Original article

Effect of Zinc supplementation in treatment of acute diarrhoea among 2-59 months children treated in Black Lion Hospital, Addis Ababa, Ethiopia

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Abstract

Background: Diarrhoeal disease is one of the major causes of morbidity and mortality in under five children. Worldwide, there are about 1.3 million under five children deaths attributable to diarrhea. Health status in Ethiopia is one of the lowest in the world with estimated health service coverage of 60%; and diarrhoeal disease remains one of the major causes of under five morbidity and mortality. Treatment with ORS does not affect the duration and severity of diarrhoea, hence acceptance of ORS is low and diarrhoea still remains the major cause of child morbidity and mortality. Diarrhoea is a commonly associated problem in children with Zinc deficiency and also leads to excess zinc losses.

Objective: To assess variations in the usage of antimicrobial and/or antidiarreals in children with acute watery diarrhoea randomized to receive zinc supplementation as compared to those who do not receive it; and assess the adherence to zinc supplementation given with ORS in the management of an episode of acute watery diarrhoea.

Methodology: This is part of a multicentre, multi-disciplinary, randomized and open effectiveness trial conducted in out-patient settings in Addis Ababa, Black Lion Hospital at the Department of Paediatrics. The sample size has been calculated for a two-tailed alpha of 0.05 and power of 0.2. Children aged 2-59 months and who presented with acute watery diarrhoea for less than 7 days were recruited.

Results: There were 188 children randomized to the Zinc plus ORS arm and 226 children to the ORS arm. There were 193 (46.6%) females and 221 (53.4%) males. Fifty two percent of the cases were between 2-11 months of age and decreasing trend of proportion of older children was observed in the study population (P=0.0001). Zinc adherence rate was 95%. Seventy three (39.3%) patients from Zinc + ORS group and 71 (32.3%) patients from ORS group took ORS when they came for the first follow up visit (P-value=0.115). From the total study subjects 16.1% took antibiotic or antidiarhael tablets before randomization which was significantly higher than the second follow up visit observation with only 1.7% (P=0.0001). Only 3 (1.7%) patients from Zinc arm and 4 (1.8%) patients from ORS arms took antibiotic/anti diarrhoeal on the second follow up visits.

Conclusion: Proper counselling of care takers significantly reduces unnecessary use of antibiotic/anti diarrhoea drugs in the treatment of childhood diarrhoea. Zinc supplementation in the treatment of childhood diarrhoea is well tolerated by patients and there is good compliance of care takers. However, we could not observe any significant difference in antibiotic/antidiarheal drug use between ORS and ORS plus Zinc groups. [*Ethiop.J.Health Dev.* 2008;22(2):187-190]

Background

Diarrheal disease is one of the major causes of morbidity and mortality in under five children (1, 2). Worldwide, there are about 1.3 million under five children deaths attributable to diarrhea. Health status in Ethiopia is one of the lowest in the world with estimated health service coverage of 60%. Various reports have shown that diarrheal disease is one of the major causes of mortality and morbidity in under five children next to lower respiratory tract infection. In a nationwide rural survey 12.5% of 6-59 months of children had diarrhea in the two weeks period prior to the survey. It is estimated that 230,000 under five children die due to diarrhea. The median incidence of diarrhea was estimated to be 5 episodes /child/ year (3-6). Since the introduction of ORS, many lives have been saved by oral rehydration therapy. Treatment with ORS does not affect the duration and severity of diarrhea so that the acceptance of ORS is low and hence diarrhea still remains the major cause of child morbidity and mortality. Diarrhea is a commonly associated problem in children with Zinc deficiency and diarrhea also leads to excess zinc losses (7-14). Evidence over the years has shown that zinc supplementation reduces the duration and severity of diarrhea (9). Zinc is found to be safe in HIV infected children and also is known to reduce morbidity in these children (13). The focus of this research is on the implementation of adjunctive Zinc therapy as part of the management of acute diarrhea, and on feasibility and cost-effectiveness of zinc supplementation. The primary and secondary specific objectives of this study are:

The primary objectives of the study wer to assess variations in the usage of antimicrobial and/or antidiarreals, along with the duration of use, in children with acute watery diarrhea randomized to receive zinc supplementation as compared to those who do not receive it, and to assess the adherence to zinc supplementation given with ORS in the management of an episode of acute watery diarrhea.

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Secondary objectives include: to assess the frequency of adverse effects of zinc supplementation, namely vomiting as compared to those who do not receive it, assess variations in treatment failures in children with acute watery diarrhea randomized to receive zinc supplementation as compared to those who do not receive it, and to characterize children most susceptible to acute watery diarrhea disease

Methods

This is part of a multicentre, multi-disciplinary, randomized and open effectiveness trial which was conducted in out-patient settings in Addis Ababa, Black Lion Hospital at the Department of Pediatrics. The sample size has been calculated to detect a difference of US $ 2.00 with a standard deviation of US $ 2.00 for a two-tailed alpha of 0.05 and power of 0.2. We require a minimum of 20 subjects with clinical failures or clinical cure in each arm of the trial. Since we assumed a 10% failure rate, the adequate sample size became 400 subjects for analyzing differences in the cost of treatment of failures and cures. The protocol was submitted to the local ethics review committee and ethical clearance was obtained before the start of the study. In the initial formative component of the study, appropriate messages were identified and that was given along with ORS or Zinc + ORS. Baseline assessment was done for eligibility of children and consent forms signed.

Children aged 2-59 months and who presented with acute watery diarrhea for less than 7 days were recruited. Children residing in areas too far or unsafe for follow up, requiring antimicrobial for other conditions, immuno-compromized (severely malnourished or with known primary immune deficiency) excluding cases of measles or those with reported HIV positive status, those with special fluid requirements such as those with renal diseases, heart and hepatic failure, with chronic or persistent diarrhea and dysentery, requiring hospitalization or admitted for in-patient care or on zinc supplementation and whose parents/guardians do not consent to participate were excluded.

Assignment to Zinc + ORS or ORS alone was based on randomly selected days and preformed questionnaires were filled. The day allocated to a particular treatment type was known only on the day of recruitment. The parents were given the intervention along with appropriate messages verbally. The care giver was instructed to give two tablets of Zinc dissolved in 5 ml of clean water or breast milk (each containing 10 mg) once daily between meals for 14 days. The first dose was given before the children leave the hospital. The care givers are then advised to bring unused zinc tablets when they come for follow up. If a child is allocated to the ORS group, instructions were given on how to give and prepare ORS and demonstrations were conducted before the parent leaves from the hospital. The parents were given appointments to come on day 3 and then day 15. Outcomes of interventions were assessed on the first and second follow-up visits. Data entry, cleaning and analysis was done using SPSS software version 11.

Results

From Nov 2003-Dec 2004, 783 children within the age range of 2-59 months and with the problem of acute watery diarrhea attended our diarrheal disease treatment unit. 369 children who did not fulfill the criteria were excluded from the study. 414 eligible children were randomized. There were 188 children randomized to the Zinc plus ORS arm and 226 children to the ORS arm. There were 193 (46.6%) females and 221 (53.4%) males (Table 1). Fifty two percent of the cases were between 2-11 months of age and decreasing trend of proportion of older children was seen in the study population (P=0.0001) (Table 1).

Table 1: **Sex and age distribution of children with acute watery diarrhea recruited in the study, Black Lion Hospital, Addis Ababa, November 2003-December 2004**

	No	Percent
Sex		
Male	221	53.3
Female	193	46.7
Age		
2-11 months	218	52.5%
12-24 months	148	35.7%
25-36 months	29	7%
37-59 months	19	4.5%

From Zinc and ORS groups 179 and 222 children successfully completed the study respectively. The response rate was 96.9%. The maximum number of children was recruited in December 2003 and the lowest in June 2003 (Table 2). Thirteen (3.1%) patients were lost to follow up on day 3, while one patient (0.2%) was lost to follow up on day 15. There were 9 non-adherent cases from Zinc arm. Zinc adherence rate was 95% (Table 2). Seventy three (39.3%) patients from Zinc + ORS group and 71 (32.3%) patients from ORS group took ORS when they came for the first follow up visit (P-value=0.115). Only 35% of the study population took ORS a day before the first day of follow up. There were 2 patients from Zinc arm who were hospitalized due to severe illness and treated according to hospital protocol and were discharged improved. No deaths were reported.

The mean age of the recruited patients was 13 months (9.7 SD), while the mean weight was 8.37 kg (2.49 SD). The mean duration of illness was 3.7 days. There was vomiting in 110 (58.8%) and 150 (66.7%) of the Zinc and ORS group respectively (P-Value=0.502). From the total recruited patients 261 (63.2%) had vomiting during presentation. The average number of tablets consumed during day 3 was 6.4 and 170 (94.9%) of the patients took four or more tablets on day 3. The average number

Table 2: **Comparison of treatment performance in Zinc and ORS group among acute watery diarrhea cases recruited in the study, Black Lion Hospital, Addis Ababa, November 2003- December 2004.**

Intervention type	Zinc plus ORS	ORS	Chi-square	P-Value
Total recruitment	188	226		
Zinc supplementation adherence (%)	170 (90.4%)	-		
ORS use: Day 3 (N, %)	73(39.6%)	71 (32.1%)	2.48	0.115
Antibiotic/ anti diarrheal use: Day 3(N, %)	1(0.6%)	3 (2.5%)	3.2	0.94
Antibiotic/antidiarrheal use: Day 15-17 (N, %)	2 (1.7%)	1 (0.8%)	0.55	0.46
Loss to follow up (day 3)	9 (4.7%)	4 (1.7%)	3.06	0.08
Loss to follow up (day 15-17)	1	0	1.2	0.27

of tablets consumed during day 15-17 was 27.9 and 170 (94.9%) patients took 23 or more tablets on day 15-17. From the study subjects 16.1% took antibiotic or antidiarhael tablets before randomization. This was significantly higher than the second follow up visit observation with only 1.7% (P=0.0001) (Table 3). Only 3 (1.7%) patients from Zinc arm and 4 (1.8%) patients from ORS arms took antibiotic/anti diarrheal on the second follow up visits. The mean duration of antimicrobial/anti diarrheal used on the second follow up visit was 2.2 days and 2.5 days for ORS and Zinc arms respectively. Forty six (25%) patients and 37 (16.1%) patients from zinc and ORS groups respectively did have vomiting on the first follow up visit (P=0.04). Seven (4%) of patients and 6 (2.7%) of patients from Zinc and ORS groups respectively had vomiting on the second follow up visit. Three (0.8%) patients and 4 (1%) of patients from Zinc and ORS groups respectively had therapeutic failure on the first follow up visit but non had therapeutic failure on the second follow up visit (Table 4).

Table 3: **Use of antibiotic/antidiarheal drugs before and after intervention among the study population, Black Lion Hospital, Addis Ababa, November 2003- December 2004**

Use of	Antibiotics/Antidiarheal		Total	Chi-square	P-Value
	Yes	No			
Before intervention	16.1%	83.8%	100%	50.97	0.0003
After intervention	1.8%	98.2%	100%		

Table 4: **Outcome of the intervention in the two arms in the first follow up visit, Black Lion Hospital, Addis Ababa, November 2003- December 2004.**

Intervention type	Outcome of treatment (3-5 days)				X^2	P-Value
	Diarrhea Stopped	frequency decreased	same	worsened		
Zinc plus ORS (No= 179)	99 (53.8%)	62 (32.7%)	20 (10.9%)	2 (1.6%)	1.099	0.777
ORS (No=222)	121 (53.8%)	75 (33.9%)	19 (8.6)%	6 (2.7%)		

Discussion

In this study, the numbers of male patients is some how similar to the number the females. Gastroenteritis affects both sexes almost equally. About 53% of the cases were in the age range of 2-11 months and decreasing trend of proportion of older children was observed in the study population. This indicates that infants and younger age children are more susceptible for acute diarrhea causing organisms. The seasonal distribution of patients was in agreement with previous observations in our diarrheal unit in Addis Ababa.

There were two picks of patient enrolment during November-Dec 2004 and Mar-April 2004. Almost equal number of patients from Zinc arm and ORS arm took ORS when they came for the first appointment visit which showed that Zinc supplementation during acute watery diarrhea did not affect use of ORS. The average number of tablets consumed during the second follow up visit was 27.9. There was high consumption (>90%) of the recommended Zinc tablets. Though pre-randomization medical costs were not calculated, it was observed that the use of antimicrobials/anti diarrheals on both arms was significantly reduced after the randomization. This could be an indirect indicator of reduction in the medical cost of treatment which resulted following proper consultation. There was no difference in using antimicrobials/anti diarrheas between the two arms probably because of the project staff's instructions during recruitment. Therapeutic failure rate as defined in this study was 2.5% from Zinc arm and 3.3% from ORS arm. There was no difference in the clinical failure rates in the two arms of the trial. Diarrhea associated vomiting in our patients (66.9%) is very high as compared to other reports. On the first follow up visit the number of cases who had vomiting was reduced to 84 (21%). There were significantly higher numbers of cases of vomiting in the Zinc arm as compared the ORS arm. Previous studies have shown that vomiting is one of the most important side effects of zinc administration (15). This was also observed in our study during the first follow up visit. In the second follow up visit, vomiting was reported on 7

(1.8%) of cases in Zinc arm and 6 (1.5%) of cases in ORS arm. The rate of vomiting was significantly reduced in both arms and there was no significant difference between the two arms during the second follow up visit. During the first follow up visit, 160 (89.4%) of children among Zinc arm had their diarrhea stopped or markedly decreased in frequency while 18 (10.0%) of children had their diarrhea remained the same or worsened. In the ORS arm, 187 (84.2%) of children had their diarrhea stopped or markedly decreased in frequency while 35 (15.7%) of children had their diarrhea remained the same or worsened. In the second follow up visit, the outcome was the same. Though the outcome of treatment in the two arms was not statistically different (P=0.61), children in the zinc arm had their general well-being and appetite improved in the appetite scale, their care takers were also happy in the first follow up visit. Previous reports have shown that 20 mg of zinc daily for 14 days not only reduces the duration of diarrhea, but also subsequent episodes of diarrhea (17, 18).

Conclusion

Children of under one year of age were at increased risk of developing acute watery diarrhea than the older children. Apart from promoting good hygiene and sanitation practice, identifying the cause of acute diarrhea in young children is warranting in designing appropriate strategy to reduce diarrhea diseases morbidity and mortality among children.

Proper counselling of care takers significantly reduces unnecessary use of antibiotic/anti diarrhea drugs in the treatment of childhood diarrhea. Zinc supplementation in the treatment of childhood diarrhea was well tolerated by patients and there was good compliance of care takers. However, we might need to conduct further large scale study to investigate the impact of zinc supplementation in the treatment of childhood diarrhea in our set up.

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