ClinicSearch

International Journal of Clinical and Medical Case Reports

Louis Edwin Wirya *

Open Access

Review Article

Nitazoxanide in Self-limiting Viral Gastroenteritis a Systematic Review and Meta-Analysis

Louis Edwin Wirya [1]*, Suryanti2, Henry Lie [1], Epistel Pangujian Simatupang [1,3]

[1]Departement of Internal Medicine Siloam Hospitals Kebon Jeruk, Jakarta

[2]Magister Program of Esa Unggul University, Kebon Jeruk, Jakarta

[3]Division of Gastroentero Hepatologi Siloam Hospitals Kebon Jeruk, Jakarta

***Corresponding Author**: Louis Edwin Wirya, Departement of Internal Medicine Siloam Hospitals Kebon Jeruk, Jakarta.

Received Date: September 06, 2024; Accepted Date: September 18, 2024; Published Date: September 30, 2024.

Citation: Louis E Wirya, Suryanti2, H Lie , Epistel P Simatupang,(2024), Nitazoxanide in Self-limiting Viral Gastroenteritis A Systematic Review and Meta-Analysis , *International Journal of clinical and Medical Case Reports*, 3(5); **Doi:**10.31579/2834-8664/058

Abstract:

Introduction: Acute gastroenteritis (AGE) is a condition where there is an inflammation of the stomach and small and large intestines, with characteristic of vomiting, fever, abdominal pain, increased bowel movement and resulting in diarrhea. Mostly, AGE was cause by viral infection. Up to this date, AGE accounts for a burden in public health, especially in low-income and middle-income countries and also the eighth leading cause of mortality among all ages. This systematic review and meta-analysis aim to summarize the evidence regarding the use of Nitazoxanide in improving the outcome of viral gastroenteritis in all ages.

Methods: We conducted a systematic review and meta analysis, collecting studies from EuropePMC, Pubmed, Scopus, and clinicaltrial.gov. The inclusion criteria for selecting the study were as follows: (1) Types of studies: observational studies (cohort, case-control, cross-sectional), randomized or non-randomized clinical trials; (2) Types of participants: patients at any age who present with acute diarrhea or gastroenteritis caused by viral pathogens (rotavirus, norovirus, or adenovirus); (3) Types of intervention: received nitazoxanide in any dose and any formulations for the treatment of viral diarrhea/gastroenteritis; (4) Types of comparison: receiving only standard of care (rehydration solutions) or placebo; Studies in which diarrhea or gastroenteritis caused by other pathogens than virus (such as bacteria, parasite or fungal infections) were excluded. The primary outcome was duration of diarrhea and duration of hospitalization.

Results: A total of 874 studies were retrieved, resulting in the final number of six studies included, with a total of 580 patients. Out of 6 studies, 3 were double-blind RCTs, 1 was single-blind RCT, while the remaining 3 were retrospective cohort studies. Sample sizes ranged from 26 to 330. Three out of six studies include adults gastroenteritis patients, while the rest 3 articles were studies on paediatric populations. The majority of the causative viral pathogens in the included studies were rotavirus (dominant pathogens in 4 out of 6 studies), and the remaining two studies were dominated by norovirus infection. The doses of nitazoxanide used in the included studies were ranged from 7.5 mg/kg/day to 500 mg twice daily, administered for 3 days. The use of nitazoxanide was associated with shorter duration of diarrhea [Mean Difference -1.25 days, (CI 95% -1.68, -0.82), $p < 0.00001$) and shorter duration of hospitalization [Mean Difference -0.82 days, (CI 95% -1.10, -0.54), $p < 0.00001$). when compared with standard of care/placebo in patients with viral gastroenteritis.

Conclusion: The use of Nitazoxanide in viral gastroenteritis was associated with shorter duration of diarrhea and shorter duration of hospitalization when compared with standard of care/placebo in adult and child population. However, further randomized clinical trials are still needed to confirm the results of our study.

Keywords: Nitazoxanide, Viral, Gastroenteritis

Introduction

Acute gastroenteritis (AGE) is a condition where there is an inflammation of the stomach and small and large intestines, with characteristic of vomiting, fever, abdominal pain, increased bowel movement and resulting in diarrhea.[1,2] The focus on the prevention and control of AGE is on children, but it also needs to be remembered that AGE could happen in all ages, and most of the deaths caused by AGE in United States were in older adults. Based on data by the National Outbreak Reporting System, it is estimated that more than 350,000,000 cases of acute gastroenteritis occur annually in the United States.[1,3] AGE also causes 1 million

hospitalizations annually and accounts for more than 1.6 million deaths globally every year in all ages.[3,4,5] Up to this date, AGE accounts for a burden in public health, especially in low-income and middle-income countries and also the eighth leading cause of mortality among all ages.[5,6,7]Meanwhile, AGE is also still one of the leading cause of morbidity and mortality in children and infants, and also still one of the most common infection in children and infants.[8,9] Based on data published by the Global Health Data Exchange in 2016, diarrhea was the fifth leading cause of mortality among children younger than 5 years, which is 446,000 deaths. In South Asia and sub-Saharan Africa, diarrhea accounts for more than a quarter of leading cause of mortality in children younger than 5 years, which is 26.93%.[5] There are numerous etiologies for GAE, which are viral, bacterial, and parasitic pathogens.[10]Norovirus and Rotavirus are the most common etiology of viral gastroenteritis. Other less common etiology of viral gastroenteritis are Astrovirus and Adenovirus.[1,10,11] Incidence rate of Norovirus as the causative agent of AGE worldwide is 17–18%, especially among developed countries. Norovirus infection can occur in all ages, while Rotavirus is found as the most common causative agent of AGE in children. Rotavirus was mostly found in children aged 0–14 years old, with the highest incidence rate was in children less than 5 years.[2,12]Nitazoxanide or 2-(acetyloxy)-*N*-(5-nitro-2-thiazolyl) benzamide is a new thiazolide broad-spectrum antiviral agent which has been gaining more attention in recent years because of its ability as a broad-spectrum antiviral agent. Nitazoxanide plays a role through multiple mechanisms of action of virus and interfere with host-regulated pathways in viral replication.[13,14] Nitazoxanide as a new broad-spectrum antiviral agent is expected to provide greater protection against virus and reduce the risks of resistance and costs associated with medication, and also prevent further viral infection and transmission so that eradication could occur.[14,15,16] Nitazoxanide's antiviral mechanisms is through the inhibition of viral RNA and DNA replication and modulate host's innate immune response when a pathogen has entered a susceptible cellular target.[15]This systematic review and meta-analysis aim to summarize the evidence regarding the use of Nitazoxanide in improving the outcome of viral gastroenteritis in all ages.

Materials & Methods

Eligibility Criteria

The inclusion criteria for selecting the study were as follows: (1) Types of studies: observational studies (cohort, case-control, cross-sectional), randomized or non-randomized clinical trials; (2) Types of participants: patients at any age who present with acute diarrhea or gastroenteritis caused by viral pathogens (rotavirus, norovirus, or adenovirus); (3) Types of intervention: received nitazoxanide in any dose and any formulations for the treatment of viral diarrhea/gastroenteritis; (4) Types of comparison: receiving only standard of care (rehydration solutions) or placebo; (5) Types of outcome: duration of diarrhea and duration of hospitalization. Studies in which diarrhea or gastroenteritis caused by other pathogens than virus (such as bacteria, parasite or fungal infections) were excluded. Studies without the control group, any other articles besides primary studies (review articles, editorials, correspondences), and articles in non-English language will also be excluded.

Literature Search And Study Selection

Literature search was done on EuropePMC, PubMed, Scopus, and ClinicalTrials.gov with English-language restriction until August 26th, 2022 with the following keywords "(nitazoxanide OR thiazolides OR alinia OR heliton OR daxon) AND (viral OR virus OR rotavirus OR norovirus OR adenovirus) AND (diarrhea OR gastroenteritis OR enteritis)". The initial step was the identification of eligible articles through screening of titles and abstracts by two reviewers. Additional evaluation of references from found eligible studies were also conducted to search for more potential articles. Duplicate articles were removed. Finally, full-text articles were independently screened by 2 reviewers, with discrepancies resolved through discussion. Meta-analysis of Observational Studies in Epidemiology (MOOSE)[17] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed for our study.[18]according to the Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines

Data Extraction

Two independent authors performed data extraction process using a standardized form which included authors' names, publication year, study design, sample characteristic, and outcomes measured. Sample characteristics will include sample size, type of participants, viral pathogens, age, and nitazoxanide dose. Extracted data were then compared with any discrepancies will be resolved through discussion. The quality of the included clinical trial studies will be assessed by using Risk of Bias version 2 (RoB v2) from Cochrane Collaborations.[19] This tool includes five domains for methodological evaluation: (a) randomization process; (b) deviations from intended interventions; (c) missing outcome data; (d) measurement of the outcome; and (e) selection of the reported result. The RCT was classified as low risk of bias (low risk of bias for all domains), high risk (high risk of bias for one or more domains) or unclear risk (unclear risk of bias for one or more key domains). Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of case-control and cohort studies. The assessment process included reviewing the comparability, selection, and outcome of each study, then each research was assigned a total score beginning with zero until nine. Research is graded good if it scores ≥ 7.[20]

Statistical Analysis

Meta-analysis was done using Review Manager 5.4 (Cochrane Collaboration) software. Application of Mantel-Haenszel formula with random-effect models, regardless of heterogeneity was employed to calculate risk ratio (RR) and its 95% confidence interval (95% CI) for the dichotomous variable outcomes. Meanwhile, Inverse-Variance formula with random effect models was used to calculate standardized mean difference (SMD) and its standard deviations (SD) for the continuous variable outcomes. In this meta-analysis, heterogeneity between studies was assessed by I-squared (I^2; Inconsistency). The I^2 statistic with a value of <25% considered as a low degree of heterogeneity, 26-50% moderate degree of heterogeneity, and >50% considered high degree of heterogeneity. I^2 of at least 50% is considered substantial heterogeneity; it means that at least half of the total variability among effect sizes is due to true heterogeneity between studies. When data were reported as medians and interquartile ranges or as medians and minimum-to-maximum ranges, we converted them to means and standard deviations for meta-analysis pooling using the

formula by Wan X et al.[21] Funnel plot analysis was utilized to assess the qualitative risk of publication bias.

Results

Study Selection And Characteristics

A total of 874 studies were retrieved from Europe PMC, ClinicalTrials.gov, PubMed, and Scopus. After screening titles, abstracts and removing the duplicates, 18 articles were assessed for eligibility through reading the full-text form. Of these eligible studies, 12 articles were further excluded, seven articles did not have control or comparison group, three were review articles, and two articles were not exclusively performed on viral gastroenteritis populations, therefore resulting in the final number of 6 clinical trial and observational studies[22-27] with a total of 580 patients with viral gastroenteritis for the analysis (Figure 1). Out of 6 studies, 3 were double-blind RCTs, 1 was single-blind RCT, while the remaining 3 were retrospective cohort studies. Sample sizes ranged from 26 to 330. Three out of six studies include adults gastroenteritis patients, while the rest 3 articles were studies on paediatric populations. The majority of the causative viral pathogens in the included studies were rotavirus (dominant pathogens in 4 out of 6 studies), and the remaining two studies were dominated by norovirus infection. The doses of nitazoxanide used in the included studies were ranged from 7.5 mg/kg/day to 500 mg twice daily, administered for 3 days through syrup or tablet formulations. The details of each included studies were summarized in Table.1

Study	Sample size	Design	Participants	Viral pathogen	Age (years)		Nitazoxanide dose	Control group
					NTZ	Control		
Brooks T et al.[22] 2021	26	Retrospective cohort	Adults (age >18 years) who had either: 1) underwent stem cell transplantation; or 2) received myeloablative chemotherapy within 4 weeks of NV diagnosis by positive test on gastrointestinal pathogen panel	Norovirus (100%)	68.2 ± 20.2	54.4 ± 18.9	Not mentioned	Supportive care
Ghosh N et al.[23] 2016	97	Retrospective cohort	Immunocompromised and cancer patients with viral associated diarrhea (VAD)	Norovirus (50.5%) Rotavirus (35%) Adenovirus (14.5%)	43.1 ± 18.3		Not mentioned	Supportive care
Mahapatro S et al.[24] 2017	330	Double-blind RCT	Children aged 12 months – 5 years with acute onset diarrhea of <48 hours duration, some to severe dehydration	Rotavirus (100%)	2.1 ± 0.7	2.1 ± 0.7	100 mg (12 – 47 months) or 200 mg (≥4 years), twice daily for 3 days in syrup formulation	Placebo
Rossignol JF et al.[25] 2006 (a)	38	Double-blind RCT	Children aged <12 years presenting with watery diarrhea and subsequently hospitalised in the paediatric gastroenterology department because of the severity of their illness	Rotavirus (100%)	1.4 ± 1.8	1.1 ± 0.4	7.5 mg/kg (<12 months) or 100 mg (12 – 47 months) or 200 mg (4 – 11 years), twice daily for 3 days in syrup formulation	Placebo
Rossignol JF et al.[26] 2006 (b)	45	Double-blind RCT	Children aged >12 years presenting with gastroenteritis	Rotavirus (100%)	34.1 ± 16.2	32.9 ± 12.9	500 mg, twice daily for 3 days in tablet formulation	Placebo
Teran CG et al.[27] 2008	50	Single-blind RCT	Infants aged 28 days to 24 months with a history of acute watery diarrhea positive for rotavirus of less than 72 h duration and a moderate to severe degree of dehydration	Rotavirus (100%)	0.8 ± 0.5	0.9 ± 0.4	15 mg/kg/day divided into 2 doses for 3 days in syrup formulation	Oral or systemic rehydration solution

Table 1. Characteristics of included studies

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	
Mahapatro S (2017)	+	+	+	+	+		+ Low risk
Rossignol JF (2006) (a)	+	+	+	+	+		? Some concerns
Rossignol JF (2006) (b)	+	+	+	+	+		- High risk
Teran CG (2008)	-	+	+	+	+	-	

Table 2. Risk of Bias assessment of the included studies using RoB v2 tool

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Brooks T et al.[22] 2021	Cohort	***	**	**	7	Good
Ghosh N et al.[23] 2016	Cohort	***	**	**	7	Good

Table 3. Newcastle-Ottawa quality assessment of observational studies

a(1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was no present at start of study

b(1) comparability of cohorts on the basis of design or analysis, (maximum two stars)

c(1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow up of cohorts

Quality Of Study Assessment

Risk of Bias version 2 (RoB v2) from Cochrane was used to evaluate the quality of randomized clinical trial studies. Three out of four included RCTs have low-risk of bias in all five domains of methodological evaluation, while one RCT have high-risk of bias because of randomization method was not described in details and there were some differences in the baseline characteristics (age and malnutrition status) among groups of patients which suggest some problems during randomization process (Table 2). NOS scale was used to evaluate the quality of cohort and case-control studies, which indicated all included studies had good quality (Table 3).

Nitazoxanide vs control

Duration of diarrhea (in days)

In overall six studies (n = 292) reported on the duration of diarrhea outcome, our pooled analysis showed that the use of nitazoxanide was associated with shorter duration of diarrhea when compared with standard of care/placebo in patients with viral gastroenteritis [Mean Difference -1.25 days (95% CI -1.68, -0.82), $p < 0.00001$, $I^2 = 44\%$, random-effect modelling] (Figure 2).Three studies (n = 168) in adult population reported on the duration of diarrhea outcome. Our pooled analysis showed that the use of nitazoxanide was associated with shorter duration of diarrhea when compared with standard of care/placebo in adult population with viral gastroenteritis [Mean Difference -1.39 days (95% CI -2.50, -0.27), $p=0.32$, $I^2 = 0\%$, random-effect modelling] (Figure 2A).Three studies (n = 124) in child population reported on the duration of diarrhea outcome. Our pooled analysis showed that the use of nitazoxanide was associated with shorter duration of diarrhea when compared with standard of care/placebo in children population with viral gastroenteritis [Mean Difference -1.23 days (95% CI -1.81, -0.65), $p < 0.00001$, $I^2 = 77\%$, random-effect modelling] (Figure 2B).

Duration Of Hospitalization (In Days)

In overall three studies (n = 126) reported on the duration of hospitalization outcome, our pooled analysis showed that the use of nitazoxanide was associated with shorter duration of hospitalization when compared with standard of care/placebo in patients with viral gastroenteritis [Mean Difference -0.82 days (95% CI -1.10, -0.54), $p < 0.00001$, $I^2 = 0\%$, random-effect modelling] (Figure 3).There was only one study sub-group in adult population (n = 26) reported on the duration of hospitalization outcome, so the outcome cannot be interpreted. (Figure 3A) Two studies (n = 100) in child population reported on the duration of hospitalization outcome. Our pooled analysis showed that the use of nitazoxanide was associated with shorter duration of hospitalization when compared with standard of care/placebo in patients with viral gastroenteritis [Mean Difference -0.82 days (95% CI -1.10, -0.54), $p < 0.00001$, $I^2 = 0\%$, random-effect modelling] (Figure 3B)

Publication Bias

Because the number of included studies in each outcome is fewer than 10 studies, the funnel plots and statistical tests for detecting publication bias are not reliable when compared with whenever there are more than 10 included studies in each outcome.[28,29] Therefore, the test for publication bias was not performed in this study.

Discussion

According to our overall pooled analysis, it was discovered that nitazoxanide was associated with reduction of duration of diarrhea and duration of hospitalization, the same outcome was seen in our sub-group pooled analysis, adult and child population. The use of nitazoxanide in treating viral gastroenteritis is still controversional,

because viral gastroenteritis is a self-limiting gastrointestinal infection.[30,31,32] There are many clinical practices guidelines (CPG) available for the treatment of AGE, including WHO recommendation.[33,34,35] The main goal for treating acute gastroenteritis is to prevent dehydration, and the first-line therapy recommended in all of the CPG for this is oral rehydration solution (ORS). The only active treatment recommended by WHO for AGE is zinc.[33,35,36] Meanwhile, the use of other pharmaceutical agents is still controversial and still has a high variability in practice.[36] As already known, Nitazoxanide (2-(acetolyoxy)-N-(5-nitro-2-thiazolyl)benzamide) is a broad-spectrum parasiticidal agent. The use of Nitazoxanide has already been approved by the US Food and Drug Administration (FDA) and other health agencies worldwide as the first-line treatment for Cryptosporidium parvum or Giardia lamblia infection in healthy individual, therefore, Nitazoxanide is commonly know as antiprotozoal. Other common indication for the use of Nitazoxanide is helminth infection.[4,37] Nitazoxanide has been used in millions of children and adults with mild adverse effects.[16] Nitazoxanide has 2 major active metabolites, which are tizoxanide and tizoxanide glucuronide.[37] Nitazoxanide and its known metabolite, tizoxanide have been reported to have a role as a broad-spectrum antiviral agent, against many kind of viruses in the recent years.[38,39] Previous studies regarding the antiviral effect of Nitazoxanide have been reported, including reduced duration of symptoms in individu with acute uncomplicated influenza[40], hepatitis B and C[41,42], Japanese encephalitis[43], and coronavirus[39,44].Norovirus and Rotavirus are the most common etiology of viral gastroenteritis. Other less common etiology of viral gastroenteritis are Astrovirus and Adenovirus.[1,10,11] Acute gastroenteritis, however, accounts for a burden in public health, especially in low-income and middle-income countries, and still have a high rates of morbidity and mortality, especially in children and infants.[8,9] Its burden in public health includes, higher total cost because of hospitalization rates, missing productive days, and care seeking rates.[45]Many studies have also reported that Nitazoxanide has an antiviral activity for the etiology of viral gastroenteritis, which is rotavirus and norovirus.[32] Based on our population in this study, the cause of viral gastroenteritis in adult population was Norovirus, Rotavirus, and Adenovirus, and Norovirus accounts for the highest number in two of the studies. Meanwhile, the cause of viral gastroenteritis in child population was Rotavirus. Norovirus (NoV) infection is characterized by a non-febrile, non-bloody, and watery gastroenteritis often accompanied with vomiting, abdominal cramps. Norovirus (NoV) infection usually lasting for 12–60 hours. In infant aged less than 1 year, the symptoms can last until 6 days, and in individu ages more than 85 years, the symptoms can last until 4 days.[46,47] Norovirus (NoV) is a non-enveloped single-stranded RNA virus belongs to Caliciviridae family. The genome has 3 open reading frames (ORF), which are: ORF-1 (codes non-structural protein); ORF-2 (codes mayor capsid protein VP1); and ORF-3 (codes minor capsid protein VP2). NoV has been divided into 10 genogroup (GI-GX), but only GI, GII, and GIV could cause acute gastroenteritis in human.[48,49]Rotavirus is a most common etiology of acute watery diarrhea, especially in children younger than 5 years old. The symptoms can last until 5 days on previous studies, and was associated with dehydration.[50,51] Rotavirus (RV) is a non-enveloped double-stranded RNA genome belongs to Reoviridae family. Rotavirus consists of 11 RNA gene segments, which encodes viral protein with multilayered protein capsid. In the 11 gene segments, there are 6 structural proteins, which are VP1, VP2, VP3, VP4, VP6, and VP7, and the rest 5 are non-structural protein (NSP). RV has two surface proteins in its virion, VP7 and VP4. These surface proteins will stimulated the production of G type and P type, which are the neutralizing antibodies when infection occurs.[50,52,53]Up to this date, the use of Nitazoxanide in million of adults and children is proven safe and is already been marketed globally, for many purposes.[15] The use of Nitazoxanide in viral gastroenteritis is based on its antiviral effect on the virus, which is Norovirus and Rotavirus.[22-27] There are several mechanism regarding antiviral effect of Nitazoxanide. Based on the previous studies, Nitazoxanide has no effect on virus infectivity and binding or entry into target cells. Nitazoxanide also do not inhibit protein expression. The antiviral action of Nitazoxanide is targeted in reducing the size of viroplasms and altered the virus' cytoplasmic structures, where the replication of the virus genome takes place, and later will disturb the virus' replication process.[16,54]There are numerous non-structural and structural proteins in viroplasm, such as NSP5 and NSP2, and VP1, VP2, VP3 and VP6, respectively. Meanwhile, interaction between NSP5 and NSP2 oligomers plays a major role in rotavirus viroplasm formation. However, the detailed mechanism for the impaired NSP2/NSP5 interaction caused by Nitazoxanide is still unknown.[16,55,56]In previous study showed that Nitazoxanide inhibit virus replication by activating host cellular antiviral response, and inducing the expression of interferon-stimulated genes (ISGs). Interferon is still one of the important component of the innate immunity in response to virus infection. Interferon will then activated the JAK-STAT pathway, the principal cascade for IFN signaling. The ISG activated includes interferon regulatory factor 1 (IRF-1), IRF-9, RIG-I, IFI27, PKR, ISG15, Mx1, and MDA5, and some of this has activity against many viruses.[57,58,59] Some of the previous data regarding ISG antiviral activity includes: ISG15, which mitigates MNV-1 replication *in vitro* and *in vivo* in the early phase of the viral life cycle[60]; MDA5, a cellular sensor, which recognized MNV-1 and then triggered a host immune respons[61]; and PKR mediated type II IFN, which will inhibit MNV-1 translation[62]. Another mechanism based on previous data showed that nitazoxanide also played a role in the host antiviral pathway. Nitazoxanide can activated the protein kinase by double stranded RNA (PKR). PKR is a serine/threonine kinase that is expressed in all differentiated cells within low level. PKR is activated by dsRNA. Binding of dsRNA to PKR will promote dimerization and autophosphorylation. Later, the activated PKR will phosphorylate the translational eukaryotic initiation factor 2 alpha (eIF2α), which is a halting viral protein synthesis. PKR is also known as an interferon induced effector of cellular immunity.[46,54]However, the exact antiviral mechanism of nitazoxanide is still unclear and not well known until now. And up to date, there is still no consensus or guideline regarding the antiviral mechanism of nitazoxanide. All of the previous studies showed that the antiviral mechanism depend on the virus and host cells.[57]This study still has several limitations. There are currently small number of studies that specifically asses the use of Nitazoxanide in improving the outcome of viral gastroenteritis, and this study still lacks the sub-group population data, especially in adult population. Most of the included studies in these systematic review and meta-analysis also only have a small number of samples. More studies with larger sample sizes and good methodological design might still be needed to confirm the results of our study.

Conclusion

Our systematic review and meta-analysis indicated that the use of Nitazoxanide in viral gastroenteritis was associated with shorter duration of diarrhea and shorter duration of hospitalization when compared with standard of care/placebo in adult and child population. However, further randomized clinical trials are still needed to confirm the results of our study.

References

1. Jassas BA, Khayat M, Alzahran H, et al.(2018).Gastrosenteritis in adults. *Int J Community Med Public Health*;5(11):4959-4964
2. Hasan H, Nasirudeen NA, Ruzlan MAF, et al.(2021)Acute infectious gastroenteritis: the causative agents, omics-based *detection of antigens and novel biomarkers*. Children.;8(12):1112.
3. Cardemil CV, Balachandran N, Kambhampati A, et al.(2021) Incidence, etiology, and severity of acute gastroenteritis among prospectively enrolled patients in 4 Veterans Affairs Hospitals and Outpatient Centers, 2016–2018. *Clinical Infectious Diseases*;73(9):e2729–e2738.
4. GBD Diarrhoeal Diseases Collaborators.(2015). Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study . *Lancet Infect Dis*. 2017;17(9):909–948.
5. GBD 2016 Diarrhoeal Disease Collaborators (2018) Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 18(11): 1211–1228
6. Stanyevic B, Sepich M, Biondi S, at al.(2022). The evolving epidemiology of acute gastroenteritis in hospitalized children in Italy. *Eur J Pediatr*;181(1):349–358.
7. Farfán-García AE, Imdad A, Zhang C, et al.(2020). Etiology of acute gastroenteritis among children less than 5 years of age in Bucaramanga, Colombia: A case-control study. *PLOS Neglected Tropical Diseases*. 2020;14(6):e0008375.
8. Hartman S, Brown E, Loomis E, et al.(2019). Gastroenteritis in Children. afp. 2019;99(3):159–165.
9. Guarino A, Aguilar J, Berkley J, et al.(2020). Acute gastroenteritis in children of the world: what needs to be done? *Journal of Pediatric Gastroenterology and Nutrition*;70(5):694–701.
10. Salami A, Fakih H, Chakkour M, et al.(2019). Prevalence, risk factors and seasonal variations of different Enteropathogens in Lebanese hospitalized children with acute gastroenteritis. BMC Pediatrics. 2019;19(1):137.
11. van Dongen JAP, Rouers EDM, Schuurman R, et al.(2021). Acute gastroenteritis disease burden in infants with medical risk conditions in the Netherlands. The Pediatric Infectious Disease Journal;40(4):300–305.
12. Matsuyama R, Miura F, Tsuzuki S, et al.(2018). Household transmission of acute gastroenteritis during the winter season in Japan. J Int Med Res;46(7):2866–2874.
13. La Frazia S, Ciucci A, Arnoldi F, et al.(2013). Thiazolides, a new class of antiviral agents effective against rotavirus infection, target viral morphogenesis inhibiting *viroplasm formation*. J. Virol. 2013;83:11096–11101.
14. Geller M, Blum VF, Oliveira L, et al. Nitazoxanide: antiviral properties relevant to current global situation. International Journal of Current Research. 2020; 12(05):11733-11737
15. Rossignol JF.(2014). Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Res*;110:94–103.
16. Jasenosky LD, Cadena C, Mire CE, et al.(2019). The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits Ebola Virus. *iScience*;19:1279–1290.
17. Stroup DF, Berlin JA, Morton SC, et al.(2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA;283(15):2008-2012.
18. Moher D, Liberati A, Tetzlaff J, et al.(2009). Preferred reporting items for systematic reviews and meta-analyses: the *PRISMA statement. BMJ*;339:b2535.
19. Sterne JAC, Savović J, Page MJ, et al.(2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
20. Margulis AV, Pladevall M, Riera-Guardia N, et al.(2014). Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. Clin Epidemiol;6:359-368.
21. Wan X, Wang W, Liu J, et al.(2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol;14:135.
22. Brooks T, Crilley TA, Russell GB, et al.(2021). Clinical Characteristics and Outcomes of Norovirus Infection in Patients with Hematologic Malignancies: A Retrospective, Single Center Study. *Open Forum Infect Dis*;8(Suppl 1):S555–S556.
23. Ghosh N, Malik FA, Daver RG, et al.(2017). Viral associated diarrhea in immunocompromised and cancer patients at a large comprehensive cancer center: a 10-year retrospective study. *Infect Dis (Lond);*49(2):113-119.
24. Mahapatro S, Mahilary N, Satapathy AK, et al.(2017). Nitazoxanide in acute Rotavirus diarrhea: a randomized control trial from a developing country. J Trop Med:7942515.
25. Rossignol JF,Abu-Zekry M, Hussein A, et al.(2006). Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. Lancet;368(9530):124-129.
26. Rossignol JF, El-Gohary YM.(2006). Nitazoxanide in the treatment of viral gastroenteritis: a randomized double-blind placebo-controlled clinical trial. Aliment Pharmacol Ther;24(10):1423-1430.

27. Teran CG, Teran-Escalera CN, Villarroel P.(2009). Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Infect Dis*;13(4):518-523.
28. Thornton A, Lee P.(2000). Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol*;53(2):207-216.
29. Terrin N, Schmid CH, Lau J, et al.(2003) Adjusting for publication bias in the presence of heterogeneity. *Stat Med;22*(13):2113-2126.
30. Zollner-Schwetz I, Krause R.(2015) Therapy of acute gastroenteritis: role of antibiotics. Clinical Microbiology and Infection;21(8):744–749.
31. Orenstein R.(2020). Gastroenteritis, viral. Encyclopedia of Gastroenterology;652–657.
32. Tan EM, Cawcutt KA, Zomok CD, et al.(2017). Activity of nitazoxanide against viral gastroenteritis: a systematic review. International Journal of Travel Medicine and *Global Health*;5(4):107–112.
33. Florez ID, Veroniki AA, Khalifah RA, et al.(2018) Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. PLOS ONE;13(12):e0207701.
34. Farthing M, Salam MA, Lindberg G, et al.(2013). Acute diarrhea in adults and children: a global perspective. *Journal of Clinical Gastroenterology*;47(1):12–20.
35. Schwermer M, Längler A, Fetz K, Ostermann T, et al.(2018). Management of acute gastroenteritis in children: a *systematic review of anthroposophic therapies*. CMR;25(5):321–330
36. Vecchio AL, Dias JA, Berkley JA, et al.(2016). Comparison of recommendations in clinical practice guidelines for acute gastroenteritis in children. *J Pediatr Gastroenterol Nutr*;63(2):226–235.
37. Balderas-Acata J, Bueno E, Pérez-Becerril F, et al.(2011). Bioavailability of two oral-suspension formulations of a single dose of nitazoxanide 500 mg: an open-label, randomized-sequence, two-period crossover, comparison in healthy fasted Mexican adult volunteers. Journal of Bioequivalence & Bioavailability;03.
38. Stachulski AV, Taujanskas J, Pate SL, et al.(2020) Therapeutic potential of nitazoxanide: an appropriate choice for repurposing versus SARS-CoV-2? ACS Infect Dis;acsinfecdis.0c00478.
39. Driouich JS, Cochin M, Touret F, et al.(2022). Pre-clinical evaluation of antiviral activity of nitazoxanide against SARS-CoV-2. *eBioMedicine*;82.
40. Haffizulla J, Hartman A, Hoppers M, et al.(2014). Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. *The Lancet Infectious Diseases*;14(7):609–618.
41. Rossignol J, Bréchot C.(2019). A pilot clinical trial of Nitazoxanide in the treatment of chronic hepatitis B. *Hepatol Commun*.;3(6):744–747.
42. Nikolova K, Gluud C, Grevstad B, et al.(2014). Nitazoxanide for chronic hepatitis C. *Cochrane Database of Systematic Reviews*.;(4).
43. Shi Z, Wei J, Deng X, et al.(2014) Nitazoxanide inhibits the replication of Japanese encephalitis virus in cultured cells and in a mouse model. Virology Journal;11(1):10.
44. Pepperrell T, Pilkington V, Owen A, et al.(2020) Review of safety and minimum pricing of nitazoxanide for potential treatment of COVID-19. *J Virus Erad*. 6(2):52–60.
45. Bartsch SM, Lopman BA, Ozawa S, et al.(2016). *Global economic burden of Norovirus Gastroenteritis*. PLOS ONE.;11(4):e0151219.
46. Siddiq DM, Koo HL, Adachi JA, et al.(2011). Norovirus gastroenteritis successfully treated with nitazoxanide. *J Infect*.;63(5):394–397.
47. Kirby AE, Streby A, Moe CL.(2016). Vomiting as a symptom and transmission risk in Norovirus illness: evidence from human challenge studies. PLOS ONE;11(4):e0143759.
48. Rani M, Rajyalakshmi S, Pakalapaty S, et al.(2021). Norovirus Structure and Classification. Norovirus. IntechOpen;
49. Campillay-Véliz CP, Carvajal JJ, Avellaneda AM, et al.(2020). Human Norovirus proteins: implications in the replicative cycle, pathogenesis, and the host immune response. *Frontiers in Immunolog*.
50. Meel SK, Katewa V, Singh R, et al.(2020) The burden of Rotavirus gastroenteritis in children: a hospital-based prospective study in Western Rajasthan. *Cureus*;12(10):e11020.
51. Karampatsas K, Osborne L, Seah ML, et al.(2018). Clinical characteristics and complications of rotavirus gastroenteritis in children in east London: a retrospective case-control study. PLoS One;13(3):e0194009.
52. Kung YH, Chi H, Liu CC, et al.(2020). Hospital-based surveillance of severe rotavirus gastroenteritis and rotavirus strains in young Taiwanese children. *Journal of the Formosan Medical Association*;119(7):1158–1166.
53. Bányai K, László B, Duque J, et al.(2012). Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: Insights for understanding the impact of rotavirus vaccination programs. Vaccine30:A122–A130.
54. Ashiru O, Howe JD, Butters TD. (2014).Nitazoxanide, an antiviral thiazolide, depletes ATP-sensitive intracellular Ca2+ stores. Virology;462–463:135–148.
55. Lestari FB, Vongpunsawad S, Wanlapakorn N, et al.(2020) Rotavirus infection in children in Southeast Asia 2008–2018: disease burden, genotype distribution, seasonality, and vaccination. Journal of Biomedical Science.May 21;27(1):66.
56. Amit LN, Mori D, John JL, et al.(2021). Emergence of equine-like G3 strains as the dominant rotavirus among children under five with diarrhea in Sabah, Malaysia during 2018–2019. PLOS ONE;16(7):e0254784.
57. Dang W, Xu L, Ma B, et al.(2018). Nitazoxanide inhibits human Norovirus replication and synergizes with Ribavirin

by activation of cellular antiviral response. Antimicrobial Agents and Chemotherapy;62(11):e00707-e00718.
58. Schoggins JW, Wilson SJ, Panis M, et al.(2011). A diverse array of gene products are effectors of the type I interferon antiviral response. Nature;472(7344):481–485.
59. Xu L, Wang W, Peppelenbosch MP, et al.(2017). Noncanonical antiviral mechanisms of ISGs: dispensability of inducible interferons. *Trends Immunol*;38(1):1–2.
60. Rodriguez MR, Monte K, Thackray LB, et al.(2014). ISG15 functions as an interferon-mediated antiviral effector early in the murine norovirus life cycle. J Virol;88(16):9277–9286.
61. McCartney SA, Thackray LB, Gitlin L, et al.(2008) Correction: *MDA-5 Recognition of a Murine Norovirus. PLoS Pathog.*;4(10):10.
62. Changotra H, Jia Y, Moore TN, et al.(2009) Type I and Type II interferons inhibit the translation of Murine Norovirus *Proteins*. *J Virol;*83(11):5683–5692