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# NITAZOXANIDE IN TREATMENT OF ROTAVIRUS DIARRHEA IN CHILDREN: A SINGLE CENTER STUDY

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## ABSTRACT:

**BACKGROUND & OBJECTIVE:** As Rotavirus leads to significant morbidity in children 2 months to 5 years, this study was done to observe the effect of one dose of nitazoxanide on the total duration of rotavirus diarrhea. The primary objective was to evaluate the reduction in the mean duration of viral diarrhea in children after administration of first dose of Nitazoxanide.

**METHODOLOGY:** This descriptive study was done in the Department of Pediatric Medicine Unit I, Mayo Hospital, Lahore from Jan 2016 to June 2016 after approval from the ethical review committee. Sample size calculated was 175 using WHO sample size calculator. Patients of 4–5 years were given 200 mg nitazoxanide twice daily for 3 days; 100 mg nitazoxanide was given twice daily to 12–47 months age group, and patient of <12 months age were given 7.5 mg/kgtwice day along with routine care and were followed 12 hourly till the passage of normally formed stools. Duration of diarrhea was recorded.

**RESULTS:** Out of 175 cases, 58.9%(n=103) were between 2-36 months age while 41.2%(n=72) were 37-60 months age, mean+SD was calculated as 35.06+13.34 months, mean reduction in duration of rotavirus diarrhea in children after administration of first dose of Nitazoxanide was recorded as 32.85+2.32 hours.

**CONCLUSION:** With the use of nitazoxanide along with routine care for rotavirus diarrhea children, the mean duration of rotavirus diarrhea was reported to be less than 1.5 days.

**KEYWORDS:** Rotavirus, Nitazoxanide, Diarrhea, Antidiarrheal, Hospital stay.

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## INTRODUCTION:

Diarrhea caused with infection of the rotavirus is a common diagnosis of infants in the pediatric ward and outpatient department. Acute infection of the gut leading to watery stools in children <5 years is mostly caused by rotavirus, even leading to around 5% mortality. Since the development of vaccine for rotavirus,its morbidity and mortality have reduced significantly and it has been declared as an effective health strategy for prevention as well as reduced severity. Trials done at multiple centers have shown its efficacy of around 65 to 85% varying from developing and developed countries [1].Still some factors can affect the efficacy of the oral vaccines in under developed countries[2].

Previously it was thought that a better standard of living, improved hygiene and better sanitation can control the incidence of rotavirus infection, but studies have shown that these are not sufficient, as incidence of rotavirus diarrhea was same in developed and developing countries before the development of vaccine against rotavirus. This virus transmits through the feco-oral route. After initial two days of infection, patientsstart to have fever with vomiting, later followed by severe watery diarrhea, which last for at least five to seven days [3]. Management of rotavirus diarrhea mainly include the electrolyte correction along with oral rehydration, but in some cases, antibiotics are also prescribed[4]. Nitazoxanide is among the few antimicrobial drugs which can be used in the treatment of diarrheas due to parasitic infection as well as for viral infections, as it has broad antiviral activity. Few studies have been done to see the role of Nitazoxanide in the management of viral infections involving the gut [5]. It is one of the anti-infectiveagents used now in the field of medicine, which can disturb the growth of the various types of protozoans, helminthes and even few anaerobes and viruses [6].

Previously a study recorded 35.6+28.9 hours for duration of diarrhea after administration of first dose of Nitazoxanide[7] while another study recorded this finding as 31.0±6.87 hours which shows a significant difference between the two studies[4].

A systemic review of various randomized controlled trials on the role of Nitazoxanide in patients of viral diarrheas showed that with the first dose of Nitazoxanide symptoms start to resolve and total duration of diarrhea is reduced. It was concluded that although it is a viral disease and is self-limiting, but with the use of Nitazoxanide beneficial effects can be achieved by controlling the outbreaks [8,9].

The rationale of the study is that Nitazoxanide is cost effective but no local data is available evaluating mean duration of diarrhea after first dose of Nitazoxanide in children with rotavirus, while the above studies were conducted on smaller sample size which needs a local study to be conducted in our population so that we may get the real scenario on our local population that may help to reduce the disease burden.

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## METHODLOGY:

This research was conducted in Department of Pediatric Medicine Unit I, Mayo Hospital, Lahore,six months after approval from the hospital ethical review committee. Children having age from 2 months to 5years of age from both genders diagnosed as the cases of rotavirus diarrhea (as per operational definition) during last 24 hours were included in the study though non probability, conservative sampling technique.

Rotavirus Diarrhea was defined as the children with more than or equal to three loose stools or watery stools in 24 hours lasting not more than 14 days with the symptoms including vomiting, fever (100.4`F), and abdominal pain. (Assessed on history and clinical examination) caused by Rota Virus diagnosed by ELISA technique.

Mean duration was defined as the duration of diarrhea andcalculated from the administration of first dose of Nitazoxanide till the normal formed stools less than 3 episodes per day (assessed on physical examination) and resolution of associated symptoms with diarrhea i.e. fever, vomiting and abdominal pain. Patients were assessed after every 12 hours.

**Exclusion criteria:** Patients having history of diarrhea for more than 14 days and patients with dysentery (Assessed on physical examination considering more than or equal to three loose stools or watery stools in 24 hours lasting not more than 14 days with blood in stools) including patients already have received rotavirus vaccines, coexisting severe infection e.g. pneumonia (patchy infiltration on chest xray), sepsis (TLC >11000 or <4000/mm3),severe malnourished patients (weight for height < 3SD) and patients previously taken any antibiotic therapy by checking medical record in last 7 days before current illness, patients with serum creatinine of more than 2.0 mg/dl were excluded from the study.

Sample size of 175 was calculated using WHO sample size calculator, taking absolute precision of 1%, 95% confidence level and taking expected mean duration of diarrhea after first dose of administration of Nitazoxanide i.e. 31.0±6.87 hours[7].

All 175 patients fulfilling the inclusion/exclusion criteria admitted to Department of Pediatric Medicine Unit I, Mayo Hospital, Lahore were included in the study. An informed consent to include their data with the assurance of confidentiality was obtained from their parents. All study cases were administered by the nursing staff as (200 mg nitazoxanide) twice a day for 3 days in patients 4–5 years of age, (100 mg nitazoxanide) twice a day in patients 12–47 months of age, and (7.5 mg/kg nitazoxanide) twice a day in patients younger than 12 months. In addition to the study medication, all patients were receiving routine care including fluid replacement therapy and nutritional and metabolic management of diarrhea. The nursing staff followed the children for every 12 hours till the normal formed stools. All this information was recorded on a pre-designed proforma. Duration of diarrhea was recorded as per operational definitions.

The data was entered in computer software Statistical Package for Social Sciences (SPSS version 17.0). Categorical variables i.e., gender was described as frequency and percentages. Continuous variables i.e., age and duration of rotavirus diarrhea in children after administration of first dose of Nitazoxanide was recorded and presented as mean±SD. The data was stratified for age, gender, no. of stools per day of the children to control the effect modifier. Independent sample t-test was applied $p<0.05$ was significant.

## RESULTS:

A total of 175 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the mean duration of rotavirus diarrhea in children after administration of first dose of Nitazoxanide. Patients were distributed according to age of the patients, it shows that 58.86%(n=103) were between 2-36 months of age while 41.14%(n=72) were between 37-60 months of age, mean±sd was calculated as 35.06+13.34 months.

Patients were distributed according to gender; it shows that 56%(n=98) were females and 44%(n=77) were male.Mean duration of rotavirus diarrhea in children after administration of first dose of Nitazoxanide was recorded as 32.85±2.32 hours. The data was stratified for age, gender, no. of stools per day of the children to control the effect modifier. Independent sample t-test was applied and $p\leq0.05$ was significant (Table: I-III).

**Table-I: Stratification for Mean Duration of Rotavirus Diarrhea in Children After Administration of First Dose of Nitazoxanide with Regards to Age (n=175).**

| Age (in months) | Duration of rotavirus (Hours) | | p-value |
|---|---|---|---|
| | Mean | SD | |
| 2-36 (n=103) | 32.73 | 2.34 | 0.433 |
| 37-60 (n=72) | 33.01 | 2.30 | |

As p-value is insignificant, it shows that the mean duration of diarrhea after treatment with the drug was same in both age groups showing that its effect on the duration of diarrhea is same from 2 months to 60 months.

**Table-II: Stratification for Mean Duration of Rotavirus Diarrhea in Children After Administration of First Dose of Nitazoxanide with Regards to Gender (n=175).**

| Gender | Duration of Rotavirus (Hours) | | p-value |
|---|---|---|---|
| | Mean | SD | |
| Male (n=77) | 33.13 | 2.34 | 0.151 |
| Female (n=98) | 32.62 | 2.30 | |

This shows that the mean duration of diarrhea after treatment with the drug was same in both genders showing that the duration of diarrhea after treatment with nitazoxanide reduced equally in both genders.

**Table-III: Stratification for Mean Duration of Rotavirus Diarrhea in Children After Administration of First Dose of Nitazoxanide with Regards to no. of Stools (n=175).**

| No. of Stools | Duration of Rotavirus (Hours) | | p-value |
|---|---|---|---|
| | Mean | SD | |
| 3-8 | 32.88 | 2.36 | 0.43 |
| >8 | 32.84 | 2.33 | |

Interpretation of this analysis is that the mean duration of diarrhea after treatment with the drug was same irrespective of the no of stools per day at presentation.

Rotavirus is a leading cause of morbidity and mortality in children younger than 5 years. This study was planned to recordreductionin the mean duration of rotavirus diarrhea in children after administration of first dose of nitazoxanide as this drug is cost effective but no local data is available evaluating mean duration of diarrhea after first dose of Nitazoxanide in children with rotavirus, while the previous studies were conducted on smaller sample size [10].

In the 20th century, nitazoxanide was used to treat parasitic infections mostly. Although with the use of nitazoxanide some side effects can occur. These include headache, bronchitis, and oropharyngeal pain in around 3-5% of the children [11]. The cost of treatment for nitazoxanide and probiotics are almost the same for 5 days. The cost of treatment is seen in developing countries where the incidence of rotavirus is still significance among the children. With significant reduction in diarrhea duration and stay in the hospital, nitazoxanide can be a better treatment strategy for rotavirus infection. In our study, out of 175 cases, 58.86%(n=103) were between 2-36 months of age while 41.14%(n=72) were between 37-60 months of age, mean±SD was calculated as 35.06±13.34 months, 44%(n=77) were male and 56%(n=98) were females, mean duration of rotavirus diarrhea in children after administration of first dose of Nitazoxanide was recorded as 32.85±2.32 hours. We compared our results with a previous study 6 recorded 35.6+28.9 hours for duration of diarrhea after administration of first dose of Nitazoxanide while another study 4 recorded this finding as 31.0+6.87 hours which shows a significant difference between the two studies. However, our findings are in agreement with the successive study.

Teran CG, et al[7] conducted a controlled trial to determine the efficacy of nitazoxanide treatment alone and compared with the probiotic's

treatment group and oral rehydration group. After comparing the results, they reported that the hospital stay was reduced significantly (p = 0.017) among the case group who were given nitazoxanide (81 hours) and probiotics (72 hours) and ORS group (108 hours). The duration of disease (diarrhea) also reduced; it was 54 hours in nitazoxanide group and 48 hours in the probiotics group and 79 hours in the) RS group. They were of the conclusion that nitazoxanide is more effective as compared to just probiotic use or oral rehydration treatment for acute rotavirus diarrhea.

Another study conducted to observe the effect of nitazoxanide on duration of diarrhea showed that median duration (hrs.) of diarrhea was 54 versus 80 hrs. The duration of rotavirus diarrhea was significantly shorter in the nitazoxanide group. There was no report of any adverse events. Comparison of the median diarrhea duration between the trial group of patients and control group showed that difference of around 26 hrs. was observed [95% CI: −13.2 to −38.8][12]. Our study didn't have any control group, it is one of the limitations of our study, further studies should be done in our population by adding a control group in the trial. Unlike our study, fever and other adverse effects were also noted in this study.

Studies have shown that nitazoxanide has anti-viral properties by inhibiting the replication process of a group of viruses[7]. Nitazoxanide and probiotics are together alternative for the other OTC medications used for management of rotavirus cases in populations where rotavirus vaccination is not a routine and for children with contraindications of immunizations or who cannot buildup proper immune response in the body. Although preliminary results have proven effectiveness of nitazoxanide as compared to probiotics alone and the standard treatment groups, we still recommend more trials to be conducted including a large number of patients to obtain better and more reliable results.

As studies have shown broad spectrum anti-microbial activity of nitazoxanide, it is now approved in USA as an anti-parasitic drug for the management of conditions like cryptosporidiosis and giardiasis[13,14]. Few Studies have been conducted to evaluate the antiviral activity against certain viral illnesses like rotavirus, novo virus and influenza virus. with a wide range of antiviral activity and its safe use in children, it is currently in trial to see its response in COVID -19 as well [15].

## CONCLUSION:

With the use of nitazoxanide along with routine care for rotavirus diarrhea children, the mean duration of rotavirus diarrhea was reported to be less than 1.5 days. This drug might be suitable for the management of rotavirus diarrhea, but a larger study involving children of all age groups can help in reaching a better conclusion.

## LIMITATION OF THE STUDY:

This was done at a single center; this trial should be done at a larger scale involving multiple centers and large number of populations. Only the duration of diarrhea was compared, other variables like complications of the drug under trial, volume of stool output, and cost-effective analysis should be done.

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**Author's Contribution:**

**Aneeqa Adnan:** Designed the study, collected the data and manuscript writing.
**Abdul Ahad Jamshaid:** Manuscript writing and data analysis.
**Muhammad Azhar Farooq:** Drafting of the work and final approval of the version to be published.
**Tehreem Fatima:** Interpretation of data for the work.

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