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Original Article

Comparison of zinc-probiotic combination therapy to zinc therapy alone in reducing the severity of acute diarrhea

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Abstract

Background Although the incidence of diarrhea in Indonesia has declined in the last five years, the mortality rate in children under five years old is still high. Therefore, appropriate and comprehensive management of diarrhea is essential. There have been many studies on the role of zinc therapy and probiotic therapy in reducing the severity of acute diarrhea, but not many studies have compared the use of a combination of the two therapies to zinc therapy alone.

Objective To compare the efficacy of zinc-probiotic combination therapy to zinc alone in reducing the severity of acute diarrhea.

Methods We conducted a randomized, open-label, controlled trial from July 2009 to January 2010 in Adam Malik Hospital and Pirngadi Hospital, Medan. Children aged between 1 month and 5 years who met the criteria were divided into two groups. Group I received zinc sulphate (aged <6 months: 10mg/day; aged ≥6 months: 20mg/day) combined with heat-killed *Lactobacillus acidophilus* ($3x10^{10}$ CFU/day) for 10 days. Group II received only zinc sulphate at the same dosage as group I. Measurement of disease severity was based on the frequency of diarrhea (times/day) and the duration of diarrhea (hours) after initial drug consumption.

Results Eighty subjects were enrolled, randomised, and divided equally into two groups. 40 children received zinc-probiotic in combination (group I) and the remainder (group II) received zinc alone. We observed significant differences in frequency of diarrhea (2.1 vs 3.1 times/day, P=0.001, 95%CI -1.62 to -0.49), and duration of diarrhea (52.1 vs 72.6 hours, P=0.001, 95%CI -30.91 to -10.18) in the two groups.

Conclusion Combination of zinc-probiotic therapy was more effective in reducing the severity of acute diarrhea than zinc therapy alone in children under five years of age. **[Paediatr Indones. 2011;51:1-6].**

Keywords: *acute diarrhea, zinc, probiotic, Lactobacillus acidophilus*

Diarrhea is defined as the passage of unusually loose or watery stools, at least three times in a 24-hour period, accompanied by changes in stool consistency, with or without blood or mucus in the stool, sometimes accompanied by vomiting.[1] Episodes of diarrhea are generally acute, and in certain circumstances may last for weeks, a condition termed, persistent diarrhea.[2]

In Indonesia, diarrhea remains a leading cause of death in infants and children. Based on the Household Health Survey (SKRT) 2001, diarrhea was ranked third of 10 causes of death in children under five years of age.[3] There have been many studies conducted on treatment of acute diarrhea in the last few years, especially involving the use of zinc and probiotics. Zinc has been shown to significantly reduce the frequency, severity, and morbidity of acute diarrhea.[4-6] The World Health Organization (WHO) recommends zinc therapy for acute diarrhea

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at a dose of 10 mg for children <6 months, and 20 mg for children ≥ 6 months, for 10 to 14 days.[7] Giving probiotics (Lactobacillus sp) has also proved to be effective for treatment of acute diarrhea.[8] The combination of both zinc and probiotics in the diets of children aged less than 1 year has been shown to significantly reduce the severity and duration of diarrhea.[9]

Zinc and probiotics work by different mechanisms to reduce the severity of acute diarrhea,[10-14] but it is not known whether a combination of both is more effective than zinc alone in reducing the severity of acute diarrhea. This study was designed to compare the efficacy of zinc-probiotic combination therapy with zinc therapy alone in reducing the severity of acute diarrhea.

Methods

We conducted an open, randomized, controlled trial from July 2009 until January 2010, in the pediatric ward of Adam Malik Hospital and Pirngadi Hospital, Medan, North Sumatra. We included children aged 1 month to 5 years with acute diarrhea. We excluded those with severe malnutrition, encephalitis, meningitis, sepsis, bronchopneumonia, immunocompromised state, or those who had been given probiotics or zinc in the last 10 days. Subjects were divided into two groups by simple randomization using random tables. Group I received zinc sulfate (10 mg/day for age <6 months and 20 mg/day for ≥ 6 months) and heat-killed Lactobacillus acidophilus (3x1010 CFU/day) orally for 10 days. Group II received zinc sulfate at a the same dose as Group I. The probiotics were mixed into milk or boiled water. Zinc sulfate tablets were dissolved in 5 ml of boiled water. Both doctors and parents were aware of the therapies given.

We did not perform stool examination because of the high cost required. The cause of diarrhea was distinguished only by the stool consistency. Dysentery was characterized by acute diarrhea mixed with blood, while cholera and diarrhea caused by rotavirus was characterized by acute watery diarrhea. We suspected cholera if: 1) symptoms occurred during known diarrheal outbreaks involving children and adults; or 2) frequent, voluminous, loose stools quickly led to severe dehydration with hypovolemic shock; or 3) severe dehydration occurred and antibiotics shortened the duration of diarrhea.[7]

Monitoring of the duration and frequency of diarrhea was done during hospitalization and after the patient was discharged. Toxicity and side effects relating to the administration of zinc and probiotics were also observed (nausea, vomiting, abdominal pain, and sepsis). We defined recovery from diarrhea as 8 hours after passage of formed stool and/or discharge of the patient. Home monitoring was done by contacting the parents or caregivers by telephone. This study was approved by the Medical Ethics Committee of the Medical School, University of North Sumatra.

We used SPSS version 15 for data analysis. Independent t-test was used to assess the relationship between zinc-probiotic combination therapy and zinc alone as nominal scale with the duration and frequency of diarrhea as numerical scale. Differences were considered significant at a probability value of $P<0.05$, and 95% CI. Our study was an intention-to-treat analysis-based study.

Results

There were 80 children who met the inclusion criteria. We divided them into two groups of 40 subjects each: those who received zinc-probiotic combination therapy (Group I) and those who received zinc therapy alone (Group II). (**Figure 1**)

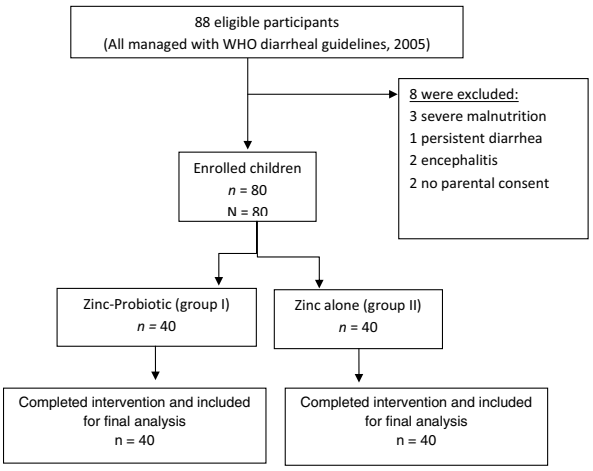

Figure 1. Study algorithm.

The mean frequency of diarrhea before treatment was 8.2 times/day in the combination group, and 9.2 times/day in the zinc group. The duration of diarrhea before treatment was 62.4 hours (2.6 days) in the combination group, and 56 hours (2.3 days) in the zinc group. (**Table 1**)

During treatment, there were significant differences in diarrheal frequency in the two groups from the first to fourth days. (**Table 2**) No parents or caregivers in either group reported recurrent diarrhea or complained of toxicity or side effects often associated with zinc and probiotics.

Table 1. Baseline characteristics

Characteristic	Zinc-Probiotic n=40	Zinc n=40
Mean age, month (SD)	27.4 (21.04)	21.5 (16.57)
Sex, n		
Male	23	21
Female	17	19
Degree of dehydration, n		
None	0	0
Mild-moderate	40	40
Severe	0	0
Parental education		
Father, n		
Elementary School	4	1
Junior High School	2	4
Senior High School	22	19
Undergraduate	10	14
Graduate	2	2
Mother, n		
Elementary School	3	0
Junior High School	7	5
Senior High School	22	28
Undergraduate	8	3
Graduate	0	4
Parental Income/month		
Father, n		
< Rp. 500.000	2	0
Rp. 500.000 – Rp. 1.000.000	15	22
Rp. 1.000.000 – Rp. 3.000.000	18	18
> Rp. 3.000.000	5	0
Mother, n		
< Rp. 500.000	26	27
Rp. 500.000 – Rp. 1.000.000	8	9
Rp. 1.000.000 – Rp. 3.000.000	6	4
> Rp. 3.000.000	0	0
Mean frequency of diarrhea before treatment, times/day (SD)	8.2 (3.19)	9.2 (2.41)
Mean duration of diarrhea before treatment, hours (SD)	62.4(18.67)	56 (23.05)

Table 2. Frequency of diarrhea, times/day

Day of Intervention	Group I (Zinc-Probiotic) mean (SD)	Group II (Zinc) mean (SD)	95% CI	**P**
1st day	7.2 (2.72)	8.8 (2.44)	- 2.72 to - 0.42	0.008
2nd day	4.6 (2.38)	6.6 (2.59)	- 3.40 to - 1.19	0.001
3th day	2.1 (1.66)	3.8 (2.30)	- 2.59 to - 0.80	0.001
4th day	0.8 (1.44)	1.8 (2.03)	- 1.86 to - 0.28	0.008
5th day	0.2 (0.54)	0.7 (1.47)	- 0.97 to 0.21	0.60
6th day	0.0 (0.00)	0.3 (1.00)	- 0.56 to 0.67	0.120
7th day	0.0 (0.00)	0.0 (0.15)	- 0.75 to 0.02	0.320

In this study, the frequency and duration of diarrhea, as well as length of hospital stay were lower in the combination group than in the zinc group (P=0.001). (**Table 3**)

Table 3. Frequency and duration of diarrhea, and length of hospital stay

	Group I (Zinc-Probiotic) mean (SD)	Group II (Zinc) mean (SD)	95% CI	P
Frequency of diarrhea (times/day)	2.1 (1.04)	3.1 (1.44)	- 1.62 to - 0.49	0.001
Duration of diarrhea (hours)	52.1 (22.54)	72.6 (23.99)	- 30.91 to - 10.18	0.001
Length of stay (hours)	56.7 (19.39)	98.5 (23.82)	- 51.49 to - 32.15	0.001

Where does 2.1 and 3.1 in table 3 come from?

Discussion

The mean age of children with acute diarrhea was 27.4 months in the combination group, and 21.5 months in the zinc group. There were more males in each group. (Table 1) Previous epidemiological studies found that children with acute diarrhea caused by rotavirus were aged 0 to 12 months.[15,16] The majority of previous studies did not analyze the difference in diarrhea incidence between sexes. One study of diarrhea in hospitalized children aged 0 to 36 months found that the incidence of acute diarrhea was higher in boys, but did not discuss possible theories for this occurrence.[17]

In children under five years old, acute diarrhea is usually caused by rotavirus infection.[15,18] Previous studies using live Lactobacillus acidophilus reported a significant benefit in reducing the severity of diarrhea caused by rotavirus infection.[8] However, Indonesians often dissolve milk or food in hot water, thus killing the Lactobacillus acidophilus. This habit may not be a problem, as several studies found that heat-killed Lactobacillus acidophilus is still able to stimulate gastrointestinal immunity.[20,21] Furthermore, one study found that heat-killed Lactobacillus acidophilus was even more effective in reducing symptoms of persistent diarrhea than live Lactobacillus acidophilus. It is thought that in addition to improving gastrointestinal immunity, heat-killed Lactobacillus acidophilus can also prevent the adhesion of enteropathogens to enterocytes.[19,22]

Also, occurrence of sepsis in premature infants, the elderly, and immunocompromised patients has been reported after live, probiotic administration.[25] For these reasons, we used heat-killed Lactobacillus acidophilus, as it may be just as effective and may have fewer side effects compared to live probiotics. There was no standard dose of probiotic administration for acute diarrhea. Often the provisions of probiotic manufacturers were used. In our study, we gave probiotics once per day at a dose of 3x1010 CFU, for ten days to coincide with the duration of zinc administration.

Zinc toxicity may occur if more than 2 grams per day is consumed for long periods.[23] Manifestations of zinc toxicity are nausea, vomiting, abdominal pain and fever.[24] We gave 10 mg-20 mg of zinc per day. The possibility of zinc toxicity in our subjects was small, but it would be difficult to attribute symptoms (nausea, vomiting, abdominal pain, and fever) to zinc toxicity during the diarrheal illness.

Previous studies assessed the severity of diarrhea based on the frequency, duration, and stool consistency.8 In our study, we assessed the severity of diarrhea based on frequency (times/day) and duration (hours). Assessment of the stool consistency was not included because it was subjective and difficult to agree to a standard assessment scale.

We found a significant difference in the decrease in diarrheal severity in the two groups. Shamir et al. reported similar results, but with shorter duration and lower frequency. A possible reason for this difference is their use of live, multi-strain probiotics (Streptococcus thermophilus, Bifidobacterium lactis, and Lactobacillus acidophilus), which may be more effective than a single strain of heat-killed Lactobacillus acidophilus.[9] One in vitro study concluded that live Lactobacillus acidophilus improved the transport of electrolytes in intestinal epithelial cells better than heat-killed Lactobacillus acidophilus.[26] However, heat-killed probiotics are still useful in the therapy of acute diarrhea in children, because they are still effective even if mixed with hot water, and they are less expensive than live, multi-strain probiotics.[20,21,27]

We found no obvious reasons why the frequency of diarrhea in the fifth to seventh days of therapy did not differ in both groups.

Anggarwal et al. used zinc supplementation and found that the duration of diarrhea after therapy was 3 days.[4] We had similar results in our study. Length of hospital stay cannot be used as an indicator of therapeutic success due to many other factors that affect the length of patient hospitalization, such as time delays in hospital discharge caused by the parents' requests or payment issues. In our study, we monitored the results only up to 7 days because no diarrhea was present by the 8th day of therapy. However, therapy was given for 10 days. It appears that intestinal recovery in acute diarrhea occurs within 7 to 10 days.[28]

Limitations of this study were that the etiology of diarrhea was unknown, and this was not a double-blind study, although randomization was done to reduce bias. We conclude that a combination of zinc and probiotic therapy is more effective than zinc therapy alone in reducing the severity of acute diarrhea in children under five years.

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