologic diagnosis), an initial empiric therapy may be appropriate in case of a severe illness, particularly in infancy and the immunocompromised. Moreover, a major concern is the emergence of antibacterial-resistant strains due to the widespread use of antibacterial agents: a continuous monitoring of antibiotic resistance in diarrhea-related bacterial pathogens is recommended. The benefits and risks of adverse drug reactions should be weighed before prescribing any kind of drug.

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