The Role of Zinc and Vitamin A Supplementation in Young Children with Persistent Diarrhea

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دور إعطاء عنصر الزنك(الخارصين) وفيتامين A في علاج الأطفال المصابين بحالات الإسهال المتواصل

خلاصة البحث

إن نقص عنصر الزنك و فيتامين A حالة شائعة عند الأطفال في العالم الثالث.المعروف أن إعطاء عنصر الزنك و فيتامين A ذا تأثير علاجي فعال في معالجة الأطفال المصابين بسوء التغذية و الإسهال المتواصل persistent diarrhea .

الهدف من هذه الدراسة هو إثبات مدى تأثير إعطاء عنصر الزنك و فيتامين A للمرضى المصابين بسوء التغذية و الإسهال المتواصل persistent diarrhea .

أجريت هذه الدراسة في مستشفى كربلاء التعليمي للأطفال على ١١٧ طفلا مصابين بسوء التغذية و الإسهال المتواصل (persistent diarrhea) الذي يعرف بأنه (الإسهال المتواصل لأسبوعين على الأقل و مصحوبا بتأثير سلبي على النمو) وبعمر ٦- ٢٤ شهرا .قسم الأطفال تحت الدراسة إلى مجموعتين : المجموعة (أ) العلاجية (Zinc and vitamin A Group) وعددها ٥٩ والمجموعة (ب) مجموعة المقارنة(control group) و عددها ٥٨ .

المجموعة (أ) قد أعطيت عنصر الزنك و فيتامين A إضافة للعلاج الغذائي والمجموعة (ب) مجموعة المقارنة أعطيت العلاج الغذائي فقط.

قياسات الوزن و الطول وحسب جداول النمو إضافة لعلامات الاستجابة السريرية أخذت للمجموعتين لغرض المقارنة عند الدخول الى المستشفى وبعد ٧ و ١٤ و ٢٨ يوما على التوالي بعد خروج المريض من المستشفى.

وكانت نتائج البحث كما يلي:كانت المعلومات الأولية عند الدخول مقارنة بين المجموعتين محل البحث ومعدل الاستجابة للعلاج و التحسن ألسريري كانت أعلى (٨٦ %) في المجموعة (أ) بالمقارنة مع المجموعة(ب) ٤٨ %.

النتيجة النهائية التراكمية لزيادة الوزن بعد ٢٨ يوما من المعالجة كانت واضحة إحصائيا عند أطفال المجموعة(أ).

نتائج البحث دلت على إن إعطاء الزنك و فيتامينA تقلل من كمية و عدد مرات الخروج stool output و تؤدي إلى استجابة و تحسن مبكر للحالة مما يعني لنا ضرورة جعل المادتين ضمن البرنامج المعتمد في معالجة الأطفال المصابين بسوء التغذية و الإسهال المتواصل .

Abstract

Background: Zinc deficiency is prevalent in children in developing countries. Supplemental zinc and vitamin A provides therapeutic benefits in persistent diarrhea.

Objective: To evaluate the effect of supplemental zinc given with vitamin A therapy in the management of persistent diarrhea.

Design: The study was conducted in Karbala Teaching Hospital for Children. Children of the age 6-24 months with persistent diarrhea (diarrhea that last for at least 14 days with growth faltering)were enrolled in this study. The children randomly assigned to two groups; group A(n=59) received zinc supplement 3-5 mg/kg/day of elemental zinc sulfate in a single daily dose for 14 days and vitamin A 100000 units to children 6-12 months old and 200000 units to children above 12 months and control group (group B) (n=58).Both groups received nutritional support with a rice-lentil (Khitchri), yogurt and home available diets was initiated, Breastfeeding was continued as required and low osmolality oral rehydration solution was used also .Stool output, (consistency, frequency) and body weight were recorded daily during days of admission (3-5 days). Stature, occipito-frontal circumference, weight-for-age, stature-for-age percentile are defined on standard growth charts and weight for height SD were determined. These anthropometric measurements were repeated at days 7, 14, and 28 after discharge from hospital.

Results: The baseline characteristics of the 2 study groups were comparable. The total diarrheal stool output, (consistency, frequency) among the 2 groups over 3-5 days were significantly different. The percentage of children who had clinical recovery (passage of soft stool was taken as recovery) within 5 days were significantly greater in the zinc and vitamin A group (86%) compared to the control group (48%). The net gain in the body weight over the 28day study period was significant only in the children receiving zinc and vitamin A group compared to the control group.

Conclusion: Zinc and vitamin A supplementation in persistent diarrhoea reduces stool output along with frequency, and promotes earlier recovery.

Introduction

Globally diarrheal diseases account for almost fifth of all deaths of children less than 5 years, with an estimated 2.3 million deaths annually [(1)]. Of these deaths, significant proportions are related to episodes of persistent diarrhea.

Persistent diarrhea (PD) is defined as episodes that began acutely but last for at least 14 days with growth faltering [(2)] .These criteria identify children with a substantially increased diarrheal burden and an increased rate of diarrhea-related deaths. Such episodes were recognized to account for 3 to 20% of all diarrheal episodes in children under 5 years [(3)] .In several large community-based studies of diarrhea it has been shown that PD is directly responsible for about 36% - 54% of all diarrhea related deaths. [(4,5)] It has, however, been pointed out that such differences in mortality between different regions may be related to environmental characteristics and differences in the utilization of health care and oral rehydration therapy [(6)]. Although PD accounted for only 5% of all diarrheal episodes in a large prospective study of diarrhea in north India, the case fatality rate for PD was 14% in comparison with 0.7% for episodes of shorter duration (acute) [(7)] .It is important to recognize that most cases of PD in developing countries represent post-infectious diarrhea. The majorities of cases of diarrhea in developing countries are of acute onset and are shorter than one week in duration. However, a group of children develop episodes of longer duration, some lasting longer than 14 days [(8)]. Although the aforementioned division of diarrheal episodes into acute

and PD may be arbitrary, this operational definition identifies children with significantly increased diarrheal burdens. It is recognized widely that most undernourished children with PD have associated deficiencies of micronutrients including zinc, and vitamin A. This may be a consequence of poor intake and continued enteral losses by frequent recurrences of acute diarrheal episodes which result in nutritional compromise and may predispose these children to develop PD.

Zinc plays an important role in intestinal structure and function. In animal models, zinc deficiency is associated with mild villus atrophy and decreased brush border disaccharidase activity [(9)].This phenomenon is reversible by dietary replenishment [(8)]. In malnourished Bangladeshi children with acute diarrhea, zinc supplementation resulted in a rapid reversal of the abnormal lactulose-mannitol ratio [(10)] .Mannitol is absorbed across epithelial cells and lactulose through the intraepithelial space. In mucosal damage, the former is less absorbed than the latter. Given these biologic effects of zinc deficiency, it seems highly plausible that zinc has an important role in determining the risk of acquiring enteric infection, in the severity of the resultant pathophysiologic disturbances, and in the recovery process.

There is increasing recognition of the importance of zinc and vitamin A in childhood growth and development [(11)] and subclinical zinc deficiency has been widely recognized as a significant limiting factor for growth among children in both developing and developed countries[(12)], reflecting the close association of zinc deficiency with stunting in apparently normal as well as malnourished children [(13)]. The disorder has been labeled by many as a public health problem in developing countries[(14)] .Although the optimal method of assessment of body zinc status is uncertain, plasma levels currently offer the best means of evaluation[(15)] and it has also been suggested that the best indication of a deficient state may be the clinical response to supplementation [(16)] .

The clinical response to zinc supplementation in pathologic states is, however, variable. Although some zinc supplementation studies of malnourished children have suggested improved growth and morbidity [(17)], others have failed to identify any improvement in linear growth, despite impressive reduction in morbidity rates.

Vitamin A is an essential nutrient needed in small amounts for normal functioning of the visual system, growth and development, maintenance of epithelial cell integrity, immune function, and reproduction. Vitamin A maintains the physical and functional integrity of epithelial tissues that serve as a barrier against infection. It acts at multiple sites in the immune system. In vitamin A deficient state, there is an impairment in the antibody response to bacterial polysaccharides and proteins, as well as cytotoxic activity, and natural killer cells numbers are decreased. Vitamin A also plays a role in the production of cell glycoprotein and in the regulation of cell division in the intestine [(18)], which has a bearing on intestinal epithelial renewal during and after acute enteric infections and thereby on the absorption of water, electrolytes, and other nutrients. Recently, it was shown that although vitamin A deficiency by itself caused little change in the jejunal epithelium, the jejunal atrophy induced by rotavirus infection was greater in vitamin A deficient than in replete animals [(19)].

Although in general the standard WHO oral rehydration solution is adequate for replacing on-going losses, recent evidence indicates that low osmolality oral rehydration fluids may be advantageous in undernourished children with persistent diarrhea with no associated risk of hyponatremia (Figure 1).

Figure 1: Comparisons between standard ORS and low osmolality oral rehydration fluids(*)

	Standard ORS	***Low osmolality ORS***
Ingredients	mmol/L	mmol/L
Sodium	90	75
Potassium	20	20
Chloride	80	65
Citrate	10	10
Glucose	111	75
Osmolarity	311 mosmol/L	245 mosmol/
Recommended in 1976		Recommended in July, 2001

(*)The United Nations Children's Fund (UNICEF), Supply Division, April 2004.

Materials And Methods

A total of 117 children (age 6-24 months) with persistent diarrhea (PD), (four or more unformed stools per day continuously for at least 14 days with evidence of malnutrition [weight-for-height ≤ -2.0 SD according to WHO Weight-for- Height growth charts]) were recruited for the study between July, 2005 to September, 2007 in Karbala Teaching Hospital for Children..

For each patient a data sheet was filled including, name, age, sex, residence, history of diarrhea, and feeding habit. The children were clinically evaluated at admission for dehydration and signs of intercurrent illnesses.

Stool sample from each patient was sent for microscopy, pH and culture, blood was also aspirated for serum electrolytes, complete blood count, C-reactive protein, albumin and blood urea. The degree of dehydration, body temperature, vital signs, and clinical status was recorded twice daily. In cases of suspected septicemia a blood culture was obtained before initiation of broad-spectrum antibiotics. Chest radiograph was ordered when indicated.

For all children weight, length and occipito-frontal circumference were measured on admission and plotted on growth chart . Length was obtained on an infant measure board. Weight-for-age, stature-for-age percentile on standard growth charts and weight for height SD were determined.

These anthropometric measurements were repeated at days 7, 14, and 28 after discharge from hospital.

All children were resuscitated 3- 5 days stabilization period, in which intravenous (IV) fluid give when strongly indicated in addition to the low osmolality oral rehydration solution. Electrolyte imbalance was corrected and antibiotic therapy for concomitant non enteric infections was initiated. During this period the stool output frequency was quantified. Dietary therapy with a rice-lentil (Khitchri)' yogurt and home available diets was initiated. Breastfeeding was continued as required.

The children were allocated to two groups, group A(received zinc supplement 3-5 mg/kg/d of elemental zinc sulfate in a single daily dose for 14 days and vitamin A the dose 100,000 units to age group from 6-12 months or 200,000 units to age group above 12 months) and control group (group B).

At discharge, appropriate amounts of zinc was provided to the caregiver of the enrolled children and advised to continue the supplement for a further 14 days and compliance of therapy was assessed by estimation of the remaining supplement amount at return appointment.

To assess the rapidity of recovery, two main endpoints for estimation of therapeutic response were defined. The "time-to-weight gain" was defined as the time taken to

achieve weight gain for 3 or more days consecutively, whereas the "time-to-diarrheal recovery" was defined as the time taken to achieve a reduction in stool frequency and achievement of a semiformed stool consistency. Weight gain (g/kg/d) according to WHO program(W2 (second body weight/kg) - W1(first body weight/kg) multiplied by 1000= grams gained / number of days between W1 and W2= Weight gain (g/kg/d)[20]

Results

A total of 180 children admitted to Karbala teaching hospital for children. fourteen(7.7%) children were excluded from the study because of concomitant infections. The remaining 166 children thus randomized for allocation to the two treatment groups, 22 (10 in zinc and 12 in control group, respectively) could not stay in the ward and were discharged prematurely on their family responsibility; a further 24 children (13 in zinc and 11 in control group) were also excluded because they didn't complete the study. Two children in the control group died during the intervention period, one due to septicemia and the other from pneumonia; one severely malnourished child in the treatment group died, likely from a systemic infection.

Overall therefore, 117 children completed the study protocol for 3-5days stabilization period in the hospital, followed by a further 14 days of either zinc supplementation or control group at home and 14 days follow-up without zinc or vitamin A. Details comparison of admission characteristics of the two groups were shown in Table 1.

Table 1: Details Comparison of Admission Characteristics of the two groups

Admission Characteristics	Studied Group	Control Group
Number of patients	59	58
Gender (M:F)	32:27	30:28
Age (months)	6-24	6-24
Weight (kg)	4- 9.5	3.800-9.250
Weight-for-age percentile		
<5 n (%)	40(67.79)	37(63.79)
5-10 n (%)	15 (25.43)	16(27.59)
>10 n (%)	4(6.78)	5 (8.62)
stature -for-age percentile		
<5 n (%)	5 (8.47)	4 (6.89)
5-10 n (%)	20 (33.89)	21(36.21)
>10 n (%)	34 (57.64)	33(59.90)
Weight-for-stature percentile		
<5 n (%)	30 (50.85)	28(48.28)
5-10 n (%)	20 (33.90)	19(32.76)
>10 n (%)	9 (15.25)	11(18.96)
Total protein (g/L)	56.8 ± 8.9	55.0 ± 9.2
Serum albumin (g/L)	33.5 ± 6.5	33.7 ± 7.8
Haemoglobin (g/dL)	9.23 ± 1.82	9.16 ± 1.90
Hematocrit (%)	29.8 ± 4.9	29.9 ± 4.3

Most children had significant malnutrition, but were closely comparable for all admissions regarding the clinical, nutritional, and laboratory parameters.

The two groups were also comparable for the duration and severity of diarrhea, as assessed by history as well as actual quantification of purging rates during the period of stabilization. The degree of dehydration, duration of diarrhea, type of stool, stool frequency / day and electrolytes disturbances at admission were approximately similar in both groups of children as shown in Table 2.

Table 2 Comparison of Diarrhea Characteristics at Admission

Diarrhea Characteristics	Studied Group	Control Group
Number	59	58
Duration of diarrhea		
14-20 days n, (%)	45(76.27)	46(79.31)
>20 days n, (%)	14(23.73)	12(20.69)
Type of stools at admission		
Watery. n, (%)	50(84.75)	50(86.21)
Bloody. n, (%)	2(3.39)	3(5.17)
Mixed. n, (%)	7(11.86)	5(8.62)
Stool frequency /day		
3-6 n, (%)	10(16.95)	8(13.79)
7-10 n, (%)	40(67.79)	40(68.97)
>10 n, (%)	9(15.26)	10(17.24)
Vomiting n (%)	10(16.95)	12(20.69)
Duration of vomiting(h)		
<24 (h) n, (%)	6(10.17)	9(15.52)
>24(h) n, (%)	4(6.78)	3(5.17)
Vomiting frequency/day		
1-3 n, (%)	8(13.56)	10(17.24)
>3 n, (%)	2(3.38)	2(3.45)
Degree of dehydration at admission		
None n, (%)	11(18.64)	12(20.69)
Some dehydration n, (%)	40(67.80)	39(67.24)
Severe n, (%)	8(13.56)	7(12.07)
Fever n (%)	20(33.8)	19(32.76)
Duration of fever		
<24 h n, (%)	12(20.33)	10(17.24)
> 24h n, (%)	8(13.55)	9(15.52)
Serum sodium mEq/L		
>135 n, (%)	50(84.75)	47(81.03)
<135 n, (%)	9(15.25)	11(18.97)
Serum potassium mEq/L n (%)		
>3.5	10(16.95)	8(13.79)
<3.5	49(83.05)	50(86.21)

Table 3 Post enrollment outcomes in the studied (zinc with vitamin A) and control groups

Post enrollment outcomes	Studied Group	Control Group
Stool frequency (n/d)		
Day 1	10.4 ± 5.4	10.2 ± 6.4
Day 3	5.3 ± 3.7	5.9 ± 5.6
Day 7	1.9 ± 1.6	3.0 ± 2.2
Decrease in stool frequency (n/d)	6.1 ± 6.2	4 ± 5.2
Weight gain (g/kg/d)		
Day 7	5 ± 2.5	3 ± 2.7
Day 14	8 ± 2.2	6 ± 2.4
Day 28	8 ± 2.7	7.13± 2.6
Weight-for-stature percentile Day 14		
<5 n (%)	20(33.8)	25 (43)
5-10 n (%)	19 (32)	18(31)
>10 n (%)	20(33.8)	15 (25.86)
Weight-for-stature percentile Day 28		
<5 n (%)	14(23.7)	21 (36)
5-10 n (%)	15 (25.4)	18(31)
>10 n (%)	30(50.8)	20(34.5)
Serum protein (g/L)		
Day 14	57.6 ± 7.8	56.0± 8.2
Day 28	58.2 ± 6.6	57.1± 6.8
Serum albumin (g/L)	33.5± 6.5	33.7± 7.2
Day 14	35.3± 5.5	34± 6.5
Day 28	38.2± 5.2	36± 5.5

DISCUSSION

In this study all the patients with persistent diarrhea (PD) admitted to pediatric hospital were enrolled for immediate assessment and planning for subsequent therapy and nutritional instructions to their families.

The study reviel that 18% of the patients presented with acute exacerbations of diarrhea associated with vomiting required brief periods of intravenous rehydration with Ringer's lactate. Electrolyte imbalances such as hypokalemia and acidosis necessitated correction; these data are similar to data in other studies[3, 4].

Most children with PD that admitted to the pediatric hospital wards have significant malnutrition (82.9% of patients less than 10 percentile). Total serum protein, serum albumin, hematocrit and hemoglobin were lower than normal in agreement with findings in other studies [2, 3, 4]. Most of the patients showed mild to moderate degree of dehydration, only (13.55%) were severely dehydrated this result is similar to some extent to another study [21]. The percentage of children who had clinical recovery (passage of soft stool was taken as recovery) within 5 days was significantly greater in the zinc and vitamin A group compared to the control group, similar finding also found in other studies [22]. Systemic infections have been recognized in severely

undernourished children with PD requiring antimicrobial therapy, this is in agreement with other studies [22,23].

This study shows that the use of zinc and vitamin A in the management of persistent diarrhea significantly reduces the duration of persistent diarrhea, decrease stool frequency, better weight gain and early improvement regarding total serum protein, serum albumin and hemoglobin in comparison with control group, these results are similar to some extent to other studies[24,25] but in contrast to a study done in Pakistan[26].

The results of this study and additional information from other published randomized trials indicate that zinc and vitamin A, given during persistent diarrhea, can have a substantial clinical benefit and suggest that this adjunctive therapy could reduce the risks of death from diarrhea[27].

The findings indicate that therapeutic use of zinc and vitamin A may have wide applicability. Perhaps the use of this effective and inexpensive supplement would be helpful in the efforts to reduce the now common treatment of diarrhea with unnecessary antibiotics and other drugs [28] .At the same time, it will be important to continue the promotion of appropriate low osmolality oral rehydration fluids and dietary therapy as the mainstay of efforts to reduce mortality from persistent diarrhea in children [29].

The beneficial effect of the use of zinc and vitamin A may be due to the improvement of the immune function in affected children. [30] and reduce the incidence and prevalence of diarrhea [31] .Other possible mechanisms include effects of zinc deficiency on intestinal permeability[32], regulation of intestinal water and electrolyte transport[33], brush border enzymatic function, and intestinal epithelial tissue repair[34].

The use of zinc and vitamin A as adjunctive therapy has the potential to improve the management of diarrhea and increase survival in children, if it can be incorporated into diarrheal disease control programs in developing countries. Primary prevention of zinc deficiency would be expected to improve the growth and development of children.

Conclusion

Zinc and vitamin A supplementation in persistent diarrhea reduces stool output, frequency, and promotes earlier recovery.

RECOMMANDATION

Zinc and vitamin A supplementation in addition to nutrient supplementations in malnourished children with PD is recommended to improve the nutritional outcome and diarrheal recovery.

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