

Effect of adding tyndallized probiotics to the World Health Organization standard therapy for acute diarrhea in children

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Abstract

Background Diarrhea is the major cause of morbidity and mortality in children. Probiotics can decrease the frequency and duration of diarrhea. There are two types of probiotics, live and tyndallized. Tyndallized probiotics have been sterilized, so they are unable to produce active metabolites, but may have an effect on human immunity.

Objective To evaluate the effectiveness of supplementing WHO standard therapy with tyndallized probiotics in children with acute, watery diarrhea.

Methods We performed a randomized, single-blind, controlled trial in children aged 3-60 months who were diagnosed with acute, watery diarrhea at Gunungsitoli General Hospital, Nias, North Sumatera. Subjects were collected by consecutive sampling by way of parent interviews.

Results One hundred subjects with acute, watery diarrhea were divided into 2 groups of 50. One group was treated with only WHO standard therapy for acute, watery diarrhea. The other group was treated by WHO standard therapy with the addition of tyndallized probiotics. There were no significant differences in basic characteristics between the two groups. Diarrheal duration for the group receiving WHO standard therapy only was 3.95 ± 1.3 days, while that of the group receiving both WHO standard therapy and tyndallized probiotics was 4.6 ± 2.3 days ($P > 0.05$). Diarrheal frequency on the fifth day in the WHO standard therapy group was 1.90 ± 0.99 times per day, while that of the tyndallized probiotic group was 1.56 ± 0.67 times per day ($P > 0.05$).

Conclusion There were no significant differences between WHO standard therapy alone and WHO standard therapy with the addition of tyndallized probiotics for decreasing the duration and frequency of diarrhea in children. [Paediatr Indones. 2012;52:91-4].

Keywords: tyndallized probiotic, acute diarrhea, WHO standard therapy

Diarrhea is the major cause of morbidity and mortality in children. In Indonesia, based on National Basic Health Research (Riskesmas) 2007 results, diarrhea was the major cause of death in infants (42%), followed by pneumonia (24%). In children aged 1-4 years, it caused 25.2% of deaths, followed by pneumonia (15.5%).^{1,2}

Currently, the five steps for diarrhea treatment used, known as the five pillars of rehydration, nutritional support, zinc supplementation, selective antibiotic use and parental education. These pillars are in agreement with the WHO standards of management for acute diarrhea, consisting of rehydration, administration of zinc and continued feeding.^{3,4}

Probiotics are food and drinks that contain live microorganisms which may provide beneficial physiological effects for the host through microbial action.⁵ Previous studies have reported that live

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probiotics may reduce the duration and frequency of diarrhea.^{5,6,7} In addition to live probiotics, tyndallized probiotics have also been used. Tyndallization sterilizes the probiotics, so that active metabolites are not produced. However, this form of probiotic may still have an effect on human immunity. Since micororganisms in tyndallized probiotics are unable to reproduce, tyndallized probiotics have an advantage over the live form, in that gene resistance cannot be inherited and there is no possibility of it causing sepsis. A number of studies on tyndallized probiotics have shown that they stimulate Th1 cytokines and suppress the production of immunoglobulin E, enhancing the systemic and mucosal immune responses, particulary the production of immunoglobulin A.^{8,9} Since there have been few studies on the effectiveness of tyndallized probiotics on acute watery diarrhea in children, we aimed to evaluate their effect on diarrhea duration and frequency.

Methods

From August to October 2009, we performed a randomized, single-blind, controlled trial comparing two groups of subjects with acute watery diarrhea. One group received WHO standard therapy and the other group received WHO standard therapy with tyndallized probiotics. Subjects were children aged 3-60 months living in Gunungsitoli, Nias who suffered from watery stool 3 or more times per day for less than 14 days and whose parents gave written informed consent. We excluded children suffering from acute diarrhea accompanied by a severe disease and/or with malnutrition (**Figure 1**).

The estimated required sample size was 100, calculated by unpaired categorical analysis formula, with $\alpha = 0.05$ and $\beta = 0.20$. By consecutive sampling, subjects were divided into two groups of 50 subjects each. WHO standard treatment consisted of rehydration,

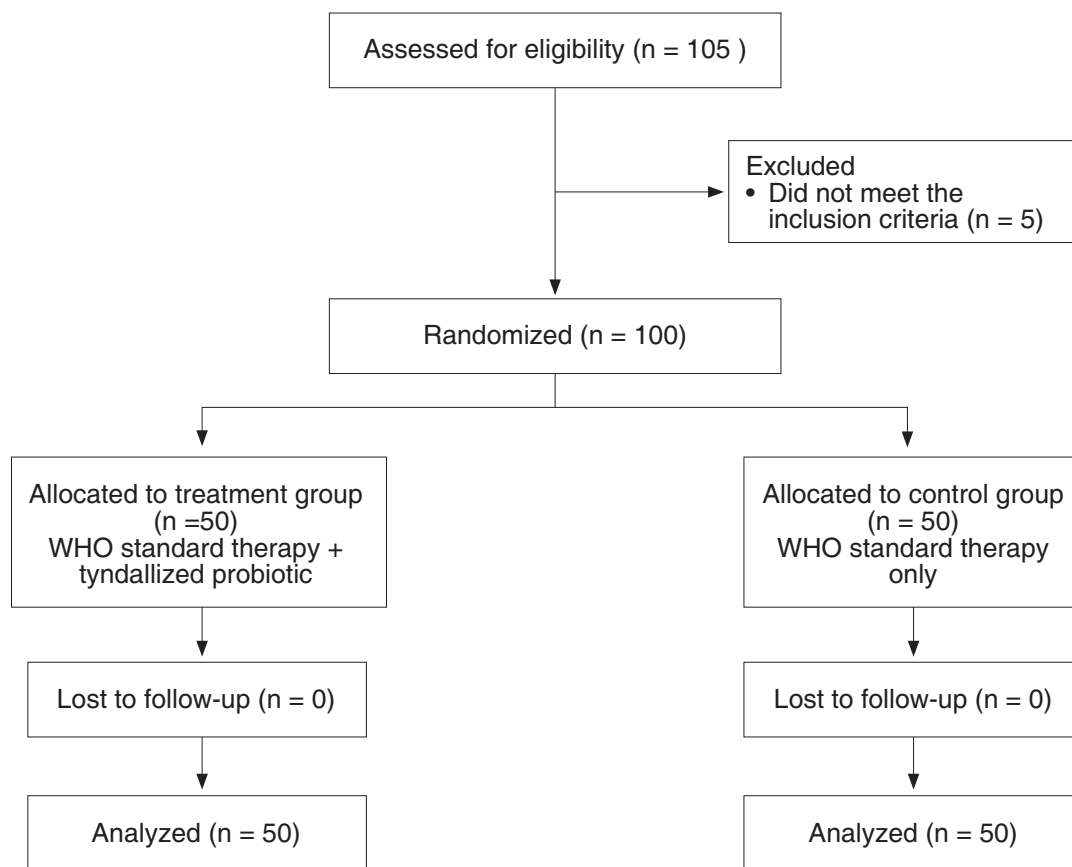


Figure 1. Study flow chart

oral zinc and continued feeding. The treatment group received tyndallized probiotic (Dialac® 1 sachet twice daily, @ 340 mg tyndallized probiotics per dose) for five days in addition to the WHO standard treatment. The control group received only the WHO standard treatment. We confirmed that outpatient subjects received treatment by telephoning their parents. Nurses confirmed administration of therapy for the inpatient subjects. Frequency of diarrhea and the side effects of the therapy were recorded by parents or nurses on a standardized form. The outcomes of the study were the duration and frequency of diarrhea.

This study was approved by the Commission on Medical Research Ethics and Health, Gadjah Mada University Medical School. All subjects' parents provided written informed consent.

Data was analyzed with SPSS for Windows 16.0. The effect of tyndallized probiotics with WHO standard therapy was analyzed by independent t-test and Chi-square test. Results were considered statistically significant if $P < 0.05$ with a 95% confidence interval (CI).

Results

There were 100 subjects divided into two groups. Characteristics of subjects are shown in **Table 1**.

There were no significant differences in the duration or frequency of diarrhea between the two groups as shown in **Table 2**. Mean duration of diarrhea in the probiotic group was 4.6 ± 2.3 days, while that of the WHO standard therapy group was 3.95 ± 1.3 days ($P = 0.98$). The frequency of diarrhea after the fifth day of treatment was 1.56 (SD 0.67) times/day in the probiotic group, and 1.9 (SD 0.99) times/day in the WHO standard therapy group ($P = 0.106$). In this study, no side effects, such as sepsis or bacteremia due to the use of tyndallized probiotics, were observed. According to parents' and nurses' reports, all subjects received their therapy with a 100% compliance.

Discussion

The addition of tyndallized probiotics did not shorten the duration or reduce the frequency of acute diarrhea. Several meta-analysis studies have concluded that the addition of probiotics can reduce the duration of diarrhea, however, these studies used live probiotics.^{5,6,7}

Results similar to ours were obtained by Khanna *et al*¹⁰ in India and Pramono *et al*¹¹ in Indonesia. According to Khanna *et al*, to observe a therapeutic effect from probiotics, microbial colonization should have occurred before their administration.

Table 1. Baseline characteristics of subjects

Characteristics	WHO standard therapy + tyndallized probiotic n = 50	WHO standard therapy alone n = 50
Male gender, n (%)	29(58.0)	25(50)
Mean age, months (SD)	17.46 (15.82)	12.74 (9.84)
Dehydration status		
Not dehydrated, n (%)	36 (72)	30 (60)
Dehydrated, n (%)	14(28)	20(40)
Mean diarrhea frequency, n (SD)	7.20 (2.16)	7.26(2.0)
Nutritional status		
Well-nourished, n (%)	30 (60)	30(60)
Undernourished, n (%)	20 (40)	20(40)

Table 2. Diarrhea duration and frequency

Results	WHO standard therapy + tyndallized probiotics	WHO standard therapy alone	P*
Mean duration of diarrhea, days (SD)	4.60 (2.3)	3.95 (1.3)	0.98
Mean frequency of diarrhea on 5th day, times/day (SD)	1.56 (0.67)	1.90 (0.99)	0.11

*t-test

However, microbial colonization means the duration of diarrhea would be longer. In acute diarrhea, colonization may not yet have taken place, so the addition of tyndallized probiotics would not provide the optimal effect.¹²

Since stool cultures were not examined, we do not know the microbial pathogens causing diarrhea in our study. From past stool examination studies, probiotics were reported to provide good therapeutic effect on rotavirus diarrhea.⁹

A limitation of our study was the lack of intensive supervision after treatment administration to each group. As such, co-intervention may have occurred beyond our monitoring efforts due to the exchange of information between study groups. Furthermore, with the single-blind study design, study contamination between groups may have occurred if parents or relatives gave other drugs to the subjects, influencing the outcome of the study. Therefore, further research may be needed, using a larger sample size and more intensive monitoring for each subject. Nevertheless, our results were similar to previous research, concluding that tyndallized probiotics did not reduce the duration and frequency of acute diarrhea in children.

There were no significant differences in duration and frequency of diarrhea between the WHO standard therapy group and the WHO standard therapy with tyndallized probiotics group.

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