EFFICACY OF LACTOSE-FREE FORMULA AS A 24-HOUR MANAGEMENT APPROACH FOR ACUTE DIARRHEA AMONG CHILDREN

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Abstract

Background: Diarrhea continues to be a prominent contributor to morbidity and mortality among young children under five years, especially in developing nations. Secondary lactose intolerance is a significant complication that can arise from acute diarrhea. However, it can be effectively managed with lactose-free formula.

Objective: This study aimed to compare the rate of diarrhea resolution within a 24-hour period among children receiving lactose-free formula and those receiving lactose-containing formula.

Methods: This retrospective cohort study took place at Naresuan University Hospital and included 153 children aged between one month and five years admitted with acute diarrhea. Participants with bloody mucous diarrhea suspected to be bacterial in nature, positive stool culture, breastfeeding and chronic diarrhea (including cow's milk protein allergy and inflammatory bowel disease) were excluded. We compared the effectiveness of lactose-free formula (n=48) and lactose-containing formula in improving clinical diarrhea within a 24-hour (n=105).

Results: The study findings indicated the lactose-free formula group demonstrated a statistically significant increase in efficacy, with a 3.90 fold improvement in diarrhea within 24 hours compared with that of the group receiving lactose-containing formula. These results were obtained after the confounding factors were adjusted using multivariable regression analysis. The adjusted relative risk (RR) for a 24-hour improvement in diarrhea was 3.90 (95% CI: 1.91-7.95). However, this study encountered limitations regarding the sample size and accurate measurement of stool output.

Conclusion: Lactose-free formula showed the potential for greater effectiveness in improving acute diarrhea within a 24-hour timeframe compared with lactose-containing formula.

Keywords: Acute diarrhea, Lactose intolerance, Lactose-free formula

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Introduction

Diarrhea remains a significant cause of morbidity and mortality among children, particularly those under five years, especially in developing countries.[1, 2] The etiology of diarrhea can be attributed to bacterial and viral pathogens. In 2019, the Department of Disease Control in Thailand reported that the leading viral causes of diarrhea were rotaviruses (48.8%), followed by norovirus GII (21.3%). The most affected age group was children aged 0 to 4 years, accounting for 74.7% of cases. [3]

Secondary lactose intolerance is a notable complication of acute diarrhea, particularly in cases of viral origin. Younger children with acute viral diarrhea may experience mucosal damage that hinders lactose absorption, leading to lactose intolerance.[4] This intolerance can further exacerbate symptoms of diarrhea and prolong recovery. [5]

The standard approach for lactose intolerance involves using lactose-free formula and restricting foods containing lactose.[6] The ESPGHAN Guidelines for the Management of Acute Gastroenteritis in Children in Europe (2014 update) recommend lactose-free formula among hospitalized children under five years with acute diarrhea but do not routine recommend in outpatient settings.[7] Related studies have investigated the effects of lactose-free formula as an adjunctive treatment for acute diarrhea among children. Ngoenmak conducted a study demonstrating that lactose-free formula reduced the time to reach normal stool consistency to an average of 1.60±0.96 days.[8] Simakachorn et al. reported a median reduction in the duration of diarrhea by 20.5 hours by incorporating lactose-free formula.[9] Furthermore, Hartawan et al. specifically studied children with acute rotaviral diarrhea and observed a mean reduction in duration by 28.38 hours compared with that of the lactose-containing formula.[10] These findings suggest that lactose-free formula may offer a promising approach to shortening the duration of diarrhea and promote faster recovery.

In addition to individual studies, a systematic review conducted by Cochrane in 2013 evaluated lactose-free formula's overall efficacy in reducing diarrhea duration. The review concluded that lactose-free formula resulted in an average reduction of 18.6 hours in the duration of diarrhea.[11] However, a need exists to investigate the effectiveness of lactose-free formula in improving acute viral diarrhea within a 24-hour treatment period, specifically in our community and considering the present time. This study aimed to evaluate the efficacy of lactose-free formula in improving acute viral diarrhea within a 24-hour treatment period.

Methods

This study was approved by the ethics committee of Naresuan University Hospital (COA No. 034/2023. IRB No. P3-0006/2566). A retrospective cohort study collected data from medical hospital records between January 2017 and December 2022. The study population comprised children between the ages of one month and five years who were admitted to the Pediatric Ward at Naresuan University Hospital, Thailand, due to acute viral diarrhea lasting less than seven days, based on clinical manifestations such as fever and URI symptoms. Laboratory investigations revealed no bacterial growth in stool culture and no leukocytosis from CBC. We identified acute diarrhea based on loose stool diarrhea >3 times/day or at least one/day watery stool diarrhea within seven days. Exclusion criteria included bloody mucous stool, suspected bacterial diarrhea, positive stool culture, cow's milk protein allergy, breastfeeding and chronic diarrhea. Data were collected from medical hospital records including age, sex, underlying diseases, time to recover from diarrhea and adjunctive treatment received. The primary objective was to compare the effectiveness of lactose-free formula versus lactose-containing formula in managing acute viral diarrhea. Clinical improvement in 24 hours was defined as the presence of normal stool consistency or decreased frequency of diarrhea.

Statistical Analysis

Baseline characteristics were presented as frequencies and percentages reported using Fisher's exact test. Univariate and multivariable regression analyses were performed to compare

the efficacy between the two groups, reporting crude relative risks (RR) and adjusted RR. Statistical analysis was conducted using the Stata Program.

Results

Of the initial 191 patients considered for inclusion, 38 were excluded based on the predetermined exclusion criteria. The final analysis included 153 patients, with 48 receiving lactose-free formula and 105 receiving lactose-containing formula **(Figure 1)**. The study population consisted of 56.21% male and 43.79% female patients, with 35.95% of patients being below 1 year old (**Table 1**). Most patients had no underlying diseases. Both groups (lactose-free formula and lactose-containing formula) exhibited a mean diarrhea at 1.60±0.10 days before admission. Most presented moderate dehydration (86.72%) and the initial laboratory results showed no metabolic acidosis, either the lactose-free formula or lactose-containing group (**Table 1**). All patients in this study received initial intravenous infusion for rehydration upon admission. Totally, 46 patients did not receive any of the administered adjunctive treatments including zinc solution,

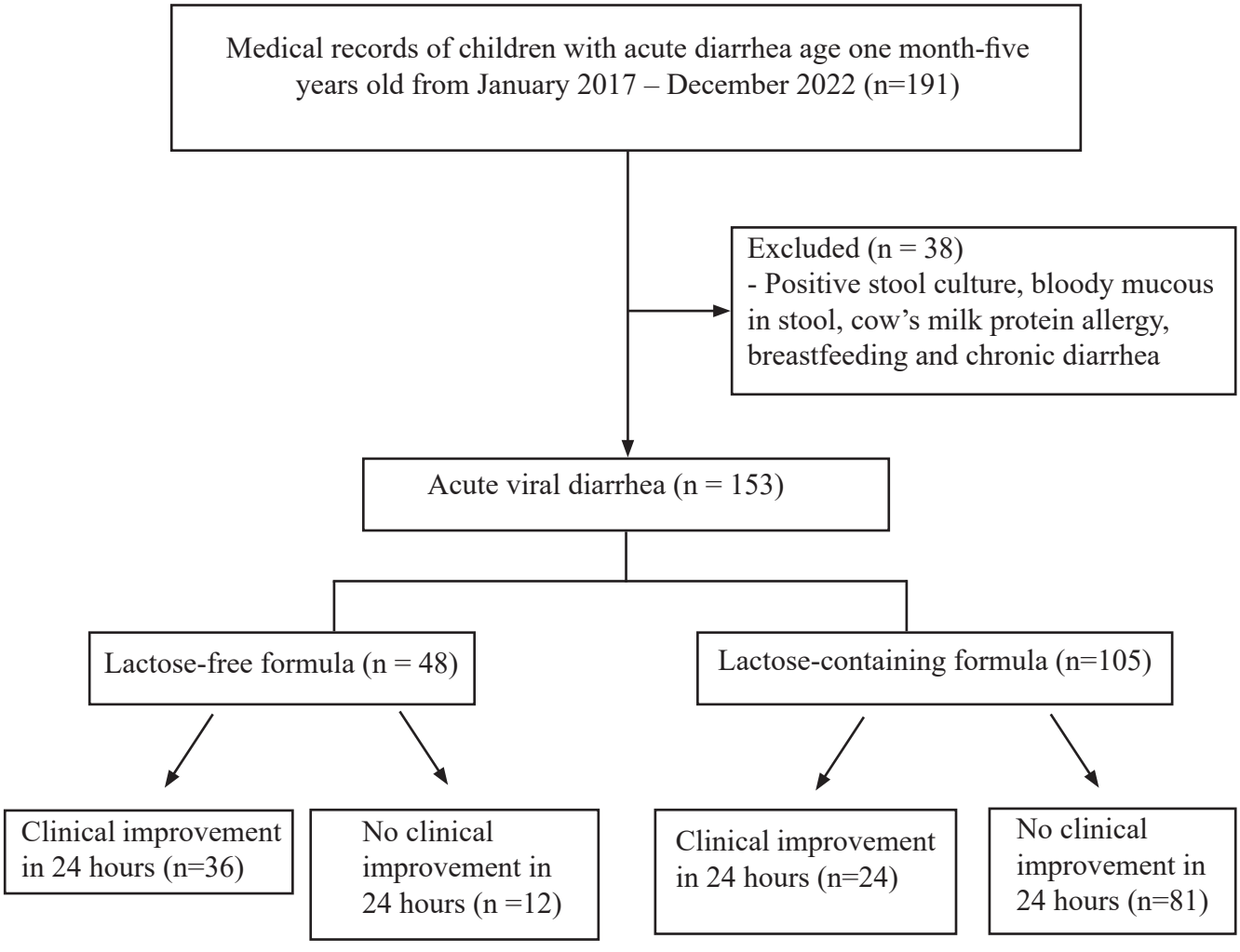

Figure 1. Study flow diagram

Table 1. Demographics and characteristics of children with acute viral diarrhea

Characteristics	Lactose-free formula (n = 48)	Lactose-containing formula (n = 105)	*p*-value
Age (%)			0.366
< 1 year old	20 (41.67)	35 (33.33)	
1 -5 years old	28 (58.33)	70 (66.67)	
Sex (%)			0.861
Male	28 (58.33)	58 (55.24)	
Female	20 (41.67)	47 (44.76)	
Degree of dehydration (%)			0.509
Mild	4 (8.33)	15 (14.29)	
Moderate	43 (89.58)	89 (84.76)	
Severe	1 (2.08)	1 (0.95)	
Stool pH < 5.5 (%)	34 (73.91)	21 (33.33)	< 0.001
Metabolic acidosis (%)			0.656
Yes (serum bicarbonate ≤ 15 mmol/L)	10 (21.74)	18 (18.37)	
No (serum bicarbonate > 15 mmol/L)	36 (78.26)	80 (81.63)	
Adjustive Therapy			
None	15 (31.25)	31 (29.52)	0.851
Racecadotril	4 (8.33)	3 (2.86)	0.679
Zinc solution	11 (22.92)	21 (20.00)	0.674
Zinc + Racecadotril	15 (31.25)	40 (38.10)	0.470
Probiotic+Racecadotril	0 (0)	2 (1.90)	0.470
Zinc solution, Racecadotril, and Probiotics	3 (6.25)	8 (7.62)	0.528

racecadotril and probiotics. Seven patients received racecadotril alone, 32 patients were administered zinc solution, 55 patients received zinc solution and racecadotril combined, 2 patients received racecadotril and probiotics and 11 patients received racecadotril along with zinc solution and probiotics. When comparing the two groups (lactose-free and lactose-containing formula), no significant difference was observed, except in the lactose-free formula group, 34 patients (73.91%) presented a stool pH value of <5.5. This finding significantly differed from the lactose-containing group, where only 21 patients (33.33%) had a stool pH of <5.5 (**Table 1**).

Table 2. The primary outcome of the study

Outcome	Crude RR (95%CI)	Adjusted RR (95%CI)
Diarrhea improvement in 24 hours after treatment	3.28 (2.23- 4.83)	3.90 (1.91-7.95) *

* Adjusted age, gender, dehydration, stool pH, metabolic acidosis, and adjunctive therapy.

The efficacy of lactose-free formula in treating acute diarrhea was determined by measuring the improved clinical diarrhea within 24 hours. Multivariable regression analysis revealed that the lactose-free formula group had a 3.90 fold higher rate of improvement than that of the lactose-containing formula group. Crude relative risk (RR) was calculated as 3.28 (2.23-4.83). Furthermore, after adjusting the age, sex, dehydration, stool pH, metabolic acidosis and adjunctive therapy, the adjusted RR was 3.90 (1.91 to 7.95) (**Table 2**). Using subgroup analysis within the lactose-free formula group (n=48), a comparison was made between the zinc solution-only with the other three groups: (1) no adjunctive treatment, (2) racecadotril group and (3) zinc solution combined with racecadotril. The analysis revealed that the improved rate in these groups was lower by 15% ($p = 0.851$), 8.33% ($p = 0.679$) and 15% ($p = 0.470$), respectively.

Discussion

Lactose intolerance frequently arises as a complication of acute viral diarrhea, particularly among children under 5 years. In our study involving 153 children, 75% of participants receiving lactose-free formula demonstrated improvement within 24 hours. We specifically selected this time frame to assess the efficacy of treatment in cases of acute diarrhea. Related studies demonstrated the ability of the lactose-free formula to reduce the duration of diarrhea.[7-10] Specifically, among children aged 1 month to 5 years admitted with acute viral diarrhea, the rate of improved clinical diarrhea within 24 hours was 3.90 times higher in the lactose-free formula group compared with that in the lactose-containing group. These results aligned with the recommendations outlined in the clinical practice guidelines for acute diarrhea among children. The Thai Society of Pediatric Gastroenterology and Hepatology, 2019 guidelines recommend[2] using lactose-free formula as a viable option for children under 5 years requiring hospital admission and those exhibiting evidence of lactose intolerance. Similarly, the ESPGHAN guidelines to manage acute gastroenteritis among children in Europe[7] advocate using lactose-free formula among hospitalized children under 5 years with acute diarrhea. Most children enrolled in our study required hospital admission due to moderate dehydration, further emphasizing the practical relevance of our findings in real-world clinical settings. In our study, stool pH emerged as a statistically significant factor, with a higher proportion of patients in the lactose-free formula group exhibiting a stool pH <5.5. Stool pH has been used as a screening tool for carbohydrate malabsorption in related studies.[12] Despite its limitations in terms of sensitivity and specificity [13] this diagnostic tool can provide valuable information in certain clinical contexts. Regarding adjunctive therapy for acute diarrhea, our study did not identify any statistically significant differences between the groups administered with lactose-free and lactose-containing formulas. However, subgroup analysis performed on patients receiving lactose-free formula revealed a better trend regarding improvement within 24 hours when treatment consisted solely of zinc solution, as compared with other groups with different treatment interventions (no adjunctive treatment, racecadotril only and combined therapy of zinc solution and racecadotril). Interestingly, our findings showed that the group receiving zinc solution alone had a shorter mean length of stay (2.91 ± 0.10 days) compared with the other groups (no adjunctive treatment, racecadotril and zinc solution combined with racecadotril), which indicated a mean length of stay of three days. Although the participants in this study demonstrated clinical improvement in diarrhea within 24 hours, a hospital observation period of 2 to 3 days remained necessary before their discharge. However, acknowledging the limitations of our study is important, including incomplete data regarding the length of the hospital stay and a small sample size. Additionally, the accuracy of stool output measurement was not ensured, and certain data were unavailable. Further research using larger sample sizes and comprehensive data collection is warranted to validate and expand upon our findings.

Conclusion

Our study provides evidence supporting the superior efficacy of lactose-free formula compared with lactose-containing formula in the dietary management of acute viral diarrhea among children aged 1 month to 5 years old, within a 24-hour timeframe. The concurrent administration of zinc solution and lactose-free formula may lead to a higher rate of improvement and shorter hospital stays. These findings suggest that including lactose-free formula as a complementary measure in the dietary management plan has the potential to reduce costs and shorten the duration of hospitalization for children receiving a diagnosis of acute diarrhea.

Conflicts of Interest

The authors declare they have no conflict of interest regarding the publication of this article.

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