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Original Article

Zinc therapy for different causes of diarrhea

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Abstract

Background The incidence of diarrhea in Indonesia has declined in the past five years. In spite of the increasing number of studies on the treatment for acute diarrhea, especially the use of zinc, it is not known if bacterial vs. non-bacterial etiology makes a difference in the reduction of severity of acute diarrhea in children on zinc therapy.

Objective To assess the effect of zinc therapy in reducing the severity of acute bacterial and non-bacterial diarrhea.

Methods We performed a cross-sectional study in the Secanggang District, Langkat Regency of North Sumatera, from August to November 2009 in children aged 2 months to 14 years. Microscopic stool examinations were undertaken to separate subjects into the acute bacterial or non-bacterial diarrhea groups. Both groups received 10 mg/day of zinc sulphate for subjects aged <6 months or 20 mg/day for those aged ≥6 months for 10 days. Measurement of disease severity was based on the frequency of diarrhea (times/day) and the duration of diarrhea (hours) after initial drug consumption. We performed independent T-test for statistical analysis.

Results Sixty-two children participated in this study, with 31 children in the acute bacterial group, and the remainder in the non-bacterial group. There were no significant differences between the two groups in frequency of diarrhea (2.61 vs 2.70 times/day, respectively, P=0.27) or in duration of diarrhea (63.39 vs 66.68 hours, respectively, P=0.06).

Conclusion Zinc is not more effective in reducing the severity of acute bacterial diarrhea compared to non-bacterial diarrhea in children. **[Paediatr Indones. 2013;53:334-8.]**

Keywords: *acute non-bacterial diarrhea, zinc, acute bacterial diarrhea*

In Indonesia, diarrhea remains to be a leading cause of death in infants and children. In the *2001 Household Health Survey* (SKRT), diarrhea ranked third of 10 causes of death in children under five years of age.[1] Diarrhea is defined as the passage of unusually loose or watery stool, at least three times in a 24-hour period, accompanied by changes in stool consistency, with or without blood or mucus in the stool, and sometimes accompanied by vomiting.[2] Episodes of diarrhea are generally acute, and in certain circumstances may last for weeks, a condition termed persistent diarrhea.[3]

There have been many studies conducted on the treatment of acute diarrhea in the past few years, especially involving the use of zinc. 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 at a dose of 10 mg for children <6 months of age, and 20 mg for children ≥6 months of age, for 10 to 14 days.[7] Zinc in the diets of children with diarrhea aged less than 1 year has been shown to significantly reduce the severity and duration of diarrhea.[8]

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Zinc works by different mechanisms to reduce the severity of acute bacterial diarrhea and non-bacterial diarrhea,[9-13] but is not yet known if zinc is more effective in reducing the severity of acute bacterial diarrhea compared to non-bacterial diarrhea. The aim of this study was to assess the effect of zinc therapy in reducing the severity of acute bacterial and nonbacterial diarrhea.

Methods

We conducted a cross-sectional study in the Secanggang District, Langkat Regency in North Sumatera, from August to November 2009. We included all children aged 2 months to 14 years with acute diarrhea. All subjects received zinc therapy. We excluded children with severe malnutrition, encephalitis, meningitis, sepsis, bronchopneumonia, or persistent diarrhea. Informed consent was obtained from all parents and the study was approved by the Research Ethics Committee of the University of North Sumatera Medical School.

Sample recruitment was centered at the Hinai Kiri, Secanggang, and Tanjung Ibus Community Health Centers (*Puskesmas*), the local government clinics in the Secanggang District. Before starting the study, we explained the study methods, the effects of diarrhea and diarrheal treatment to subjects and their parents. On admission, a standard history was taken and a thorough physical examination was performed by a physician. Parents were asked to fill questionnaires. Dehydration was assessed and treated according to WHO 2005 guidelines with oral or parenteral rehydration solutions.

Microscopic stool examinations were performed on subjects to separate them into the acute bacterial or nonbacterial diarrhea groups. Bacterial diarrhea was defined as 10-20 leukocytes/high power field (L/hpf), 200x magnification) in the microscopic stool examination with 1-2% eosin staining. Both groups received zinc sulphate for 10-14 days at dosages of 10 mg/day for subjects <6 months of age or 20 mg/day for those ≥6 months of age.

Zinc treatment was given at enrollment. Subjects with dehydration were rehydrated prior to therapy. Parents were asked to monitor the diarrheal frequency. Monitoring of the frequency and duration was done during hospitalization and after the patient was discharged. A diarrheal monitoring chart was given to parents and they were informed on how to fill the monitoring chart. All subjects were visited (at the local government clinic or by home visit) every day until recovered. At every visit we looked at the monitoring chart and obtained information about zinc toxicity and potential side effects (vomiting, nausea, or abdominal pain). We defined recovered from diarrhea as 8 hours after passage of formed stool and/or discharge of the patient.

We used *SPSS version 14.0* and *Microsoft Excel 2007* for data processing. Independent T-test was used to evaluate the relationship between acute bacterial diarrhea and non-bacterial diarrhea (nominal scale) to diarrheal frequency and diarrheal duration (numeric scale). Differences were considered to be statistically significant at $P < 0.05$.

Results

Sixty-seven children with diarrhea were recruited into the study, but 5 children were subsequently excluded (2 children with severe malnutrition, 1 with persistent diarrhea, and 2 children who did not get parental consent). The 62 children who were included underwent microscopic stool examinations to separate them into the acute bacterial or non-bacterial diarrhea groups.

The mean frequency of diarrhea before treatment was 7.3 times/day in the bacterial diarrhea group and 7.8 times/day in the non-bacterial diarrhea group. The mean duration of diarrhea before treatment was 53.1 (SD 13.86) hours in the bacterial diarrhea group, and 44.3 (SD 16.10) hours in the non-bacterial diarrhea group. The mean age of children with nonbacterial diarrhea was less than those with bacterial diarrhea (**Table 1**).

During treatment, the frequency of diarrhea was not significantly different between the two groups on any day from the first to sixth days (**Table 2**). No parents or caregivers in either group reported recurrent diarrhea or complained of toxicity or side effects associated zinc.

In this study, the frequency and duration of diarrhea, as well as the length of hospital stay were not significantly different between the two groups (**Table 3**).

Table 1. Characteristics of subjects

Characteristics	Non-bacterial diarrhea (n=31)	Bacterial diarrhea (n=31)
Mean age (SD), months	47.8 (27.58)	82.4 (21.88)
Gender, n (%)		
Male	17 (54.8)	12 (38.7)
Female	14 (45.2)	19 (61.3)
Degree of dehydration, n (%)		
None	7 (22.6)	12 (38.7)
Mild-moderate	24 (77.4)	19 (61.3)
Severe	0 (0)	0 (0)
Mean fecal leukocytes (SD), L/hpf*	1.7 (1.22)	13.4 (3.02)
Mean frequency of diarrhea before treatment (SD), times/day	7.8 (0.98)	7.3 (1.02)
Mean duration of diarrhea before treatment (SD), hours	44.3 (16.10)	53.1(13.86)

*L/hpf=leukocytes/high power field

Table 2. Mean frequency of diarrhea after initiation of zinc treatment

Day of observation	Non-bacterial diarrhea mean (SD) times/day	Bacterial diarrhea mean (SD) times/day	95% CI of mean difference	P value
1st day	8 (0.82)	8 (0.86)	- 0.42 to 0.42	1.000
2nd day	6 (0.82)	6.1 (0.85)	- 0.53 to 0.40	0.762
3th day	2.9 (0.84)	3.1 (0.81)	- 0.60 to 0.41	0.646
4th day	1 (0.84)	1.2 (0.64)	- 0.52 to 0.26	0.497
5th day	0.4 (0.53)	0.5 (0.51)	- 0.53 to 0.01	0.064
6th day	0.1 (0.18)	0.1(0.30)	- 0.20 to 0.07	0.310
7th day	0 (0.00)	0 (0.00)		

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

	Non-bacterial diarrhea	Bacterial diarrhea	95% CI of mean difference	P value
Mean frequency of diarrhea (SD), times/day	2.6 (0.32)	2.7 (0.30)	- 0.22 to 0.04	0.27
Mean duration of diarrhea (SD), hours	63.4 (10.31)	66.6 (10.66)	- 12.40 to 0.01	0.06
Mean length of hospital stay (SD), hours	56.2 (14.52)	58.4 (16.09)	- 10.47 to 5.57	0.53

Discussion

Our study was conducted in a village within this developing country, with an area of 223.27 km^2 divided into eight districts. The total number of inhabitants was 69,940 of which 29,406 (42.04%) were children. The most common parental occupations were fishing and farming. The mean age of children with acute diarrhea was 47.8 (SD 27.58) months in the non-bacterial diarrhea group, and 82.4 (SD 21.88) months in the bacterial diarrhea group. Previous epidemiological studies found that children with acute diarrhea caused by rotavirus were aged 0 to 12 months.[14,15] The majority of previous studies did not analyze the difference in diarrheal incidence between gender. 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 reasons for this occurrence.[16]

In children under five years of age, acute diarrhea is usually caused by rotavirus infection.[14,17] Previous study on the use of zinc reported a significant benefit in reducing the severity of diarrhea caused by rotavirus infection.[18] Zinc toxicity may occur if more than 2 grams per day is consumed for long periods.[19] Manifestations of zinc toxicity are nausea, vomiting, abdominal pain, and fever.[20] We gave 10-20 mg of zinc per day to our subjects in order to minimize the risk of zinc toxicity. However, it would be difficult to attribute symptoms (nausea, vomiting, abdominal pain, and fever) to zinc toxicity as they are often inherent in diarrheal illnesses.

Previous studies assessed the severity of diarrhea based on frequency, duration, and stool consistency.[9]

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

Anggarwal *et al*. used zinc supplementation and found that the duration of diarrhea after therapy was 3 days,[4] similar to our results. 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. In our study, we monitored the results only up to 7 days and no diarrhea was present by the 7th day of therapy. However, zinc therapy was given for 10 days. It appears that intestinal recovery in acute diarrhea occurs within 7 to 10 days.[21]

The aim of microscopic stool examinations in patients with diarrhea is to discover leukocytes in the stool. In normal circumstances, leukocytes can be found in the stool. We defined bacterial diarrhea as diarrhea with 10-20 L/hpf (200x magnification) in microscopic stool examinations with eosin 1-2% staining.[3] The mean fecal leukocyte counts of children with acute diarrhea was 1.7 L/hpf in the non-bacterial diarrhea group, and 13.4 L/hpf in the bacterial diarrhea group. We used microscopic stool examinations to separate subjects into the acute bacterial or non-bacterial diarrhea groups, not as a method to evaluate the therapeutic efficacy of zinc.

Zinc is needed for growth, regeneration, and restoration of intestinal mucosa function and been shown to increase absorption of water and electrolytes. Zinc is also needed to enhance the immune system, including cellular and humoral antibody responses, thus speeding up the clearance of pathogens causing intestinal diarrhea.[22,23]

A limitation of our study was that we did not measure subjects' zinc level before and after treatment, therefore we cannot conclude a reciprocal relationship between diarrhea and zinc. We also did not objectively assess the daily recovery process of the subjects, so our data was based only on parental or caregiver reports. Another limitation was that the etiological agent of diarrhea was unknown.

In conclusion, zinc is not more effective in reducing the severity of acute bacterial diarrhea compared to non-bacterial diarrhea in children.

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