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ORIGINAL ARTICLE

Effectiveness of nitazoxanide in the treatment of COVID-19 related diarrhoea

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Abstract

Background: *Diarrhoea is becoming one of the most prominent and troublesome manifestations in COVID-19 infection but no definitive treatment is available. So Nitazoxanide was used to see whether it can shorten the duration and sufferings form COVID-19 related diarrhoea.*

Objective: *To see the efficacy of Nitazoxanide in decreasing frequency and improving the consistency of stool in COVID-19 related diarrhoea.*

Methods: *This randomized comparative study was done in private chambers of medicine specialists in Khulna and patients admitted in corona dedicated hospital, Khulna from July 2020 to June 2021. 100 patients were enrolled in the study using Nitazoxanide & ORS (oral rehydration solution) in 50 patients and only ORS in another 50 patients. Decreased frequency and volume of stool at 24, 48 and 72 hours of both groups were compared.*

Results: *After giving Nitazoxanide in diarrhoea of COVID-19 patients, improvement was in 90% patients at 24 hours: in 96% patients in 48 hours and in 98% cases at 72 hours. On the other hand, without Nitazoxanide improvement was found in 30%, 40% and 50% cases at 24, 48 and 72 hours respectively. So Nitazoxanide was effective ($p < 0.05$) at reducing frequency of diarrhoea and improving the consistency of stool.*

Conclusion: *Nitazoxanide significantly improves diarrhoea in COVID-19 patients by reducing duration of diarrhoea and improving consistency of stool.*

Keywords: Nitazoxanide, COVID-19, Diarrhoea

Introduction

COVID-19 disease, the current pandemic is a huge challenge for whole of the world. Till 3 September, 2021 more than 218,946,836 confirmed cases were found and more than 4,539,723 deaths are reported globally.[1] Transmission of COVID-19 occurs mainly through respiratory droplets and close contact are the main means of transmission. Clinically fever, fatigue, and dry cough are the main manifestations and diarrhea is the first or accompanying symptom in some patients. In a study of 99 patients with COVID-19 in Wuhan showed that most of them had fever or cough when they were admitted to hospital, but 2% had diarrhea and 1% had nausea and vomiting.[2] A statistical analysis on 1,099 COVID-19 patients was done and found that about 3.7% of them had diarrhea and 5.0% had vomiting.[3] Another study on 138 COVID-19 patients reported that 10.1% had diarrhea, while 16.7% of 36 patients admitted to the intensive care unit had diarrhea.[4] In case reports of the United States and Vietnam, gastrointestinal symptoms such as diarrhea and nausea have been described.[5,6] No such type of study is available in Bangladesh.

Till now no specific drug is available to combat COVID-19 related diarrhoea. Nitazoxanide is a broad-spectrum antiparasitic and broad-spectrum antiviral medication that is used in medicine for the treatment of various helminthic, protozoal and viral infections.[7-10] Chemically, Nitazoxanide is the prototype member of the thiazolides, a class of drugs which are synthetic nitrothiazolyl-salicylamide derivatives with antiparasitic and antiviral activity. Nitazoxanide has been shown to inhibit replication of SARS (severe acute respiratory syndrome), MERS (middle east respiratory syndrome) and other coronaviruses as well as influenza viruses, rhinoviruses, parainfluenza

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viruses, RSV (respiratory syncytial virus) and other respiratory viruses in cell culture studies.[9,11,12] Therefore, in patients with COVID-19 diarrhea, Nitazoxanide may be a therapeutic choice for clinicians. However, there is still a lack of evidence to support Nitazoxanide in the treatment of patients with COVID-19 with diarrhea. So it was necessary to conduct further review and provide evidence to clinicians. This study aims to assess the effectiveness of Nitazoxanide in treatment of COVID-19 diarrhea.

Materials and methods

This was a prospective, longitudinal, comparative study. Study period was July 2020 to June 2021 The patients attending in private chambers of medicine specialists and patients admitted in Dedicated corona hospital were enrolled in the study. Total number of cases were 100. COVID-19 infection was diagnosed on clinical features like fever, headache, body ache, cough, respiratory distress, anosmia, loss of taste etc. supported by positive rapid antigen test or positive RT-PCR for covid-19 or imaging evidence of ground glass opacities in both lungs mainly basal regions. Diarrhoea was diagnosed on history of loose stool - one / more in 24 hours or more than 3 form stools in 24 hours. Stool for routine and microscopic examination was done to exclude other causes of diarrhoea.

Inclusion criteria was - 1) Symptoms of covid-19; 2) Supportive investigations: Positive Rapid Ag test or RT-PCR for COVID-19 or imaging evidence of COVID-19 infection 3) Diarrhoea Exclusion criteria was 1) Suspected other causes of diarrhoea like drug induced diarrhoea; other infectious diarrhoea 2) Patients having H/O chronic diarrhoeal disease like IBS

Ethical clearance was taken from KMCH. Pre-formed data collection sheet was used. Informed written consent was taken from patient. Total patients were alternatively allocated into 2 groups. History of stool frequency, stool consistency, stool volume was recorded. 50 patients of Group A were treated with Nitazoxanide and ORS. Another 50 patients of Group B were treated with ORS only. Improvement of the patients was assessed daily by decreased frequency of bowel movement, decreased stool volume and improvement of stool consistency and recorded in data collection sheet. These data were analyzed using SPSS version 21. P value was calculated by Chi Square test.

Results

100 patients were alternatively allocated into 2 groups. 50 patients of group A were treated with Nitazoxanide (500mg bd for 5 days) and ORS. Another 50 patients of group B were treated with ORS only. Improvement of the patients was assessed daily by decreased frequency of bowel movement, decreased stool volume and improvement of stool consistency and recorded in data collection sheet

Table I

Frequency and Consistency of Stool in study cases

	Group A (50) (%)	Group B (50) (%)
Stool frequency		
>10 stool/day	15 (30)	16 (32)
5-10 stools/day	30 (60)	28 (56)
<5 stools/day	5 (10)	6 (12)
Stool Consistency		
Watery	40 (80)	41(82)
Loose	6 (12)	7(14)
Semisolid	4 (8)	2 (4)

Mean age was 40 + 21.3 years. Fever was the most common symptom (100%); other symptoms were cough (89%), headache (85%), body ache (79%), generalized weakness (75%), anosmia (56%), Vomiting (15%). In group A 30% patients and in group B 32% patients had stool frequency >10 stools/day. 80% of group A patients and 82% of group B patients had watery stool. (Table 1) After 24 hours total 45 (90%) patients of Group A showed improvement (20 patients showed full recovery & 25 patients showed some improvement); whereas 15 (30%) patients of Group B showed improvement (5 patients showed full recovery & 10 patient showed some improvement) (Table II).

Table II

Improvement of diarrhoea with time

Time	Complete recovery		Some improvement		No improvement	
	A	B	A	B	A	B
24 hours	20	5	25	10	5	35
hours	30	15	18	5	2	30
hours	45	16	4	9	1	25

After 48 hours total 48 (96%) patients of group A showed improvement (30 patients showed full recovery & 18 showed some improvement); whereas 20 (40%) patients of Group B showed improvement (15 patients showed full recovery & 5 some improvement). After 72 hours total 49 (98%) patients of group A showed improvement (45 patients showed full recovery & 4 some improvement); whereas 25 (50%) patients of Group B showed improvement (16 patients full recovery & 9 some improvement); (Table II).

Table III

Comparison of Improvement between two groups

Time	Group A (n=50)	Group B (n=50)	p value	Comment
At 24 hours	45	15	<0.05	Significant
At 48 hours	48	20	<0.05	Significant
At 72 hours	49	25	<0.05	Significant

Comparison between the response of two groups by Chi Square test shows p value <0.05. So the treatment with Nitazoxanide is better (Table III).

Discussion Covid-19 is highly contagious, has a variety of transmission routes, and is unpredictable in its development, seriously affecting social life and human health. Although the number of cures is increasing, there is no specific drug for the new coronavirus. In the current SARS-CoV-2 pandemic, most of the attention is still exclusively focused on the respiratory symptoms of the disease. However, it is important to emphasize that the number of COVID-19 patients experiencing diarrhea is significant and cannot be overlooked. We found high variability among published studies in the percentage of patients with diarrhea, ranging from 2% to 16.7 % of cases.

Currently there is no specific treatment for COVID-19 related diarrhoea and its management is mainly based on supportive care. No evidence on the efficacy of antidiarrheal drugs is available, but an adequate rehydration and serum electrolytes monitoring should be performed as in all patients with diarrhea. China's National Health Commission recommended the use of probiotics for the treatment of patients with severe COVID-19 to preserve intestinal balance and to prevent secondary bacterial infections.[13] Moreover, a rapid improvement in diarrhea was also found after starting antiviral therapy.[14] Although no antiviral drug was specifically designed for the treatment of diarrhea, several molecules could have beneficial effects.

The use of Baricitinib, a JAK kinase inhibitor, was proposed for the treatment of COVID-19.15 It blocks the AP2-associated protein kinase 1 and the cyclin G-associated kinase, which are 2 important regulators of cellular endocytosis, resulting in a theoretical reduction of the viral passage into the host cell. The anti-inflammatory function and the antiendocytic activity of Baricitinib could be effective in diarrhea and deserve further studies.

Study shows Nitazoxanide may play an important role in managing norovirus and rotaviral gastroenteritis in adults.9 Benefit of Nitazoxanide in reducing duration of illness from viral gastroenteritis was also demonstrated for children.[16] Nitazoxanide exhibits in vitro activity against Middle East respiratory syndrome coronavirus (MERS-CoV) and other coronaviruses, inhibiting expression of the viral N protein.12 Nitazoxanide also suppresses production of pro-inflammatory cytokines in peripheral blood mononuclear cells and suppresses interleukin 6 production in mice.[17] It has been recently reported that NTZ exhibited in vitro inhibition of SARS-CoV-2 at a small micromolar concentration. Additionally, NTZ suppresses the production of cytokines emphasizing its potential to manage COVID-19-induced cytokine storm.[17]

In our study after giving Nitazoxanide along with ORS in COVID-19 related diarrhoea improvement was in 90% patients at 24 hours; in 96% patients in 48 hours and in 98% cases at 72 hours. On the other hand, in patients receiving only ORS without Nitazoxanide improvement was found in 30%, 40% and 50% cases at 24, 48 and 72 hours respectively. p value (<0.05) was significant. So Nitazoxanide reduces duration of diarrhoea and improves the consistency of stool. Thus Nitazoxanide can cause early significant improvement in diarrhoea of covid-19 patients. Therefore, further patients' sufferings can be minimized with symptomatic improvement.

Limitation of our study was that evolution of different variants of SARS COV-2 has resulted in variable response to different therapeutic agents. Our study has not considered this response to different variants of SARS COV-2 and sample size was small.

Conclusion

Nitazoxanide significantly improves diarrhoea in COVID-19 patients by reducing frequency and duration of diarrhoea and improving consistency of

stool. Large scale study on new variants of SARS COV-2 is recommended for further confirmation.

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