Sultan Qaboos University Medical Journal
December 2007 Vol 7, No. 3, p. 219-225
Sultan Qaboos University©
Submitted - 1st April 2007
Accepted - 29th July 2007

Effect of Zinc Supplementation on Morbidity due to Acute Diarrhoea in Infants and Children in Sanaa, Yemen

A randomized controlled double blind clinical trial

***Muna A M Elnemr[1] and Ahmed K Abdullah[2]**

تأثير امداد الزنك على المراضة المصاحبة لحالات الاسهال الحاد عند الأطفال في صنعاء (اليمن)

دراسة سريرية مضبطة العشوائية مزدوجة التعمية

منى عبده محمد النمر ، أحمد قائد عبد الله

الملخص: الهدف: دراسة تأثير إعطاء الزنك على المراضة والوفيات المصاحبة للإسهال الحاد لدى الأطفال دون سن الخامسة. **الطريقة:** هذه دراسة سريرية مضبطة العشوائية مزدوجة التعمية . أجريت في الفترة بين سبتمبر 2005 وأكتوبر 2006 في مستشفى السابين للأمومة والطفولة في صنعاء باليمن ل 180طفلا (دون سن الخامسة) أصيبوا بالإسهال الحاد. تراوحت أعمارهم بين 6-48شهرا. تم تقسيم الحالات عشوائيا إلى مجموعتين أعطيت المجموعة الأولى محلول اسيتيت الزنك بالفم لمدة أسبوعين بينما تم إعطاء المجموعة الثانية عقارا كاذبا. وتمت متابعة الحالات لمدة شهرين. **النتائج:** أظهرت النتائج أن إعطاء الزنك قلل من متوسط عدد نوبات الإسهال 1.39 عند الأطفال الذين أخذوا الزنك مقابل 2:59 في العينة الضابطة. كذلك قلل مرات التغوط باليوم في كل نوبة إسهال (3.57 في العينة التي أخذت الزنك مقابل 5.47 في العينة الضابطة) كما هو الحال في حجم البراز في كل نوبة إسهال في مدة المتابعة. **الخلاصة:** إعطاء الزنك لمدة أسبوعين أثناء الإصابة بنوبات الإسهال قلل من حدوث نوبات الإسهال وكذلك قلل شدة هذه النوبات. إن تقليل معدلات المراضة المصاحبة للإسهال الحاد باستعمال الزنك يعتبر ذو فائدة كبيرة وذلك لسهولة استعماله ولرخص ثمنه . ولهذا يمكن أن يستعمل للسيطرة على إسهال الأطفال.

مفتاح الكلمات: زنك . إسهال . اليمن.

ABSTRACT ***Objectives:*** To study the impact of zinc administration on the morbidity and mortality attributed to diarrhoea among children less than 5 years old. ***Methods:*** The study design was a randomized double blinded controlled clinical trial, held at Elsabeen Hospital for Maternity and Childhood, Sana'a, Yemen. The study was conducted during the period September 2005 to October 2006 on 180 children less than 5 years old with acute diarrhoeal episodes. They were randomly allocated to two groups; one of them received a placebo and the other received zinc acetate syrup for 14 days. Both groups were followed up for 2 months. ***Results:*** Zinc was able to decrease the mean number of diarrhoeal episodes: 1.39 in the intervention group versus 2.59 in the control group. It also reduced the mean frequency of stools per day in each attack (3.57 in the intervention group versus 5.47 in the control group) and the volume of stool in each attack during the follow-up period. Moreover, zinc was significantly more palatable. ***Conclusion:*** We can conclude from the study that administration of zinc for two weeks during acute diarrhoeal episodes could decrease the incidence of further diarrhoeal episodes as well as the severity of these episodes. The lower rates of child morbidity with zinc treatment represent substantial benefits from a simple and inexpensive intervention that can be incorporated in existing efforts to control diarrhoeal disease.

Key Words: Zinc; Diarrhoea; Children; Yemen.

[1]Department of Pediatrics, Faculty of Medicine, University of Science and Technology, Sana'a, Yemen; [2]Department of Physiology, Faculty of Medicine, Thamar University, Sana'a, Yemen

**To whom correspondence should be addressed. Email: munaabdo@hotmail.com*

Advances in Knowledge

In contrast to previous studies, this is the first study in Yemen to utilise a special liquid preparation containing only zinc (dose = 20mg/ 5ml) with an acceptable taste. This study supports the efficacy of zinc in acute diarrhoea among children under five years.

Applications to Patient Care

Efficacy of zinc as an agent that could reduce the recurrence and duration of episodes of diarrhoea in children less than five years which, in turn, implies that zinc supplementation could be used routinely for every child with acute diarrhoea as a prophylactic measure.

Diarrhoea represents a leading cause of under 5 mortality in developing countries, including Yemen and many other countries of the Eastern Mediterranean.[1] Overall under 5 mortality was estimated by World Health report to be 113 per 100,000 live births of which diarrhoea accounted for 17%, while that of measles represented only 4% and that of malaria 3%. Hence, reducing the burden of diarrhoea in these countries will significantly reduce overall mortality in such countries. Zinc deficiency is highly prevalent among children in developing countries.[2] Diarrhoea causes loss of zinc in the stools, which exacerbates the zinc deficiency in children with acute diarrhoea. Provision of zinc during diarrhoea is thus rationalized.[3]

Therapeutic studies of giving zinc during diarrhoea proved that zinc administration during and for 14 days from the onset of acute attack will reduce the severity of diarrhoea.[4] Moreover, zinc therapy for diarrhoea has been shown to be beneficial in controlled trails, in reducing the need for antibiotic therapy and increasing the use of ORT (oral rehydration therapy).[5] In another study in 2004, Baqui et al. found that zinc sulphate has an antimicrobial effect on the enteric pathogens in vitro.[6]

Unlike other essential micronutrients such as iron and vitamin A, there are no conventional tissue reserves of zinc that can be released or sequestered quickly in response to variations in dietary supply. It is recognized that the equivalent of approximately one third (~450 mg) of total body zinc exchanges between the blood stream and other tissues.[7] The major source of zinc intake is through diet, with the transcellular uptake occurring in the distal duodenum and proximal jejunum, potentially facilitated by specific transporters, such as zinc transporter protein-1 (ZnTP-1).[8] The intestine also serves as the major conduit for zinc elimination from the body with almost 50% of the daily zinc losses occurring in the gut. However, much of the zinc that is secreted into the intestine is subsequently reabsorbed and this process serves as an important point of regulation of zinc balance. Other routes of zinc excretion include the urine, which accounts for approximately 15% of total zinc losses, and epithelial cell desquamation, sweat, semen, hair, and menstrual blood, which together account for approximately 17% of total zinc losses.[9] The mechanism by which zinc (Zn) improves diarrhoea is not known but could result from the fact that Zn inhibits cAMP-induced Cl secretion by blocking basolateral membrane K channels.

Given the high prevalence of micronutrient deficiencies and infectious diseases in children of developing countries, interventions to reduce infant and pre-school morbidity are a public health priority.[10]

METHODS

This study was conducted in the Oral Rehydration Therapy Centre at Elsabeen Teaching Hospital in Sana'a,Yemen.

The following criteria were used to include subjects in the study: infants and children with acute diarrhoeal episodes aged 3 months to 2 years of both sexes either admitted to the medical ward or not.

The following subjects were excluded from this study: infants with malnutrition (body weight <60% of the median for age and sex and/or stunting (low height for age) or wasting (low weight for height) according to the 1995 WHO Standard Deviation Classification (The Use and Interpretation of Anthropometry , Geneva,1995). Infants with co-infections were also excluded as well as those with bloody diarrhoea.

The study was a prospective randomized double blinded controlled clinical trial. Sample size was calculated according to the suitable formula: employing the EpiInfo package using an expected reduction of mortality and morbidity of 20%. The confidence interval was 95%; power of the test 90%; unexposed: exposed ratio:

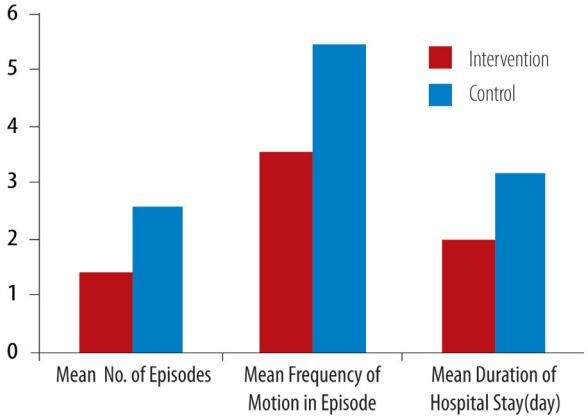

Figure 1: ***Mean number of episodes, mean frequency of stool in these attacks, and mean duration of hospital stay during follow up.***

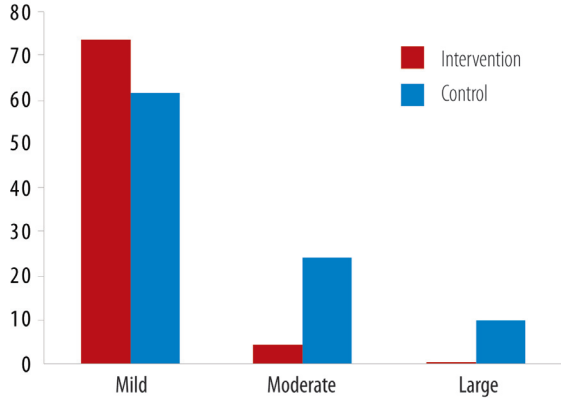

Figure 2: ***Average amount of stools per motion during follow up period***

1:1. Disease in unexposed: 30% (in Yemen); Risk Ratio: .33. Using the sample size collection of EpiInfo 2000, the number of children was 100 per group. The total number of children was 200.

The following sampling technique was used: the children were randomly allocated into two groups as soon as the enrolment was completed. The randomization was undertaken by blinded trained co-investigators in the study location and by the principal investigators.

The control group received ORT and advice to the mothers on feeding during diarrhoeal episodes. The intervention group received zinc acetate 20mg daily in the form of Diazar syrup from Indimedica Pharmaceuticals, India, which was undistinguishable from the placebo bottles. Treatment began as soon as the episode of diarrhoea started and continued for 14 days, in addition to ORT and the advice to the parents.

The data collectors taught the mothers how to use the zinc syrup, and visited or called on the mother or the care taker at day 7 and day 14 and then every 2 weeks for 2 months. Children and infants eligible for the study were enrolled during the acute attack of diarrhoea. Each infant and child in the first episode was submitted to the following:

1. A detailed and complete clinical history including previous diarrhoeal episodes and their duration;
2. An evaluation using a questionnaire designed to collect: personal data; regular follow up of the acute episodes and the subsequent attacks; adherence to the zinc therapy and occurrence of death and
3. Complete clinical examination with special attention to nutritional status, dehydration status and chest examination.

Both groups were followed by observing and reporting the different outcomes mentioned in the record data form: name, age, sex, residency, weight, height, date of the first episode and its duration and frequency of stools, acceptability of the zinc medication, adherence to the treatment, as well as the number of episodes, amount and frequency in each episode, the duration of hospital stay, if any, and death and its cause, if any. It was very difficult to measure the amount of each motion so that we trained the data collectors and the parents to approximate the amount. Training was given to the care givers and data collectors to approximate the amount of stools per motion according to accommodation of the diaper to each motion.

Study definitions

An acute diarrhoeal episode was defined as three or more loose, liquid stools or at least one loose stool containing blood in a 24 hour period. An acute diarrhoeal episode, which led to inclusion of the patient, was defined as one that started during the 48 hours before the visit to the centre. Resolution is defined as three consecutive days free from disease. The diagnosis of under nutrition was based on the WHO's The Use and Interpretation of Anthropometry, which uses using weight for age, weight for height and height for age. Stunting was defined as height for age <2 standard deviations, while wasting was defined as weight for height < 2 standard deviations and under weight as weight for age < 2 standard deviations.

Table 1: ***Distribution of enrolled children, both groups, according to age, sex, and height***

Treatment group		Mean	Std. deviation	Std. error Mean	P value
Age	Intervention	months 14.10	9.778	1.042	<0.05
	control	months 14.38	11.383	1.187	
weight	Intervention	KG 8.167	2.2953	0.2447	<0.05
	control	KG 8.776	5.9102	0.6162	
Height	Intervention	cm 71.856	9.9799	1.0639	<0.05
	control	cm 71.217	11.1639	1.1639	

statistical analysis

Data were collected and analysed using the SSPS programme for data analysis, and appropriate tests were used to test significant differences; *p* value of less than 0.05 was considered significant.

ethics

The ethical review committees of the hospital approved the study procedures. Because this was a community based treatment trial, we obtained consent from parents that explained the purpose of the study and the potential risks and benefits of the new treatment. We obtained verbal or written informed consent for data collection (depending on education of the parent) from parents of both the intervention and comparison group children. Verbal consent was taken from the few who were illiterate or where the data collectors did not take the written consent in the first visit. The majority provided written consent.

results

In this double blind controlled randomized study, 180 children were enrolled with 92 in the control group and 88 in the intervention group. Ten children were excluded from the study because of the discovery of underlying chronic diseases after enrolment and other ten children dropped out during the period of follow up due to difficult communication, 6 from the intervention group and the rest from the control group. The mean age of the children was14.10 months in the intervention group and 14.38 months in the control group. In the intervention group, 56 (63.6%) were males; 32 (36.4%) were females. In the control group, 51 (55.4%) were males and 41 (44.6%) were females. The two group were not statistical significant in term of gender.

Mean weight and height among the enrolled children are illustrated in Table 1. It shows that there were no significant differences in the age, weight and height between the intervention and control groups.

There were no significant differences in the mean duration of the initial attacks of diarrhoea (before starting intervention) between the two groups [Table 2].

The mean durations of the initial attack (in days) in both groups were not significant; for the intervention group = 6.62 ±1.369; for the control group = 6.43 ±1.181.

The mean number of diarrhoeal episodes during the follow up period was significantly lower in the intervention group compared to the control group (Table 2 and Figure 1]. The mean frequency of motions in each

Table 2: ***Mean number of episodes, mean frequency of stool in these attacks and mean duration of hospital stay during follow up***

	Treatment group	Mean	Std. Deviation	Std. Error mean	*p* value
Mean No. of episodes during follow up	Intervention	1.39	1.077	0.115	<0.05
	control	2.59	1.224	0.128	
Mean frequency of motions in episodes during follow up	intervention	3.57	2.116	0.226	<0.05
	control	5.47	1.708	0.179	
Mean Duration of hospital stay(day)	Intervention	2.00	0.000	0.000	<0.05
	Control	3.17	0.983	0.401	

Table 3: ***Acceptability of Zinc syrup and placebo to children in both groups***

	Treatment group	Yes		No			*p* value
		n	% within group	n	% within group	Total	
Acceptability	Intervention	80	90.9%	8	9.1%	88	<0.05
	Control	70	76.1%	22	23.9%	92	<0.05

episode during the period of follow up was significantly lower in the intervention group.

Zinc was acceptable regarding palatability more than the control syrup, as shown in Table 3.

The data collectors had trained the mothers to assess approximately the amount of stools; the results showed that Zinc was able to reduce the average amount of stools per motion during the follow up period as shown in Table 4 and Figure 2.

On the whole, the present study suggests that zinc did not decrease the duration or the frequency of diarrhoea in the initial attack. No mortality was reported during the study or subsequent the follow up period in either group.

DISCUSSION

In our study population, 88 children received zinc supplementation during and after diarrhoea, with ages ranging from 3 months to four years. There was a downward trend in the incidence of further episodes of diarrhoea and in the mean frequency of motions in each episode during the follow up period in the zinc treatment group, but not in the comparison group, suggested a benefit of zinc. The reductions in duration of diarrhoea, although not significant, also suggest a benefit of zinc.

In a randomized controlled study in India in 2002, [11]zinc supplementation substantially reduced the incidence and severity of diarrhoea, the two important determinants of diarrhoea-related mortality and malnutrition. This intervention also substantially reduced the proportion of children who experienced recurrent diarrhoea.

The reduction in the duration of diarrhoeal episodes is consistent with earlier studies.[12] A meta-analysis of five studies of zinc treatment for acute diarrhoea found a summary estimate for reduction in duration of 16%. Possible mechanisms for the effect of zinc treatment on the duration of diarrhoea include improved absorption of water and electrolytes by the intestine, [13] faster regeneration of gut epithelium, increased levels of enterocyte brush border enzymes, [14] and enhanced immune response, leading to early clearance of diarrhoeal pathogens from the intestine.

Several controlled trials have shown a preventive effect of routine zinc supplementation on the incidence of diarrhoea[15] and acute lower respiratory infection. However, these studies provided daily zinc supplementation for a period of 6-12 months, which is often not feasible in large scale programmes. Three studies, in which zinc was given for two weeks during and after diarrhoea, found reductions in episodes of diarrhoea in the subsequent two to three months period without additional zinc.[4, 11, 16] The same result were found in a previous study, in which the zinc-supplementation group showed a decrease of 39 percent (95 percent confidence interval, 6 percent to 70 percent) in the mean number of watery stools per day ($p = 0.02$).[17]

Table 4: ***Average amount of stools per motion during follow up period***

	Average Amount of stool per motion in attacks during follow up period						***p* value**
	Mild		**Moderate**		**Large**		
	No.	**% within group**	**No.**	**% within group**	**No**	**% within group**	
Intervention	64	73.6%	4	4.6%	0	O%	< 0.05
Control	56	61.5%	22	24.2%	9	9.9%	
Total	120	67.4%	26	14.6%	9	5.1%	

The lower rates of additional episodes of diarrhoea in this and other studies indicate that the reduction in incidence could be due to a systemic effect of zinc, probably through enhanced immune function. The reduction in hospital admissions for diarrhoea could have been due to effects of zinc on episode duration, or reduced incidence. An important aspect of our study is that it shows a reduction in the volume of each bowel motion in the subsequent episodes from the use of zinc as a treatment for diarrhoea, although in this study we depended on the care taker evaluation in determining the stool volume. Three acute-diarrhoea trials with appropriate outcome measures all found reductions in diarrhoeal severity in zinc-supplemented children compared with control children. Of the two trials conducted in India, one found 18% fewer diarrhoeal stools per day ($p < 0.1$) [11] and the other found 39% fewer watery stools per day ($p < 0.02$). [15] In the only hospital-based trial of acute diarrhoea, zinc-supplemented children had a 28% lower measured diarrhoeal stool output per day ($p = 0.06$) [18.] The trial conducted in India reported a 21% lower diarrhoeal stool frequency ($p = 0.08$).[11] Two hospital-based trials in Bangladesh and India found a 37% lower measured stool output ($p < 0.02$) in zinc-supplemented children.[17, 19]

In a study that investigated the effect of zinc on the duration of illness and the stool quantity in acute watery diarrhoea of infants aged less than 6 months in 2002, Zinc supplementation did not affect diarrhoea duration or stool volume in young infants, although young infants tolerated zinc doses.[20]

A recently published randomised trial from India found a large reduction in overall mortality in infants who were small for gestational age and supplemented daily with zinc from 1 to 9 months of age.[11] In our study, there were no differences in mortality between the two groups and this may be due to a relatively small sample.

CONCLUSION

Zinc supplementation in this study substantially reduced the subsequent incidence of severe diarrhoea and frequency of motions, the two important determinants of diarrhoea-related mortality and malnutrition. This intervention also substantially reduced the proportion of children who experienced recurrent diarrhoea. The effects are large enough to merit routine use of zinc during acute diarrhoea in developing countries.

Prompt measures to improve the zinc status of deficient populations are warranted. The potential approaches to achieve this goal include: food fortification; dietary diversification; cultivation of plants that are zinc dense or have a decreased concentration of zinc absorption inhibitors; zinc supplementation for selected groups of children.

Future studies should assess the impact of increased zinc intakes on childhood mortality in developing countries. For facilitating intervention, there is a need to obtain reliable estimates of zinc deficiency, particularly in developing countries. Moreover, longer duration of zinc administration after the initial attack should be studied, for example a duration of 3-4 months of daily zinc supplementation. The intervention we evaluated is simple and inexpensive and can be incorporated into existing diarrhoeal disease control efforts.

ACKNOWLEDGEMENTS

This investigation received technical and financial support jointly from WHO Eastern Meditranean Region (EMRO), Division of communicable Diseases (DCD), and the Special Programme for Research and Training in Tropical Diseases (TDR)).

We also grateful to Professor Yeha Raja, Sanaa University, Department of Community Medicine, for his help and support during statistical analysis. We would like also to thank with appreciation Dr Omar Ali Baashour, paediatric specialist, Elsabeen Paediatric Teaching Hospital, Sanaa, and the rest of the paediatricians, general practitioners and nursing stuff in that hospital for their cooperation and support during the perod of data collection and follow up.

REFERENCES

1. Sazawal S, Black RE, Menon VP, Dinghra P, Caulfield LE, Dinghra U, et al. Zinc supplementation in infants born small for gestational age reduces mortality: a prospective, randomized, controlled trial. Pediatrics 2001; 108:1280-1286.

2. Sandest HH. Zinc deficiency : a public health problem. Am J Child 1991; 145:853-859.

3. Zinc investigators collaborative group.Therapeutic effect of oral zinc in acute diarrhoea. Am J Clin Nutr 2000; 72:1516-1522.

4. Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhoea and respiratory infections among rural Guatemalan children. Pediatrics 1997; 99:808-813.

5. Baqui AH, Black RE, El-Arifeen S, Yunus M, Zaman K, Begum N, et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of

antibiotics in Bangladeshi children. J Health Popul Nutr 2004; 22:440-442.

6. Surjawidjaja, Hidajat A, Lesmana M. Growth inhibition of enteric pathogens by zinc sulphate: an in vitro study. Med Princ Pract 2004; 13:286-289.

7. Juyal R, Osmamy M, Black RE, Dhingra U, Sarkar A, Dhingra P, et al. Efficacy of micronutrient fortification of milk on morbidity in preschool children. Am J Clin Nutr 2005; 82:1032-1039.

8. Walker CF, Black RE. Zinc and the risk for infectios disease. Ann Rev Nutr 2004; 24:255-275.

9. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of immune system and zinc status. Nutr 2000; 130:1399-1406.

10. Bhutta ZA. The Role of Zinc in health in developing countries. Indian Pediatr 2004; 41:429-433.

11. Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Mahalanabis D, Fuchs G. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997; 77:196-200.

12. Golden BE, Golden, MHN. Zinc, sodium and potassium losses in the diarrhoeas of malnutrition and zinc deficiency. In: Mills CF, Bremner I, Chesters JK, eds. Trace elements in man and animals TEMA 5. Aberdeen: Rowett Research Institute, 1985. p. 228-232.

13. Bettger WJ, O'Dell BL. A critical physiological role of zinc in the structure and function of biomembranes. Life Sci 1981; 28:1425–1438.

14. Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhoea and respiratory infections among rural Guatemalan children. Pediatrics. 1997; 99:808-813.

15. Sachdev HPS, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 1988; 7:877-781.

16. Sazawal S, Black RE, Bhan MK, Jalla S, Bhandari N, Sinha A, et al. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995; 333:839-844.

17. Sachdev HPS, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhoea in infants. Ann Trop Paediatr 1990;10:63-69.

18. Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D, et al. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997; 77:196-200.

19. Bhandari N, Bahl R, Taneja S, Strand T, Molbak K, Ulvik RJ et al. Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children. Pediatrics 2002; 109:e86.