Original Article

A Comparative Study between Zinc Alone and Zinc with Racecadotril in Acute Watery Diarrhoea

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Abstract

Background: *Diarrhoea is one of the most common causes of morbidity and mortality in children under 5 years in the developing world. Racecadotril is a diesterified derivative of thiorphan. The objective of the study is to compare the effects of zinc alone and zinc with racecadotril in acute watery diarrhoea.* ***Materials and Methods:*** *This prospective comparative study was carried out in the Department of Paediatrics, Abdul Malek Ukil Medical College & Jononeta Nurul Hoque Adhunik Hospital, Noakhali during July 2021 to December 2021 with ethical clearance from respective IERB. Total 86 Children aged between 3-60 months requiring admission for severe acute gastroenteritis, as evidenced by a Modified Vesikari Score of >11 was included in this study. Patients were divided into two groups, Group-A: Zinc with racecadotril and Group-B: Zinc alone. All the information was recorded in the fixed protocol. Collected data were classified, edited, coded and entered into the computer for statistical analysis by using SPSS-23.* ***Results:*** *Mean duration of diarrhoea was found 35.32±9.25 hrs in group-A and 31.57±11.38 hrs in group-B. The mean duration of hospital stay was 30.39±16.10 hrs in group-A and 41.53±18.38 hrs in group-B. Mean remission time was 49.7±23.22 hrs in group-A and 66.25±29.41 in group-B. The difference was statistically significant between the two groups. Skin rashes were found 4 (9.3%) in group-A and 6 (14.0%) in group-B. Angioedema was 3 (7.0%) and 1 (2.3%) in group-A and group-B respectively. Tonsilitis was 2 (4.7%) in group-B but no tonsilitis was found in group-A. Convulsion was 2 (4.7%) in group-A and 1 (2.3%) in group-B.* ***Conclusion:*** *When comparing the zinc plus racecadotril group to the zinc alone group, the mean frequency of diarrhoea, the mean length of hospital stays, and the mean remission time were all considerably lower. There was no discernible difference in the adverse occurrences between the two groups.*

Keywords: Acute Watery Diarrhoea, Zinc, Racecadotril.
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Introduction

Diarrhoea is a common problem in our country, especially in children. There are many treatment options for acute watery diarrhoea in addition to oral rehydration saline for reducing the severity of acute watery diarrhoea[1]. Diarrhoea is defined as loose or watery stool passing more than three times in a day, with or without blood or mucus in stool[2]. Diarrhoeal episodes are usually acute but sometimes these may last even for weeks[3].

Diarrhoeal disorders in childhood accounts for a large proportion (18%) of childhood deaths, with an estimated 1.5 million deaths per year globally, making it the second most common cause of child deaths worldwide[4,5]. The World Health Organization (WHO) and UNICEF estimate that almost 2.5 billion episodes of diarrhoea occur annually in children <5 year of age in developing countries, with more than 80% of the episodes occurring in Africa and South Asia (46% and 38%, respectively). Global mortality rates may be decreasing, but the frequency of diarrhoea remains constant at around 3.6 episodes per child per year[4].

For children with acute diarrhoea, racecadotril (acetorphan), an enkephalinase inhibitor with antisecretory and anti-diarrhoeal properties, is a safe and efficient treatment[6]. Several reviews and meta-analyses have examined the safety and efficacy of racecadotril in the treatment of acute diarrhoea in children[7,8]. Based on such data, international

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guidelines recommend racecadotril as a treatment option in children with acute diarrhoea[9]. The current study compared racecadotril efficacy and tolerability to placebo in hospitalized babies and children, as well as the effect of racecadotril as an addition to rehydration therapy in infants and children in Bangladesh.

Materials and Methods

The prospective comparative study was conducted in the Department of Paediatrics, Abdul Malek Ukil Medical College & Jononeta Nurul Haque Adhunik Hospital, Noakhali during July 2021 to December 2021. Among children aged 3–60 months requiring admission for severe acute gastroenteritis, as evidenced by a Vesikari score of >11 with written parental consent. The protocol was approved by the institutional ethical committee (ref: BCPS/712/2021) and written informed consent was obtained from parents of all participating children. A total of 86 patients were included by convenient sampling. Then the patients were divided into two groups, Group-A: Zinc with racecadotril and Group-B: Zinc alone.

The Inclusion criteria were children aged 3-60 months requiring admission for severe acute gastroenteritis. Exclusion criteria were clinical diagnosis of dysentery or a known diagnosis of liver or renal failure, children who had prescriptions of probiotics or any other anti diarrhoeal medication. The attending physician admitted all the children and began treating them according to the World Health Organization's guidelines. They received either intravenous fluids as per WHO plan C (30 mL/kg followed by 70 mL/kg over 1 and 5 hours respectively, in infants and over 30 min and 2.5 hours for those over 12 months of age) or low osmolality ORS as per WHO plan B (75 mL/kg over 4 hours). Zinc was prescribed at 10-20 mg/day. Participants were recruited within 24 hours of admission, following the completion of initial hydration. The granules were applied as granules dissolved in 10 ml of water and taken three times a day for up to 3 days. The test arm received zinc and racecadotril at a dose recommended by the researcher: 10 mg for children under 12 months of age and 30 mg for those over 12 months of age. This was administered as granules dissolved in 10 mL of water and taken three times a day for a maximum duration of 3 days. The control arm has zinc only preparation administered in the same way. An initial dose of either racecadotril or zinc was administered at the time of enrollment. The parents were taught how to administer the drug at this time, and this was confirmed by return demonstration. The participants were followed up using daily interviews asking about: the number of stools, the presence of blood in stools, any new symptoms and the introduction of an anti-diarrhoeal or other medication. Treatment was given either until the stools were formed or for a total of 3 days, whichever comes first. Before their symptoms were completely resolved, children who were released from the hospital underwent phone interviews until they recovered. The primary measure was the number of stools recorded in the first 48 hours following the introduction of the drug. The secondary outcomes included the duration of inpatient stay, the duration of illness and the number of adverse events associated with racecadotril.

All the data was collected with the above-mentioned methods and was entered into SPSS v23. The patients were examined by the researcher for certain signs and those were recorded in the checklist. Investigations were done to support the diagnoses. According to the participants' understanding level, sometimes the questions were described in the native language so that the patients can understand the questions perfectly and answer accurately. All the data was collected by the researcher to avoid errors. Statistical inference was based on 95% confidence interval and p-value <0.05 was considered statistically significant. Variables were expressed as mean±standard deviation (SD), frequency and percentage.

The summarized data were presented in the form of tables and figures. At the very beginning it was clarified that the participants have the right to refuse to answer any question while completing the questionnaire. They can be withdrawn from the study at any time and refusing to participate did not affect his/her treatment in any way. It also clarified to all participants about the aim of the study. Participants were assured that no personal information was published anywhere.

Results

In this study it showed that majority patients belonged to the age group 6-24 months in both groups. The mean age was found 16.5±8.3 months in group-A & 15.7±9.6 months in group-B (table-I).

Table-I: Age distribution of the study patients (n=86)

Age (months)	Group-A (n=43)		Group-B (n=43)		p-value (Significance)
	n	%	n	%	
<6	11	25.6	12	27.9	p=0.68 Not Significant
6-24	19	44.2	21	48.8	
25-48	10	23.3	8	18.6	
>48	3	7.0	2	4.7	
Mean±SD	16.5±8.3		15.7±9.6		

Male patients were predominant in both groups, that was 24 (55.8%) in group-A and 26 (60.5%) in group-B (figure-1). Present study showed that mean duration of diarrhoea was found 35.32±9.25 hours in group-A and 31.57±11.38 hours in group-B. The difference was not significant (p>0.05) between two groups (table-II).

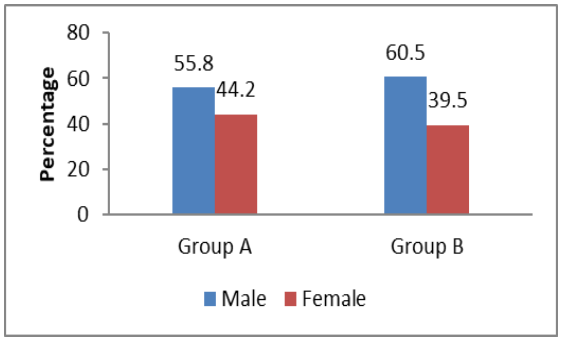

Figure-1: Gender distribution of the study population

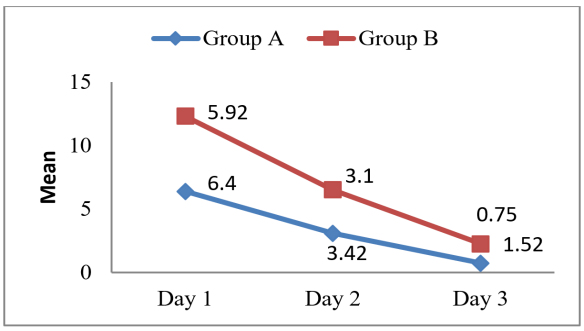

Figure-2: Mean frequency of diarrhoea between two groups

Table-II: Mean duration of diarrhoea before treatment between two groups (n=86)

Mean duration of diarrhoea (hours)	Group-A (n=43)	Group-B (n=43)	p-value (Significance)
	mean±SD	mean±SD	
Mean duration of diarrhoea	35.32±9.25	31.57±11.38	0.09 (Not Significant)
Duration of hospital stay	30.39±16.10	41.53±18.38	0.003 (Significant)
Remission time	49.7±23.22	66.25±29.41	0.001 (Significant)

Table-III: Distribution of the study patients by degree of dehydration (n=86)

Degree of dehydration	Group-A (n=43)		Group-B (n=43)		p-value (Significance)
	number	%	number	%	
No sign of dehydration	16	37.2	13	30.2	0.62 (Not Significant)
Some sign of dehydration	25	58.1	29	67.4	
Severe sign of dehydration	2	4.7	1	2.3	

Table-IV: Distribution of the study patients by adverse events (n=86)

Adverse events	Group-A (n=43)		Group-B (n=43)		p-value (Significance)
	number	%	number	%	
Skin rashes	4	9.3	6	14.0	0.501 (Not Significant)
Angioedema	3	7.0	1	2.3	0.305 (Not Significant)
Tonsilitis	0	0.0	2	4.7	0.152 (Not Significant)
Convulsions	2	4.7	1	2.3	0.556 (Not Significant)

In this study, it showed that some dehydration was found in 25 (58.1%) in group-A and 29 (67.4%) in group-B. Severe dehydration was 2 (4.7%) in group-A and 1 (2.3%) in group-B. No dehydration was 16 (37.2%) in group-A and 13 (30.2%) in group-B. The difference was not statistically significant (p>0.05) compared between two groups (table-III). In table-IV shows the adverse effects of the patients like skin rashes, angioedema, tonsilitis and convulsion of two groups.

Discussion

In this study, it showed that majority of the patients belonged to the age group 6-24 months in both groups. The mean age was found 16.5±8.3 months in group-A and 15.7±9.6 months in group-B. Male patients were predominant in both groups, that was 24 (55.8%) in group-A and 26 (60.5%) in group-B. Sultana, et al.[1] reported the mean age of month in Probiotics plus zinc group (14.01±6.72) and Zinc alone group (13.31±8.02) were almost similar with in this study. In group-A male 56% & female 44% and in group-B male 58% & female 42%. Greater number of the patients was male in both groups (56.36% vs. 58.18%). Ramadas, et al.[10] observed the mean age was 14±6.38 months in group-A (Single drug) and 11±5.19 months in group-B (combination drug). Male children were found 18 (60.0%) in group-A and 22 (79.33%) in group-B. Female was 40.0% and 26.67% in group-A and group-B respectively.

In this study showed that at day 2 mean frequency of diarrhoea was found 3.10±0.57 in group-A and 3.42±0.62 in group-B. At day 3 mean frequency of diarrhoea was 0.75±0.41 and 1.52±0.35 in group-A and group-B respectively. The difference was statistically significant between the two groups.

Similar observation was found in the study by Ramadas, et al.[10] and Sultana, et al[1]. There was no significant difference between the mean frequency of diarrhoea on day 1 in the two groups. Present study showed that mean duration of diarrhoea was found 35.32±9.25 hrs in group-A and 31.57±11.38 hrs in group-B. The difference was not significant between the two groups. Sultana, et al[1]. reported duration of acute watery diarrhoea was significantly reduced in group-A than group-B (56.22 vs 70.69 hrs). Duration of diarrhoea before treatment was shorter than Aggarwal, et al.[11] study. Gharial, et al.[12] observed the duration from the introduction of the drug until the occurrence of ≤3 formed stools within a 24-hour period.

Current study showed that mean duration of hospital stay was 30.39±16.10 hrs in group-A and 41.53±18.38 hrs in group-B. Mean remission time was 49.7±23.22 hrs in group-A and 66.25±29.41 hrs in group-B. The difference was statistically significant between the two groups. Sultana et al.[1] showed that the length of hospital stay was shorter in the combination group than in the zinc group. Besides Gharial, et al.[12] who also reported a shorter hospital stay in Racecadotril group.

This study showed that some dehydration was found in 25 (58.1%) in group-A and 29 (67.4%) in group-B. Severe dehydration was 2 (4.7%) in group-A and 1 (2.3%) in group-B. No dehydration was 16 (37.2%) in group-A and 13 (30.2%) in group-B. The difference was not statistically significant between the two groups. Gharial, et al.[12] found that there was no significant difference in the degree of dehydration between groups. It was noted that most children in the study were mild to moderately dehydrated with severe dehydration present in only 15% of the drug group and 27% of the placebo group. Similar results were found in the study carried out by Schnadower, et al[13].

Present study showed that skin rashes were found 4 (9.3%) in group-A and 6 (14.0%) in group-B. Angioedema was 3 (7.0%) and 1 (2.3%) in group-A and group-B respectively. Tonsilitis was 2 (4.7%) in group-B but no patient of tonsilitis was found in group-A. Convulsion was 2 (4.7%) in group-A and 1 (2.3%) in group-B. The difference was not statistically significant between the two groups. Gharial, et al.[12] reported the proportion of patients experiencing any adverse event was similar for the two groups (23%). There were four mortalities overall, two in each group. Convulsions were observed in three children (5%) who received the drug, while no convulsions occurred in the children given the placebo. All three children were investigated for concurrent meningitis and this diagnosis was confirmed in one. Overall, the proportion of children experiencing adverse reactions in the racecadotril group was not statistically significant when compared to the placebo group.

The World Health Organization has recommended that drug treatment be added to rehydration therapy, if the drug used has proven safety and efficacy in the paediatric population[14,15].

Racecadotril decreases intestinal hypersecretion but not motility[16-18]. It has proven efficacy and safety use in children and adults with acute watery diarrhoea when taken orally[19,20].

Limitations of the study

The study population was selected from one selected hospital in Noakhali city, so that the results of the study may not reflect the exact picture of the country. Small sample size was also a limitation of the present study. Therefore, further study may be undertaken with large sample sizes.

Conclusion

The mean frequency of diarrhoea was considerably lower in the Zinc plus Racecadotril group than in the Zinc alone group. The average length of hospital stays, and average remission time were also significantly shorter in the Zinc with racecadotril group.

Conflict of interest

The authors declared that they have no conflict of interest.

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