JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH, 2020
VOL 11, NO. 5

RESEARCH ARTICLE

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Determining the Effect of Lactose-Free Formula on The Improvement of Acute Diarrhea Among Infants Aged 3 To 24 Months

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ABSTRACT

Introduction: Diarrhea is a very common disease in children, Acute diarrhea is a major cause of mortality and morbidity in infants and children. So the aim of this study was to determine the effect of lactose-free formula in improving acute diarrhea in infants aged 3 to 24 months.

Materials and Methods: This randomized clinical trial was performed on infants aged 3 to 24 months who were referred to the hospital following acute diarrhea. Patients were randomly divided into two groups of 52 by quadruple blocking method. The infants received lactose-free formula in the intervention group and normal lactose-containing formula in the control group. The diarrhea frequency during the first three days and weight gain after two, three and seven days from the start of hospitalization were recorded. All patients were weighed at admission time 48 to 72 hours and one week after intervention. Data analysis was performed using SPSS software version 20. A P value level of 0.05 was considered to be statistically significant.

Results: A total of 104 patients were included in the study. The results showed that the administration of lactose-free formula in the diet of infants with acute diarrhea (3 days) was capable of reducing the frequency of diarrhea in these infants. However, the use of lactose-free formula in the study group did not cause a difference in weight gain when compared with infants in the control group. Our results also showed that prolonged diarrhea is more related to the better effectiveness of lactose-free formula feeding in the treatment of acute childhood diarrhea.

Conclusion: Lactose-free formula feeding was capable of reducing acute childhood diarrhea frequencies (3 days), but has no effect on improving the consistency of infant feces.

ARTICLE HISTORY

Received October 13, 2020
Accepted November 10, 2020 Published December 11, 2020

KEYWORDS

Formula, Lactose, Acute diarrhea, Infants.

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INTRODUCTION

Acute diarrhea is a frequent discharge of semisolid or fluid fecal matter with a loose consistency of more than 10 cc/kg in infants and more than 200 g in older children and adults within 24 hours (2, 1). The main cause of acute diarrhea in children is infectious agents that affect the mucosa of the small or large intestine. However, there are many other causes of diarrhea in children, including malabsorption syndromes and viral enteropathies. Acute diarrhea is usually self-limiting and resolves without the need for special interventions, although some infectious diarrhea can last longer (3, 4). Diarrhea episodes are classically and chronologically divided into three categories: acute diarrhea, prolonged diarrhea, and chronic diarrhea. Acute diarrhea is a diarrhea that lasts less than 14 days. Prolonged diarrhea lasts between 14 and 28 days and chronic diarrhea lasts for more than 28 days (1).

Pathophysiologically, diarrhea is the result of a disturbance in the normal state of absorption of the body in which the ratio of water absorption and electrolyte is reversed relative to its secretion. Such a disorder can be caused by osmotic pressure inside the intestinal lumen, or by active secretion of water into the intestinal lumen. On this basis, another classification of diarrhea can be presented in which diarrhea is classified into two categories, osmotic and secretory diarrhea. Osmotic diarrhea is a diarrhea that usually occurs as a result of eating unabsorbed sugars such as lactulose or lactose in patients with lactase deficiency (5, 6). Lactose is a disaccharide found in mammalian milk. This sugar is broken down into glucose and galactose by the enzyme lactase in intestinal enterocyte appendages. Lactose seems to increase the absorption of a number of minerals, including calcium, magnesium and zinc (8, 7). It also promotes the growth of bifidobacterium in the colon and is a source of galactose. Galactose is defined to be involved in the formation of brain galactolipids. Lactose intolerance is a common problem in adults caused by a genetic disorder in which the activity of the enzyme lactase progressively disappears. In most of these patients, the expression of lactase decreases from around 2 years of age, and about 4 million people suffer from lactose intolerance worldwide, but the clinical signs of lactose intolerance are rare in children under 6 years of age (9, 10).

The production of the enzyme lactase may be temporarily stopped in children with acute diarrhea, which is usually caused by infectious gastroenteritis. For example, this problem has been proven in children with infectious gastroenteritis caused by rotavirus (11, 12). Therefore, these children may not be able to digest lactose as the main sugar in milk, leading to worsening of their diarrhea or prolonged illness.

Therefore, our study aimed to evaluate the effect of lactose-free formula versus lactose-containing formula on formula-fed infants with acute diarrhea.

MATERIALS AND METHODS

This randomized clinical trial was performed on infants aged 3 to 24 months who referred to Golestan and Abuzar hospitals in Ahvaz, Iran following acute diarrhea in spring and summer 2015. The data collection tool and method was a questionnaire and patients with inclusion and exclusion criteria were included in the study.

Inclusion criteria: having informed consent, Formula fed infants aged between 3 to 24 months and having acute diarrhea. Exclusion criteria: diarrhea more than one week from the start of treatment, infants with congenital disease, underlying systemic disease, severe malnutrition, severe vomiting, history of antibiotic use in the last two weeks, having bloody stools and history of using therapeutic formula.

Taking into account the first type error of 0.05 and power 80%, the sample size for each group was calculated to be about 42 patients, which for each group was considered to be 52 patients to cover potential sample losses. It is noteworthy that reference (13) and G-POWER software version 3.1.9.2 were used to calculate the sample size.

Procedure

After obtaining informed consent, patients were randomly divided into two groups of 52 patients using the quadruple block. After the initial emergency and fluid therapy procedures for the patients, the infants received lactose-free formula in the intervention group and normal lactose-containing formula in the control group. Demographic information of patients including age, sex, date of hospitalization, infant weight at the time of admission, duration of diarrhea before admission, diarrhea frequency during the first three days and weight gain after two, three and seven days of hospitalization. If patients were hospitalized for less than a week, their parents were asked to go to the relevant medical center to examine their child. All patients were weighed at baseline, followed by 48 to 72 hours and one week later. Criteria for improving patients' diarrhea are the frequency of diarrheal stools (≤3 times) and the absence of dehydration symptoms.

Descriptive statistics such as mean, ratio, standard deviation, table and graph were used to compare the variables. ANOVA test was also used to measure changes in weight, frequency of diarrhea and the effect of infant formula administration

based on the duration of diarrhea. Data analysis was performed using SPSS software version 20. A p value level of 0.05 was considered to be statistically significant.

Ethical considerations

A written letter of introduction was obtained from university officials and research center officials. The purpose of the study was described for the research units and written consent was obtained from them. Patients' information were kept confidential.

Statements of ethics in Helsinki declaration and ethical principles of research ethics committee of the University of Medical Sciences were observed. The study has been approved by the Research Council of the Medical School (Code IRCT20201011048995N1).

RESULTS

A total of 104 patients were examined in the age range of 3 to 24 months (mean age: 13.71 ± 4.78 months). Two of these children were aged 3 to 6 months, 48 were aged 7 to 12 months and 54 were over 13 months old. Meanwhile, a 12-month-old girl was excluded from the study due to lack of cooperation in follow-up. Of the remaining 103 infants, 51 consumed lactose-free-formula and 52 consumed lactose containing formula.

The duration of diarrhea before hospitalization showed a minimum of 3 and maximum of 10 days (mean: 5.66 ± 1.56 days). Also, the minimum and maximum hospital stay were determined to be 3 and 8 days, respectively (mean: 4.43 ± 1.31 days). Children's weight information was recorded at the time of referral, the third day and the seventh day. At the time of referral, the minimum weight of children was 6100 grams and the maximum was 12300 grams. On the third and seventh days, the minimum and maximum weights of children were 7 kg and 12100 g, respectively. ANOVA results showed that weight changes in the whole study population were not significant over time (P = 0.387), but the number of diarrhea episodes decreased significantly in this population (P <0.001).

The frequency of diarrhea in the study population was assessed. On the first day, the minimum and maximum diarrhea was 4 and 15 times, respectively, followed by, 1 and 13 times on the second day, 2 and 10 times on the third day, and 1 time on the seventh day. During the study period, the patients had the highest diarrhea frequency on the first day (average: 8 times) and the lowest on the seventh day. As shown in Table 1, the stool consistency in most children was initially watery and gradually hardened in 92% of cases by the seventh day.

Table 1: Stool consistency changes

Stool consistency	watery	Semi-watery	Normal	P-value
Day1	102 (100%)	0	0	
Day 2	69 (71.07%)	34 (28.93%)	0	
Day 3	48 (49.4%)	11 (11.33%)	44 (39.27%)	
Day 7	7 (7.21%)	0 (0%)	96 (92.79%)	<0.001

Table 2 compared the frequency of diarrhea in infants during different time periods based on the type of infant formula consumed. According to the ANOVA test, the trend of changes in the diarrhea frequency was significant in the two groups, the diarrhea frequency on the second and third days in children consuming lactose-free formula was significantly lower (P <0.001).

Table 2: Comparison of diarrhea frequency in infants in different time periods based on the type of infant formula consumed.

the number of diarrhea frequency	Milk type formula										
	Lactose free					Compare groups	Lactose-containing				
	Mean	Min	Max	SD	Median	P-value	Mean	Min	Max	SD	Median
Day 1	7.98	4.00	11.00	1.67	8.00	0.188	8.58	6.00	15.00	1.75	8.00
Day 2	4.98	3.00	7.00	1.12	5.00	<0.001	7.38	1.00	13.00	2.24	7.00
Day 3	2.67	2.00	4.00	.59	3.00	<0.001	6.23	4.00	10.00	1.46	6.00
Day 7	0	0	0	0	0	0.163	0.04	0.00	1.00	0.19	0

The results of ANOVA analysis showed no significant difference in terms of weight changes in infants with acute diarrhea between lactose-free formula versus lactose-containing formula (P = 0.711). Also, no significant difference was found between these two types of formula in terms of infants' weight at different time points (Table 3).

Table 3: Investigation of the effect of formula types on infants' weight

Check weight (g)	Milk type formula						
	Lactose free			Compare groups	Lactose-containing		
	Mean	SD	Median	P-value	Mean	SD	Median
Referral day	10015.69	1063.08	9800.00	0.333	9969.23	2225.48	10100.00
Day 3	9841.18	1050.56	9600.00	0.843	9746.15	1504.30	9750.00
Day 7	10092.16	1062.42	9800.00	0.957	9756.00	2361.27	10000.00

Comparisons are based on Mann-Whitney U Test

The process of improving diarrhea was evaluated based on the type of formula in 7 to 12 month old male infants. There were only two infants under the age of 6 months, both of whom used lactose-containing formula. Therefore, it was not possible to compare the effects of formula in this age group of boys. The results of ANOVA test showed a significant difference in the process of reducing the severity of diarrhea between formulas among male infants aged 7-12 months (P <0.001) and over 13 months (P <0.001). Thus, the process of improving diarrhea in infants consuming lactose-free formula was significantly better (Figures 1, 2).

Fig.1: Comparison of diarrhea improvement process by type of formula in 7 to 12 month old male infants

Fig.2: Comparison of the improvement of diarrhea by type of formula in male infants over 13 months

Our findings revealed no significant effect of lactose-free formula in reducing the severity of diarrhea in the age range of 13-17 months and above 13 months (P = 0.938), (Figure 3).

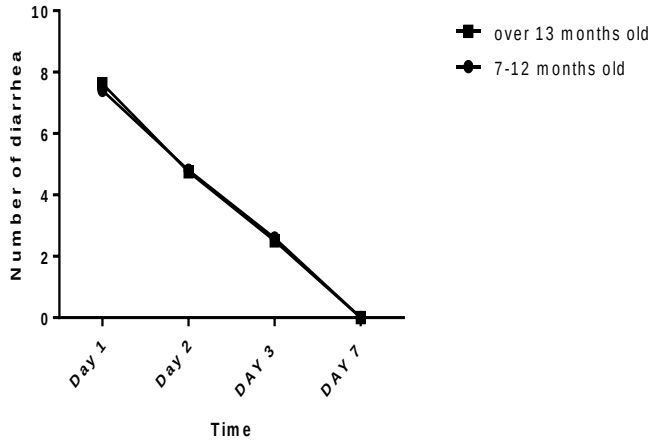

Fig.3: Comparison of the improvement in diarrhea in male infants after consuming lactose-free formula

In this study, there were no female infants in the age group under 6 months, so it was not possible to compare the effects of formula in this age group. The results of ANOVA test showed a significant difference in the process of reducing the severity of diarrhea between types of formula among female infants in the age range of 13-17 months and over 13 months (P <0.001), therefore, the improvement of diarrhea was significantly better in infants receiving lactose-free formula (Figure 4, and 5).

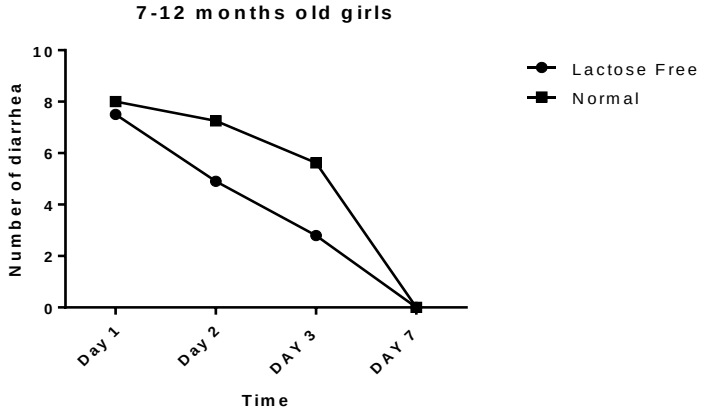

Fig.4: Comparison of the improvement of diarrhea by formula type in 7 to 12 month old female infants

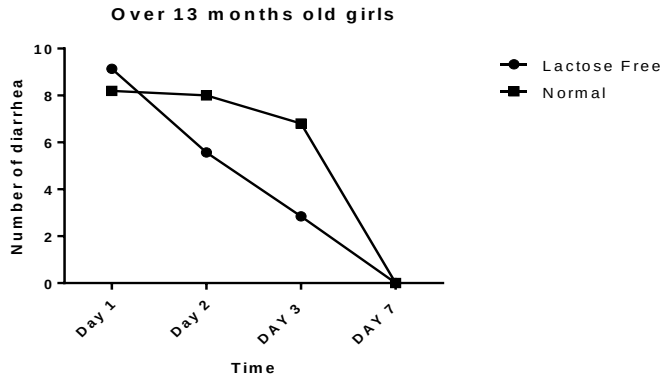

Fig.5: Comparison of the improvement of diarrhea by formula type in female infants over 13 months

No significant difference was found between two age groups 7-12 months and over 13 months in terms of the effectiveness of lactose-free formula in reducing the severity of diarrhea (P = 0.073), (Figure 6).

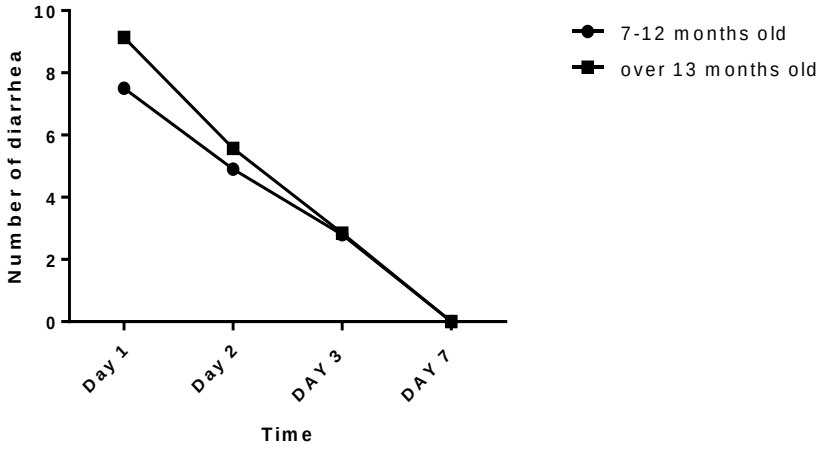

Fig.6: The improvement in the diarrhea frequency in female infants consuming lactose-free formula

All infants receiving lactose-free formula had diarrhea for more than 3 days before starting treatment. Accordingly, the comparison was made in these infants in two groups of diarrhea between 3 to 7 days and more than 7 days before treatment. The results of ANOVA analysis demonstrated the decreasing trend in the severity of diarrhea for infants who had the disease for longer duration of disease before the start of lactose-free formula (> 7 days) was significantly better than those with diarrhea between 3 and 7 days (P = 0.040), (Figure 7).

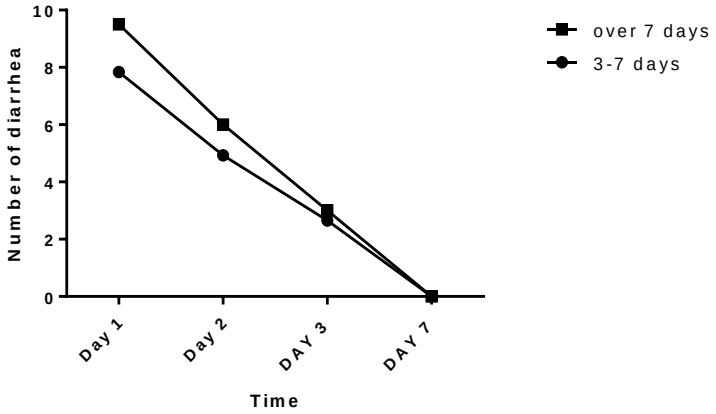

Fig.7: The effect of lactose-free formula on infant diarrhea based on the time of onset of diarrhea

DISCUSSION

A number of considerations are important in the treatment of acute diarrhea and effective nutritional interventions, including the time of onset of feeding in infants with diarrhea, milk diet and the type of formula suitable for patients, as well as the use of micronutrients in the treatment of these patients (14). The World Health Organization estimates that approximately 1.5 million children under the age of 5 die each year from diarrhea, half of which occur in developing countries (5). Therefore, the aim of this study was to determine the effect of lactose-free formula on the improvement of acute diarrhea in infants aged 3-24 months. The findings of this study showed that the use of lactose-free formula in the diet of infants with acute diarrhea lasted at least three days, reduced the frequency of diarrhea compared to regular baby formula. However, the use of lactose-free formula in the study group did not cause a difference in weight gain with infants compared with the control group. This study also showed that the longer the duration of diarrhea, the better the effectiveness of lactose-free milk feeding in the treatment of acute diarrhea in infants.

This study also showed that the longer diarrhea would be more associated with the effectiveness of lactose-free formula feeding in the treatment of acute diarrhea in infants.

In this regard, various studies have been conducted. Saneian et al., evaluated the effect of consuming lactose-free formula in infants aged 1 to 24 months referring with acute non-bloody diarrhea. Their results showed that infants treated with lactose-free formula had a shorter duration of diarrhea than infants treated with regular formula (13). Another study by Sadoon in 2009 examined the effect of lactose-free formula in infants with acute diarrhea compared to regular baby formula. Lactose-free formula reduced the length of hospital stay and improved hydration in infants (15).

Another study by Simakachorn et al., showed that lactose-free formula was effective in the dietary management of acute childhood diarrhea, where its use was linked to shorter duration of diarrhea, weight gain and less stool frequency when compared with lactose-containing formula (16). A study by Xu et al. in China showed that the use of lactose-free formula feeding in infants with acute diarrhea was capable of reducing the duration of the disease course compared to conventional formula feeding (17).

As can be seen, the results of similar studies in this field have a significant convergence with each other. Limited studies have also shown the opposite, such as Dalgic et al., in which the use of lactose-free formula had no effect on patient improvement more than the control group (18).

Overall, it can be concluded that the use of lactose-free formula feeding in infants with prolonged acute diarrhea accelerates the recovery of infants, reduces the duration of the disease, the length of hospital stay and the severity of symptoms.

In the present study, there was an innovative finding that was not mentioned in other studies. In fact, the analysis of the findings of this study showed that the effectiveness of lactose-free formula in the recovery of infants with prolonged acute watery diarrhea was associated with the duration of diarrhea. As a matter of fact, the effect of lactose-free formula feeding on the improvement of acute diarrhea was significantly greater in infants with a diarrhea period of >2 days than in infants with a diarrhea period of 3 to 7 days. This suggests that the duration of the acute diarrhea period is probably more related to the better effect of lactose-free formula. This issue can be justified from a pathophysiological point of view. As mentioned, infectious gastroenteritis, especially rotavirus-induced gastroenteritis, causes temporary lactase deficiency in patients, therefore, longer diarrhea period will lead to more lactase deficiency in patients. The use of lactose-free formula will be more effective in improving these patients and reducing the duration of their disease (11). Another finding in this study was that long-term lactose-free formula feeding in infants with acute diarrhea had no greater effect on improving infant fecal consistency than conventional formula feeding. This finding differed from the results of a study by AL Sadoon et al. The AL Sadoon study showed a strong correlation between the feeding of infants with lactose-free formula and their stool consistency (15). This controversial nature of the research findings may be probably due to the lack of objective criteria for measuring the consistency of feces as well as the evaluation of fecal consistency by different people, because it is natural to expect as a person decreases during the day, the consistency of the patient's stool increases accordingly because it is expected that reducing the frequency of diarrhea during the day will lead to better consistency of the patient's feces.

CONCLUSION

Lactose-free formula feeding in infants referring with acute diarrhea (<3 days) was capable of reducing daily stools frequency but has no effect on improving the stool consistency.

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