
Research Article

Safety and Efficacy of a Zinc Gluconate Solution in Management of Paediatric Diarrhoea

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Abstract:

Introduction: Diarrhoea is worldwide health problem in paediatric patients. It is the second leading and primary cause of morbidity and mortality in childhood in India. Zinc deficiency is prevalent among children in developing countries and is one of the reasons which cause diarrhoea. WHO, UNICEF, IAP and NRHM have advocated the use of Zinc for the treatment of paediatric diarrhoea. This study was conducted to evaluate the safety and efficacy of Zinc gluconate in Indian paediatric diarrhoea patients.

Methodology: Study was planned in 200 patients. The duration of the study was 5 days. There were 3 visits (Baseline, Day 3 and Day 5) planned. Efficacy assessment was made by studying the change in stool consistency (hard/soft/semisolid/watery) and reduction in average stool frequency. Safety assessment was made by analysing the adverse events during the clinical trial. All the patients received Zinc gluconate solution (20mg/day) with ORS.

Results: Out of 200 patients, 182 patients completed the study. Efficacy assessment was made by analysis of change in stool consistency and frequency. As compared to baseline visit, it was found that in conclusion visit the patients with watery stools are shifted to soft and semisolid stool and some patients were found with hard stools. The average stool frequency at baseline visit was 7.07 which reduced to 3.5 in conclusion visit.

Conclusion: Zinc gluconate with ORS therapy is safe and efficacious in treatment of diarrhoea in Indian paediatric patients.

Keywords: Zinc gluconate, Acute Infective Diarrhoea, Stool Consistency and Stool Frequency

Introduction

Diarrhoea is a most common childhood disease worldwide. In developing countries, diarrhoea is the second leading and primary cause of morbidity and mortality in childhood, globally. According to the World Health Organization, 1.87 million children of less than 5 years died from diarrhoea in 2003 and 80 percent of these deaths occur in children below 2 years. Persistent diarrhoea with malnutrition is also important cause of death. Diarrhoea in patients of severe malnutrition, especially vitamin A deficiency and zinc deficiency, is praiseworthy of its own category due to its increased risk of severe complications and death.^{1,2}

The majority of diarrhoeal illnesses occur due to acute infectious diarrhoea that is commonly referred as acute gastroenteritis (AGE). The passage of stools more frequent or loose in consistency than an individual's regular bowel habits is termed as diarrhoea. Diarrhoea is usually not more 7 days but if it persists longer than 14 days, it is called protracted diarrhoea that may be infectious and may represent chronic illness or complication of AGE. Most children with infectious diarrhoea are not dehydrated and can be successfully treated with replacement of ongoing fluid losses using oral rehydration solution (ORS).^{2,3}

Zinc deficiency is prevalent among children in developing

countries and is one of the reason which causes diarrhoea. Zinc plays critical role in synthesis of metallo-enzymes and poly-ribosomes along with the cellular/cell membrane functions. It also plays an important role in cellular growth and in functions of immune system. In developing countries, the role of zinc supplementation in children with acute gastroenteritis is well established where malnutrition is a sententious risk factor.¹

Zinc is usually given as nutritional supplement in the form of zinc gluconate, zinc sulphate, or zinc acetate, which are water-soluble compounds. Zinc restores the mucosal barrier integrity and enterocyte brush-border enzyme activity; it also promotes the production of antibodies and circulating lymphocytes against intestinal pathogens. It has a direct effect on ion channels and it also act as a potassium channel blocker of adenosine 3-5-cyclic monophosphate (cAMP pump)-mediated chlorine secretion.⁴

Zinc supplementation is safe and effective measure to shorten diarrhoea related illness in children and to reduce other complications including death. Although according to the WHO jointly with UNICEF and USAID have recommended that all the children with acute diarrhoeal illness should be given Zinc supplementation in addition with ORS and continued for the next 10–14 days. The IAP and the Govt. of

India has initiated providing Zinc in addition to ORS through its National Rural Health Mission.⁵ The zinc lost during diarrhoea can fully replace by continuing zinc supplementation up to 14 days, and the risk of the child having new episodes of diarrhoea in the following 2 to 3 months is reduced.¹

Zinc supplements are readily available in market in the form of zinc sulphate, zinc acetate, zinc citrate, zinc gluconate etc. and very popular for use in acute infective diarrhoea or persistent diarrhoea. Zinc gluconate supplementation is preferred now a day as it contain zinc salt of gluconic acid which has greater solubility, higher bioavailability. Patients of AGE have occasional vomiting with diarrhoea, other zinc salt has strong metallic taste which on administration influence vomiting. The metallic taste of zinc salt of sulphates or acetate need to be masked, whereas zinc gluconate has naturally better taste, which is palatable. Abundant clinical studies are done with zinc sulphate supplementation in Indian paediatric patients having diarrhoea whereas there is dearth of clinical studies data available with Zinc gluconate. Hence this study was conducted to document the safety and efficacy of Zinc gluconate in Indian paediatric patients suffering from diarrhoea.

Materials and Methods

A Phase IV Clinical study was conducted with 12 Paediatric speciality centres all across India from July 2017 to October 2017. Total 200 patients were enrolled out of which 182 patients completed the study and 18 patients were lost to follow-up.

Inclusion and Exclusion criteria

Patients of either sex having age group from 1 to 5 years, suffering from acute diarrhoea were included for the study. Patient's guardians willing to sign informed consent form and ready to adhere to the protocol were only selected for the Phase IV study. Patients having hypersensitivity to the study drug or excipient of study formulation were excluded. Patients who cannot adhere to the protocol (Mentally ill and Patients with Psychological problem) were excluded from the Phase IV study.

Study Intervention

Each 5 ml of study drug contains 20 mg Zinc Gluconate in non-syrupy base. Patients were dispensed with two 50 ml bottles of study drug as free sample by the investigator and asked to consume 5 ml along with ORS per day for 14 days.

Study procedure

Registered paediatricians were involved in the conduction of the study. The duration of the study was kept for 5 days to determine the efficacy and safety of the study drug. Patients with acute infective diarrhoea or persistent diarrhoea who fulfil exclusion/inclusion criteria were mustered for the study. Each patient was clinically examined and a detailed medical history was obtained. Two 50 ml bottle of study drug as free sample was dispensed to patients and ask to consume 5 ml along with ORS per day. Patient's guardians were asked to avoid food with high in calcium and phosphate in the patient's diet. Patient's guardians were instructed to keep a diary note

of daily symptoms.

Three visits were schedule for all the patients recruited in the study. The first visit (V1) on day 0 was baseline visit i.e. before treating patient with the study drug medication. The second visit (V2) on day 3 was reevaluation visit and third visit (V3) on day 5 was conclusion visit. The adverse events occurring and symptoms of diarrhoea analysing by stool frequency and consistency were noted by the investigator at each visit. In case of any adverse events or serious adverse events and safety-related issues, the investigator can withdraw the patient from the clinical study and treat according to the symptoms severity.

Concomitant therapy

No Pharmacological interventions were allowed during study duration of 5 days. Prolonged diarrhoea causes to the body to lose salt and water which is essential for survival. Therefore to rehydrate the body, consuming of ORS powder along with sufficient quantity of water and drinking of water at regular interval was encouraged. In case severe dehydrated patients the fluids can be given by IV route of administration. Patient's guardians were suggested to feed the food having fibre and high nutrition value.

Efficacy assessment

Before treating the patient with the study drug, the stool frequency per day and stool consistency i.e. watery, semisolid, soft or hard was recorded in the case report form. Patient guardian were asked to give the study drug orally to the patient and the same parameters were recorded at visit 2 (day 3) and visit 3 (day 5).

Safety assessment

Investigators asked patients for any adverse events during each post- dose visit throughout the study, if any adverse events are observed, it was noted in the case report form. The noted adverse events were classified into 2 different categories as serious or non-serious adverse events. Adverse event were classified as drug related or non-drug related adverse events by using Naranjo's scale of probability. Adverse events observed in patients were followed up and if necessary treated by the investigators till their resolution.

Regulatory and ethical matters

In India, Zinc gluconate is approved as OTC drug. WHO, UNICEF, USAID, IAP and NRHM has supported the use of zinc in diarrhoea. All Parents or guardians of the participated patients in the study have to read and signed the Inform consent form (ICF).

Results

Total 200 patients were mustered at 12 centres all across India for the study. 182 patients completed the study, analysed and 18 patients were lost to follow-up during the study period.

Efficacy analysis

The primary assessment was carried out by analysing the change in stool consistency i.e. hard/ soft/ semisolid/ watery and reduction in average stool frequency of the patients. The reduction in average stool frequency and change in stool consistency in visit 2 at day 3 and visit 3 at day 5 was analysed and compared to baseline visit i.e. visit 1. At

baseline visit (V1), 144 (79.12 %) of patients were having watery stools, 34 (18.68 %) were having semisolid and 4 (2.19 %) having soft stools and no patient was having hard stools. In visit 2 on day 3, 38 (20.87 %) patients were having watery stools, 126 (69.23 %) were having semisolid, 17 (9.34 %) having soft stools and 1 (0.54 %) patient was having hard stools. Here in re-evaluation (V2), after medication of it was found that there was a decrease in number of patients having watery stool consistency, increase in number of patients having semisolid and soft stool consistency. In visit 3 on day 5, 10 (5.49%) patient were having watery stools, 37 (20.32 %) were having semisolid, 123 (67.58 %) were having soft stools and 12 (6.59 %) patients were having hard stools. Therefore as compared to baseline visit, in conclusion visit (V2) there was a decrease in patients having watery and semi-solid stool consistency whereas there was an increase in patients having soft and hard stool consistency.

Table no. 1: Change in stool consistency at visit 1, 2 and 3 for all the patients.

Change In Stool Consistency	Number of patients		
	V1 (Day 0) (Baseline Visit)	V2 (Day 3) (Re-Evaluation Visit)	V3 (Day 5) (Conclusion Visit)
WATERY	144	38	10
SEMI-SOLID	34	126	37
SOFT	4	17	123
HARD	0	1	12

The average stool frequency at baseline visit (V1) was found out to be 7.07. In visit 2 (V3) the average stool frequency reduced to 4.68 and further in visit 3 (V3) it was reduced to 3.05. Therefore it was found that through medication there was change in stool consistency and reduction in average stool frequency.

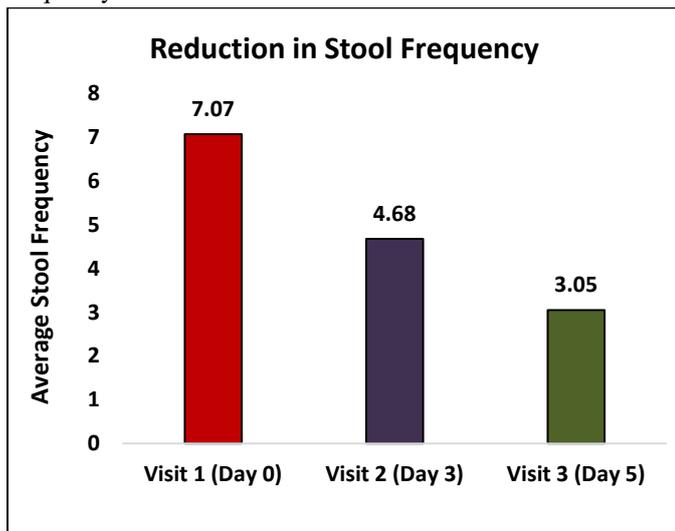


Fig no. 1: Reduction in Average Stool Frequency

Safety analysis

Six overall incidences was reported as study drug related adverse events were seen in 4 patients. The list, number of adverse events with the number of episodes is mentioned below in Table 2.

Table 2: List of adverse events, number of episodes, and number of patients and percentage of patients experienced the adverse events from total population

Adverse event	No. of event	No of patient	% of patients
Vomiting	4	3	1.64
Excessive Crying	2	2	1.09
Total	6	4	2.19

Discussion:

From the last three decades, Indian infants and young children with diarrhoea have been treated with standard ORS solution. Due to severe diarrhoea there is loss of essential minerals from the body such as zinc which plays a significant role for growth and immunity. Recent clinical studies has showed that zinc supplementation has important role in reducing the frequency and duration of diarrhoea in children suffering from Zinc deficiency. The strength of the study is the both parameter which leads to reduction in diarrhoea i.e. change in stool consistency and reduction in average stool frequency were clinically studied over a period of 5 days study duration.

At baseline visit (V1), it was found that 144 (79.12 %) patients were having watery stools, 34 (18.68 %) were having semisolid and 4 (2.19 %) having soft stools and no patient was having hard stools. After medication on re-evaluation visit 2 on day 3, it was found that 38 (20.87 %) patients were having watery stools, 126 (69.23 %) were having semisolid, 17 (9.34 %) having soft stools and 1 (0.54 %) patient was having hard stools. On conclusion visit 3 on day 5, it was found that 10 (5.49%) patient were having watery stools, 37 (20.32 %) were having semisolid, 123 (67.58 %) were having soft stools and 12 (6.59 %) patients were having hard stools. Here in re-evaluation (V2), after medication of it was found that there was a decrease in number of patients having watery stool consistency, increase in number of patients having semisolid and soft stool consistency. Therefore as compared to baseline visit, in conclusion visit (V2) there was a decrease in patients having watery and semi-solid stool consistency whereas there was an increase in patients having soft and hard stool consistency.

The average stool frequency at baseline visit (V1) was found out to be 7.07. In visit 2 (V3) the average stool frequency reduced to 4.68 and further in visit 3 (V3) it was reduced to 3.05. Therefore it was found that through medication there was change in stool consistency and reduction in average stool frequency. Six overall incidences was reported as study drug related adverse events. Vomiting and excessive crying most probably due to colicky pain in abdomen was the documented adverse event in this study affecting 2.19% of the study population.

Dutta, P., et al.⁶ has conducted a randomised, double-blind, clinical trial on 80 male malnourished children aged between 3 to 24 months suffering from diarrhoea to evaluate the efficacy of zinc supplement (zinc sulphate) with ORS. This study was conducted in Calcutta, India. 44 children were placed in zinc supplementation group and 36 were in placebo group. 100%

children with zinc supplement group and 89% with placebo group were recovered from Diarrhoea in 5 days. The difference in cure rate in two different groups was significant ($P = 0.004$). As compared to placebo group, children with zinc supplementation has shorter duration of diarrhoea ($P = 0.0001$), passed less liquid stools ($P = 0.0001$) and consume less ORS ($P = 0.0001$).

Bhatnagar, S., et al.⁷ has conducted a controlled, randomised, double blind clinical trial to evaluate the effect of zinc supplement in addition therapy of ORS in children with acute diarrhoea with dehydration. The main parameter of the study is stool outcome and duration. Around 287 patients with acute diarrhoea were recruited of age group from 3 to 36 months. The dose 15 mg or 30 mg of elemental zinc was given daily to patients in three divided doses for 14 days. In this study it was found that after zinc treatment the stool output reduced (the ratio of geometric means: 0.69) and stool output per day (the ratio of geometric means: 0.76). The risk of diarrhoea was lowered and the proportion of diarrhoeal episode lasting more than 5 days was found out as odd ratio of 0.49 and for more than 7 days was 0.09 which is lesser.

Bhutta, Z., et al.⁸ has conducted a pooled analyses including controlled and randomised trial to measure the effect of zinc supplementation along with ORS therapy in children aged less than 5 years with acute or persistent diarrhoea. This study was conducted in various cities of different developing countries which include New Delhi, India; Dhaka, Bangladesh etc. The authors use Cox survival regression analysis to appraise the overall effect of zinc supplementation on continuation of diarrhoea and possible differential effects in subgroups which was divided in two groups in which sex, age, weight-for-height was in one group, and initial plasma zinc concentration was in another and therefore by using logistic regression the Dichotomous outcomes were analysed. To evaluate the effects of studies without original data from the pooled analyses, effect-size was projected for all studies by using random-effects models. As a result, Zinc-supplemented children was found out with 15% lower probability of continuing diarrhoea on a given day (95% CI: 5%, 24%) in the acute-diarrhoea trials and a 24% lower probability of continuing diarrhoea (95% CI: 9%, 37%) and a 42% lower rate of treatment failure or death (95% CI: 10%, 63%) in the persistent diarrhoea trials. The 2 sub-group which were analyses of each pair were significantly different from each other.

Conclusion

Zinc gluconate with ORS therapy is safe and efficacious in treatment of diarrhoea in Indian paediatric patients

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Disclosure

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