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Original Research Article

Nitazoxanide in Acute Rotavirus Diarrhea- A Randomized Controlled Trial Study in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Acute rotavirus diarrhea is one of the leading cause of morbidity and mortality in children younger than 5 years. Nitazoxanide, an antiparasitic agent, acts by inhibiting the maturation of rotavirus viral protein 7 thus interferes with viral morphogenesis. **Aim of the study:** was to evaluate the role of nitazoxanide in the treatment of acute rotavirus diarrhea in 6 months to 2 years aged children. **Methods:** This randomized controlled trial was conducted at Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh from June 2018 to July 2020. A total of 70 children with acute onset diarrhea of <48 hours. duration was included in this study. All the studied patients were divided into two equal groups (group I and group II) by lottery, each comprising 35 children. The groupI represented the study group who received standard treatment of diarrhea plus oral nitazoxanide (15mg/kg/day) twice daily for 3 days and the group II is the control group received standard treatment only. **Results:** Study demonstrated that maximum number of patients 22 (31.4%) were between 14-17 months of age group and 36% patients came from rural, 64% from urban areas. Study showed before commencement of treatment most of the patients in both groups experienced some dehydration, vomiting, fever, & abdominal distension. At 48 hours' improvement was observed in both groups, comparatively higher in group I. Difference of some dehydration and vomiting improvement between two groups were statistically significant ($p < 0.05$). After 3 days' treatment normal stool consistency was found in 24(68.5%) patients in group I & 10 (28.5%) in group II patients. The difference was also statistically significant ($p=<0.05$). Mean time of resolution of diarrhea 62.5 hours in Group-I and 96.5 hours in group-II. Compared to the group II, group I showed decrease in mean time of resolution of diarrhea ($p= 0.001$). The mean duration of hospital stay was prolonged in group-II (86.5 hours vs. 102.5 hours in group I & II respectively), the difference was statistically significant ($p<0.05$). **Conclusion:** In the present study, oral nitazoxanide was found effective in the treatment of acute rotavirus diarrhea in 6 months to 2 years old children.

Keywords: Acute Rotavirus Diarrhea, Nitazoxanide.

INTRODUCTION

Three or more loose or liquid stools per day (or more frequent passage than normal for the individual) is defined as diarrhea. [1] Diarrheal diseases are a major threat to human health and still represent a leading cause of morbidity and mortality worldwide. The burden of diarrheal diseases is much lower in developed countries but a significant public health problem in low and middle-income countries like Bangladesh. [2] The World Health Organization (WHO) and UNICEF reported that about two billion

people suffer from diarrheal diseases worldwide every year. Among them 1.9 million children younger than 5 years of age die due to diarrhea each year, mostly in developing countries. [3] Some different groups of viruses have been shown to be responsible for high incidence of acute viral gastroenteritis among children during their first few years of life. Four major categories of viruses are recognized as clinically important including Rotavirus, Astrovirus, Adenovirus and Calcivirus. [4] Rotavirus is the most common cause of severe dehydrating diarrhea and gastroenteritis in young children worldwide and is a major cause of mortality. [5] The disease causes an estimated 440 000 deaths every year globally, an estimated 1205 children die from rotavirus disease each day and around 80% of these deaths occur in children in the poorest countries. [6] In developed nations, around 1 in 40 children younger than 5 years are hospitalized every year because of rotavirus diarrhea. [7] The disease is more severe in infants aged 3 to 24 months. [8] After pneumonia, diarrhea is the second commonest cause of death in under five children of Bangladesh. During the year 2001 to 2004, between 5756 to 13,430 children died from severe rotavirus gastroenteritis each year. While overall deaths from diarrhea are declining in Bangladeshi children, the proportion of diarrheal deaths due to rotavirus have actually increased. [9] The prevalence of rotavirus diarrhea in Bangladesh below 5 years aged children is about 25%. [10] Poor hygienic practices, home overcrowding, neglect, lack of health education with poor health services, poor sanitation, infants on artificial formula responsible for the continuing high prevalence of acute rotavirus diarrhea. [11] Bangladesh is a riverine country, which is prone to severe flooding. Flooding has been shown to cause epidemics of water-borne and vector-borne disease. During flood-associated epidemics, Rotavirus, *Vibrio cholerae* is the most commonly identified cause of diarrhea, and rotavirus considered the second most frequently identified flood-associated pathogen, although the proportion of cases caused by rotavirus infection decreased during floods compared with matched periods. [12] Due to the high incidence of rotavirus infection in both developing and the developed countries, the development of vaccines took shape in the early 1980s. [8] Since 2006, 2 rotavirus vaccines have been licensed and used globally-Rotarix and Rota Teq. Rotarix is a live, attenuated vaccine containing a single G1P human rotavirus strain. Rota Teq is a live, attenuated vaccine containing 5 human-bovine reassortant rotavirus strains-G1P7[5], G2P7[5], G3P7[5], G4P7[5], and G6P1A. [13] Both vaccines are administered orally to infants starting at a minimum age of 6 weeks, with a minimum 4 weeks. interval between doses. [13] The treatment of individuals with acute rotavirus diarrhea is predominantly based on fluid resuscitation. Approximation of fluid deficit and the requirement in children with some dehydration or severe dehydration should be carried out by weighing them without clothing. [14] Fluid, electrolytes and acid base disturbances are responsible for most deaths due to acute diarrhea. [15] Timely recognition, a high index of suspicion, and a thorough understanding of common electrolyte abnormalities is essential to ensure their correction. [16] Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salts by consumption of water, juices, sports drinks, soups, and salting crackers. [17] Individuals who are unconscious or unable to intake ORS by mouth can be treated by repleting fluids and electrolytes intravenously. [14] Aims of ORT to prevent or reverse dehydration and has no effect either on the duration or on the stool output. Zinc is also not universally effective and has been used mainly in developing country. [18] There is currently no drug for treating rotavirus infection. Racecadotril, an enkephalinase inhibitor, inhibits intestinal hypersecretion and has been shown to reduce stool output and duration of rotavirus diarrhea have shown that use of probiotics early in the course of diarrhea can reduce duration of illness and rotavirus shedding. [19-21] Nitazoxanide is a new nitrothiazole benzamide compound notable for its activity in treating both intestinal protozoal and helminthic infections with a low range of minor adverse effects. [22] Nitazoxanide has been reported to be effective against a broad range of parasites, including Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, and Ascaris lumbricoides. [23] The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism. [24] The first research on the antiviral effects of nitazoxanide was published in 2006 stated that tizoxanide showed a cytoprotective effect in rotavirus infected cells in others studies carried out in vitro. [25] Tizoxanide inhibits the maturation of rotavirus viral protein 7 (VP7), a glycoprotein that forming the outer part of the virion, and one of the six structural glycoproteins involved in rotavirus replication, alters viroplasm formation and interferes with viral morphogenesis. [26] Till the vaccination is universal in developing countries, this drug can be an effective low cost treatment to control rotavirus diarrhea. So, the purpose of this study to evaluate the effectiveness of nitazoxanide in the treatment of acute rotavirus diarrhea between 6 months to 2 years old children.

OBJECTIVES

General objective:

The general object of this study was to evaluate the effectiveness of nitazoxanide in acute rotavirus diarrhea.

Specific objectives:

- To find out the duration of clinical recovery in nitazoxanide group and control group.
- To find out the length of hospital stay in nitazoxanide group and control group.

- To compare the treatment outcome in both groups.

METHODOLOGY

It was randomized controlled study; the study was conducted from June 2018 to July 2020. Age group was 6 months to 2 years old children of rotavirus diarrhea at the Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh.

Inclusion criteria

- Patient with rotavirus diarrhea.
- Duration of diarrhea <48 hours.
- Patient with some to severe dehydration.
- Patient between 6 months to 2 years of age.

Exclusion criteria

- Patient with bloody diarrhea.
- Patient with severe malnutrition.
- Patient with systemic infections requiring antibiotic therapy.
- Patient with chronic disease.

Study procedure

This randomized controlled clinical trial was conducted at Bangladesh Shishu & Hospital Institute, Dhaka, Bangladesh to evaluate the role of nitazoxanide in acute rotavirus diarrhea. Children with acute onset diarrhea of <48 hour's duration and positive stool rotavirus antigen test (by ELISA) were selected for study. A total of 70 patients were selected divided into two arms (group I and group II). Group I: 35 patients of case were enrolled in this arm and were treated with nitazoxanide with standard treatment. group II: 35 patients of control were enrolled in this arm and were treated with only standard treatment diarrhea only. After fulfilling the inclusion and exclusion criteria, patient was enrolled with unique ID. Patient's guardian were briefed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. Informed consent was obtained accordingly. Patient was managed accordingly. All patients were interviewed and their particulars and disease history were documented in a prescribed data collection sheet. Diagnosis was made on the basis of patient's guardian statement, statement of the witness, characteristic features of illness, clinical examination and available medical records. The clinical examinations were done properly. Relevant available investigations, such as complete blood count, stool R/M/E, stool for culture & sensitivity, serum creatinine, serum electrolyte were done. The treatments of the patients were given by the following sequences. Treatment: group I or intervention group was received nitazoxanide suspension at a dose of 15 mg/kg/day twice daily for 3 days along with rehydration solution and syrup zinc sulphate monohydrate and group II or control groups received rehydration solution and syrup zinc sulphate monohydrate. The children were discharged after improvement in their clinical condition and followed up at day 7. Follow-up: All participants were given standardized clinical care as inpatients based on WHO guidelines and standard operating procedures. During hospitalization, they were monitored for frequency and consistency of stools and time since last loose stool. They were also monitored for adverse events. All the patients were fed according to their age. Patients aged more than 6 months received milk formula or breast milk and solid food based on chicken meal, potatoes, rice, carrots, and vegetable oil. Outcome measures: Duration of acute diarrhea was defined as the time from the first to the last abnormal (loose or liquid) stools preceding a normal stool output. Consistency of stool was evaluated through a score system and stool was graded as 1 (normal), 2 (loose), 3 (semiliquid), and 4 (liquid). Duration of hospitalization was defined as the time from admission till discharge. Children were discharged 24 hours. after resolution of diarrhea. Adverse effects of nitazoxanide were also studied.

Statistical Analysis

Data were checked and cleaned before incorporating into statistical software (SPSS- version 22) and analyzed. Descriptive statistics were expressed as percent, mean & standard deviation. For categorical variables Chi-square test was done to find out the association. Continuous variables were compared by unpaired t-test. In all tests of significance p below <0.05 was considered as significant.

Ethical Implications

Ethical Review Committee (ERC) of Bangladesh Shishu Hospital & Institute, Dhaka had been approved the study.

RESULTS

Study demonstrates that maximum number of patients 22(31.4%) were between 14-17 months of age group. Mean age of the patient was 17.37±8.50 months in group I and 16.31±7.86 months in group II. The mean difference was not statistically significant (p>0.05) between the arms. Most of the patients were male in both arms. Male and Female ratio was 3.3:1. Maximum number of the studied subjects were belonging to lower class socio-economic status. The difference was not statistically significant (p-value>0.05) between the groups.

Table 1: Demographic characteristics of the studied subjects (N=70)

Variables	Group-I (n=35) n (%)	Group-II (n=35) n (%)	P value
Age (Months)			
6-9 months	7 (20.0)	9 (25.7)	
10-13 months	7 (20.0)	2 (5.7)	
14-17 months	11 (31.4)	11 (31.4)	
18-21 months	8 (22.5)	4 (11.5)	
22-24 months	2 (5.7)	9 (25.7)	
Mean ± SD	17.37 ± 8.50	16.31 ± 7.86	0.786
Gender			
Male	29 (82.8)	25 (71.5)	0.086
Female	6 (17.2)	10 (28.5)	
Socio-economic status			
Lower class	18 (51.4)	21 (60.0)	
Middle class	12 (34.3)	10 (28.6)	0.086
Upper class	5 (14.3)	4 (11.4)	

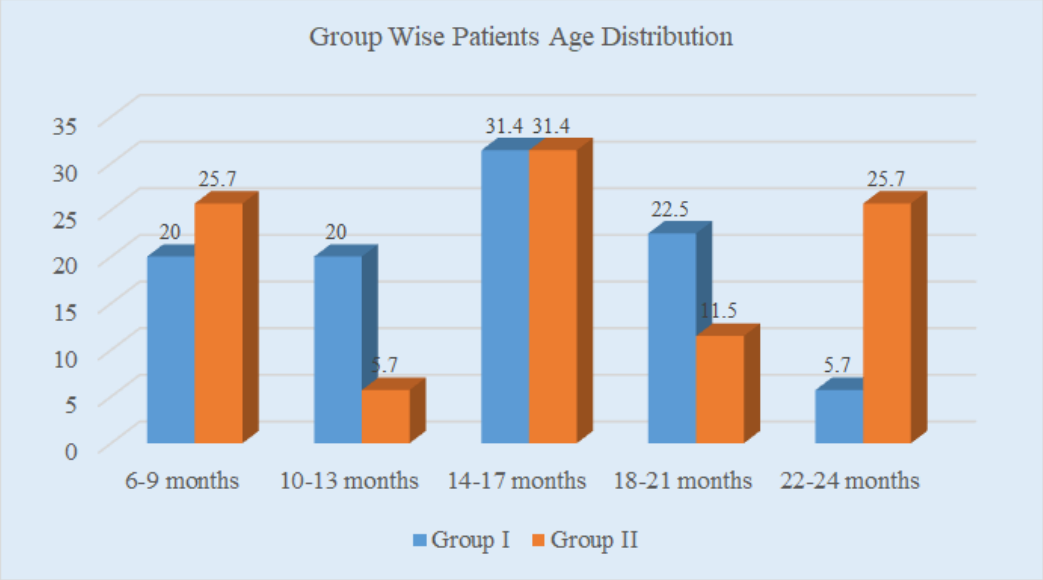

Figure 1: Bar chart showed Patients group wise age distribution

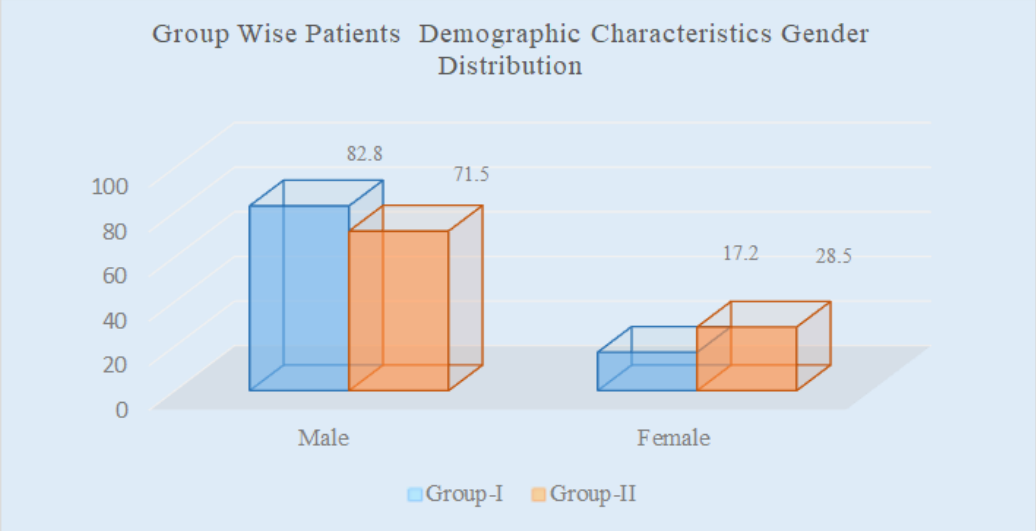

Figure 2: Bar chart showed Patients Group Wise Gender Distribution

Table II: Distribution of patients according to clinical symptoms (N=70)

Clinical symptoms	Group-I (n=35) n (%)		Group-II (n=35) n (%)	
	n	%	n	%
Passage of loose stools	35	100.0	35	100.0
Vomiting	35	100.0	35	100.0
Fever	28	80.0	32	91.4
Feeding difficulties	15	42.9	12	34.3
Abdominal pain	11	31.4	10	28.6
Restlessness	18	51.4	14	40.0

Table II showed the distribution of the patients according to clinical symptoms. Common symptoms were passage of loose stools, vomiting & fever.

Table III: Distribution of the Patients according to physical sign (N=70)

Physical sign	Group-I (n=35) n (%)		Group-II (n=35) n (%)	
	n	%	n	%
Some dehydration	35	100.0	35	100.0
Abdominal distension	23	65.7	25	71.4
Tachycardia	15	42.9	12	34.3
Abdominal tenderness	5	14.3	4	11.4
Lethargy	12	34.3	11	31.4
Altered consciousness	7	20.0	8	22.9

Table III showed the distribution of the patients according to physical sign. Common signs were some dehydration, abdominal distension and tachycardia.

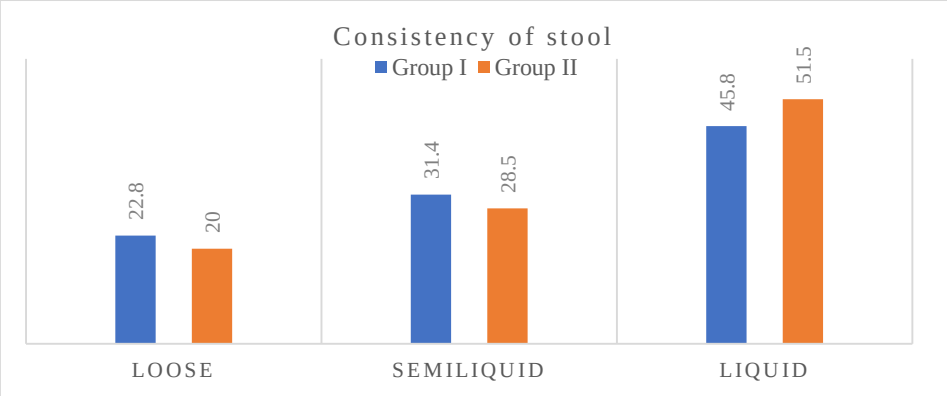

Figure 3: Distribution of the studied patients according to group wise consistency of stool (N=70)

Figure-3 shows the stool consistency of the studied patients. It was observed that most common findings were liquid consistency as 16(45.8%) patients in group I & 18(51.5%) in group II patients. Semiliquid stool was found in 11 (31.4%) patients in group I & 10(28.5%) in group II patients. Loose stool found in 8(22.8%) patients in group I & 7(20.0%) in group II patients. The difference was statistically non-significant.

Table IV: Assessment of major symptomatic improvement/ deterioration at different follow-up time (N=70)

	Clinical manifestations	Group-I (n=35) n (%)		Group-II (n=35) n (%)		P value
At 48 hours	Some dehydration	18	51.4	26	74.3	0.048
	Vomiting	17	48.6	29	82.9	0.003
	Fever	12	34.3	18	51.4	0.227
	Abdominal distension	13	37.1	20	57.1	0.094
At 72 hours	Some dehydration	12	34.3	19	54.3	0.092
	Vomiting	15	42.9	17	48.6	0.631
	Fever	9	25.7	14	40.0	0.203

	Clinical manifestations	Group-I (n=35) n (%)		Group-II (n=35) n (%)		P value
	Abdominal distension	5	14.3	11	31.4	0.088
At 168 hours	Some dehydration	0	0.0	5	14.3	
	Vomiting	8	22.9	13	37.1	0.192
	Fever	3	8.6	6	17.1	0.151
	Abdominal distension	0	0.0	0	0.0	-

Table IV showed the major symptomatic improvement/ deterioration at different follow-up time. Before commencement of treatment most of the patients in both groups experienced some dehydration, vomiting, fever, & abdominal distension. At 48 hours' improvement was observed in both groups, comparatively higher in group I. Difference of some dehydration and vomiting improvement between two groups were statistically significant (p <0.05).

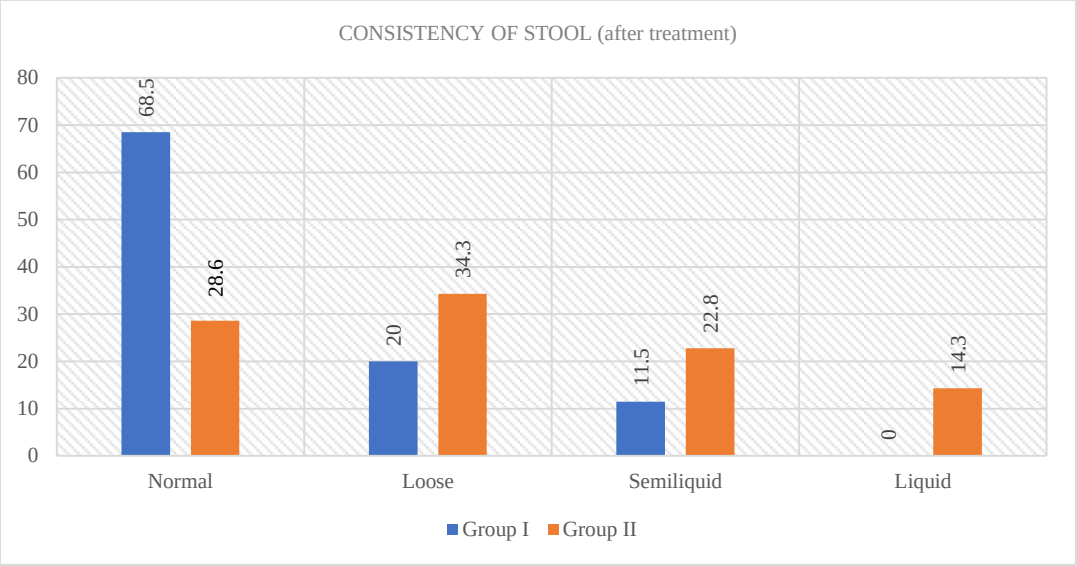

Figure 4: Evaluation of group wise stool consistency improvement after treatment (N=70)

Figure- 4 showed the stool consistency improvement of the study patients after treatment and observed that improvement almost similar in both groups, but slightly better in group I. Normal in consistency was found in 24(68.5%) patients in group I & 10 (28.6%) in group II patients. The difference was statistically significant (p=<0.05).

Table V: Distribution of the studied subjects according to overall outcome (N=70)

Outcome	Group-I (n=35) n (%	Group-II (n=35) n (%)	p value
Complete recovery	33 (94.3)	32 (91.4)	0.652
Need further management	2 (5.7)	3 (8.6)	0.712
Expired	0 (0.0)	0 (0.0)	

Table V showed the outcome between groups. Although recovery rate was high in Group-I, but overall outcome was almost similar. Complete recovery was 94.2% patients in Group-I and 91.4% patients in group-II, the difference was statistically non-significant (p>0.05).

Table VI: Comparison of complications between groups (N=70)

Complications	Group-I (n=35) n (%	Group-II (n=35) n (%)	p value
AKI	0 (0.0)	1 (2.9)	0.086ns
Electrolyte imbalance (hypokalaemia)	2 (5.7)	2 (5.7)	
No complications	33 (94.3)	32 (91.4)	

Table VI showed different complications between groups. Study revealed hypokalaemia developed in 2 (5.7%) patients of Group-I and 2 (5.7%) patients in group-II. The difference was statistically non-significant.

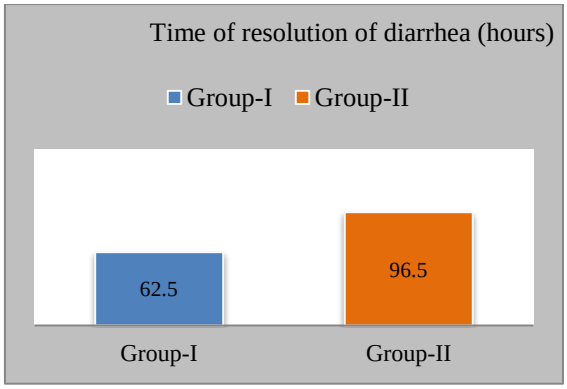

Figure 5: Bar chart showed, group wise time of resolution of diarrhea

Figure- 5 showed the mean time of resolution of diarrhea. Mean duration was 62.5 hour in group I and 96.5 hour in group-II. Compared to the control group (group II), the treatment group (group I) showed decrease in duration of diarrhea which was statistically significant (p= 0.001).

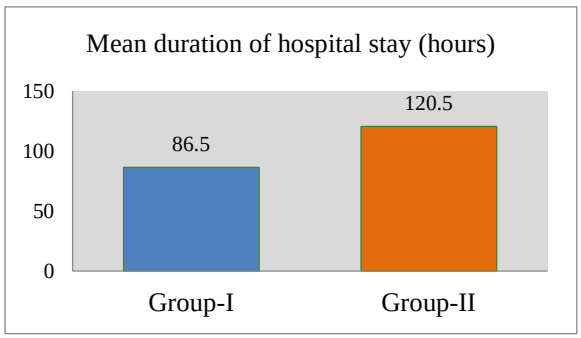

Figure 6: Bar chart showed group wise comparison of length of hospital stay

DISCUSSION

The study was carried out in Bangladesh Shishu & Hospital Institute, Dhaka, Bangladesh, from June 2018 to July 2020. This was the first randomized prospective clinical study of children between 6 months to 2 years old diagnosed with rotavirus diarrhea in Bangladesh, that has compared the nitazoxanide along with standard care and standard care alone. According to the questionnaire, history of all the 70 selected cases were taken, the clinical examination was carried out meticulously. Study demonstrated that maximum number of patients 22(31.4%) were between 14-17 months of age group. Ahmed et al., (2009) was found that highest prevalence in children from 7-12 months of age. [27] The highest prevalence rate during this age period most probably due to increased encourage to complementary feeding and decreased demand of breast feeding causing declining immunity. Mean age of the patient was 17.37±8.50 months in group I and 16.31±7.86 months in group II. Ahmed et al., (2009) Rossignol et al., (2006) also found similar findings in their studies. [27,28] Out of 70 cases 54(77.2%) cases were male and 16(22.8%) female. Male and Female ratio was 3.3:1. The clarification to this male predominance remains unclear. [27] It might be occurred due to gender bias among the parents of these children who seek medical care for their male children and this difference bears no statistical significance. Rossignol et al., (2012) also found similar findings in their studies. [29] Study showed lower class comprising the major percentage of the studied children. It might be occurred due to inadequate hand washing, unsafe & insufficient drinking water, and inadequate sanitation. [30] Alemayehua at el., 2020 [30] stated that major percentage of rotavirus diarrhea occurred in lower class family due to mother with low educational status, limited knowledge of mothers about diarrhea, absence of hand washing among mothers/caregivers, and sharing of the residence with domestic animals. [31] In this study, common clinical manifestations were found as some dehydration 35(100%) patients in both groups, vomiting 35(100%) patients in both groups, fever 28(80%) patients in group I & 32(91.4%) patients in group II and abdominal distension 23(65.7%) in group I & 25(71.4%) patients in group II. Severe dehydration in studied children was not found most probably due to increased awareness of mothers/caregivers about their children, availability of oral rehydration solution at community level, and improved health care facilities. Ahmed et al., (2009) studied 601 children aged from 1 month to 5 years in Bangladesh and they found fever 58.4% and vomiting in 63.7% patients which differs from this study. [27] In this study, liquid consistency was found in 16 (45.8%) patients in group I & 18(51.5%) in group II patients. Semisolid was found in 11(31.4%) patients in group I & 10 (28.5%) in group II patients. Loose stool was found in 8(22.8%) patients in group I & 7 (20.0%) in group II patients. The difference was statistically non-significant between two arms. In this randomized controlled trial, nitazoxanide given orally twice daily for 3 days to children aged 6 months to 2 years during an acute episode of rotavirus diarrhea resulted in significant decrease in the duration of diarrhea and hospitalization without any remarkable adverse events. Present study showed the stool consistency improvement of the patients after treatment and observed that improvement was almost similar in both groups, but slightly better in group I. Previous trial among 38 children (5 months to 7 years) were included and the intervention group received 7.5 mg/kg nitazoxanide orally twice daily for 3 days. [28] The median time to resolution of illness was 31 hours for the nitazoxanide group compared with 75 hours for the control group (p=0.0137), and no significant adverse effect was reported. In the second trial, 75 children (28 days to 24 months) were included and the intervention group (n=25) received oral nitazoxanide (15 mg/kg/day) twice daily for 3 days. [32] The median duration of hospitalization (nitazoxanide, 81 hours. control, 108 hours.; p=0.017) and diarrhea (nitazoxanide, 54 hours, control, 79 hours. p=0.009) was significantly reduced in the nitazoxanide group. The only adverse effect noted was greenish discoloration of body fluid that spontaneously disappeared in follow-up. The

present study result was in accordance with these trials without report of any adverse effect and provides evidence that nitazoxanide is helpful in children with <10% dehydration. Mean time of resolution of diarrhea decreased in intervention group might be due to decreasing viral load by tizoxanide which inhibits rotavirus viral protein 7. The strength of the present study is that it studied the effect of nitazoxanide in Bangladesh setting with high morbidity & mortality due to rotavirus diarrhea. As previous trials have been conducted in western countries, their findings cannot be extrapolated on Bangladeshi children due to a higher breast feeding rate, poor hygienic condition, and a distinct gut colonization status. The age range included 12 months to 5 years which is important, as diarrhea is an important cause of under-five mortality in developing countries in this age group. The effect on the requirement of rehydration was evaluated which is important from public health point of view. Similar observation reported median duration of hospitalization was significantly shorter (p= 0.017) in patients who received nitazoxanide (81 hours) and probiotics (72 hours) compared to patients who received oral rehydration solution alone (108 hours). Similarly, the median duration of diarrhea was significantly reduced (p= 0.009) in children who received nitazoxanide (54 h) and probiotics (48 hours) compared to the control group (79 hours). [32] In this study, the baseline clinical manifestations before randomization were almost same in both arms but after 3 days' treatment clinical manifestations significantly reduced in arm I compared to arm II. So, it is concluded that treatment with nitazoxanide is effective in the management of studied children with acute rotavirus diarrhea.

LIMITATIONS

Potential limitations include the following:

- No genotyping of rotavirus strain was done due to cost constraints.
- Measurement of the volume of stool output (g/kg) was not done.
- Cost-effective analysis was not done.

RECOMMENDATION

Further multicenter studies with advanced laboratory facilities and large sample is recommended.

CONCLUSION

Present study concluded that treatment with nitazoxanide was effective in the treatment of studied children with acute rotavirus diarrhea.

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