

Double blind clinical trial on a lactose-free and a lactose-containing formula in the treatment of acute diarrhea in children

Sri Lestari, Agus Firmansyah, Zakiudin Munasir

ABSTRACT

Background Lactose intolerance is a common complication of diarrhea in young children particularly that due to rotaviral infection. A meta-analysis study evaluated the use of undiluted lactose containing formula or cow's milk during an episode of diarrhea. It was concluded that routine dilution of milk and the use of lactose-free milk formula are not necessary.

Objective To evaluate the effect of lactose free formula compared with lactose-containing milk formula during acute diarrheal episode in outpatient setting.

Methods A total of 56 children with acute diarrhea with mild-moderate or no dehydration attending to the outpatient clinic were randomly assigned to receive a lactose-free formula (Nestle Nan[®] free lactose) or lactose-containing milk formula (Nestle Nan 2[®] formula) after initial rehydration. Comparisons of stool frequency, duration of diarrhea and treatment failure rates were noted. Treatment failure was defined as clinical requirement for intravenous infusion after rehydration or prolonged diarrhea (>7 days).

Results The duration of diarrhea was similar between the two groups (P=0.195) in spite of two children who received lactose free formula did not resolve from diarrhea within 7 days of treatment. The median of stool frequency was indifferent in the two groups (P=0.199) in rotavirus gastroenteritis; there were no differences in the duration of diarrhea or the stool frequency.

Conclusion Children without dehydration or with mild dehydration tolerated to lactose-containing formula as well as lactose-free formula for the treatment of acute diarrhea [Paediatr Indones 2006;46:271-275].

Keywords: diarrhea, milk formula, lactose-free formula, lactose intolerance.

Acute diarrheal disease is still a major public health problem in developing countries.¹ In Indonesia, the disease consistently ranked among the top 5 causes of morbidity and mortality of children between the age of 0-4 years.² Lactose intolerance is a common complication of diarrhea in young children particularly that due to rotaviral infection.^{3,4} It occurred when rotavirus destroyed the villus cells and diminished disaccharide, especially lactose absorption.^{5,6} This condition had been the reason to delay refeeding milk-based formula; when feeding is introduced, often began with low-lactose formula or lactose-free formula. Suharjono *et al*,⁷ found that the incidence of lactose intolerance was 52.8% in 838 patients with acute diarrhea and Hegar *et al*⁸ found 23.1% lactose intolerance of hospitalized patients. Since it causes a high incidence of lactose intolerance, we had been using low-lactose formula or dilution of milk in the treatment of acute diarrhea in our practice, especially for children with clinically presentation of lactose intolerance.

From the Department of Child Health, Medical School, University of Indonesia, Jakarta, Indonesia.

Reprint request to: Sri Lestari, MD, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital Jakarta, Jl. Salemba No. 6, Jakarta 10430, Indonesia. Email: sriaisha@yahoo.co.id

Recently Brown *et al*⁹ performed a meta-analysis study that evaluated the use of undiluted lactose containing formula or cow's milk during an episode of diarrhea. It was concluded that routine dilution of milk and the use of lactose-free milk formula are not necessary. No controlled trial to compare lactose-free milk formula with lactose-containing formula during acute diarrhea in our outpatient's case had been reported. At the same time, we need the data to change our policy. The purpose of this study was to compare the effect of lactose-free milk formula with lactose-containing formula during acute diarrhea in the outpatient clinic setting.

Methods

This study was a randomized, double blind controlled clinical trial conducted at the outpatient clinic of Cipto Mangunkusumo (CM) Hospital, Jakarta, from July to September 2005. The sample size was 28 patients per treatment group according to standard statistical methods.¹⁰ The inclusion criteria were children aged 6-24 months who suffered from diarrhea (defined as the passage of unusually or watery stools, usually at least three times in a 24 hour period¹¹) for less than 7 days duration, who were not breast fed, with weight-for-age not less than 70% of median of National Center for Health Statistics Standards, and had no intake of any antibiotics during the 7 days preceding enrollment. They were excluded if they had sign of severe dehydration, failed to have their stool specimens taken on the same day of their visits to the clinic, presence of a major systemic illness like pneumonia and sepsis, bloody diarrhea, or if their parents refused to join the study.

The study was approved by The Committee for Medical Research Ethics, Medical School, University of Indonesia. Informed consent was obtained from parents or caregivers of the children who served as subjects in the study. After informed consent was obtained, the parents or caregivers were interviewed to get detailed information, regarding clinical history of the illness. All subjects underwent physical examination to assess clinical status and degree of dehydration (based on the WHO standard¹¹). A stool specimen was collected during enrollment. The specimens were plated at the bedside on Cary Blair transport

media and then plated on Mac Conkey agar to identify Enteropathogenic *E. coli* (EPEC) and on SS agar to identify *Salmonella spp.* Portions of each stool specimen were also tested at the bedside for stool reducing substance using clinitest (Ames, Ltd[®]) and for measuring the pH using pH meter (special indicator, Merck) and the rest for rotavirus antigen using a commercial ELISA preparation (Quick Stripe[®], Savyon).

Oral rehydration therapy was provided according to WHO guidelines (children with mild-moderate dehydration received 75 ml/kg).¹¹ Rehydration was completed within four hours by administering oral rehydration solution (ORS) recommended by WHO. After initial rehydration phase, children were randomly allocated to receive either a lactose-free or a lactose-containing formula. Children were fed with free lactose food as appropriate to age and ORS 10 ml/kg after each watery stool. Milk formula was randomized in blocks of four (two lactose-free Nestle Nan FL[®] and two lactose-containing formula Nestle Nan 2[®]) and coded to ensure sequential distribution. We educated the parents how to manage diarrhea at home before children were discharged from hospital. The parents were asked to record the time, frequency and duration of diarrhea in the research form. The parents were asked to come to the hospital if their children fall into deeper dehydration and could not receive ORS. We monitored the progress of illness by making phone call to the parents or doing home visit everyday.

The total duration of diarrhea was defined as the duration in hours from the time of the first diarrhea to the last watery or loose stool or no stool in 24 hours period. Treatment failure was defined as clinical requirement for intravenous infusion after rehydration or prolonged diarrhea (>7 days). Frequency of diarrhea was defined as number of stools in hour from the first diarrhea until diarrhea stops.

The primary outcome measurement in this intervention was the duration of diarrhea and stool frequency. A therapeutic failure rate was the secondary outcome.

Data collected from completed forms were processed using computer program SPSS 12.0. An independent t-test was performed if the data were continuous variables with normal distribution and the Mann-Whitney test was used when the distribution was not normal. Probabilities (P) less than 0.05 were considered statistically significant.

Results

The characteristics of the 28 children on admission are showed in **Table 1**.

None of the differences between the groups was statistically significant. Twenty five subjects had rotavirus in their stool. EPEC was only found in 1 subject. Most subjects were well-nourished. Twenty nine subjects showed clinical signs of mild-moderate dehydration.

TABLE 1. CHARACTERISTICS OF SUBJECTS AT THE TIME OF ADMISSION

	Lactose containing formula n	Lactose free formula n	Total
Age (months)			
6-11	13	11	24
12-24	15	17	32
Sex			
Male	21	18	39
Female	7	10	17
Nutritional status			
Well-nourished	20	18	38
Undernourished	8	10	18
Degree of dehydration			
No dehydration	16	11	27
Mild-moderate	12	17	29
Duration of symptoms before admission (hours)			
24-72	25	24	49
96-168	3	4	7
Frequency of diarrhea (times/day)			
<5	13	8	21
5-10	12	16	28
>10	3	4	7
Stool culture			
Negative	28	27	56
Positive	-	1	-
Rotavirus			
Negative	17	14	31
Positive	11	14	25
Reducing substance			
Negative	19	20	39
Positive	9	8	17
Stool pH			
<6	13	12	25
≥6	15	16	31

TABLE 2. DURATION OF DIARRHEA ACCORDING TO MILK FORMULA

	Mean (SD) (hours)	Median (range) (hours)	P
Lactose-containing formula (n=28)	106.5 (29.2)	102.5 (55-160)	0.195
Lactose-free formula (n=28)	116.8 (29.1)	120 (68-170)	

Unpaired t test

TABLE 3. DURATION OF ROTAVIRUS DIARRHEA ACCORDING TO MILK FORMULA

	Mean (SD) (hours)	Median (range) (hours)	P
Lactose-containing formula (n=11)	110.3 (28.0)	110 (55-154)	0.288
Lactose-free formula (n=14)	120.8 (20.5)	120 (92-1154)	

Unpaired t test

TABLE 4. STOOL FREQUENCY ACCORDING TO MILK FORMULA

	Mean (SD) (times/day)	Median (range) (times/day)	P
Lactose-containing formula (n=28)	4.0 (1.5)	3.4 (3-10)	0.199
Lactose-free formula (n=28)	4.5 (1.9)	4.0 (3-10.5)	

Mann-Whitney test

Table 2 shows the mean duration of diarrhea in subjects receiving lactose-free formula compared with those receiving lactose-containing formula (116.8 hours vs 106.5 hours; $P=0.195$). The duration of rotaviral diarrhea is also similar between the two group ($P=0.288$) (**Table 3**). There were no significant differences between the two groups in stool frequency (4 times/day vs 3.4 times/day; $P=0.199$) (**Table 4**).

Two of the subjects receiving lactose-free formula were considered to be treatment failure. These subjects had continuous diarrhea for more than seven days (7 days 2 hours).

Discussion

In 2003, an estimated 1.87 million children below 5 years old in developing countries died from diarrhea. Eight out of 10 of these deaths occurred in the first two years of life.¹¹ The incidence of diarrhea was higher in infant aged 6-11 months followed by children aged 12-24 months.² This is in accordance with the findings of Ariani *et al*¹² and Tjitrasari *et al*¹³ in their studies at CM Hospital that the incidence rate of acute diarrhea was higher among the 6-11 months age group than that in the 12-24 months age group. Infants who are younger than 6 months are protected by transplacental antibody and breast feeding, whereas 80-100% of older children are

protected by antibody produced by previous infection.^{5,14} As the children begin to crawl, contamination of wearing food and poor domestic hygiene give the chances to get diarrhea.⁵ On the other hand, we found that the incidence rate of diarrhea was higher among the 12-24 months age group than that in the 6-11 months age group. We excluded breast-fed children mostly under 12 months of age,¹⁵ because breast feeding exerts a beneficial effect on the course and outcome of acute diarrhea by reducing the number and volume of diarrhea stools.¹⁶ In a case control study on Bangladeshi children <3 years, discontinuation of breast feeding during the illness was associated with a five-fold increase in the incidence of dehydration.¹⁷ Furthermore, Hafeehee *et al*¹⁸ found that in rotaviral gastroenteritis, breast feeding significantly reduced the duration of acute diarrhea compared to cow's milk formula feeding. We also excluded children who suffered from severe malnutrition because of gastrointestinal mucosal atrophy will increase the possibility of lactose malabsorption. Most of the patients in our study were well-nourished.

Lactose intolerance is a common complication of some episodes of diarrhea. Increase rates of lactose malabsorption have been demonstrated in acute diarrhea, particularly in children with rotaviral infection. Our study identified rotaviral infection in 25 patients. This finding was still within the range with other findings i.e. Frühwirth *et al*¹⁹ (Austria) and Hegar *et al*²⁰ (Indonesia) who found the prevalence of 34% and 61.1%, respectively.

Recently Tjitrasari *et al*¹³ identified 35.7% rotaviral infection in pediatric outpatient. We just identified 1.7% EPEC as the causing factor of diarrhea. This data is similar to other studies which showed the rotavirus as the most common cause of acute diarrhea.^{5,12,20}

The appropriate use of lactose-containing formula, non human milk for young children with acute diarrhea is still in debates. Whereas some clinicians routinely withdraw milk from the diets of children during diarrhea, primarily to avoid the potential consequences of lactose malabsorption, others continue to offer milk without apparent evidence of increased clinical complications. As mentioned above, a meta-analysis performed by Brown *et al*⁹, concluded that routine use of lactose-free milk formula during an epi-

sode of diarrhea is not necessary.

In contrast, Yasman *et al*²¹ found that the duration of diarrhea with lactose intolerance was shortened by 17.5 hours after receiving lactose-free formula compared to that receiving lactose-containing formula. This study was done on hospitalized patients with various degree of dehydration. Children with severe dehydration were included in this study. This is similar with that found by Simakachorn *et al*.²²

Our study showed that there were no differences in stool frequency or in the duration of diarrhea between lactose-free formula and lactose-containing formula. It is likely that the degree of dehydration of our patient was in a level of no dehydration or mild-moderate dehydration. Besides, most of our patients were well-nourished. Therefore, they could recover better from diarrhea. When substantial absorptive function is lost because of an inflammatory lesion, enteral nutrition is generally still well tolerated. This is assumed that viral infection of gastrointestinal tract may not affect all regions of the small bowel equally and the residual function is sufficient for successful enteral nutrition.²³ The mixed feeding of milk with other foods resulted in a more absorption of lactose than when milk is given alone.^{9,23} We used mixed diet in our study because we believe that the lactose load may be decreased by adding other food stuffs to the milk.

The treatment failure rate in our study was very small (only 2 patients who received lactose-free formula). This is unlikely to be of clinical importance because the duration of diarrhea was only 7 days and 2 hours. We succeeded to treat the diarrhea because we followed the WHO guidelines to use oral rehydration therapy for children with acute diarrhea. In addition, the new standard WHO-ORS reduces the incidences of vomiting by 30% and stool volume by 20% and also reduces the requirement of intravenous rehydration therapy by 33%.¹¹

We concluded that routine use of lactose-free milk formula in well-nourished children with diarrhea without dehydration or with mild-moderate dehydration does not influence the stool frequency and the duration of diarrhea.

Considering many limitations within this study, there is a need to do further multicenter study to give a better result. Stool output, treatment failure rate, stool frequency and duration of diarrhea must be more considered in the next study.

Acknowledgments

The authors wish to thank PT. Nestle Indonesia that provided financial support for this study.

References

1. WHO. Major causes of death among children under five world wide 2001. Available from URL: www.who.int/child-adolescent-health/overview/child-health/map00world.jpg.andmap01world.jpg.
2. Afifah T, Djaja Sarimawar, Irianto Joko. Kecenderungan penyakit penyebab kematian bayi dan anak balita di Indonesia: 1992-2001. *Bul Penel Kesehatan* 2003;31 :48-59.
3. Firmansyah A. Kontroversi mengenai formula rendah dan bebas laktosa dalam tata laksana diare pada anak. *Maj Kes Masy Indones* 2002;1:27-35.
4. Lebenthal E, Kretchmer N, Alliet P. Lactase deficiency, lactose malabsorption and lactose intolerance. In: Lebenthal E, editor. *Textbook of gastroenterology and nutrition in infancy*. New York: Raven Press; 1989. p. 459-72.
5. Departemen Kesehatan RI. Epidemiologi dan etiologi diare. In: Ditjen PPM & PLP Departemen Kesehatan, editor. *Buku ajar diare*. Jakarta: Depkes; 1999. p. 3-14.
6. Frye RE. Diarrhea. Available from <http://www.emedicine.com>.
7. Suharjono, Sunoto, Sutedjo. Lactose intolerance in Indonesian children. *Ann Inst Child Health* 1971;1:7.
8. Hegar B, Firmansyah A. Evaluasi penderita diare yang dirawat di bangsal anak RSCM 1994. *Maj Kes Masy Indones* 1995;8:563-5.
9. Brown KH, Reerson JM, Fontaine O. Use of nonhuman milks in the dietary management of young children with acute diarrhoea: A meta-analysis of clinical trials. *Pediatrics* 1994;93:17-27.
10. Madiyono B, Mz Moeslichan S, Sastroasmoro S, Budiman I, Purwanto HS. Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. *Dasar-dasar metodologi penelitian klinis*. 2nd ed. Jakarta: CV Sagung Seto; 2002. p. 259-86.
11. World Health Organization. *The treatment of diarrhea: A manual for physicians and other senior health workers*. WHO/CDD/SER/80.2 rev.3. Geneva, Switzerland: World Health Organization, 1995.
12. Ariani A. Gambaran diare akut serta hubungannya dengan gejala yang ditemukan pada anak 0-2 tahun yang dirawat di SMF anak RSUPNCM periode September 1996-Januari 1997 [thesis]. Jakarta: Bagian Patologi Klinik FKUI, 1998.
13. Tjitrasari T, Firmansyah A, Chair I. Clinical manifestations of rotavirus diarrhea in the outpatient clinic of Cipto Mangunkusumo Hospital, Jakarta. *Pediatr Indones* 2005;45:69-75.
14. DuPont HL, Miranda AG. Small intestine: Infectious with common bacterial and viral pathogens. In: Yamada T, Alpers DH, Powell DW, Owyang C, Silverstein EE, editors. *Textbook of gastroenterology*. 2nd ed. Philadelphia: JB Lippincott; 1995. p. 1605-29.
15. Santoshan M, Foster S, Reid R, Bertrando R, Yolken R, Burns B, et al. Role of soy-based, lactose-free formula during treatment of acute diarrhea. *Pediatrics* 1985;76:292-8.
16. Khin-Maung-U, Nyunt-Nyunt-Wai, Myo-Khin, Mu-Mu-Khin, Tin-U, Thane-Toe. Effect of clinical outcome of breast feeding during acute diarrhea. *British Medical Journal* 1985;290:587-9.
17. Faruque AS, Mahalabis D, Islam A, Haque SS, Hasnat A. Breast feeding and oral rehydration at home during diarrhea to prevent dehydration. *Arch Dis Child* 1992;67:1027-9.
18. Haffejee IE. Cow's milk-based formula, human milk, and soy feeds in acute infantile diarrhea: A therapeutic trial. *J Pediatr Gastroenterol Nutr* 1990;10:193-8.
19. Frühwirth M, Karmaus W, Moll-Schüler, Brösl S, Mutz I. A prospective evaluation of community acquired gastroenteritis in paediatric practices: Impact and disease burden of rotavirus infection. *Arch Dis Child* 2001;84:393-7.
20. Hegar B, Kadim M, Pasaribu A. Karakteristik mikroorganisme saluran cerna pada anak dengan diare akut. *Maj Kedokt Indon* 2004;54:367-71.
21. Yasman. Perbandingan manfaat pemberian susu semula, susu rendah laktosa dan susu bebas laktosa pada diare akut [thesis]. Palembang: Bagian Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Sriwijaya Palembang 1997.
22. Simakachorn N, Tonoenyai Y, Tongtan O, Varavithya W. Randomized, double-blind clinical trial of a lactose-free and a lactose-containing formula in dietary management of acute childhood diarrhea. *J Med Assoc Thai* 2004;87:641-9.
23. Duggan C, Nurko S. Feeding the gut: The scientific basis for continued enteral nutrition during acute diarrhea. *J Pediatr* 1997;131:238-46.