

## The effect of zinc supplementation in children under three years of age with acute diarrhea in Indonesia

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### Abstrak

Diare masih merupakan penyebab terpenting kematian anak di Indonesia. Anak yang menderita diare akut mengalami penurunan kadar seng dalam serum. Kekurangan seng dapat menghambat proses regenerasi epitel pada mukosa usus halus sehingga penyembuhan diare terlambat. Untuk menilai pengaruh pemberian seng terhadap masa berlangsungnya diare dilakukan penelitian secara random, kontrol dan tersamar ganda. Kelompok perlakuan diberikan seng dengan dosis 4-5 mg unsur seng/kg berat badan/hari dua kali sehari dan kelompok kontrol diberikan plasebo. Sebanyak 1185 anak batita dikunjungi di rumahnya masing-masing setiap minggu selama duabelas bulan. Selama pengamatan jumlah episode diare akut dikumpulkan sebanyak 2410, tetapi 131 (5,4%) tidak dianalisis karena informasi tidak lengkap. Pemberian seng berhubungan dengan penurunan risiko berlanjutnya diare sebesar 11% (95% interval kepercayaan 3 sampai 18%). Bila anak batita mengalami episode diare akut cair, lama berlangsungnya diare menurun sebesar 12% (95% interval kepercayaan 3 sampai 21%) pada kelompok yang diberikan seng. Hasil penelitian menunjukkan bahwa pemberian seng pada anak batita yang mengalami episode diare akut  $\geq 3$  kali dalam setahun menyebabkan risiko berlanjutnya diare 0,79 kali lebih kecil dibandingkan kelompok kontrol (95% interval kepercayaan 0,64 sampai 0,97). Pemberian seng pada anak batita yang mengalami diare akut memperpendek masa berlangsungnya diare secara bermakna. Penurunan risiko berlanjutnya diare sangat bermanfaat dalam mencegah terjadinya dehidrasi dan kematian akibat diare yang berlanjut.

### Abstract

Diarrheal diseases continue to be an important cause of childhood mortality in Indonesia. Diarrhea leads to excess zinc losses and could contribute to zinc deficiency. Zinc deficiency in particular is known to limit regeneration of gut epithelium and consequently to delay recovery from diarrhea. To evaluate the effect of zinc supplementation in children on the duration of diarrhea we conducted a randomized, double blind, controlled trial. The treatment group received syrup incorporating zinc acetate providing 4-5 mg elemental zinc/kg body weight/day in two divided doses for the consecutive days during diarrhea. The control group received syrup without elemental zinc. One thousand one hundred and eighty five children under three years of age were visited at home every week for 12 months. During observations there were 2410 diarrheal episodes, 131 (5.4%) were excluded due to lack of information. Among children of zinc supplementation group there was an 11% reduction (95% confidence intervals 3 to 18%) in the risk of continued diarrhea. In children with watery diarrhea there was a decrease of 12% (95% confidence intervals 3 to 21%) in the number of days in the zinc supplementation group. Children who had  $\geq 3$  episodes during 12 months observations had a greater reduction in diarrheal duration (hazard ratio in the zinc supplementation group = 0.79; 95% confidence intervals 0.64 to 0.97). Zinc supplementation in children with acute diarrhea significantly reduced the duration of diarrhea. Reduction in the number of days may decrease the risk of dehydration and mortality due to diarrhea.

**Keywords :** zinc, diarrheal duration, dehydration, child mortality

Diarrheal disease remains a leading cause of childhood morbidity and mortality in Indonesia. Approximately 15% deaths among infants and 25% among children aged 1 - 4 years are caused by diarrhea.<sup>1</sup> The

availability of oral rehydration solution (ORS) and the widespread use of ORS can greatly reduce death due to acute watery diarrhea (< 7 days), but is unlikely reduce the mortality due to persistent and dysenteric diarrhea. Oral rehydration therapy with the present ORS does not reduce the duration of illness, the volume of stool output or frequency of diarrhea, which are what most caretakers desire.<sup>2,3</sup>

Children with diarrhea have been reported to have transient depression of serum zinc levels during diar-

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reha. The studies showed a linear correlation between serum zinc levels and the duration of diarrhea.<sup>4-6</sup> Diarrhea may determine zinc status by reduction of dietary intake, impaired intestinal absorption, or increased intestinal loss of endogenous store. Zinc has many important and diverse functions in human metabolism. Experiments in humans and animal models have established the essential role of zinc in many physiologic functions including immunity, taste acuity, wound healing, sexual function, and cognition.<sup>7-9</sup> Diarrhea leads to excess zinc losses and could contribute to zinc deficiency; zinc deficiency in particular is known to limit the regeneration of gut epithelium and consequently delay the recovery from diarrhea. To evaluate the protective effect of zinc supplementation in children on the duration of diarrhea we conducted a community-based, double blind, controlled trial.

## METHODS

### Selection of cases

The trial was conducted in two subdistricts in Indramayu Regency, West Java, about 200 km from Jakarta, between April 1995 and March 1996. Children under 3 years of age with the following criteria were included in the study: had 3 or more loose stools or one or more loose stools containing blood/mucus in 24 hours, with the duration of diarrhea of less than 7 days. Children under 3 years of age with any of the following conditions were included to the study: fever ( $> 39^{\circ}\text{C}$ ), measles, acute respiratory tract infection or severe dehydration. A diarrheal episode was considered terminated on the last day of diarrhea followed by a subsequent period  $\geq 48$  h of not reaching the diarrheal definition. The study was approved by the Graduate Program in Public Health Committee, School of Graduate Studies, University of Indonesia. The consent form was read to the parent and verbal informed consent was obtained for each child's enrollment.

### Follow-up visits

Study children were visited at home by trained field workers every week, and information for each of the previous seven days of diarrheal episode, including the number and consistency of stools were recorded. Children were weighted unclothed using a Tanita baby scale with a sensitivity of 100 mg. Recumbent length was measured to the nearest 0.1 cm using wooden height board. All anthropometric instruments were checked and calibrated daily. Axillary temperature was measured using mercurial thermometer. Base-line as-

essment at enrollment included age, birth date, socioeconomic status, education and occupation of parents, symptoms before enrollment with their duration, frequency and consistency of stools, vomiting, fever, blood in stools, any treatment given for diarrhea before enrollment, description of the feeding status, hydration status, and anthropometric measurement.

### Randomization and intervention

Children under 3 years of age with diarrhea were recruited in a double blind, controlled, randomized by episode trial to either the treatment or control group. Randomization schedules with permuted blocks were assigned using random serial numbers indicating whether they would receive the zinc preparation or placebo.<sup>10</sup> Children who had been recruited were randomized again if they were subsequently met the inclusion criteria during the observation period. The treatment group received syrup incorporating zinc acetate providing 4-5 mg elemental zinc/kg body weight/day as a daily dose in two divided doses for the consecutive days during diarrhea. The control group received syrup without elemental zinc. The two syrups were indistinguishable in appearance and were prepared and coded by PT Dankos Laboratories. Each 5 ml syrup contained 20 mg elemental zinc. They also underwent oral rehydration therapy. Bottles were given to each child's mother and the mother gave the syrup to their children at home during the diarrheal episode. To assess compliance, a card was given to the mothers. They had to make a cross if they gave the syrup to their children. In the next visit the field workers compared the card's and the bottle's volume.

### Statistical analysis

Statistical analyses were performed using SPSSPC+ (version 6.0) and Epi-Info (version 6.0).<sup>11,12</sup> The total duration of episodes was modelled with Cox survival regression, the covariate was assigned a value of 0 for children in the control group or 1 for those in the zinc-supplementation group. Anthropometric Z values were calculated using Epi-Info (version 6.0). Children with less than -2.0 Z scores for height for age, using the National Centre for Health Statistics reference population, were considered stunted.<sup>13</sup>

## RESULTS

### Comparability of base-line characteristics

One thousand one hundred and eighty five children under 3 years of age were followed-up for 12 months.



During observation there were 2410 diarrheal episodes, 131 (5.44%) were excluded due to lack of information. The base-line characteristics of the diarrheal episodes in the two groups were similar for child, socioeconomic status, family, features of the episodes of diarrhea and nutritional status, except for weight for height (Table 1). Analysis post-stratification was used to assess modification effect between the treatment and the duration after enrollment for varying levels of nutritional status for weight for height. There was no modification effect after the post-stratification analysis.

Table 1. Base-line characteristic of diarrheal episodes according to zinc and control group.

| Characteristic                                | Zinc group<br>(N=1165) | Control group<br>(N=1114) |
|---|------------------------|---------------------------|
| Age at enrollment (%)                         |                        |                           |
| 0 - 11 mo.                                    | 41.5                   | 43.5                      |
| 12 - 23 mo.                                   | 36.7                   | 37.3                      |
| 24 - 35 mo.                                   | 21.8                   | 19.2                      |
| Sex (%)                                       |                        |                           |
| Male  | 58.9                   | 58.7                      |
| Female  | 41.1                   | 41.3                      |
| Mother's education (%)                        |                        |                           |
| No formal education                           | 30.6                   | 30.0                      |
| Formal education 1 - 6 yr                     | 59.5                   | 58.6                      |
| Formal education 7 - 11 yr                    | 9.9                    | 11.4                      |
| Family income monthly (Rp)                    | 45,968<br>(SD 35,165)  | 47,075<br>(SD 42,662)     |
| Duration of diarrhea before enrollment (days) | 1.89<br>(SD 1.49)      | 1.93<br>(SD 1.50)         |
| No. of unformed stools in previous 24 hrs     | 4.3<br>(SD 1.9)        | 4.3<br>(SD 2.0)           |
| Any breast feeding before enrollment (%)      | 81.3                   | 84.1                      |
| Fever during episode (%)                      | 46.6                   | 46.3                      |
| Vomit during episode (%)                      | 23.9                   | 25.2                      |
| Intake of drugs during episode (%)            | 27.4                   | 31.3                      |
| Z-score for weight for age -2.0 (%)           | 35.8                   | 32.2                      |
| Z-score for height for age -2.0 (%)           | 27.1                   | 27.2                      |
| Z-score for weight for height -2.0 (%)        | 15.7                   | 12.1*                     |

\* Not similar between the zinc and control groups, post-stratification analysis was done

### Duration of episodes of diarrhea

Of 2279 episodes of diarrhea, 49.3 percent resolved within three days after enrollment and 81.0 percent resolved after five days. From Table 2, the hazard ratio for continued diarrhea of the zinc supplementation group was 0.89 (95% CI 0.82 to 0.97), this means that the supplementation with zinc was associated with

11% reduction in the risk of continued diarrhea (95% CI 3 - 18%). In children with watery diarrhea, the estimated risk of continued diarrhea was 0.88 (95% CI 0.64 to 0.97) times smaller for an episode with zinc supplementation compared with an episode with placebo. This means there was a reduction of 12% in the risk of continued diarrhea (95% CI 3 to 21%). The effect of zinc on the number of days in children given antibiotics before enrollment was smaller than that of the control group (hazard ratio in the zinc group as compared with the controls, 0.82 (95% CI 0.68 to 0.99). Children who had  $\geq 3$  episodes during 12 months observation had a greater reduction in diarrheal duration (hazard ratio in the zinc supplementation group = 0.79; 95% confidence interval 0.64 to 0.97). In stunted children (z score for height for age  $< -2.0$ ), there was 8% reduction in the number of days of diarrhea, but statistically this was not significant (95% CI to -9 to 21%).

### DISCUSSION

The effect of zinc supplementation on the duration of diarrhea showed a protective effect and statistically significant with 11% reduction of the risk of continued diarrhea. This finding was consistent with Sazawal's *et al.* (1995)<sup>14</sup> study, which reported a 23% reduction in the duration of diarrhea when zinc was provided early in the episode. A trial of supplementation with 20 mg zinc daily in children 6-18 months with acute diarrhea showed no differences in overall outcomes, but children with low zinc concentration in the rectal mucosa had shorter episodes of diarrhea.<sup>15</sup> In a small study of children 6-18 months with persistent diarrhea, the diarrheal duration in the zinc supplementation group was lower than in placebo group, but the difference was not statistically significant.<sup>16</sup> The protective effect of zinc supplementation was consistent among subgroups of the study (Table 2). Reduction in the number of days with watery stools may decrease the risk of dehydration and the need for fluid and electrolyte replacement. Antibiotics are primarily indicated for cholera and diarrhea with visible blood (dysentery), which account for only 5 to 10 percent of all episodes in developing countries.<sup>17</sup> The development of effective antidiarrheal agents, such as zinc, should facilitate a more rational approach to treatment. The study was conducted with the children at home rather than in the hospital, and the mother gave the syrup to their children at home during diarrhea. This method was different from Sazawal's *et al.* (1995) study, where the supplementation was given by the field workers.

Table 2. Hazard ratio of continued diarrhea in the Cox regression models according to the study group in all episodes and subgroups

| Characteristics                     | Zinc group (N) | Control group (N) | Hazard Ratio (95% C.I.)* |
|-------------------------------------|----------------|-------------------|--------------------------|
| All episodes                        | 1165           | 1114              | 0.89 (0.82 - 0.97)       |
| Episodes 3 times per yr             | 184            | 193               | 0.79 (0.64 - 0.97)       |
| Children with watery diarrhea       | 841            | 803               | 0.88 (0.79 - 0.97)       |
| Z Score for height for age < -2.0   | 315            | 303               | 0.92 (0.70 - 1.09)       |
| Given antibiotics before enrollment | 234            | 205               | 0.82 (0.68 - 0.99)       |

\* Hazard ratio is the ratio of the estimated hazard of continued diarrhea on a given day during the episodes with the zinc supplementation to that with placebo.

The possible mechanisms for the effect of zinc supplementation on diarrhea include improved absorption of water and electrolytes by the intestine,<sup>18,19</sup> regeneration of gut epithelium or the restoration of its function,<sup>20-23</sup> and enhanced immunologic mechanisms for the clearance of infection, including cellular immunity and higher levels of secretory antibodies.<sup>24</sup>

What is the implementation of the study? This study shows that administration of zinc syrup to children with acute diarrhea by the mothers at home has a protective effect on diarrheal duration. Zinc syrup is easy to administer by oral route; it is also cheap and has less side effects.

## CONCLUSION

Zinc supplementation in children under three years of age with acute diarrhea significantly reduced the duration of diarrhea. This protective effect of zinc supplementation was consistent with Sazawal's *et al.* (1995) study in India. These two findings may have important implications for the reduction of morbidity and mortality due to diarrhea in children in developing countries.

## Acknowledgments

This trial was partly supported by Trisakti University and Center for Family Welfare, University of Indonesia. The authors wish to thank the subjects and their parents for their patient co-operation. We thank the contribution of PT Dankos Laboratories for providing the syrups, and thank to dra. Ellyani Suhendra and dra. Lestari Triyanti for preparing the syrups.

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