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Original Article

Effectiveness of lactose-free formula in management of acute rotavirus diarrhea

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Abstract

Background Acute rotavirus diarrhea causes mucosal destruction, blunted villi, villus shortening, and death of cells. The process also decreases lactose secretion which responsible in lactose absorption. Non-absorbed lactose then causes the progression of osmotic and secretory diarrhea causing delayed recovery. Lactose-free formula may decrease lactose, thus shortened the duration of diarrhea episode.

Objective To compare the cure rate and duration of acute rotavirus diarrhea in children treated with lactose-free formula and lactose-containing formula.

Methods A randomized, double-blind controlled trial was performed to infants and children aged ≥ 6 to 59 months old with acute rotavirus diarrhea accompanied with mild or moderate dehydration that were admitted to pediatric gastroenterology division. Latex agglutination test was used to detect rotavirus. After an appropriate rehydration therapy had been done, they were fed with either lactose-free formula (n = 29) or lactose-containing formula (n = 31). Comparisons between duration of diarrhea, weight gain, and defecation frequency were made. Statistical analysis for comparing the two groups were independent t-test and multivariate analysis (Cox regression). Statistical significant was defined if $P < 0.05$ with 95% confidence interval.

Results The mean duration of diarrhea in lactose-free formula group was 57.59 hours (SD 9.40) and lactose-containing formula was 85.97 hours (SD 13.94), mean difference was 28.38 hours (SE 3.09) [P = 0.001; (95% CI 22.19 to 34.56)]. Decrease in stool frequency was found significantly in the lactose-free formula group. Multivariate analysis (Cox regression) revealed that the intervention was affected significantly.

Conclusion Lactose-free formula may shorten the duration of acute rotavirus diarrhea. **[Paediatr Indones. 2009;49:299-303]**.

Keyword: diarrheal rotavirus, baby formula, randomized controlled trial, double-blind study

Acute diarrhea is one of the main causes of children morbidity and mortality in developing countries, including Indonesia.[1] According to the *Sistem Surveilen Terpadu* in the year of 2000, the incidence of acute diarrhea in Indonesia was 21.45 for every 1,000 children under five.[2] Rotavirus is the leading cause of diarrhea hospitalizations and death among children under five.[3] The Asian Rotavirus Surveillance Network (ARSN) has found that rotavirus to be associated with 45% of diarrhea among children.[4] The study on the burden of rotavirus disease have been conducted at six hospitals in Indonesia, and found that the proportion of children under five who were rotavirus-positive; ranged from 39% to 67%. The proportion of children who were rotavirus-positive at Sanglah Hospital was 61%.[5] Rotavirus diarrhea causes mucosal destruction, blunted villi, villus shortening and death of cells. The process also decreases lactose secretion which responsible in lactose absorption.

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Non-absorbed lactose then causes the progression of osmotic and secretory diarrhea and causing delayed recovery afterwards.[6-8] Lactose-free formula can decrease lactose, thus may shortened the duration of diarrhea episode.

The objective of this study was to compare the cure rate of acute rotavirus diarrhea that was treated with lactose-free formula and lactose-containing formula. The secondary aim was to compare the duration of acute rotavirus diarrhea in children treated with lactose-free formula and lactose-containing formula.

Methods

This study was a double-blind randomized controlled trial, conducted at gastroenterology division, Department of Child Health, Medical School, Udayana University, Sanglah Hospital from June to October 2008. Eligible subject were chosen using consecutive sampling. The study was approved by the Ethics Committee of Medical School, Sanglah Hospital, Denpasar.

The inclusion criteria were children with mild to moderate dehydration due to rotavirus diarrhea, aged 6 to 59 months old, and duration of diarrhea before hospitalization was equal to or less than two days. Patients with complicated diarrhea, breast feeding or treated with oral neomycin, kanamycin, spasmolytic, and anti-secretory were excluded.

Sample size calculation used formula to calculate the mean of two population, with $\alpha = 0.05$; $\beta = 0.2$ and the power was 80%. The formula was:

$$n = \frac{2\,\sigma^2\,(Z_{1-\alpha} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

μ_1 = mean duration of diarrhea for free-lactose formula = 77 hours.

μ_2 = mean duration of diarrhea for lactose containing formula= 100.2 jam.

n = 27 + drop out 10% = 30. Total subjects was 60.

In this research "acute" rotavirus diarrhea was defined as the diarrhea that is caused by rotavirus in less than seven days. Duration of diarrhea in the hospital was counted as the time consumed until the consistency of the stool become normal and defecation frequency reduced to ≤ 3 times/day.

Body weight gain was the difference between body weight after rehydration therapy and body weight measured when the subject was discharged. Diarrhea with complication was defined as diarrhea episode that was accompanied with direct effect of acute diarrhea such as severe dehydration, metabolic acidosis, seizure, and paralytic ileus. Diarrhea with problems was defined as diarrhea episode accompanied with systemic disease, severe malnutrition, and congenital gastrointestinal disorders, respiratory infection, anemia, vitamin A deficiency, severe dysentery, measles and in chemotherapy treatment. Latex agglutination test was used to detect rotavirus on the feces.

Total study subjects was 60 infants and children randomly allocated using permuted block randomization to receive either lactose-free formula or lactose-containing formula. Lactose-free formula group comprised 29 subjects while 31 subjects were lactose-containing formula group. Blinded was done by giving codes to either lactose-free formula or lactose-containing formula. Researchers, nurses or the subjects knew about the codes. The codes were opened at the end of the study. All subjects were managed accordance to standard therapy. After appropriate rehydration therapy, latex agglutination test was done to detect rotavirus on the feces. Subjects were fed either a lactose-free formula or lactose-containing formula by researcher. A lactose-free formula contained; carbohidrate (maltodextrin) (7 gram/100 ml), protein (2 gram/100 ml), and fat (4 gram/100 ml). Lactose-containing formula contained carbohydrate (lactose) (11 gram/100 ml), protein (2 gram/100 ml), and fat (3 gram/100 ml). Observation was done six-hourly, while evaluation and measurement of body weight were done after the end of the study.

Data was analyzed using computer. Efficacy of treatment was analyzed by independent t-test to compare diarrhea duration, weight gain, defecation frequency and time needed for the stool to become normal consistency. The cure rate of rotavirus diarrhea between two group showed by Kaplan-Meier curve. We made adjustment on confounding variables of diarrhea duration between two group using Cox-regression analyses. Statistical significant was defined if $P < 0.05$ with 95% CI.

Results

During the study, there were 121 subjects, aged 6-59 months old admitted to Department of Child Health, Sanglah Hospital due to acute diarrhea. Sixty two subjects were suffered from acute rotavirus diarrhea but two subjects refused to participate in the study. As a result, 60 subjects were enrolled in the study **(Figure 1)**.

Mean age of lactose-free formula group was 16.97 months (SD 12.01) while that in the lactose-containing formula group was 19.23 months (SD 10.10). Baseline characteristics of those two groups are shown in **Table 1**. All of the subjects did not have any history of using kanamycin or neomycin before admitted to hospital.

The mean duration of diarrhea in lactose-free formula group was 57.59 hours (SD 9.40) while lactose-containing formula was 85.97 hours (SD 13.94), [mean difference = 28.38 hours (SE 3.09); (95% CI 22.19 to 34.56); P =0.001]. Mean duration of diarrhea was significantly shorter in the lactose-free formula group compared to lactose-containing formula group. Body weight gain between two groups at the time of hospital discharge was not significantly different [mean difference = 0.03 kg (SE 0.03); (95% CI -0.04 to 0.10); P = 0.384]. Frequency of defecation was significantly lower in the lactose-free formula group compared to lactose-containing formula [mean difference = 9.64 times (SE 1.10) (95% CI 7.44 to 11.84); P = 0.001]. Time needed for the stool to become normal consistency was significantly shorter in the lactose-free formula group compared to lactose-containing formula [mean difference = 29.93 hours (SE 3.41) (95% CI 23.10 to 36.76); P = 0.001]. The outcome was shown in **Table 2**.

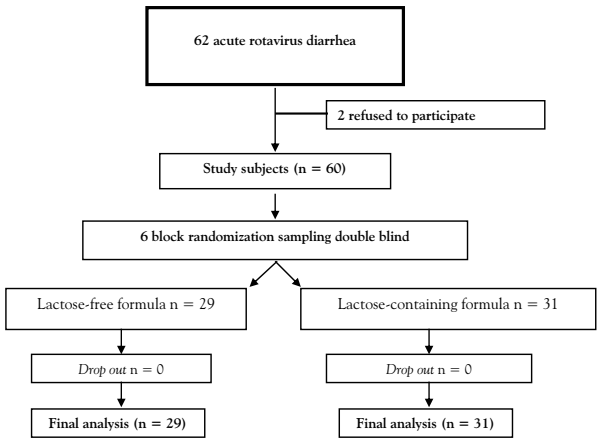

Figure 1. The schematic of enrollment, randomization, follow up, and analysis of the study subject

Based on Kaplan-Meier analysis, cure rate of diarrhea was significantly shorter in the lactose-free formula group compared to lactose-containing formula **(Figure 2)**. Mean survival time was 57.59 hours, (95% CI 54.16 to 61.01; P = 0.001) in lactose-free formula group and mean survival time was 85.97 hours (95% CI 81.06 to 90.87; P = 0.001) in lactose-containing formula group.

Using multivariate analysis (Cox-regression), we found that duration of diarrhea was only affected significantly by lactose-free formula, while other factors such as age, nutritional status, nutritional intake, pre-hospital diarrhea duration and antibiotics had no significant effects **(Table 3)**.

Discussion

Acute rotavirus diarrhea causes mucosal destruction, blunted and shortened villi, and death of cells, which might responsible for decrement of lactose enzyme production that will lead to the decrement in lactose absorption. Non-absorbable lactose increased the osmotic pressures in the gut, which leads to osmotic diarrhea. Secretory diarrhea may accompany the osmotic diarrhea thus lead to the delayment of recovery afterwards.

This study was to compare the outcome between lactose-free formula and lactose-containing formula in the management of "acute" rotavirus diarrhea. The usage of the lactose-free formula in acute diarrhea management has been reported in several studies, which showed a significant decreased of duration of acute diarrhea compared to lactose containing milk formula.[7]

Sack et al[9] showed that there was no a significant difference in the duration of acute diarrhea using the oral sucrose or glucose electrolytes solution compared to solution given intravenously. The dehydration of the acute diarrhea can be managed by oral sucrose or glucose rehydration therapy thus indicates that in the acute rotavirus diarrhea, malabsorption occurs.

Our study showed that duration of rotavirus diarrhea in the lactose-free formula group was shorter

Table 1. Baseline characteristics of subject with acute rotavirus diarrhea in lactose-free formula and lactose containing formula

Characteristics	Lactose-free formula (n=29)	Lactose-containing formula (n=31)
Age (month), mean (SD)	16.97 (12.01)	19.23 (10.10)
Boys, n (%)	14 (23.3%)	14 (23.3%)
BW (kg) at admission, (SD)	9.4 (2.2)	9.8 (2.4)
Pre-hospital diarrhea frequency, mean (SD)	10.10 (1.76)	9.74 (1.84)
Pre-hospital diarrhea (hours), mean (SD)	30.97 (9.64)	29.71 (11.27)
Volume formula consumed (ml), mean, (SD)	200.72 (26.70)	209.97 (30.70)
Nutritional status		
Overweight and wellnourhised, n (%)	24 (40)	20 (33.3)
Mild malnutrition, n (%)	5 (8.4)	11 (18.3)
Nutritional diet		
poridge	5	1
poridge + steam rice	3	3
steam rice	9	13
table food	12	14
Antibiotics before admission, yes, n (%)	11 (18.3)	12 (20)
Simptomatics before admission, no, n (%)	29 (48.3)	31 (51.7)
Zinc preparation, yes, n (%)	29 (48.3)	31 (51.7)

Table 2. The independent t-test comparing diarrhea duration, weight gain, defecation frequency and time need for reaching the normal stool consistency

	lactose-free formula (n=29)	lactose containing formula (n=31)	*P*	Mean different (95% CI)
Hospital diarrhea duration (hours), mean (SD)	57.59 (9.40)	85.97 (13.94)	0.001	28.38 hours (22.19 to 34.56)
Time need for reaching the normal stool consistency (hours), mean (SD)	41.06 (11.16)	71.00 (14.84)	0.001	29.93 hours (23.10 to 36.76)
Weight gain (kg), mean (SD)	0.10 (0.15)	0.13 (0.14)	0.384	0.03 kg (-0.04 to 0.10)
Defecation frequency, mean (SD)	15.59 (3.68)	25.23 (4.71)	0.001	9.64 times (7.44 to 11.84)

Tabel 3. Inter-variable connection that affected acute rotavirus diarrhea cure rate in lactose free formula vs lactose containing formula group

	B	SE	*P*	Exp (B)	95% CI for Exp (B)
Intervention	-3.078	0.53	0.001	0.046	0.016 to 0.13
Nutritional status					
Wellnourhised and overweight	-2.44	0.314	0.436	0.783	0.423 to 0.845
Antibiotics before admission	0.146	0.300	0.626	1.157	0.643 to 2.084
Pre-hospital diarrhea	-0.014	0.014	0.340	0.987	0.960 to 1.014
Age	0.001	0,017	0.992	1.000	0.967 to 1.034
Diet intake					
poridge	0.672	0.633	0.288	1.959	0.566 to 6.779
poridge + steam rice	-0.619	0.613	0.312	0.538	0.162; 1.790
steam rice	-0.054	0.409	0.894	0.947	0.425; 2.109

B= coeficient of Cox regression; *P*= probability, Exp (B) = Odd Ratio; 95% CI= Confident interval 95%

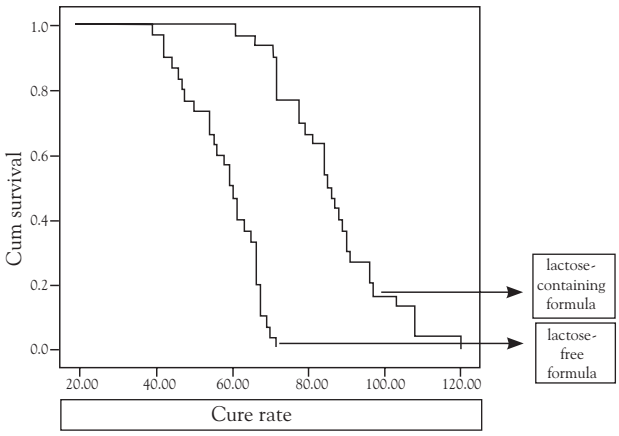

Figure 2. Kaplan Meier survival curve of cure rate of acute rotavirus diarrhea in the lactose free formula and lactose-containing formula group

compared to lactose-containing formula, and the difference was statistically significant. Our result were similar with those of Simakachron et al[7] who gave lactose-free formula in patients with acute rotavirus diarrhea resulted in shorter diarrhea duration. Meanwhile, study by Lazano et al[10] showed different result. In that study, there was no significant difference in the duration of acute diarrhea in lactose-free group compared to lactose-containing formula group. This result was probably due to small number of sample and did not mention any etiology of diarrhea.

In this study, the lactose-free formula group had smaller number in diarrhea frequency compared to lactose-containing formula group, and the different was statically significant. The similar result was also reported in the study done by Santosham et al[11].By using lactose-free formula after rehydration therapy, this study showed a decreased in diarrhea frequency. Simakachorn et al[7] also get the same result by using lactose-free formula in acute rotavirus diarrhea.

Body weight gain at the end of the study was not statistically significantly different between the lactose-free formula group and lactose-containing formula group. In Simakachorn et al[7], the increased of body weight after two days observation was not statistically significantly different. This matter was possibility caused by increasing body weight is influenced by many factors such as other nutrition during diarrhea and oral rehydration.

In our study, we did not find any adverse events due to lactose-free formula or lactose-containing formula. The limitation of this study was the taste of the formula used were different, and the immunity status was not determined. In conclusion, lactose-free formula may shorten the duration of acute rotavirus diarrhea.

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