

Efficacy of synbiotic treatment in children with acute rotavirus diarrhea

Made Ratna Dewi¹, Yati Soenarto², I Putu Gede Karyana¹

Abstract

Background Diarrhea is one of the major causes of morbidity and mortality in children throughout the world, mostly due to rotavirus infection. In daily practice, we routinely use the World Health Organization *Five steps for managing acute diarrhea*. This practice has shown great success in diarrhea management, but concerns remain on reducing the duration of diarrhea to prevent complications. Synbiotics can reduce the severity of diarrhea. However, there has been limited data on synbiotic therapy for treating acute rotavirus diarrhea in children.

Objective To compare the durations of acute rotavirus diarrhea treated with synbiotics vs. placebo.

Methods This study was a randomized, double-blind, clinical trial, performed at the Pediatric Gastrohepatology Division, Sanglah and Wangaya Hospitals in Denpasar. Subjects were children aged 6 to 59 months with acute rotavirus diarrhea. Rotavirus was diagnosed by immune chromatography assay. The synbiotic group received probiotic comprised of *Lactobacillus sp.*, *Streptococcus sp.*, *Bifidobacterium sp.* (total viable count 1.00×10^9 CFU per dose), and prebiotic consisted of 990.00 mg fructooligosaccharide (FOS). The placebo consisted of lactose monohydrate packaged similarly as the synbiotics. Subjects orally ingested 1 pack per day for 5 days.

Results Seventy children with acute rotavirus diarrhea was involved in this study. The median duration of diarrhea in the synbiotic group was 50.0 (SE 1.1); 95%CI 47.9 to 52.1 hours, while that of the placebo group was 63.0 (SE 5.9); 95%CI 51.4 to 74.6 hours. Based on Kaplan-Meier survival analysis, the duration of diarrhea in the synbiotic group was significantly shorter than that of the placebo group (log-rank test $P < 0.0001$).

Conclusion In children with acute rotaviral diarrhea, synbiotic reduces the duration of diarrhea compared to placebo. [Paediatr Indones. 2015;55:74-8.].

Keywords: acute rotavirus diarrhea, synbiotic, randomized clinical trial

The WHO definition of acute diarrhea is the release of soft or liquid stools with a frequency of three times or more per day, with or without blood or mucus in the stool, and lasting less than 2 weeks.¹ Diarrhea causes death in more than 3 million children every year.² The major cause of acute diarrhea in children is viral (60%-70%).³ Rotavirus is the most common virus associated with acute diarrhea. The main goal in implementation of the current management is to decrease morbidity. Mortality decrease can be achieved through effective governance management.^{4,5} The Department of Health launched the five steps to overcome diarrhea (“*Lima Lintas Diare*”).⁶ Management using the existing standards has been largely successful, but duration of diarrhea should be shortened to prevent complications. Intestinal mucosal healing may occur within a few days, but total healing takes more than four weeks. Probiotics can help the healing process of the intestinal mucosa.⁷

From the Department of Child Health, Udayana University Medical School /Sanglah Hospital, Denpasar¹ and Gadjah Mada University, Sardjito Hospital, Yogyakarta².

Reprint requests to: Made Ratna Dewi, Department of Child Health, Udayana University Medical School, Sanglah Hospital, Jl. Pulau Nias Denpasar, Bali 80114. Tel./Fax: +62361-244038. E-mail: ratnaupiq@yahoo.com.

Synbiotics (eubiotics) are a combination of probiotics and prebiotics. The advantage of this combination for bacterial growth, such as bifidobacterium and fructooligosaccharide (FOS) or *Lactobacillus* and lactitol, is to improve the survival of the probiotics. The specific substrates contained in synbiotics act to accelerate fermentation, benefitting the body.⁷

Previous studies have shown synbiotics to significantly shorten the duration of diarrhea compared to placebo, though not for any specific diarrheal etiology.^{8,9} However, there has been limited data on the efficacy of synbiotic therapy in treating acute rotaviral diarrhea in children. We conducted this study to compare the effects of synbiotics to that of placebo in decreasing the duration of rotaviral diarrhea.

Methods

This double-blind, randomized controlled trial was performed at the Pediatric Gastrohepatology Division of Sanglah and Wangaya Hospitals in Denpasar from May 1, 2012-April 30, 2013.

Subjects were children aged 6 to 59 months with acute rotaviral diarrhea and hospitalized during the study period. Subjects were selected by consecutive sampling. The inclusion criteria were children with acute rotaviral diarrhea and mild to moderate dehydration, length of diarrhea before hospital admission was ≤ 48 hours, had no other problems in addition to the diarrhea, and parents/guardians provided informed consent. The exclusion criteria were acute diarrhea with complications, had taken diarrheal medications before hospital admission, and had probiotic or prebiotic treatment before hospital admission. Subjects were distributed by block randomization using six permutations. This randomization was concealed. Sample size was estimated using the hypothesis average of two populations with a 5% significance level, 80% power of the study, mean difference of at least 12 hours, with standard deviations of both groups set at 44 hours. We found the minimum required sample size to be 30 subjects per group.

Acute rotaviral diarrhea was defined as diarrhea lasting up to 7 days and caused by

rotavirus (positive immunochromatography assay examinations). Subjects received either synbiotics or placebo. The probiotic composition in the synbiotic was *Lactobacillus Sp.*, *Streptococcus Sp.*, and *Bifidobacterium Sp.* Total viable count was 1.00×10^9 CFU per dose. The prebiotics consisted of 990.00 mg FOS per dose. The placebo consisted of lactose monohydrate packaged by the same manufacturer, in a similar form, taste, smell, and outer packaging as the synbiotics. Subjects orally ingested 1 pack per day for 5 days. Single pack treatments were mixed with 30 ml of boiled water. The duration of diarrhea during hospitalization was calculated from the first hour of treatment onset until the diarrhea was declared cured. Diarrhea was defined as cured when the patient did not experience loose stools more than 3 times in 24 hours. Nutritional status was determined based on body weight to height/length and weight, according to WHO protocol and classified into the following categories: (1) $> +2$ SD: overweight, (2) -2 until $+2$ SD: well-nourished, (3) -3 until < -2 SD: underweight, (4) < -3 SD: severe malnutrition. The level of dehydration was determined based on WHO guidelines.¹ Therapy was considered to be a failure if the patient did not recover by the 5th day of treatment, or if before the 5th day of treatment the patient experienced complications from the diarrhea, co-morbidities, or death.

Infants and children with acute diarrhea underwent history-taking and physical examinations. Diagnoses were made by the pediatric resident or the physician at the outpatient clinic or the emergency department, using the WHO criteria.¹ After assessment of the degree of dehydration and rehydration efforts had been done, an immunochromatography assay (IA) was performed. Examinations were conducted by the attending physician. Immunochromatography assay examinations using SD rotavirus test kits were used to detect rotavirus antigen in the stool. Patients diagnosed to have acute rotavirus diarrhea were then enrolled based on the inclusion criteria. Written informed consent was provided by subjects' parents. The subjects were then given treatment by the resident on duty at the time. One sachet of the treatment formula or placebo was mixed with 30 ml of water, taken once daily. All study subjects received fluid therapy, nutritional support, and zinc supplementation as an integral part of diarrheal management according

to WHO protocol. We followed up on subjects during their hospitalization and recorded results in a follow-up form.

Statistical analysis was performed with computer program. Normality of the data was tested by Kolmogorov-Smirnov test. Kaplan-Meier survival

analysis was used to assess the diarrhea treatment effect during the follow-up period. Level of significance was accepted to be $P < 0.05$ with a confidence interval of 95%. This study was approved by the Health and Medical Ethics Committee of the Udayana University Medical Faculty/Sanglah Hospital.

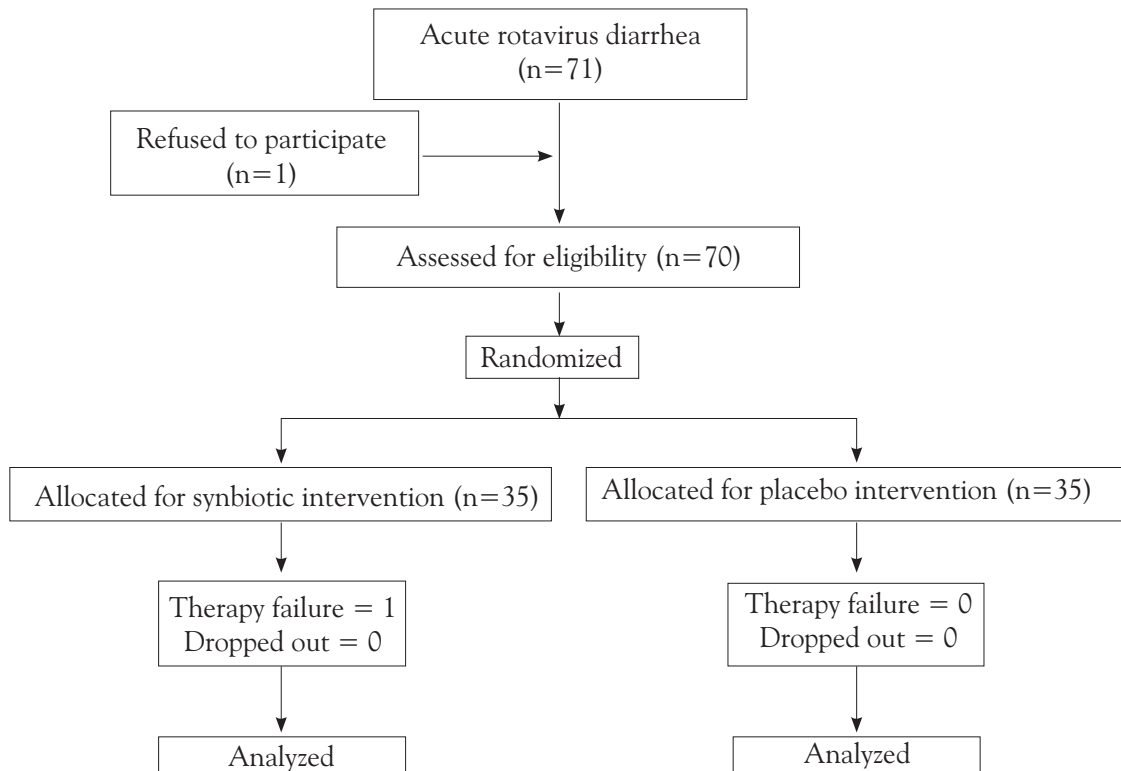


Figure 1. Study scheme

Table 1. Baseline characteristics of subjects

Characteristics	Synbiotic group (n=35)	Placebo group (n=35)
Median age (interquartile), months	15 (10-24)	17 (10-26)
Gender, male, n (%)	21 (60)	19 (54)
Nutritional status		
Well-nourished, n (%)	21 (60)	20 (57)
Undernourished, n (%)	14 (40)	15 (43)
Breastfeeding, n (%)	11 (31)	15 (43)
Median diarrheal frequency before admission (interquartile), times/day	5 (5-7)	7 (5-8)
Median diarrheal duration before admission (interquartile), hours	36 (24-48)	36 (24-48)

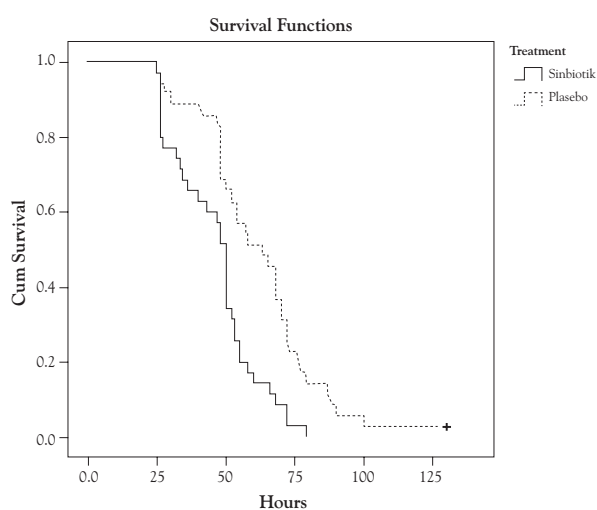


Figure 2. Kaplan-Meier curve comparison between the synbiotic and placebo groups for duration of diarrhea in 5 days of treatment.

Results

During the study period, 71 children aged 6-59 months met the study criteria of acute rotaviral diarrhea. One child refused to participate, so we had 70 children for the sample study. In the placebo group, one subject had therapy failure. The study scheme is shown in **Figure 1**.

The characteristics of the subjects are presented in **Table 1**. Subjects from both the synbiotic and placebo groups had similar characteristics. In this study, 57% of the subjects were male. The median age of all subjects was 15.5 (interquartile range 10-24) months, while that of the synbiotic group was 15 (interquartile range 10-24) months and the placebo group was 17 (interquartile range 10-26) months.

The median times for resolution of the diarrhea were 50.0 (SE 1.1); 95%CI 47.9 to 52.1 hours in the synbiotic group and 63.0 (SE 5.9); 95%CI 51.4 to 74.6 hours in the placebo group. Based on the Kaplan-Meier survival curve, 50 hours after the administration of synbiotics, 50% of the patients experienced healing. The recovery time for the synbiotic group was 13 hours shorter than that of the placebo group, a statistically significant difference in duration of diarrhea (log-rank test $P < 0.0001$) (**Figure 2**). However, there was little clinical difference as it did not affect the length of hospitalization.

Discussion

Surveys in several Asian countries found that 30-70% of hospitalizations were due to diarrhea caused by rotavirus.¹⁰ A study of the *Asian Rotavirus Surveillance Network* (ARSN) from August 2001 to July 2002 showed the incidences of rotavirus infection in Indonesia to be as high as 53%.¹⁰ A study of rotaviral diarrhea in 2006 was held at 6 hospitals in Indonesia (in Palembang, Jakarta, Bandung, Yogyakarta, Denpasar, and Mataram). The study showed the hospitalization of diarrhea in children under 5 year old was 60% due to rotavirus, and especially in Sanglah Hospital was 61% of all diarrhea cases.¹¹ In our study, 53% of the 133 children met the study criteria of having acute rotaviral diarrhea. Widowati *et al.* showed that more males were affected than females, but the difference was not statistically significant.¹² Of our subjects, 57% were male. Rotavirus can infect all ages, but is most frequently seen in children aged 6-24 months.¹³ Kadim *et al.* also showed that rotaviral diarrhea affected the age group of 12-23 months.¹⁴ The median age of our subjects was 15.5 (10-24) months, the synbiotic group 15 (10-24) months, and the placebo group 17 (10-26) months.

There are a variety of synbiotic mixtures with different strains on the market. To date, few studies have evaluated synbiotic effectiveness for the treatment of diarrhea. Dinleyici *et al.* performed a randomized clinical trial on 3-120 month old children with mild to moderate dehydration of acute diarrheal who took synbiotics consisted of *L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *B. longum*, *E. faecium*, and fructooligosaccharides. Diarrhea in the synbiotic group was 36 hours shorter than in the placebo group ($P < 0.0001$), with mean durations of diarrhea 77.9 (SD 30.5) hours in the synbiotic group and 114.6 (SD 37.4) hours in the placebo group.⁸ Similarly, Vandenplas *et al.* found that children aged 3-186 months with acute diarrhea and mild/moderate dehydration who took synbiotics comprised of *Streptococcus thermophilus*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Bifidobacterium infantis*, and fructooligosaccharides, had one day shorter duration of diarrhea than those in the placebo group.⁹ Both studies were performed in children suffering from acute diarrhea without knowing the etiology. In our study, the synbiotic contained 4.00×10^8 CFU *Lactobacillus casei*,

3.5×10^8 CFU *Lactobacillus rhamnosus*, 1.00×10^8 CFU *Streptococcus thermophiles*, 5.00×10^7 CFU *Bifidobacterium breve*, 5.00×10^7 CFU *Lactobacillus acidophilus*, 4.00×10^7 CFU *Bifidobacterium infantis*, 1.00×10^7 CFU *Lactobacillus bulgaricus*, and 990.00 mg FOS. All subjects were children with acute rotaviral diarrhea.

The US Food and Drug Administration recommends probiotics as a safe supplement. Several clinical trials showed no side effects or health problems.^{9,15} In our study, we observed no side effects from synbiotic use. A limitation of this study was not assessing patients' immune status. In conclusion, synbiotic administration for acute rotaviral diarrhea significantly decreased the duration of diarrhea without side effects. As such, synbiotic administration may be considered as an adjunctive treatment for management of acute rotaviral diarrhea in children.

Acknowledgements

Our sincere gratitude to the physician, and nurses in charge at the Jempiring Ward, Sanglah Hospital and the Kaswari Ward, Wangaya Hospital. We also extend our gratitude to I Gde Raka Widiana, MD for his help in constructing methodology and statistical analyses.

Conflict of interest

None declared

References

1. Farthing M, Linberg G, Dite P, Khalif I, Lindo ES, Ramakrishna BS, et al. Acute diarrhea. WGO practice guidelines; 2008. p. 1-28.
2. Bengmark S, Gil A. Bioecological and nutritional control of disease: Prebiotics, probiotics and synbiotics. *Nutr Hosp*. 2006;21:72-84.
3. Sandhu B, Devadason D. Management of diarrhea. In: Wyllie R, Hyams JS, editors. *Pediatric gastrointestinal & liver disease*. 3rd ed. USA: Saunders Elsevier; 2006. p. 1165-76.
4. Achmadi UF. Harapan pemerintah mengenai peranan kaum profesional dalam mendukung program penyakit saluran cerna anak di era otonomi. In: *Kumpulan Makalah Kongres Nasional II*. Badan Koordinasi Gastroenterologi Anak Indonesia; 2003 Jul 3-5; Bandung. p. 1-16.
5. Widaya WI, Gandhi. Konsistensi pelaksanaan program serta morbiditas dan mortalitas diare di era otonomi dan krisis. In: *Kumpulan Makalah Kongres Nasional II*, Badan Koordinasi Gastroenterologi Anak Indonesia; 2003 Jul 3-5; Bandung. p. 45-53.
6. Direktorat Jendral Pengendalian Penyakit dan Penyehatan Lingkungan Departemen Kesehatan Republik Indonesia. *Lintas diare*. Buku Saku Petugas Kesehatan. 2008. p. 7-18.
7. Collins MD, Gibson GR. Probiotics, prebiotics and synbiotics: approaches for modulating the microbial ecology of the gut. *Am J Clin Nutr*. 1999;69:1052S-7S.
8. Dinleyici EC, Dalgic N, Guven S, Ozen M, Kara A, Arica V, et al. The effect of a multispecies synbiotic mixture on the duration of diarrhea and length of hospital stay in children with acute diarrhea in Turkey: single blinded randomized study. *Eur J Pediatr*. 2013;172:459-64.
9. Vandenplas Y, De Hert SG, Probiotal study group. Randomised clinical trial: the synbiotic food supplement probiotal vs. placebo for acute gastroenteritis in children. *Aliment Pharmacol Ther*. 2011;34:862-7.
10. Bresee J, Fang ZY, Wang B, Nelson EA, Tam J, Soenarto Y, et al. First report from the Asian Rotavirus Surveillance Network. *Emerg Infect Dis*. 2004;10:988-95.
11. Soenarto Y, Aman AT, Bakri A, Waluya H, Firmansyah A, Kadim M, et al. Burden of severe rotavirus diarrhea in Indonesia. *J Infect Dis*. 2009;200:S188-94.
12. Widowati T, Bakrie A, Nirwati H, Soenarto Y. Surveillance of rotavirus diarrhea, *Paediatr Indones*. 2012;52:22-7.
13. Noel RJ, Cohen MB. Infectious diarrhea. In: Wyllie R, Hyams JS, editors. *Pediatric gastrointestinal and liver disease*. 3rd ed. USA: Saunders Elsevier; 2006. p. 557-81.
14. Kadim M, Soenarto Y, Hegar B, Firmansyah A. Epidemiology of rotavirus diarrhea in children under five: a hospital-based surveillance in Jakarta. *Paediatr Indones*. 2011;51:138-43.
15. Charrois LT, Sandhu G, Vohra S. Probiotics. *Pediatr Rev*. 2006;27:137-9.