Therapeutic and Biochemical Effects of Zinc Sulfate in Acute Diarrhea among Young Children

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Abstract

Background Zinc deficiency is prevalent in children in developing countries. Supplemental zinc provides therapeutic benefits in diarrhea.
Objectives: To evaluate the role of zinc supplementation in the recovery of hospitalized children on intravenous fluid for acute diarrhea.
Patients & Methods: A randomized control trial of 116 cases who were admitted to Karbala teaching hospital for children from October 2007 toAugust 2008 were enrolled in our study, the children aged 3 to 60 months old were divided into 2 groups, zinc group (57 cases) who received zinc for 14 days and control group (51 cases) who did not receive zinc. Zinc was given according to WHO guideline, 10 mg daily for infants up to 6 months of age, and 20 mg daily for older infants and children. General stool examination, serum k+, Na+, blood urea, and serum alkaline phosphates were done for all patients.
Results: Our study showed improvement in 16 patients (28.07%)of cases versus 5 (9.8%)in the control group (p value of 0.013) within the1st three days of treatment with zinc and52 patients (91.23%)versus 36 (70. 58%) [p value 0.017] 6 days after the treatment .
Conclusions: Zinc supplementation reduces the severity and duration of acute diarrhea in hospitalized children on intravenous fluid.
Abbreviations: IVF: intravenous fluid; ALP: alkaline phosphatase; ORS: oral rehydration solution.
Key words: Acute diarrhea, zinc, alkaline phosphatase, oral rehydration solution

الخلاصة

يعاني اطفال الدول النامية من نقص في الزنك, أعطاءالزنك يوفر فوائد علاجية في حالات الإسهال
الهدف: تقييم دور سلفات الزنك في علاج حالات الأسهال الحادة للأطفال اللذين يحتاجون السوائل عن طريق الوريد في المستشفيات.
الطريقة: تم تجربة مراقبة عشوائية من 116 حالة الذيدخلوا الى المستشفى التعليمي للأطفال في كربلاء من أكتوبر 2007 الى أغسطس 2008, واللذين تم تسجيلهم في دراستنا، أنقسم الأطفال ما بين 3 إلى 60 شهرا إلى مجموعتين مجموعةالزنك (57 حالة) واللذين حصلوا على سلفات الزنك لمدة 14 يوما, والمجموعة الضابطة (51 حالة) الذين لم يتلقوا الزنك. أعطيت الزنك وفقا لمبادئ منظمة الصحة العالمية ، 10 ملغ يوميا للرضع إلى 6 أشهر من العمر، و20 ملغ يوميا للاكبر عمرا من الرضع والأطفال. اجري فحص عام للبراز; البوتاسيوم, الصوديوم واليوريا في الدم، والفوسفاتيز القلوية في الدم لجميع المرضى.
النتائج:أظهرت دراستنا تحسن في 28،23٪ من الحالات مقابل 9.8٪ من مجموعة المراقبة (0،013p value) خلال ثلاثة أيام من العلاج مع الزنك و91،23٪ مقابل 70. 58٪ (0.017 p value) 6 أيام بعد العلاج.
الاستنتاج:علاج الزنك مفيد في علاج حالات الأسهال الحادة للأطفال اللذين يحتاجون السوائل عن طريق الوريد في المستشفياتويؤدي إلى خفض مدة وشدة الإسهال.

Introduction

Zinc is an essential trace element; the recommended dietary allowance for adolescent and adult males is 11 mg/day [1]. Zinc deficiency is an important problem in children and adolescents, particularly in developing countries. The true prevalence of mild zinc deficiency is

not known because of the nonspecificity of symptoms and imprecise diagnostic methods. Zinc deficiency occurs rarely in exclusively breast-fed infants (usually premature) whose mothers have a low level of zinc in their breast milk. The clinical presentation is similar to that of acrodermatitis enteropathica [2-5].Some investigators argue that plasma zinc measurements are relatively insensitive and that mild zinc deficiency occurs with normal plasma levels [7]. Zinc levels in neutrophils or lymphocytes may be more sensitive [8]. The criteria for zinc deficiency are decreased zinc level in either lymphocytes (<50 mcg/$10^{(10)}$ cells) or granulocytes (<42 mcg/$10^{(10)}$ cells) [9]. Depressed serum alkaline phosphatase levels for age provide supportive evidence for zinc deficiency [6].In one study, zinc supplementation for three or more months in children younger than 5 years of age reduced episodes of diarrhea, respiratory tract infections, severe diarrhea or dysentery, persistent diarrhea, and lower respiratory tract infections or pneumonias, with rate ratios between 0.75 and 0.95 [11].

A second study found that zinc supplementation given to children between two and five years of age in developing countries reduced the incidence of clinically confirmed pneumonia by 21 percent [12].

Zinc supplementation given to pregnant women reduces the frequency of diarrhea during infancy in their offspring [13].A possible mechanisms for the effect of zinc treatment on the duration of diarrhea include

1) Improvement absorption of water and electrolyte by the intestine [14].

2) Fast regeneration of gut epithelium [15].

3) Increase level of enterocyte brush border enzymes [16].

4) Enhancement immune response leading to early clearance of diarrheal pathogens [17,18].Although similar effects have not been demonstrated in all populations, the preponderance of evidence suggests that zinc supplementation reduces the severity and duration of acute diarrhea in children from populations in which zinc deficiency is common [20-22]. Based on these findings, the WHO recommends zinc supplementation for infants and children with acute diarrhea in developing countries,the supplements are given at a dose of 20 mg/day for children, or 10 mg/day for infants younger than 6 months old, for 10 to 14 days [21,23]. Zinc supplementation is probably helpful for treatment of acute diarrhea even in populations without zinc deficiency. A meta-analysis of 18 randomized trials concluded that the subgroup without zinc deficiency also benefitted from zinc supplementation [19]. This may be because zinc has specific local inhibitory effects on some enteric pathogens and toxins [27].The World Health Organization defines diarrheal episodes of greater than 14 days as persistent diarrhea. Persistent diarrhea is associated with higher mortality and greater adverse growth effects than is acute diarrhea [22]. Randomized, controlled trials in children with persistent diarrhea have generally shown that zinc supplementation reduces the severity and duration of acute and persistent diarrhea [10,19,20,22,24,25].Little toxicity occurs with zinc supplementation. Ingestion of up to ten times the recommended daily intake produces no symptoms. Intestinal absorption of copper is inhibited by zinc. Thus, chronic intake of zinc in excess of 100 mg per day may be associated with copper deficiency [26].

Patients and methods

The study was conducted at Karbala teaching hospital for children from October 2007 to August 2008. In this trial, children aged 3-60months who presented with diarrhea were enrolled. Diarrhea is defined as at least 3 or more loose stool per 24hr and consider terminated on the last day of diarrhea that was followed by at

least 24hr free of diarrhea. The children was considered to have acute diarrhea if duration was less than 14 days pre-enrollment.The following data base were collected:The duration of diarrhea prior to enrollment (<14days), character of stool (watery, semi formed, well formed, and bloody), degree of dehydration (no dehydration , some dehydration, severe dehydration according to standard WHO guide line), age, sex, body weight and height or lenght which are both measured by well trained person .Also the data included the diet of child (breastfed, formula fed, mixed, or family feeding), immunization status (according to primary health care system in Iraq), history of previous admission due to diarrhea, recent intake of antibiotics or zinc sulfate was also considered.Exclusion criteria included the following :

1. Recent history of drug use.
2. Failure to thrive (marasmus, kawshioerkor)
3. Extra intestinal cause of diarrhea like otitis media, tonsillitis.
4. Intractable diarrhea.
5. Respiratory distress.
7. Altered sensorium or any morbid condition that precluded the use of zinc
8. Prerenal or renal failure.
9. Vomiting the zinc frequently and did not use it.
10. Patient receives oral rehydration therapy.

The children were allocated to treatment group following a preliminary clinical assessment to determine if they had any exclusion criteria. Children who had severe dehydration (WHO guidline) or inability to drink were temporarily excluded for 4hr during which they received standard treatment, at the end of this period they reassessed for possible inclusion. The cases were divided into 2 groups

1. Zinc group2. control group

For both groups, general stool examination, blood urea, serum k+, Na+ and ALP were done.All patient provided other usual support care with antibiotics and IVF.ALP (zinc related enzyme) was used as an indicator of increasing plasma zinc which was not available in our hospital. It was measured in both groups and 2nd measurement was done in zinc group after 4 days of treatment with zinc sulfate tablet to assess indirectly the response of increasing plasma zinc. Zinc sulfate tabletsare available in 2 forms, 10mg, 20mg given to the patients (according to WHO guideline) 10 mg daily for infants up to 6 months of age, and 20 mg daily for older infants and children. If vomiting occurs within 1hr after intake of zinc, another oral dose was given (by dividing dose regime) and the patient was excluded from the study when did not tolerate the dose or because of persistent vomiting. In present study, ORS did not introduce for the patients , and we depended on the IVF onlyfor rehydration according to WHO guide line , and when the patients can tolerate oral intake we offeredto themtheir ordinary feeding prior to illness and supplemental fluids.The children were assessed at the same time every 24hr till discharge.The time taken to rehydrate the patient from time of admission, episode of vomiting , frequency and consistency of stool , amount of IVF,body weight assessment, all these were daily recorded.

The improvement of the patient was considered when all of the following present:

1. Bowel motion decrease below 3 times /day and the last day of diarrhea was considered when followed by 24hr diarrhea free period.
2. General examination reveals improvement of general condition and state of hydration.
3. No more need for IVF.
4. Patient stopped vomiting.

Results

A total of 116 children presented with acute diarrhea were enrolled in the study.

We excluded8 patients from the studybecause they had one or more exclusion criteria; 108 children were randomized to treatment.Zinc group were 57 patients while control group were 51. Males were33 patients (57%) and females were 24(43%) ;whilein control group, males were 25 patients (49%) and female were26(51%).The mean of the age in zinc group was 15.07 months while the mean in control group was 18.16months.The child diet in zinc group ,27 patients (47.3%) were breastfed,12(21.2%) were formula fed, and18(31.5%) were mixed fed; while in controle group, 25 patients (49.1%) were breastfed, 4(7.85%) were formula fed, and 22(43.14%) were mixed fed. The mean body weight in control group was 10.24 kg while in zinc group was 9.85 kg .There was an increase in body weight for both groups on discharge ,the increment in control group was 1.27% ,while in zinc group was 2.53%.The normal value of ALP is 145-420 u/l which is more than adult . Table (1) shows the mean ALP in both group and the mean of ALP in zinc group on 4th day after zinc initiation. The total days of admission for zinc group was 205 days with mean of 3.6 days versus 263 days with mean of 5.16 days in the control group. The number of patients who received IVF in zinc group were 52 (91.2%) while those who did not received IVF were 5 (8.8%), in addition vomiting was found in 43 patients (75.4%) ;while number of patients who received IVF in controle group were 47 patients (92.1%) ;Vomiting were found in 40 (78.43%) of them .

In zinc group , 2 patients (4.65%) stopped vomiting in the first 24 hours and 41 (95.35%) thereafter, while in controle group , 4 patients (10%) stopped vomiting in the first 24 hours and 36 (90%) thereafter.

After initiation of zinc to the patients, the clinical response with comparision to control group is summarized in Table (2).

The outcome of diarrheal duration of both group in breast fed child is shown in Table (3). Table (4) shows the outcome of diarrheal duration in formula fed patient for both groups. According to the age, the clinical response was different in infants and toddlers , the outcome of diarrheal response in relation to the age group is illustrated in the Tables(5,6).Table (7) lists the outcome of vomiting among them after zinc supplementation.

Table 1. The mean of ALP in both groups

Statistics	Zinc group in 1st day N=57	Zinc group in 4th day N=57	Control group in 1st day N=51
Mean ALP	124.8 U/L	164.39 U/L	123.37 U/L

Table 2. The outcome of diarrheal duration after initiation of zinc supplementation

Time	Zinc group No=57	%	Control group No=51	%	P value
≤3 days	16	28.07	5	9.8	
4-- 6 days	36	63.16	31	60.78	0.017
≥ 7 days	5	8.77	15	29.41	0.05

Table 3. The outcome of diarrheal duration of both group in breast fed children

Breast fed group	No. of patients improved in1st3days	%	Non improved	%	P valueof the improved	Total
Zinc group	11	40.74	16	59.26	0.014	27
Control group	3	12	22	88		25

Table 4. The outcome of diarrheal duration of both groups informula fed children

Bottle fed group	No. of patients improved in the 1st 3 days	%	Non improved	%	P value of the improved	Total No
Zinc group	4	33.33	8	66.67	0.019	12
Control	0	-----	4	100		4

Table 5.The outcome of diarrheal duration of both group below 1 year age

Age < 12 mo No=59	Zinc group No=35	%	Control group No=24	%	P value of improved
No. of improved In the 1st 3 days	7	20	2	8.33	0.19
Non _ improved	28	80	22	91.67	

Table 6. Theoutcome of diarrheal duration of both group above 1 year age

Age ≥12 mo No = 49	Zinc group No= 22	%	Control groupNo=27	%	P value of improved
No. of improved In 1st 3 day	9	40.9	3	11.11	0.016
Non _ improved	13	59.1	24	88.89	

Table 7. The outcome of zinc group, single versus divided dose regimen

Dose	Total No	Single dose regimen No	%	Divided dose regimen No	%	P value
10 mg	9	7	77.78	2	22.22	0.0075
20 mg	48	17	35.42	31	64.58	0.003

Discussion

In our study, children who received zinc supplementation during diarrheal episode had improvement within 72 hr in 28.07%of cases versus 9.8 %inthe control group with p value of (0.013) and after 6 days ,the improvement increased to (91.23%) versus (70.58%)in the control group with p value (0.017). This result was in line with other 3 studies in India [28,29,30].A meta analysis of 5 studies of zinc treatment for acute diarrhea found a summary estimate for reduction in duration 16% which support our study [31]. The total days of admission for zinc group was 205 days with mean of 3.6 versus 263 days with mean of 5.16 in the control group ; this indicate that zinc treatment has a direct effect to decrease duration of admission which was supported by zinc investigators Collaborative group study[31].Somewhat better results observed in other studies done in Al- Naharin hospital, Iraq (72% versus 40%) [32], Nepal [33] (65%versus 39%), West Bengal [34](70% versus 42%), and New Delhi study [35] (66%versus 38%) is probably due mixing the ORS with the zinc ,this difference in improvement is due to it's direct effect. On the other hand ,our study showed that there was a good response in breastfed zinc group compared to breastfed control group (40.74% versus 12% with p value of 0.014) and to formulafed zinc group(40.74% versus 33.33%);this probably due to the role of breast milk in enhancing the efficacy of zinc absorption from the intestine and the presence of calcium in milk in high concentration decreased zinc absorption from intestine by competition[36] .This effect of breast milk on zinc absorption may be the cause of acrodermatitis enteropathica after weaning of breast milk to cow milk [37]. Formulafed zinc group showed better response compared to bottle fed control group (33.33% versus 0% in the 1st 3 days of treatment) with p value of 0.019 which enhance the significant of zinc supplementation in treatment of acute

diarrhea in formula fed children. According to age group, infants showed 20% response compared to 8.33% in the control group with (p value of 0.19)which was statistically insignificant, this may be due to small sample in our study; while in those children > 12 months old showed better response (40.9 % in zinc group versus 11.11%) in control group [p value of 0.016].This difference in response between infants and older age group was statistically insignificant (p value of 0.1) and this was supported by other studies done in Al –Naharin hospital[32] and North India study[38]

Vomiting was very common In both groups (75.40% in zinc group versus 78% in control group)in the 1st 24 hr,it could be attributed to the illness itself , but onthe 2nd day ,all patients stopped vomiting after the initial treatment with IVF , the response to treatment were (95.35% of zinc group versus 90% in control group) . Zinc was given to those patient after 2hr of stopping vomiting and watched for 1hr if vomiting recurred. Zinc group patient who were given10 mg dose had an increased risk of vomiting (22.22%) comparedto 20mg dose regimen (64.58%). The low dose of zinc (10mg) was better tolerated as a single dose regimen with (77.78% response versus 22.22% vomiting with p value of 0.0075), while the high dose of zinc (20mg) was better tolerated as divided dose regimen rather than single dose regimen (64.58% divided doses versus 35.42% single dose regimen with p value of 0.003. This indicates that there is anincrease in the incidence of vomiting with increasing the dose andto overcome this problem by using divided dose regimen, which was similar with other study in Dhaka hospital [39].Vomiting in response to metallic taste could be expected to occur sooner while toxic zinc blood level are more likely to lead to later repeated vomiting which did not occur in our study. Although, we did not measure plasma zinc (not available in our hospital) to evaluate biochemical response, we depended on zinc related enzyme measurement which is ALP. The mean ALP in both zinc and control group at time of admission (124.8u/l versus 123.3 u/l); this indicates that there was a low level of ALP in response to decreased level of zinc in diarrheal patient. After 4 days of treatment with zinc, the mean ALP reached 164.34 u/l (normal value 145-425u/l). This indicates that there was an increase in plasma zinc which was reflected by an increased ALP.

Conclusions

1) The use of zinc sulfate in the management of acute diarrhea is effective in decreasing severity and duration of illness, even in the absence of preexisting zinc deficiency.
2) The use of divided dose regimen is preferable than single dose regimen in decreasing the incidence of vomiting

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