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Original Article

Efficacy of lactose-free formula in acute diarrheal management for children under 5 years: a systematic review and meta-analysis

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Abstract

Background Acute diarrhea is the most common gastrointestinal disease in children under five years of age with high morbidity and mortality risk. The use of lactose-free formula in the management of children with acute diarrhea was said to accelerate the diarrheal resolution time.

Objective To determine the efficacy of lactose-free formula in managing acute diarrhea in pediatric patients by systematic review and meta-analysis.

Methods A comprehensive literature search was conducted on *PubMed, Proquest, Web of Science,* and *CINAHL Plus Database* from November 1971 to July 11, 2021. The study selection process was carried out under *PRISMA 2020 Guidelines* based on several eligibility criteria. The quality of the included studies were further assessed using Modified Jadad Scores.

Results Fifteen randomized controlled trials (RCTs) were included, involving a total of 1,390 children with acute diarrhea. Shorter recovery time (mean difference/MD -0.21; 95%CI -0.50 to 0.08; P=0.16) was observed in patients receiving lactose-free formula than the control group. However, this finding was not statistically significant. The subgroup analysis showed that lactose-free formula significantly shortened the recovery time compared to oral rehydration solution (ORS) group (MD -0.70; 95%CI -0.98 to -0.41; P=0.00001). Furthermore, lactose-free formula also significantly reduced the amount of stool output (MD -0.61; 95%CI -0.86 to -0.36; P=0.00001) and the incidence of persistent diarrhea more than seven days (OR 0.22; 95%CI 0.10 to 0.51; P=0.0004) compared to the control group.

Conclusion Lactose-free formula as dietary management for acute diarrhea in children can reduce stool output and the incidence of persistent diarrhea for more than seven days. It also may shorten the recovery time compared to the administration of ORS alone. **[Paediatr Indones. 2024;64:233-43; DOI: https://doi.org/10.14238/pi64.3.2024.233-43**].

Keywords: *acute diarrhea; lactose free; children*

Diarrhea is the second leading cause of death in children under 5 years of age. Globally, there are nearly 1.7 billion cases of childhood diarrhea every year, and around 525,000 children under five die annually due to diarrhea disease. Diarrhea causes death by depleting body fluids, resulting in profound dehydration.[1,2] Diarrhea is also a leading cause of malnutrition in children under five years; this condition can have a detrimental impact on childhood growth and cognitive development.[2]

Current management of diarrhea includes fluid and electrolyte therapy, appropriate antibiotics, adequate nutrition, and zinc supplementation, as recommended by the WHO and UNICEF.[3] Lactose-free formulas have been found to help reduce the duration and frequency of acute diarrhea, increase weight gain, and ameliorate dehydration. These formulas can benefit young children by inhibiting the occurrence of lactose malabsorption, especially in children with low lactase level. However, the benefit of the lactose-free formula in the management of

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acute diarrhea is still controversial.[4-6] As such, we performed a meta-analysis of the existing literature in order to quantitatively assess the efficacy of a lactose-free formula in managing acute diarrhea in children under 5 years.

Methods

This study was performed according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020* reporting guidelines.[7] A comprehensive electronic-based literature search was conducted on *PubMed, Proquest, Web of Science,* and *CINAHL Plus Database* from November 1971 to July 11, 2021, with the following terms: ("children OR "infant" OR "toddler") AND ("lactose free" OR "low lactose" OR "lactose-free formula" OR "lactose-free regimen" OR "lactose-restricted formula" OR "lactose-restricted regimen" OR "milk formula" OR "nutritional management") AND ("acute diarrhea" OR "acute gastroenteritis" OR "acute diarrhoea").

We collected studies from the 4 databases and removed duplicate publications with the *Zotero program 5.0*. Studies were first screened by title and abstract, based on the following eligibility criteria: (1) RCT studies, (2) study populations of children under the age of five with acute diarrhea, (3) studies comparing the outcome of lactose-free formula and control [including lactose-containing formula and oral rehydration solution (ORS)], and (4) full text available in English. If there was a lack of information in the title and/or abstract, the full text was screened for further assessment. The selection process is shown in the *PRISMA 2020* flow diagram (**Figure 1**).

We recorded the following information into a data extraction table: author name, location, target population, research subjects, age, sample size (case/control), and intervention. Outcomes consisted of recovery time (the time needed from enrollment until diarrhea resolution), diarrhea frequency (mean frequency of diarrhea per day), duration of hospitalization, weight change (difference between weight at admission and after treatment), stool output (mean fecal weight), persistent vomiting (more than 3 times in an 8- hour period or persistent vomiting after treatment), and prolonged diarrhea (lasting more than 7 days).

The quality of the included studies was further assessed using *Modified Jadad Scores*.[8] The tool consists of 4 components: (1) randomization, (2) concealment, (3) blinding and (4) withdrawal and dropout. Studies with a total *Modified Jadad Scores* of 1-2 were graded as low quality, 3-4 as moderate quality, and >4 as high quality. Disagreements were resolved by discussion among the authors for a final consensus.

The main outcomes of this study were the differences in diarrhea outcomes between the lactose-free and control groups in children with acute diarrhea. Comparisons between these two groups were analyzed using mean differences (MD) or standardized mean differences (SMD) and odds ratio (OR), with a 95% confidence interval (CI). Heterogeneity was assessed using the I2 index.[9] A fixed-effects model was used if the I2 was <50%; otherwise, a random-effects model was applied. Results with P values <0.05 were considered to be statistically significant. Subgroup analysis was performed based on the control group intervention. All statistical analyses were conducted using *Review Manager version 5.4* software. The meta-analysis results are presented in forest plots alongside narratives to provide readers with additional explanation and for better understanding. Publication bias was analyzed using funnel plots.

This search process generated 467 articles from 4 databases. After removing duplicates, 383 records were screened. Of those, 32 studies were remained after removing those with inappropriate titles and/or abstracts. Finally, 15 studies were used (**Table 1**) for quantitative data synthesis. This process can be seen in our study selection flow chart (**Figure 1**).

Results

Fifteen RCTs were included, involving 1,390 children under five years of age with acute diarrhea. The range of published studies included in this meta-analysis was 35 years, from 1985 to 2020. These studies were conducted in various regions, including Asia, Africa, America, Europe, and Australia. Of these 15 studies, 10 were of high quality, 3 were moderate, and 2 were low (**Table 1**). The complete characteristics of each study can be seen in **Table 1**.

Data from 14 studies were used for this analysis (**Figure 2**). A standardized mean difference (SMD)

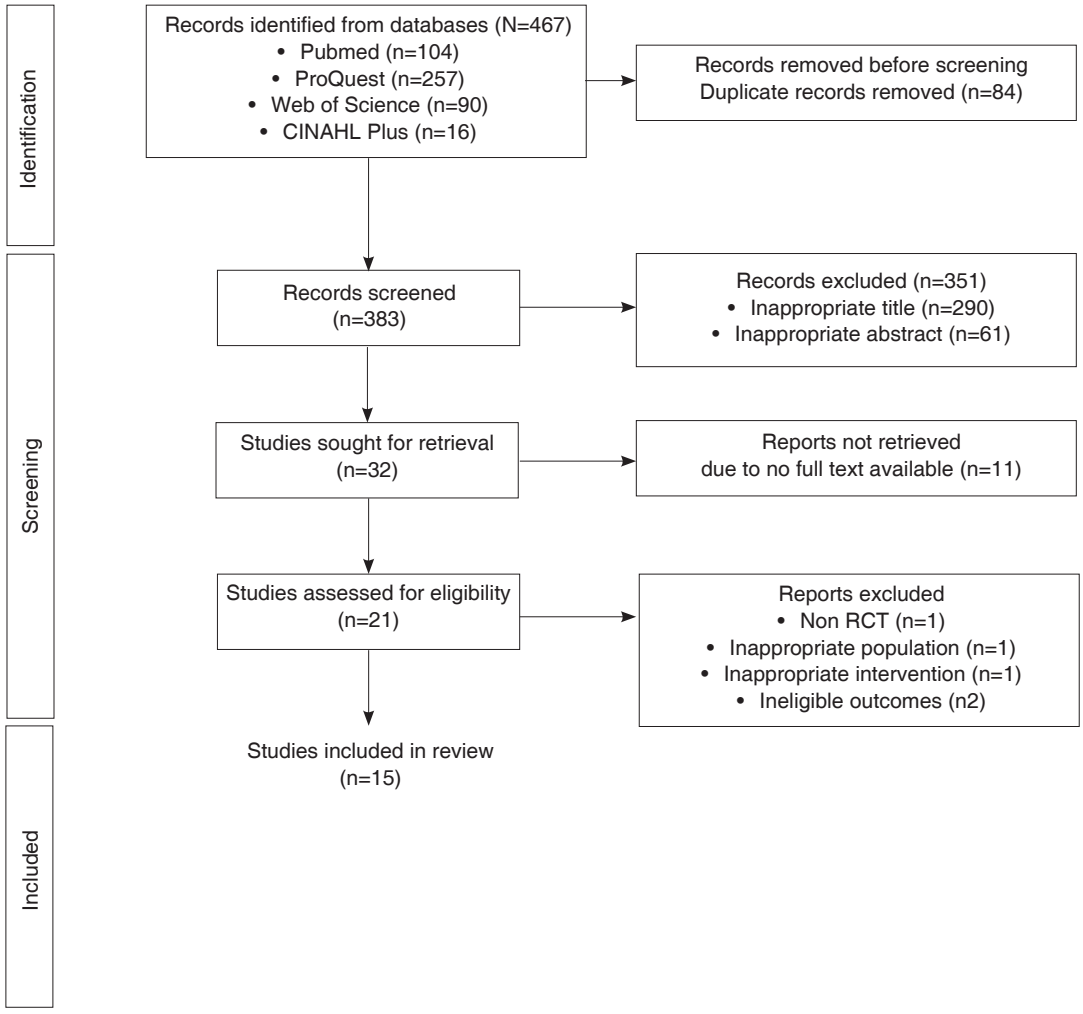

Figure 1. PRISMA fLow chart of study selection

was used in the data analysis because the criteria for evaluating recovery time in 14 studies were different. Shorter recovery time (SMD -0.21; 95%CI -0.50 to 0.08; I^2 84%) was observed in the lactose-free group compared to the control group, but this finding was not statistically significant (P>0.05). However, subgroup analysis with ORS as a control showed significantly reduced recovery time in children with acute diarrhea (SMD -0.70; 95%CI -0.98 to -0.41; I2 2%). The heterogeneity between studies in the forest plot was considered high (I^2 > 50%), but the subgroup analysis showed low heterogeneity (I^2 < 50%). The funnel plot analysis showed an asymmetrical distribution among studies, indicating a potential publication bias in the recovery time analysis (**Figure 2**).

Only three studies[6,13,14] provided data on the duration of hospitalization (**Figure 3**). The pooled results demonstrated no significant difference between the two groups (MD -0.31; 95%CI -0.95 to 0.33; I2 62%). Heterogeneity among studies was considered to be high (I^2>50%). Subgroup analysis with ORS as a control also lacked a significant result (MD -0.58; 95%CI -1.23 to 0.07; P=0.08).

Five studies reported on diarrhea frequency (**Figure 4**).[5,12,14,15,18] Pooled analysis showed that diarrhea frequency was not significantly different between the lactose-free and control groups (MD -0.12; 95%CI -0.75 to 0.50; I2 66%). Heterogeneity among studies was considered high (I^2>50%).

Four studies reported on stool output (**Figure**

Table 1. Characteristics of studies included in the meta-analysis

Author (year)	Study location	Research subjects	Mean age (SD), months	Sample size (n)		Intervention		Outcomes	Quality assessment
				Case	Control	Case	Control		
Wall *et al*., (1994)[4]	Australia	Bottle-fed infants aged 1-24 months with acute diarrhea	9.69 (4.65)	23	47	Lactose-free cow's milk	Lactose-containing cow's milk	RT, WC	5 (high)
Santosham *et al*., (1985)[10]	Arizona	Infants under 12 months with acute diarrhea	5.20 (3.34)	43	44	Lactose-free soy-based milk	ORS	RT, WC, SO, PV, PDD	1 (low)
Lifshitz *et al*., (1991)[11]	Brazil	Male infants under 12 months with acute diarrhea	-	30	20	Lactose-free soy-based and cow's milks	Lactose-containing cow's milk	SO	6 (high)
Torun *et al*., (1991)[12]	Guatemala	Infants aged 7-32 months with acute diarrhea	-	31	22	Lactose-free vegetable origin diet	Lactose-containing cow's milk	RT, DF, SO, PD	1 (low)
Simakachorn *et al*., (2004)5	Thailand	Male formula-fed infants aged 3-24 months with acute diarrhea	12.17 (4.74)	40	40	Lactose-free soy-based milk	Lactose-containing cow's milk	RT, DF, WC, SO, PDD	6 (high)
Dalgic *et al*., (2011)[6]	Turkey	Infants aged 1-28 months with acute diarrhea	12.56 (5.70)	60	60	Lactose-free cow's milk	ORS	RT, DH	6 (high)
Kukuruzovic *et al.,* (2002)[13]	Australia	Infants aged less than 36 months with acute diarrhea	15.01 (7.11)	125	55	Lactose-free cow's milk	Lactose-containing cow's milk	RT, DH, WC	7 (high)
Saneian *et al*., (2012)[3]	Iran	Formula-fed infants aged 1-24 months with acute diarrhea	7.12 (3.68)	37	34	Lactose-free formula	Lactose-containing formula	RT, WC	5 (high)
Mehrabani *et al*., (2020)[14]	Iran	Breastfed infants aged 6-24 months with acute diarrhea	14.6 (6.58)	45	45	Lactose-free plant-based formula	Breast milk	RT, DF, DH	6 (high)
Lestari *et al*., (2006)[15]	Indonesia	Infants aged 6-24 months with acute diarrhea	-	28	28	Lactose-free cow's milk	Lactose-containing cow's milk	RT, DF	6 (high)
Allen *et al*., (1994)[16]	America	Infants aged 2-12 months with acute diarrhea	7.41 (2.53)	39	34	Lactose-free, soy-based milk	Lactose-containing cow's milk	RT, WC, PV, PD	6 (high)
Haffejee *et al*., (1990)[17]	South Africa	Infants aged 3 days to 28 months with acute diarrhea	7.7 (5.5)	75	199	Lactose-free, soy-based milk	Lactose-containing cow's milk	RT	4 (moderate)

Table 1. Characteristics of studies included in the meta-analysis (continued)

Author (year)	Study location	Research subjects	Mean age (SD), months	Sample size (n)		Intervention		Outcomes	Quality assessment
				Case	Control	Case	Control		
McClean *et al.*, (1990)[18]	Northern Ireland	Infants aged less than 10 months with acute diarrhea	2.80 (1.91)	19	41	Lactose-free, soy-based milk	Lactose-containing cow's milk	RT, WC, PV	3 (moderate)
Noreen *et al.*, (2016)[19]	Pakistan	Infants aged 1-12 months with acute diarrhea	13.39 (6.01)	35	34	Lactose-free formula	Lactose-containing formula	RT	5 (high)
Bhan *et al.*, (1988)[20]	India	Infants aged 3-24 months with acute diarrhea	9.1 (4.23)	28	29	Lactose-free, plant-based cereal	Lactose-containing cow's milk	RT, WC	4 (moderate)

RT=recovery time, DF=diarrhea frequency, DH=duration of hospitalization, WC=weight change, SO=stool output, PV=persistent vomiting, PD=prolonged diarrhea

5).[5,10-12] Less stool output (SMD -0.61; 95%CI -0.86 to -0.36; I2 47%) was observed following lactose-free formula administration compared to lactose-containing formula and ORS. Pooled analysis showed that stool output was significantly lower in lactose-free group compared to control. Heterogeneity among studies was considered low ($I^2<50\%$).

Eight studies provided weight changes (**Figure 6**).[3-5,10,13,16,18,20] Lower weight change (SMD -0.09; 95%CI -0.26 to 0.07; I2 0%) was observed in the lactose-free compared to the control group. However, this finding was not statistically significant. In addition, no significant association was found in subgroup analyses with ORS as a control (SMD -0.37; 95%CI -0.79 to 0.06). Heterogeneity among studies was considered low ($I^2<50\%$).

Data from three studies were used for analysis of persistent vomiting (**Figure 7**).[10,16,18] Pooled analysis showed that the incidence of vomiting was not significantly different in the lactose-free group compared to the control group (OR 0.99; 95%CI 0.32 to 3.07; I^2 0%). Heterogeneity among studies was considered to be low ($I^2<50\%$).

Four studies reported on prolonged diarrhea of >7 days (**Figure 8**).[5,10,12,16] Pooled analysis showed that the incidence of prolonged diarrhea was significantly lower in the lactose-free group compared to the control group (OR 0.22; 95%CI 0.10 to 0.51, I^2 0%). But subgroup analysis with ORS as a control lacked a significant difference in incidence of prolonged diarrhea between the two groups (OR 0.38; 95%CI 0.07 to 2.08). Heterogeneity among studies was considered to be low ($I^2<50\%$).

Discussion

This meta-analysis showed that lactose-free formula significantly reduced stool output and prevented prolonged diarrhea for more than seven days. Other variables such as recovery time, duration of hospitalization, diarrhea frequency, weight change, and vomiting were not significantly different between the cintervention and control groups.

The sub-analysis using ORS as a control revealed a significantly decreased recovery time. This finding followed the WHO recommendation to provide nutrient-rich foods to children with acute

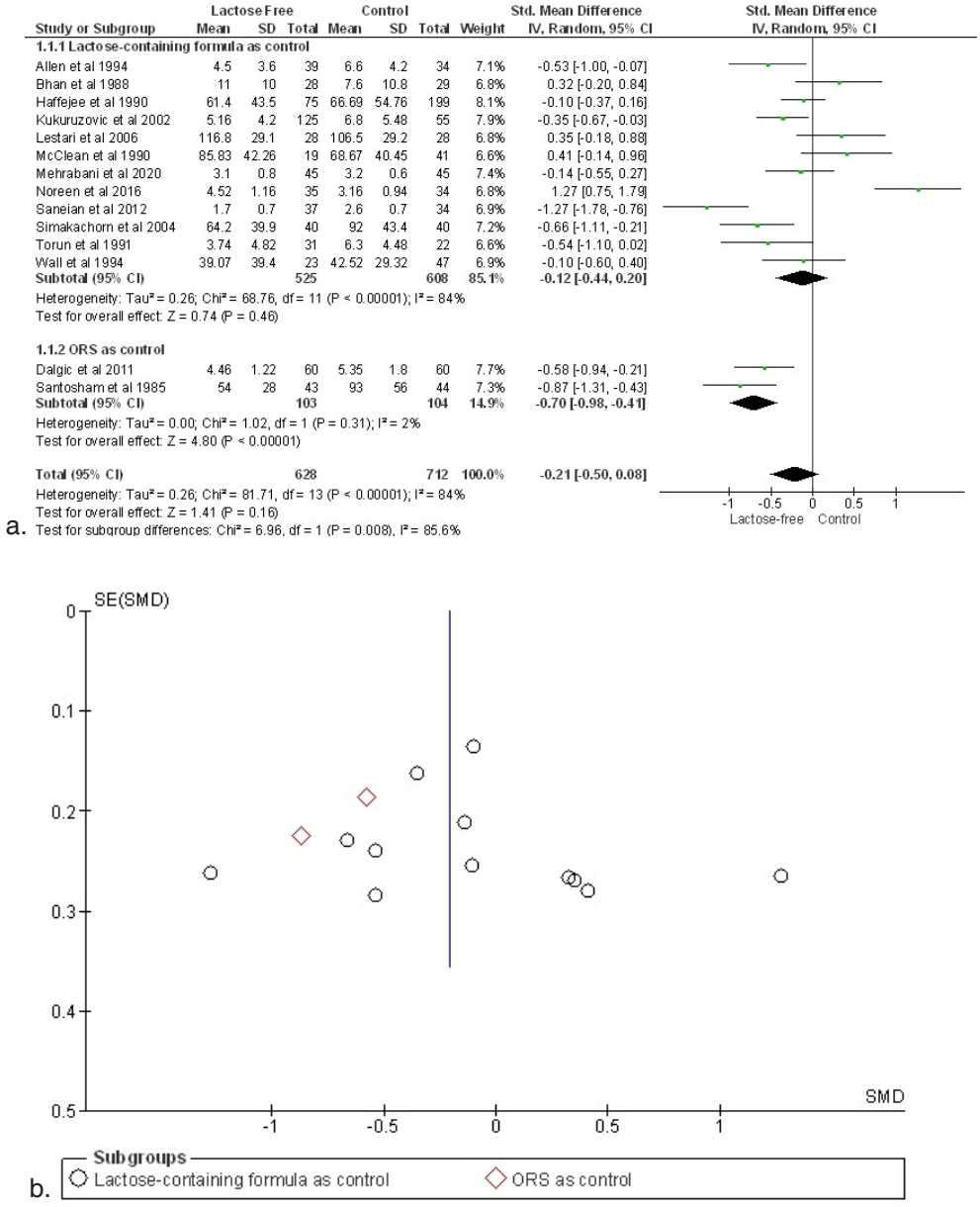

Figure 2. (a) Forest plot of the recovery time with subgroup analysis based on the therapeutic approach of the control group in children under 5 years and (b) funnel plot of the diarrhea recovery time.

diarrhea.[1] Breast milk is one such food. Children who consumed formula and breast milk had significantly reduced duration of diarrhea compared to those who consumed formula alone.[17] The content of the formula given should also be considered. A lactose-free formula with low osmolality is known to produce the best outcome. Higher osmolality is suspected of inhibiting the mucosal repair mechanism of the intestine, thereby reducing nutrient absorption.[13]

The duration of hospitalization was relatively shorter in the lactose-free formula group, although the difference was not significant. A study suggests that lactose-free formula is more effective when used in cases of prolonged diarrhea, specifically when diarrhea occurs for 14 to 28 days.[21] The subject population of the three studies analyzed in had acute diarrhea. The

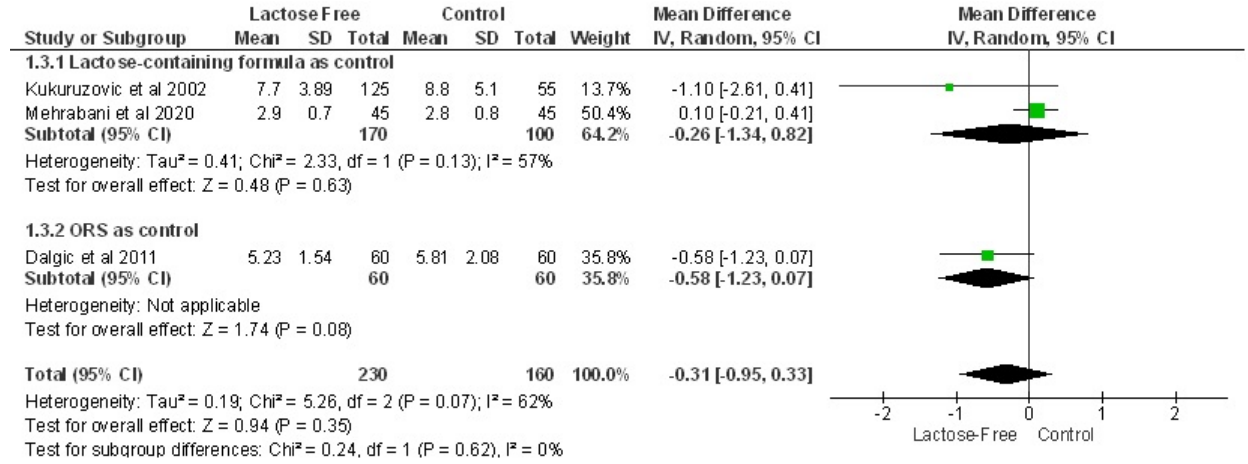

Figure 3. Forest plot of the duration of hospitalization with subgroup analysis based on the therapeutic approach of the control group in children under 5 years

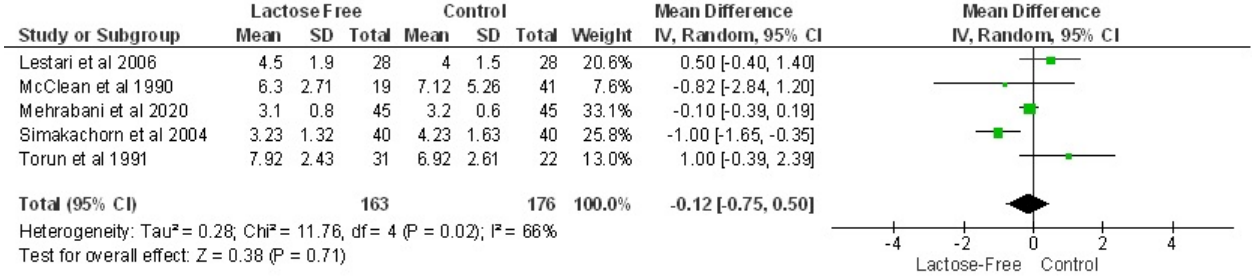

Figure 4. Forest plot of the mean difference in diarrhea frequency between the lactose-free and control groups

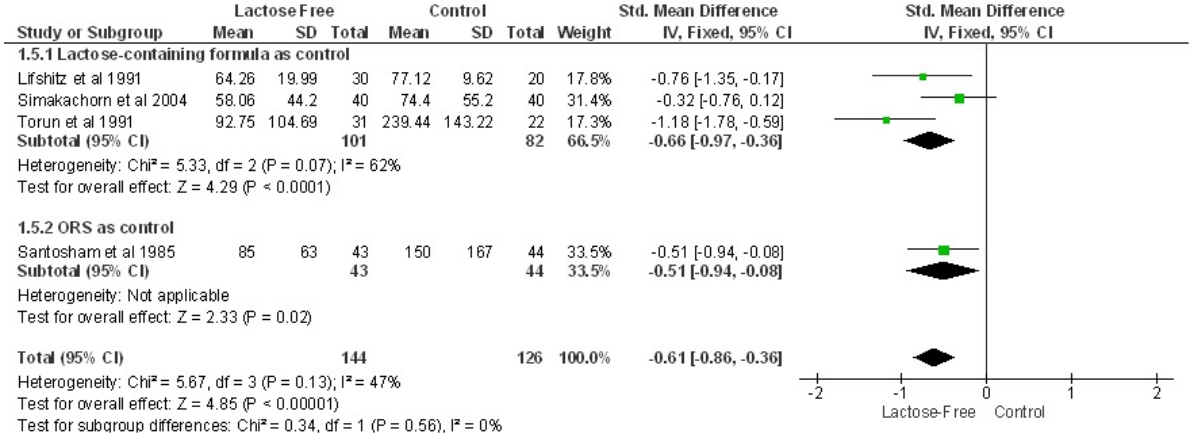

Figure 5. Forest plot of stool output with subgroup analysis based on the therapeutic approach of the control group in children under 5 years

subjects in the Dalgic *et al.*[6] study were children with diarrhea for less than 4 days, while other studies did not mention the specific number of days.[13,14]

There were no significant differences in diarrhea frequency between lactose-free formula and lactose-containing formula. This result may have been

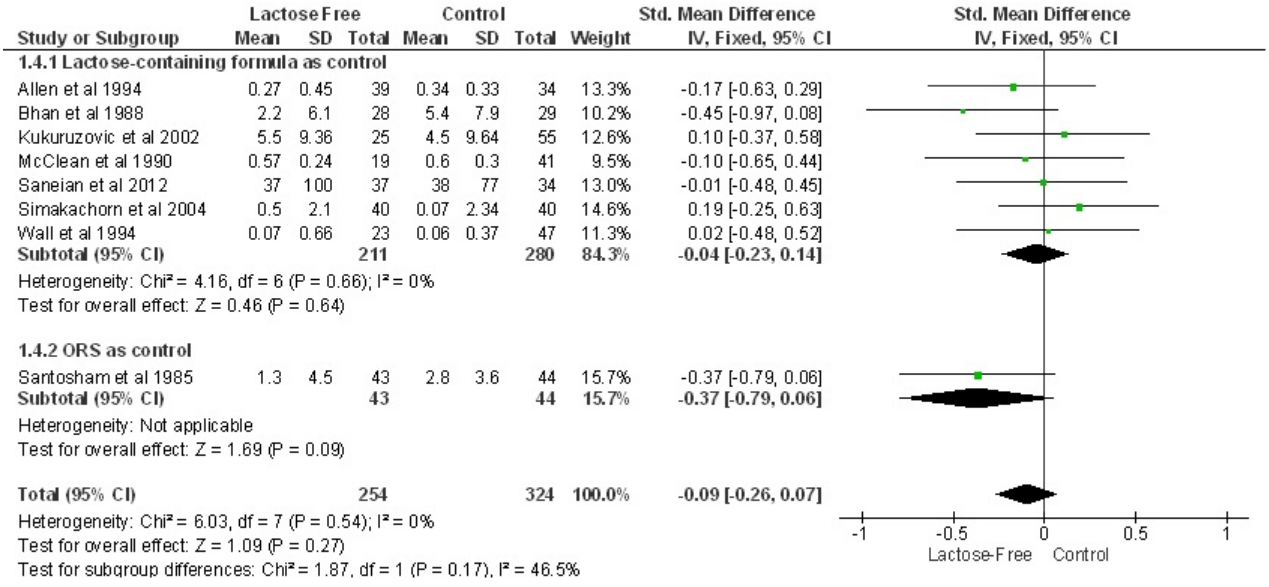

Figure 6. Forest plot of the weight change with subgroup analysis based on the therapeutic approach of the control group in children under 5 years

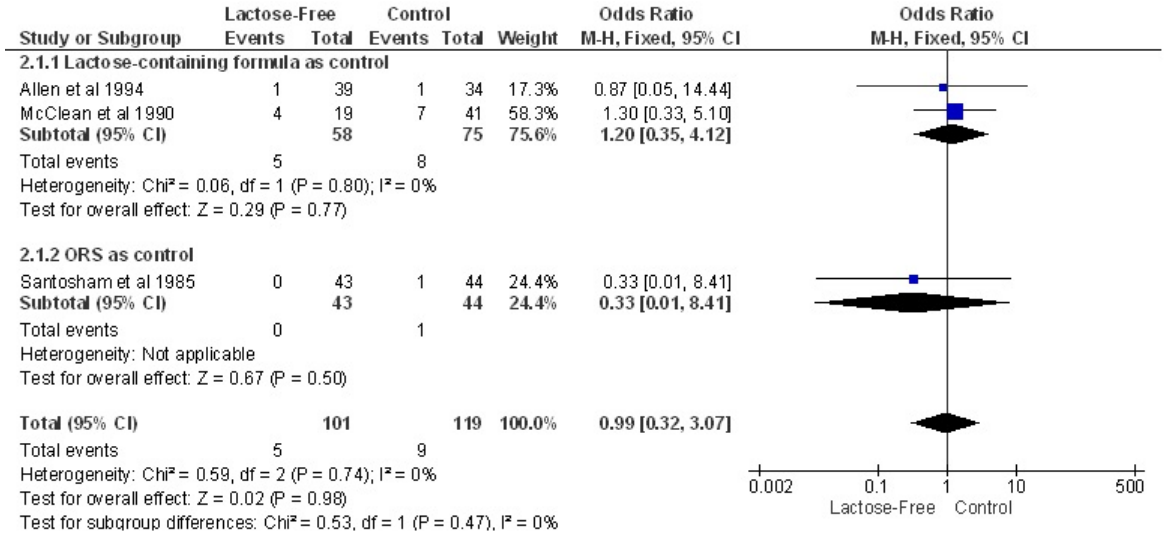

Figure 7. Forest plot of the odds ratio in persistent vomiting between the lactose-free and control groups. A subgroup analysis was made based on a control group approach to therapy in children under 5 years

influenced by subjects' degree of dehydration and their nutritional status. Routine use of lactose-free milk formula in well-nourished children with diarrhea without dehydration or with mild-moderate dehydration did not influence stool frequency or duration of diarrhea.[15] Three of five studies with diarrhea frequency data only included patients with mild-moderate dehydration or no dehydration, and well-nourished children.[5,14,15] The other two studies did not explicitly state subjects' degree of dehydration or their nutritional status.[12,18]

Stool output was significantly lower in lactose-free groups. Improvement in stool output was noticed by day 3 by Lifshitz *et al*.[11] Infants with severe diarrhea tolerated diluted cow's milk poorly in the early phases of the disease. A previous study reported

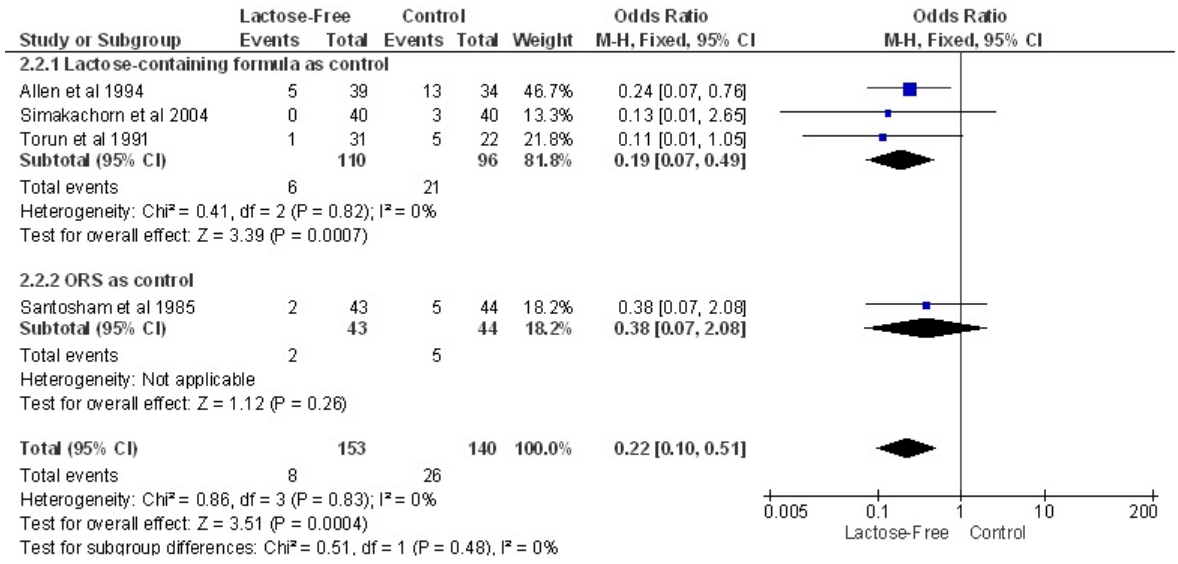

Figure 8. Forest plot of incidence of prolonged diarrhea >7 days with subgroup analysis based on the therapeutic approach of the control group in children under 5 years

no statistically significant difference in stool weight between the lactose-free formula and control groups.[5] However, another study described that patients on lactose-free formula showed significantly less mean stool output than patients on standard therapy, with a reduction in stool output of more than 50%.[10] The improved outcome in the formula-fed (soy based formula) group was probably the result of enhanced absorption of fluids, electrolytes, and nutrients from the gut. The hydrolytic products contained in the formula may have potentiated the absorption of water and electrolytes from the gut.

Giving lactose-free formula has a risk of weight loss, which can be attributed to different types of formulas in the two groups. Four out of seven studies analyzed weight change using a lactose-free sample from a vegetable-based formula,[5,10,16,18,20] while the control group used a cow's milk-based formula. Vegetable protein is less digestible than animal protein and some vegetables cannot be completely hydrolyzed.[20] As such, the formula chosen for managing acute diarrhea in children must contain ingredients that are able to be fully hydrolyzed and are easy to digest. The plant-based formula had a significantly lower number of calories compared to cow's milk formula of the same volume.[22] This difference may lead to different outcomes. Children with acute diarrhea may have anorexia, resulting in the acceptance of a semi-liquid diet less readily than a milk formula due to its greater viscosity and bulk.[13,20] Moreover, palatability is a crucial factor in the dietary management of anorexic children. Proper palatability leads to good food intake, and, thus, weight gain is easier to achieve.[4]

Prolonged diarrhea and vomiting in this study were considered to be treatment failures. Prolonged diarrhea was defined as unresolved diarrhea for more than 7 days in three studies,[5,10,16] and more than 10 days in one study.[12] Prolonged diarrhea is mostly caused by persistent infections with intestinal damage. The most prevalent causes were viral diarrhea, especially rotavirus, norovirus, and sapovirus, followed by other viruses and bacteria.[23,24] These etiologies might cause secondary mucosal damage and further impair intestinal lactase activity,[24] which explains our finding of a significantly lower risk of prolonged diarrhea in the lactose-free group compared to the control. Use of lactose-free formula might allow the intestine to recover and further lessen carbohydrate malabsorption already caused by intestinal infections. Furthermore, two of the included studies reported that 9 of 32 (28%) patients[10] and 19 of 38 (50%) patients[5] were infected by rotavirus. Simakachorn *et al.*[5] also stated that diarrhea duration in their rotavirus-

infected subjects was significantly reduced by 23.6 hours for those using lactose-free formula. This further strengthens our finding that lactose-free formula might help to reduce the duration of diarrhea and lower the risk of having prolonged diarrhea > 7 days.

The mean episodes of vomiting was identical in the lactose-containing and lactose-free groups. One subject with persistent vomiting was found in both groups.[16] McClean *et al.* [18] reported that concurrent symptoms of vomiting, fever, and anorexia were similar in the three groups. The number of children who continued to vomit after the introduction of the feeds was not significantly different between groups. Persistent vomiting in the soy-formula group may have been due to an intolerance to soy protein.[10]

A limitation of this study was that the formula used in the lactose-free and control groups may have differed in their nutritional content, besides their lactose content. Data collection, such as stool output and weight gain, was also carried out at different times, which may have affected the final result of this meta-analysis.

In conclusion, lactose-free formula as dietary management for acute diarrhea in children can reduce stool output and the incidence of persistent diarrhea for more than seven days. Further studies with longer follow-ups are needed to evaluate long-term results such as feeding problems, morbidity, and mortality.

Conflict of interest

None declared.

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