



## ROLE OF ZINC SUPPLEMENTATION IN CASES OF ACUTE AND PERSISTENT DIARRHEA IN DEVELOPING COUNTRIES: CURRENT STATUS AND ASSESSMENT

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**ABSTRACT** Diarrhea is still a major factor in mortality in children less than 5 years age group in developing countries. Reported more than 2 million child death annually worldwide. The improved treatment is established in reducing death rates however but still requires better approach. This article reviews the better outcome with ORS solution along with administration of zinc. Zinc is enlisted in WHO essential drug list under medicine for diarrhea where it is indicated in acute diarrhea as an adjunct to oral rehydration salts. Zinc is usually well tolerated. It is necessary to explore public health applications, using zinc either as a preventive Measure in children or therapeutically for diarrhea. Zinc supplementation reduces the duration and severity of acute and persistent diarrhea.

**KEYWORDS :** Diarrhea, Dehydration, Mortality, Zinc.

### INTRODUCTION –

diarrheal disease is still a major public health problem especially among children age group in developing countries like India. It is estimated that diarrheal diseases cause 1.5–2.5 million deaths each year among children younger than age 5 and contribute substantially to malnutrition in surviving children<sup>1,2</sup>. It is estimated that diarrheal diseases cause > 3 million deaths of children in developing countries each year and contribute substantially to malnutrition in surviving children<sup>3</sup>. Diarrheal episodes of longer duration, commonly called persistent diarrhea, have the greatest effect on these outcomes<sup>4,5</sup>. Treatment of acute diarrhea with oral rehydration solution has become widespread, resulting in reduced mortality from dehydrating diarrheas but no decrease in the duration of episodes or their consequences, such as malnutrition<sup>6</sup>. The critical factor for the reduction in the mortality and morbidity from diarrhea was the introduction of oral rehydration therapy for the treatment of the dehydration and metabolic acidosis associated with acute diarrhea that has been claimed by many as one of the most important therapeutic advances of the past century.<sup>7</sup> The scientific principle and rationale for this therapy is based on carrier-mediated active glucose absorption. The physiologic basis for oral rehydration solution (ORS) was the demonstration that (1) absorptive and secretory processes in the small intestine are separate and distinct, (2) cyclic nucleotides induce chlorine (Cl)-induced fluid secretion without affecting glucose-stimulated sodium (Na) absorption, and (3) glucose enhances Na and fluid absorption without modifying fluid secretion. After the introduction of standard World Health Organization (WHO) ORS more than 30 years ago, the treatment of acute diarrhea has changed dramatically and the use of ORS has become widespread. WHO ORS corrects the dehydration and metabolic acidosis that occurs as a result of fluid and bicarbonate losses and reduces mortality. However, WHO ORS does not substantially decrease either stool or the duration of diarrhea episodes or their consequences, such as malnutrition.<sup>8</sup> As a result, improved or super-ORSs and other approaches for enhancing treatment of acute diarrhea continually have been sought and evaluated. Most of these efforts have focused on the inclusion of different dietary substrates that might directly stimulate Na absorption in the small intestine. Thus, several studies evaluated L-amino acids without evidence of dramatic improvement compared with the gold standard of WHO ORS. Additional studies with food-based sources of glucose (eg, rice-based or cereal-based ORS) showed improved efficacy in the treatment of acute diarrhea. These different food-based ORSs all contained polymers that, after their digestion by pancreatic and intestinal enzymes, resulted in glucose production. As a consequence, these solutions frequently were used with a reduced osmolality. Subsequent studies proposed that the primary efficacy of these food-based solutions was their hypo-osmolar composition.<sup>9</sup> The importance of a hypoosmolar ORS is emphasized by the recent adoption by WHO and the Indian Government of a reduced Na/glucose-based (hypoosmolar) ORS solution that has prompted concerns whether such a solution may create other problems (eg, hyponatremia) in patients with cholera.<sup>10</sup> All of these solutions generally are believed to enhance small intestinal fluid absorption. In contrast, 5 years ago, Ramakrishna et al<sup>11</sup>

pointed the way to a potential new mechanism for designing an improved ORS using amylose-maize starch, a starch that is relatively resistant to pancreatic amylase digestion as substrate. The resulting non absorbed carbohydrate results in increased production of short-chain fatty acids by colonic bacteria, leading to enhanced Na and fluid absorption in the colon. These investigators showed its improved effectiveness compared with WHO ORS and rice-based ORS in adults with cholera but advised testing this amylase-resistant starch ORS intervention further in children and in other types of diarrheal disease. The incorporation of amylase resistant starch in ORS has not yet been established, although it represents a very new approach and additional studies will be required to establish the appropriate role of resistant starch-based ORS in the therapy of acute diarrhea.<sup>12</sup> Nonetheless, the development of other improved ORSs continued. Several of these more recent approaches have used Zinc (Zn) either with or without concomitant ORS as an adjunct therapy for acute childhood diarrhea in developing countries.<sup>13</sup> Zn is an essential micronutrient and is the second most abundant trace element in cells and tissues. Zn has been considered an important anti-inflammatory factor, protecting cell membranes from oxidative damage. Because there are only minimal Zn stores in the body, its bioavailability is determined by a balance among its dietary intake, intestinal absorption, and losses through urine, skin, and the intestinal tract. Diarrhea with severe Zn deficiency has been observed in children in developing countries.<sup>14</sup> Studies linking diarrheal diseases with Zn deficiency first were described in reports of low plasma Zn levels in children with diarrhea. Intestinal Zn loss has been reported in children with acute dehydrating diarrhea.<sup>15</sup> These findings prompted studies of Zn supplementation in children with diarrhea. The incidence of persistent diarrhea and dysentery also has been reduced by Zn supplementation. Recently, Zn supplementation to ORS has been shown to reduce substantially the duration and severity of diarrhea in children with both acute and persistent diarrhea.

### ROLE OF ZINC IN DIARRHEA:

Zinc is a nutritional supplement (mineral) usually given as zinc sulfate, zinc acetate, or zinc gluconate, which are all water-soluble compounds.<sup>16</sup> The association between zinc and diarrhea associated morbidity have been noted on different observational studies. It is known that increased fecal zinc loss leads to a negative zinc balance and low tissue zinc concentration among children with diarrhea. Zinc deficiency is highly prevalent in children in developing countries because overall food intake as well as consumption of animal food is low and the bioavailability of zinc from fibers, phytates rich cereal based diet is limited. The inadequacy of dietary zinc uptake is exacerbated by the net loss of zinc during diarrhea.<sup>17</sup> Based on animal studies and cell line cultures; a possible mechanism of action of zinc has been elucidated. These findings suggest that zinc is involved in regulation of intestinal fluid transport, mucosal integrity, immunity, gene expression, and oxidative stress.<sup>18</sup>

### Studies suggesting role of zinc therapy in childhood diarrhea

Studies have been conducted in recent years studying the usefulness of

zinc on both acute and persistent diarrhea. Clinical studies from India showed that regular prophylactic zinc supplementation can reduce diarrheal prevalence and diarrhea associated mortality.<sup>19,20</sup> Zinc supplementation during diarrhea is known to reduce the duration and severity of treated episodes. One of the study from the United States have found that short course of daily zinc supplementation shortens the duration (a 15-24% reduction) and severity of episodes of diarrhea.[1] Other trials from the different parts of the world have also shown similar results. The data from these studies have been analyzed and have demonstrated the clinically important benefits of zinc as supplementation. A community randomized trial undertaken in the nearby country Bangladesh have illustrated that the children who received zinc supplementation during and after diarrhea had 24% shorter duration of diarrhea, 15% lower incidence of diarrhea and a trend suggesting fewer diarrhea related hospital admission.[4] Further, zinc therapy may have a benefit over the oral rehydrate therapy alone which is currently recommended to prevent dehydration but does not reduce the duration of diarrhea. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend 10 to 20 mg of zinc per day for children with diarrhea, at least twice the recommended daily allowance.<sup>21</sup> Treatment of diarrhea with oral rehydration solution (ORS) reduces mortality due to dehydration. Zinc supplementation could help reduce the duration and the severity of diarrhea, and therefore have an additional benefit over ORS in reducing children mortality.[11] A systematic Cochrane review of 24 trials involving more than 9000 children have suggested that supplementation of zinc in the treatment of diarrhea might reduce the duration of diarrhea in children aged six months or more.

### Zinc in WHO essential drug list

Zinc is enlisted in WHO essential drug list under medicine for diarrhea where it (zinc sulfate solid oral dosage form: 20 mg) is indicated in acute diarrhea as an adjunct to oral rehydration salts. Recent, WHO recommendations on zinc include mothers, other caregivers and health workers should provide children with 20 mg per day of zinc supplementation for 10-14 days (10 mg per day for infants under the age of six months).<sup>22</sup> In addition to the several studies that have examined the effect of Zn on acute diarrhea, there also has been much attention devoted to the role of Zn in the treatment of acute lower respiratory infections.<sup>36</sup> These studies indicate that Zn is safe, well accepted, easily administered, and inexpensive. In general, these studies have established that treatment with Zn accelerates the recovery from severe pneumonia and in a recent trial was shown to be an effective treatment for severe pneumonia. <sup>37</sup> The consensus of these several reports is that Zn is a simple and inexpensive intervention and is cost effective. This experience with Zn, in conditions other than diarrhea, provides an excellent basis to support the eventual use of Zn in the treatment of acute diarrhea with the expectation that it will be safe and inexpensive.

### Zinc preparations available :

Zinc is available as 10 and 20 mg dispersible tablets manufactured by domestic manufacturers.

### Probable side effects of Oral zinc

Zinc is usually well tolerated but it may cause vomiting in some children. Although child might vomit within 30 min after swallowing the tablet, re-administration of the tablet is suggested.

### CONCLUSION :

In conclusion, a truly novel anti-diarrheal compound that provides substantial benefit in terms of induction of cation absorption and/or inhibition of anion secretion and reduction of stool output and disease duration combined with safety, selectivity of action, and low cost would be a welcome addition to the present therapies now available for the treatment of diarrheal disease. Recent studies of Zn in the treatment of acute diarrhea in children provide exciting evidence that Zn may be such an agent and soon may be established as an important adjunct to ORS in treating diarrhea. The extensive use of Zn in the treatment of pneumonia and other infections has shown that Zn is administered easily, is safe, well tolerated, and, most important in developing countries, is inexpensive. What most importantly is needed are additional laboratory-based studies that provide an understanding of the mechanism(s) by which Zn is effective in the treatment of diarrhea.

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