International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 25-09-2019; Accepted: 26-10-2019
www.medicalsciencejournal.com
Volume 5; Issue 11; November 2019; Page No. 180-184

Clinical outcomes of administration of oral zinc in children's Suffering from acute Diarrhoea

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Abstract
Zinc deficiency is common among children in low-income countries due to a variety of factors such as low food intake, particularly from animal sources; limited zinc bioavailability from local diets; and loss of zinc during recurrent diarrhoeal illnesses. Zinc deficiency is associated with immunodeficiency and increased rates of serious infectious diseases. The deficiency is widely recognized as contributing to the limited growth of children in both low-income and high-income countries. It is estimated that zinc deficiency in association with diarrhoea, pneumonia, and malaria contributes to 4.4% of deaths among children aged 6-59 months in Africa, Latin America, and Asia. The World Health Organization now recommends zinc for the treatment of children with diarrhoea because there is sufficient evidence demonstrating that supplementation reduces the severity and duration of the episode. Hence based on above findings the present study was planned for clinical outcomes of administration of oral zinc in children's suffering from acute diarrhoea.
The present study was conducted in Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India. In the designed study 100 cases of the acute diarrhoea were evaluated. The 50 cases of the childrens administered with the oral Zinc were enrolled in the study group cases. For comparative evaluation 50 number of control cases were enrolled in control group. Zinc acetate was used as salt in the dose of 20mg once a day orally either in the form of either suspension (20 mg/5ml) or dispersible tablet for 14 days to children of study group.
The data generated from present study concludes that administration of oral zinc as an adjuvant therapy in the children hospitalized with diarrhoea was found to significantly reduce the stool frequency.

Keywords: Zinc, Diarrhoea, children's, stools, etc

Introduction
Diarrhoea, also spelled diarrhoea, is the condition of having at least three loose, liquid, or watery bowel movements each day. It often lasts for a few days and can result in dehydration due to fluid loss. Signs of dehydration often begin with loss of the normal stretchiness of the skin and irritable behaviour. This can progress to decreased urination, loss of skin color, a fast heart rate, and a decrease in responsiveness as it becomes more severe. Loose but non-watery stools in babies who are exclusively breastfed, however, are normal [1].
The most common cause is an infection of the intestines due to a virus, bacteria, or parasite—a condition also known as gastroenteritis. These infections are often acquired from food or water that has been contaminated. The three types of diarrhoea are: short duration watery diarrhoea, short duration bloody diarrhoea, and persistent diarrhoea (lasting more than two weeks, which can be either watery or bloody). The short duration watery diarrhoea may be due to cholera, although this is rare in the developed world. If blood is present, it is also known as dysentery. A number of non-infectious causes can result in diarrhoea. These include lactose intolerance, irritable bowel syndrome, non-celiac gluten sensitivity, celiac disease, inflammatory bowel disease such as ulcerative colitis, hyperthyroidism, bile acid diarrhoea, and a number of medications. In most cases, stool cultures to confirm the exact cause are not required [2].
Diarrhoea can be prevented by improved sanitation, clean drinking water, and hand washing with soap. Breastfeeding for at least six months and vaccination against rotavirus is also recommended. Oral rehydration solution (ORS)—clean water with modest amounts of salts and sugar—is the treatment of choice. Zinc tablets are also recommended. These treatments have been estimated to have saved 50 million children in the past 25 years. When people have diarrhoea it is recommended that they continue to eat healthy food and babies continue to be breastfed. If commercial ORS are not available, homemade solutions may be used. In those with severe dehydration, intravenous fluids may be required. Most cases; however, can be managed well with fluids by mouth. Antibiotics, while rarely used, may be recommended in a few cases such as those who have bloody diarrhoea and a high fever, those with severe diarrhoea following travelling, and those who grow specific bacteria or parasites in their stool. Loperamide may help decrease the number of bowel movements but is not recommended in children [2].
About 1.7 to 5 billion cases of diarrhoea occur per year. It is most common in developing countries, where young children get diarrhoea on average three times a year. Total deaths from diarrhoea are estimated at 1.26 million in 2013—down from 2.58 million in 1990. In 2012, it is the second most common cause of deaths in children younger than five (0.76 million or 11%). Frequent episodes of diarrhoea are also a common cause of malnutrition and the most common cause in those younger than five years of age.

Other long term problems that can result include stunted growth and poor intellectual development [3].

Diarrhoea is defined by the World Health Organization as having three or more loose or liquid stools per day, or as having more stools than is normal for that person. Acute diarrhoea is defined as an abnormally frequent discharge of semisolid or fluid fecal matter from the bowel, lasting less than 14 days, by World Gastroenterology Organization.Secretory diarrhoea means that there is an increase in the active secretion, or there is an inhibition of absorption. There is little to no structural damage. The most common cause of this type of diarrhoea is a cholera toxin that stimulates the secretion of anions, especially chloride ions (Cl–). Therefore, to maintain a charge balance in the gastrointestinal tract, sodium (Na+) is carried with it, along with water. In this type of diarrhoea intestinal fluid secretion is isotonic with plasma even during fasting. It continues even when there is no oral food intake [4].

Osmotic diarrhoea occurs when too much water is drawn into the bowels. If a person drinks solutions with excessive sugar or excessive salt, these can draw water from the body into the bowel and cause osmotic diarrhoea. Osmotic diarrhoea can also result from maldigestion, e.g. pancreatic disease or coeliac disease in which the nutrients are left in the lumen to pull in water. Or it can be caused by osmotic laxatives (which work to alleviate constipation by drawing water into the bowels). In healthy individuals, too much magnesium or vitamin C or undigested lactose can produce osmotic diarrhoea and distention of the bowel. A person who has lactose intolerance can have difficulty absorbing lactose after an extraordinarily high intake of dairy products. In persons who have fructose malabsorption, excess fructose intake can also cause diarrhoea. High-fructose foods that also have a high glucose content are more absorbable and less likely to cause diarrhoea. Sugar alcohols such as sorbitol (often found in sugar-free foods) are difficult for the body to absorb and, in large amounts, may lead to osmotic diarrhoea [4]. In most of these cases, osmotic diarrhoea stops when the offending agent, e.g. milk or sorbitol, is stopped.

Diarrhoeal disease may have a negative impact on both physical fitness and mental development. "Early childhood malnutrition resulting from any cause reduces physical fitness and work productivity in adults," and diarrhoea is a primary cause of childhood malnutrition [20]. Further, evidence suggests that diarrhoeal disease has significant impacts on mental development and health; it has been shown that, even when controlling for helminth infection and early breastfeeding, children who had experienced severe diarrhoea had significantly lower scores on a series of tests of intelligence [5].

Diarrhoea can cause electrolyte imbalances, kidney impairment, dehydration, and defective immune system responses. When oral drugs are administered, the efficiency of the drug is to produce a therapeutic effect and the lack of this effect may be due to the medication travelling too quickly through the digestive system, limiting the time that it can be absorbed. Clinicians try to treat the diarrhoeas by reducing the dosage of medication, changing the dosing schedule, discontinuation of the drug, and rehydration. The interventions to control the diarrhoea are not often effective. Diarrhoea can have a profound effect on the quality of life because fecal incontinence is one of the leading factors for placing older adults in long term care facilities (nursing homes) [6].

There are many causes of infectious diarrhoea, which include viruses, bacteria and parasites. Infectious diarrhoea is frequently referred to as gastroenteritis. Norovirus is the most common cause of viral diarrhoea in adults, but rotavirus is the most common cause in children under five years old. Adenovirus types 40 and 41, and astroviruses cause a significant number of infections. Shiga-toxin producing Escherichia coli, such as E coli, are the most common cause of infectious bloody diarrhoea in the United States.Campylobacter spp. are a common cause of bacterial diarrhoea, but infections by Salmonella spp., Shigella spp. and some strains of Escherichia coli are also a frequent cause. In the elderly, particularly those who have been treated with antibiotics for unrelated infections, a toxin produced by Clostridioides difficile often causes severe diarrhoea [7].

Parasites, particularly protozoa e.g., Cryptosporidium spp., Giardia spp., Entamoebahistolytica, Blastocystis spp., Cyclosporacayetanensis, are frequently the cause of diarrhoea that involves chronic infection. The broad-spectrum antiparasitic agent nitazoxanide has shown efficacy against many diarrhoea-causing parasites. Other infectious agents, such as parasites or bacterial toxins, may exacerbate symptoms. In sanitary living conditions where there is ample food and a supply of clean water, an otherwise healthy person usually recovers from viral infections in a few days. However, for ill or malnourished individuals, diarrhoea can lead to severe dehydration and can become life-threatening [8].

Oral rehydration solution (ORS) (a slightly sweetened and salty water) can be used to prevent dehydration. Standard home solutions such as salted rice water, salted yogurt drinks, vegetable and chicken soups with salt can be given. Home solutions such as water in which cereal has been cooked, unsalted soup, green coconut water, weak tea (unsweetened), and unsweetened fresh fruit juices can have from half a teaspoon to full teaspoon of salt (from one-and-a-half to three grams) added per liter. Clean plain water can also be one of several fluids given. There are commercial solutions, and relief agencies such as UNICEF widely distribute packets of ORS. A WHO publication for physicians recommends a homemade ORS consisting of one liter water with one teaspoon salt (3 grams) and two tablespoons sugar (18 grams) added (approximately the "taste of tears". Rehydration Project recommends adding the same amount of sugar but only one-half a teaspoon of salt, stating that this more dilute approach is less risky with very little loss of effectiveness. Both agree that drinks with too much sugar or salt can make dehydration worse [9].

Appropriate amounts of supplemental zinc and potassium should be added if available. But the availability of these should not delay rehydration. As WHO points out, the most important thing is to begin preventing dehydration as early as possible. In another example of prompt ORS hopefully preventing dehydration, CDC recommends for the treatment of cholera continuing to give Oral Rehydration Solution during travel to medical treatment. Vomiting often occurs during the first hour or two of treatment with ORS, especially if a child drinks the solution too quickly, but this seldom prevents successful rehydration since most of the fluid is still absorbed. WHO recommends that if a child vomits, to wait five or ten minutes and then start to give the solution again more slowly [9].

Drinks especially high in simple sugars, such as soft drinks

and fruit juices, are not recommended in children under five as they may increase dehydration. A too rich solution in the gut draws water from the rest of the body, just as if the person were to drink sea water. Plain water may be used if more specific and effective ORT preparations are unavailable or are not palatable. Additionally, a mix of both plain water and drinks perhaps too rich in sugar and salt can alternatively be given to the same person, with the goal of providing a medium amount of sodium overall. A nasogastric tube can be used in young children to administer fluids if warranted [10].

Zinc deficiency is common among children in low-income countries due to a variety of factors such as low food intake, particularly from animal sources; limited zinc bioavailability from local diets; and loss of zinc during recurrent diarrhoeal illnesses. Zinc deficiency is associated with immunodeficiency and increased rates of serious infectious diseases. The deficiency is widely recognized as contributing to the limited growth of children in both low-income and high-income countries [11]. It is estimated that zinc deficiency in association with diarrhoea, pneumonia, and malaria contributes to 4.4% of deaths among children aged 6-59 months in Africa, Latin America, and Asia [12]. The World Health Organization now recommends zinc for the treatment of children with diarrhoea [13] because there is sufficient evidence demonstrating that supplementation reduces the severity and duration of the episode [14]. Hence based on above findings the present study was planned forclinical outcomes of administration of oral zinc in childrens suffered from acute diarrhoea.

Methodology

The present study was conducted in Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India. In the designed study 100 cases of the acute diarrhoeawere evaluated. The 50 cases of the childrensadministered with the oral Zincwere enrolled in the study group cases. For comparative evaluation 50 numberof control cases were enrolled in control group. Zinc acetate was used as salt in the dose of 20mg once a day orally either in the form of either suspension (20 mg/5ml) or dispersible tablet for 14 days to children of study group. (6months - 6 year) All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Age between 6 months and 6 years, suffering from acute diarrhoea of mild and moderate intensity, Guardian willing to give informed consent.

Exclusion criteria: Children suffering from: Malnutrition, Severe dehydration, Immuno-compromised children, Children on any probiotic supplementation, etc.

Results & Discussion

The rationale for use of specific nutrients as treatment of acute diarrhoea is based on their effects on immune function or on intestinal structure or function and on the epithelial recovery process during diarrhoea.

Zinc deficiency has been found to be widespread among children in developing countries, and occurs in most of Latin America, Africa, the Middle East and South Asia. Zinc has been identified to play a critical role in metallo-enzymes, polyribosomes, the cell membrane, and cellular function, leading to the belief that it also plays a central role in cellular growth and in the function of the immune system. Intestinal zinc losses during diarrhoea aggravate pre-existing zinc deficiency [15]. The zinc depleting effects of diarrhoea are most distinctly seen in adults receiving parenteral nutrition: intravenous zinc required to achieve positive zinc balance averaged 13 mg in patients with ongoing diarrhoeal fluid losses compared with 2.5 mg in patients without such losses [15-20]. Although the theoretical basis for a potential role of zinc in treatment of acute diarrhoea has been postulated for quite some time, convincing evidence for its clinical importance has come from recent randomized controlled trials of zinc supplementation [17-21].

The therapeutic benefits in acute diarrhoea may be attributed to effects of zinc on various components of the immune system and its direct gastrointestinal effects. Zinc defi- ciency is associated with lymphoid atrophy, decreased cutaneous delayed hypersensitivity responses, lower thymic hormone activity, a decreased number of antibody forming cells and impaired T killer cell activity [15]. Zinc deficiency has also been recently shown to affect the differentiation of CD4 response towards Th1 rather than Th2 pathway. The direct intestinal effects of zinc deficiency include decreased brush border activity, enhanced secretory response to cholera toxin, and altered intestinal permeability, which is reversed by supplementation [21].

Table 1: Age & Sex of Patients

Groups	**Group A**	**Group B**
Group of	**Cases**	**Control**
Patients with	Diarrhoea with Oral Zinc	Diarrhoea without Zinc
No. of Cases	50	50
Age Groups		
1 – 3 years	5	7
3 – 6 years	11	9
6 – 9 years	17	21
9 – 12 years	9	10
12 – 15 years	8	3
Sex		
Males	28	31
Females	22	19

Table 2: Dehydration type & No. of Cases

Groups	**Group A**	**Group B**
Group of	**Cases**	**Control**
Patients with	Diarrhoea with Oral Zinc	Diarrhoea without Zinc
No. of Cases	50	50
Dehydration Type		
Severe dehydration	8	5
Some dehydration	42	45
No. of Loose stools/day: initially		
4	2	1
5	12	15
6	15	22
7	11	14
8	10	8

Table 3: Frequency of loose stools on day 7

Groups	Group A	Group B
Group of	**Cases**	**Control**
Patients with	Diarrhoea with Oral Zinc	Diarrhoea without Zinc
No. of Cases	50	50
<2	2	0
2	3	4
3	15	8
4	16	14
5	7	15
6	5	5
7	1	2
8	1	2

The link between malnutrition and chronic diarrhoea is particularly strong early in life. It has been shown that intestinal permeability is exacerbated by zinc deficiency. A 5mg/day zinc supplement suffices to improve that condition, [22] although protein losses cannot be fully controlled, even with a higher dose [23]. More recently it has been shown that zinc supplements improve the speed of recovery and diminish week long diarrhoea episodes

A general feature of these trials is that infants and children who were growth retarded and malnourished improved better than others with zinc supplementation. Two mechanisms have been proposed to account for the interaction between zinc deficiency and diarrhoea. The expression of nitric oxide synthase, the enzyme involved in the formation of nitric oxide from L-arginine, is greater in the intestine of zinc deficient rats, especially after induction of the enzyme by interleukin (IL-1a) [24]. Alternatively, it has been reported that in zinc deficiency there is over expression or uroguanylin, a peptide related to the cellular receptor of thermostable E. coli toxin [25]. This would present a greater number of receptor sites for toxin attachment and thus trigger the chain of reactions leading to diarrhoea [26]. A potential benefit of the presence of zinc salts in the intestinal lumen may be that they could act as nitric oxide scavengers and reduce its intracellular biologic effects [27].

This low zinc level is possible as in southern Asia, macronutrient malnutrition and micronutrient deficiencies, especially deficiencies of zinc, are common in young children. This hypozincemia problem attributed to dietary insufficiency, limited nutrient bioavailability from local diets, and excretion of nutrients during recurrent episodes of infection [28]. Baqui A. H *et al.* [29] in their study observed that serum zinc was low in 44% of healthy children with diarrhoea. Olmez et al in their prospective study on the mean serum zinc levels in children in the age group of 2-24 months found that although the control group (n = 41) were asymptomatic, still 39% of children in this group had a mean zinc level that was below the normal standards for age [30]. In the present study among AGE, group means zinc levels in undernourished were less than mean zinc levels but it is not statistically significant may be because of the small sample size in this study. Similar findings found in Study done by Olmez *et al.* [30] in a total of 82 children (41 children suffering from acute gastroenteritis of < 7 days duration along with 41 age and sex-matched controls) showed that the baseline characteristics in the mean zinc levels in both the groups of children were the same with no statistical difference.

Future trials need to measure the efficacy of zinc treatment for probable serious bacterial infection in other settings—specifically, other studies should measure the effect of zinc supplementation on important outcomes in children who are diagnosed with serious bacterial infections without measurements of concentrations of C-reactive protein. If such trials show improvement in treatment outcomes, the use of zinc as an adjunct to antibiotic treatment might lead to substantial reductions in infant mortality, particularly in resource-constrained settings where second-line antibiotics and appropriate intensive care might be unavailable. Care providers at small health-care facilities can be trained to initiate treatment of probable serious bacterial infection with antibiotics and zinc before transferring infants to appropriately equipped facilities. Zinc syrup or dispersible tablets are already available in the public and private health-care systems for treatment of acute diarrhoea in many countries of low and middle income and the incremental costs to make this intervention available for young infants with probable serious bacterial infection would be small.

Conclusion

The data generated from present study concludes that administration of oral zinc as an adjuvant therapy in the children hospitalized with diarrhoea was found to significantly reduce the stool frequency & duration of hospital stay.

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A: home therapy to prevent dehydration and malnutrition, 4.3 Treatment Plan B: oral rehydration therapy for children with some dehydration, and 4.4 Treatment Plan C: for patients with severe dehydration on pages 8 to 16 (12–20 in PDF). See also 8. Management of Diarrhoea with Severe Malnutrition on pages 22–24 (26–30 in PDF) and "Annex 2: Oral and Intravenous Rehydration Solutions" on pages 33–37 (37–41 in PDF). World Health Organization. 2005. Archived (PDF) from the original on 19 October 2011, 2003.
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