



POST-MARKETING SURVEILLANCE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ZINC GLUCONATE IN PAEDIATRIC PATIENTS OF DIARRHOEA

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Article Received on 11/06/2021

Article Revised on 02/07/2021

Article Accepted on 23/07/2021

ABSTRACT

Introduction: Diarrhoea is characterised by loose, watery stools, nausea, stomach cramps, pains and other symptoms. Zinc supplementation is considered to be efficacious to minimise the frequency and severity of diarrhoea. Zinc has been recommended for the treatment of diarrhoea by the WHO and the UNICEF since 2004. If Zinc is paired with oral rehydration solution (ORS) and continued feeding, diarrhoeal morbidity and mortality can be minimised. This study was conducted to determine the efficacy and safety for Zinc Gluconate equivalent to elemental Zinc 20 mg per 5ml for the treatment of diarrhoea in paediatrics in Indian population. **Method:** A total 180 trial subjects were enrolled for the study. The study was conducted for the duration of 14 days in which the efficacy was analysed till day 5 as normally the diarrhoea gets managed within 5 days and the safety was analysed till day 14. The improvement in stool consistency and the decrease in average stool frequency were used to determine efficacy. To evaluate safety, the occurrence and severity of the reported adverse events were measured. **Results:** 166 trial subjects completed the study. The average stool frequency was 8.73 on day 1 reduced to 4.19 on day 3 and further reduced to 1.89 on day 5. During the study improvement in stool consistency was also observed. Adverse events reported by trial subjects were of non-serious and expected nature. **Conclusion:** Zinc Gluconate was found to be efficacious and safe for the treatment of diarrhoea when given along with the ORS.

KEYWORDS: Zinc Gluconate, Efficacy, safety, diarrhoea.

INTRODUCTION

Three or more loose or watery stools a day is referred as diarrhoea.^[1] In developing countries, children may experience several episodes of acute diarrhoea each year, each of which contributes to the infection-malnutrition cycle and results into impaired growth and development.^[2] The intestine handles 8-9 L of fluid per day in adults, but typical stool fluid losses are just 150 mL, demonstrating the intestine's incredible absorption ability. The commonest causes of infectious diarrhoea are viruses including but not limited Rotavirus, Norovirus, Enteric adenovirus, other virus including Caliciviruses, Astroviruses, Enteroviruses and bacteria like Campylobacter Jejuni, non-typhoid Salmonella sp, Enteropathogenic E. Coli, Shigella spp, Salmonella typhi, Shiga-toxin producing E. Coli (ETEC), Vibrio Cholera Protozoa, Cryptosporidium Parvum, Giardia Lamblia and Entamoeba Histolytica. The prevalence of these pathogens varies depending on patient's geographical location. Around 70% of diarrhoea cases in

developing countries are viral (40 % rotavirus), 10-20 % bacterial and 10 % of protozoal origin.^[3] Diarrhoeal illnesses affects almost 46 million children under the age of five years, with about 1 billion episodes of diarrhoea.^[4,5] The first step in treating a patient with diarrhoea is to take a thorough medical history and conduct a physical examination. Understanding the epidemiological contexts in which diarrhoea occurs (for example, community-acquired, hospital-acquired or travel-related) also aids in diagnosis and care.^[6] Lazzerini M et al., suggested that the treatment which decreases the duration and severity of diarrhoea is an important aspect in treating diarrhoea including Zinc supplementation which helps to reduce the frequency and severity of diarrhoea and thus may be more effective than oral rehydration solution (ORS) as monotherapy in reducing infant mortality and combination of Zinc supplementation with ORS also shows additional benefits for the treatment of diarrhoea.^[7]

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) have recommended Zinc for the treatment of diarrhoea since 2004. Zinc aids in the treatment of diarrhoea by assisting in the absorption of water and electrolytes by the intestine, as well as the faster regeneration of the gut epithelium, increased levels of enterocyte brush boundary enzymes and an improved immune response, both of which contribute to the clearance of the pathogens that cause diarrhoea. Zinc decreases the amount of stool produced and the duration of time diarrhoea lasts. In terms of immune response, Zinc decreases fluid secretion in the intestine by indirectly inhibiting cAMP-dependent Cl-transport across the mucosa through an action on the basolateral membrane K⁺. Zinc stimulates the immune system and assists in the regeneration of the intestinal epithelium.^[8] Zinc minimises the length and severity of diarrhoeal outbreaks, as well as the frequency of diarrhoea, when given for 10–14 days during and after the episode.^[9,10,11] In large-scale trials, researchers allocated whole populations to obtain Zinc in addition to and instead of ORS and it showed positive effects on diarrhoea duration, pneumonia incidence as well as reductions in hospitalizations and mortality.^[12] Zinc, when combined with low-osmolarity ORS and continued feeding, has the potential to minimise diarrhoea morbidity and mortality and also improves pneumonia morbidity and mortality in 2–3 months after treatment.^[13,14] This study was conducted to generate more data on efficacy and safety of a Zinc Gluconate for the treatment of diarrhoea in paediatric population in India.

METHODOLOGY

This post-marketing surveillance study was conducted at 12 paediatric speciality clinical trial sites all across India. The duration of the study was of 14 days. A total of 180 trial subjects were recruited, out of which 166 completed and rest were lost to follow-up. For the study duration of 14 days, trial subjects were requested to visit the clinical trial site on day 3, 5 and 14 considering the baseline visit as day 1.

Inclusion and Exclusion Criteria

For the post marketing surveillance study, trial subjects of both genders including male and female of age above 1 year with confirmed diagnosis of diarrhoea were recruited for the study. Also, only those patients were recruited whose guardians as well as patients were ready to willing to follow the study procedure.

Trial subjects having hypersensitivity to Zinc Gluconate were excluded. Patients or their guardians who could not adhere to the protocol including mentally ill or with psychological illness were excluded from the study.

Investigational product

The investigational product used for the post marketing surveillance study was Zinc Gluconate equivalent to elemental Zinc 20 mg per 5ml. The investigational

product was provided by the sponsor to the investigator at no cost and those investigational products were dispensed to the trial subjects at no cost by the investigator.

Study design

The Post Marketing Surveillance study was conducted on 180 trial subjects at 12 clinical trial sites. As the study was conducted on paediatric patients, all the investigators in this study were of paediatric speciality. Due to the non-randomized, non-comparative, and open label nature of the study, control drug was not used and all trial subjects, clinical research personnel, and any other people involved in the study were aware of the investigational product and its composition as well as the study procedures.

Study Procedure

Trial subjects were enrolled for the post marketing surveillance study as per inclusion and exclusion criteria by the investigator. All guardians of the eligible trial subjects as per the inclusion and exclusion criteria were well informed about the study procedure and the investigational product by the investigator. Guardians of the trial subjects were asked for their consent and if they were found to be ready to give his/ her consent for the study then the consent form for the study was taken by the investigator and then the trial subjects were recruited for the study. Consent for the study was taken by the guardians of the trial subjects before recruitment for the study as all the trial subjects were of age below 18 years. Also, all the doubts of the trial subjects or their guardians were resolved by the investigator in the language understandable by the trial subjects or the guardians of the trial subjects. A detailed medical history was obtained from all enrolled trial subjects and their guardians, which was followed by a thorough clinical examination. Each guardian of the trial subject was given with two 50 ml bottle of investigational product at no cost. All the guardians of the trial subjects were asked to give the investigational product to the trial subject in the dose of 5 ml per day for the study period of 14 days. Trial subjects and guardians of the trial subjects were instructed to record daily symptoms experienced by the trial subject to detect the adverse event if any. To evaluate efficacy and safety of the investigational product, trial subjects recruited in this study were asked to visit the clinical trial site on day 3 (Visit 2), 5 (visit 3) and 14 (visit 4) considering the baseline visit (visit 1) on day 1. Efficacy evaluation was done till day 5 (visit 3) as normally the diarrhoea is managed within 5 days but the safety evaluation was done for the study duration of 14 days.

Concomitant therapy

During the study, trial subjects were asked to take ORS as a concomitant therapy. During the study period, trial subjects were advised to strictly avoid foods rich in calcium and phosphate while taking the Zinc supplement. Non-pharmacological measures such as

drinking of clear liquid such water and juice, semisolid and low fibre food eggs, rice, soda crackers etc at regular intervals were permitted and encouraged.

Efficacy Assessment

Efficacy assessment was done by analysing the change in stool consistency as hard or soft or semisolid or watery and decrease in average stool frequency on day 3 (visit 2) and 5 (visit 3) as compared to the baseline (visit 1). The decrease in average stool frequency and improvement in stool consistency on visits 2 and 3 were analysed and compared to the baseline efficacy assessment records to analyse the efficacy.

Safety assessment

Trial subjects and their guardians were asked to report the adverse events on visit 2 (day 3), visit 3 (day 5) and visit 4 (day 14) to the investigator if any. These adverse events were categorized into serious or non-serious adverse events as well as expected or unexpected.

Regulatory Matters

In India, Zinc gluconate is approved for manufacturing and marketing. UNICEF, WHO, USAID, IAP and NRHM has supported the use of Zinc in diarrhoea. All Parents or guardians of the trial subjects in the study read and signed the Inform consent form prior to their recruitment in the post marketing surveillance study.

RESULTS

On visit 1 at day 1, trial subjects had average stool frequency of 8.73. On visit 2, day 3, the average stool frequency was reduced to 4.19, which was further reduced to 1.89 on day 5, visit 3. The average stool frequency at visit 3 (day 5) was 1.89 which could be considered as normal range of stool frequency in non-diarrhoeal human individuals. Figure 1 showed a graphical presentation of the average stool frequency at baseline, day 3 and day 5.

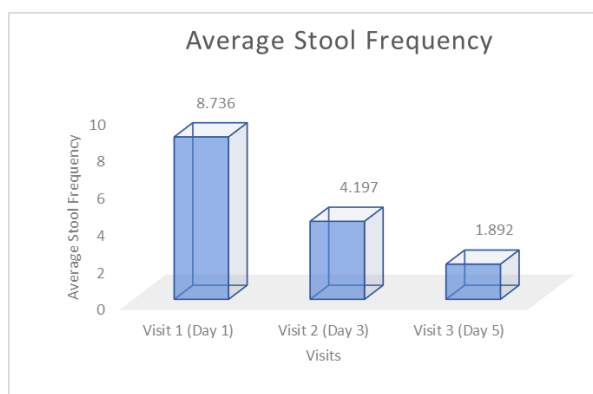


Fig.1: Average Stool Frequency at visit 1, 2 and 3.

On baseline visit, the average stool frequency was 8.37, which dropped to 4.19 on visit V2, indicated a 51.95% reduction as compared to baseline visit. On day 5, the average stool frequency was 1.89 which was a reduction of 78.34% as compared to the baseline. Graphical

presentation for the percentage reduction in the average stool frequency at visit 2 and 3 as compared to baseline is as presented below in the fig. 2.

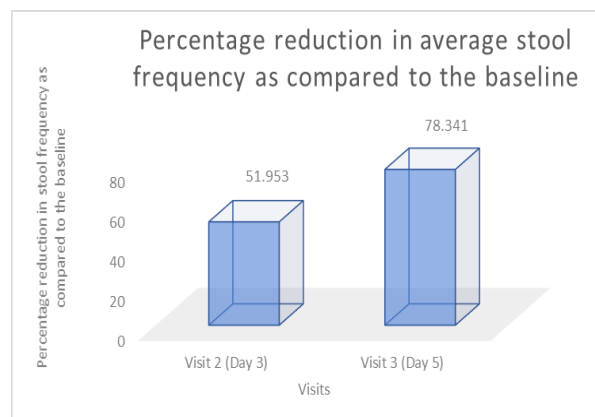


Fig. 2: Percentage reduction in average stool frequency score as compared to the baseline.

For further efficacy evaluation, the no. of trial subjects with different stool consistency as watery, semisolid, soft and hard have been calculated and graphically presented below in figure 3.

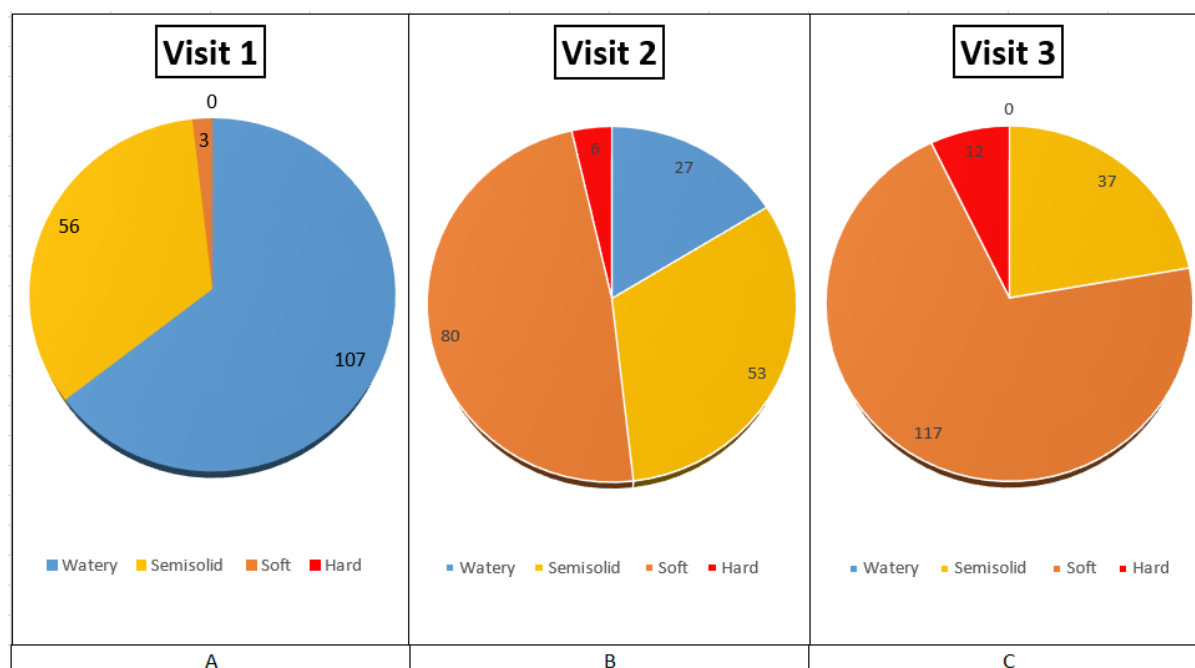


Fig.3: No. of trial subjects of watery, semisolid, soft and hard consistency at visit 1, 2 and 3 A) Visit 1 (day 1) B) Visit 2 (day 3) C) Visit 3 (day 5)

At Baseline, 107 trial subjects had watery, 56 had semisolid and 3 had soft stool consistency. At day 3, 27 trial subjects had watery, 53 had semisolid, 80 had soft and 6 had hard stool consistency. At day 5, 37 trial subjects had semisolid, 117 had soft and 12 had hard stool consistency. On day 5, no trial subjects had a watery stool consistency.

Overall efficacy evaluation showed that in the study duration of 5 days the mean stool frequency was restored to 1.89 which comes under the normal range of stool frequency and also no trial subject had watery stool consistency.

Safety analysis

Only 1 episode of adverse drug reactions was reported by a trial subject which was of metallic taste. In the study duration of 14 days, no severe or serious or un-expected adverse event was reported by any of the trial subject.

DISCUSSION

Diarrhoea is one of the leading cause of death in children under the age of five years in developing countries.⁽¹⁵⁾ Diarrhoea is characterised by loose, watery stools, nausea, stomach cramps, pains and other symptoms. The most critical aspect of treating diarrhoea is to reduce the length and severity of the diarrhoea. Zinc supplementation is considered to be reduces the incidence and severity of diarrhoea, which helps to minimise infant mortality and when Zinc is combined with ORS is considered to show the additional benefits for diarrhoea care. Zinc supplementation can be considered as useful for the management of extreme diarrhoeal morbidity and mortality. This study was conducted to test the efficacy and safety of Zinc

supplementation in the patients of diarrhoea. Total 180 trial subjects were recruited for the study out of which 166 completed the study and others were lost to follow-up. Stool consistency and reduction in average stool frequency were two parameters used to evaluate the efficacy in this post marketing surveillance study. At baseline, the average stool frequency was found 8.73 which was decreased to 4.19 at day 3 and then to 1.89 at day 5. At day 5, the average stool frequency was 1.89 which falls under the normal category and not under the diarrhoeal category. At visit 2 and 3 there was 51.95 % and 78.34 % decrease in the average stool frequency as compared to the average stool frequency at baseline. At Baseline, 107 trial subjects had watery, 56 had semisolid and 3 had soft stool consistency. At day 3, 27 trial subjects had watery, 53 had semisolid, 80 had soft and 6 had hard stool consistency. At day 5, 37 trial subjects had semisolid, 117 had soft and 12 had hard stool consistency. On day 5, no trial subjects had watery stool consistency. Overall efficacy evaluation showed that, in the study duration of 5 days the mean stool frequency was restored to normal stool frequency which was 1.89 which comes under the normal range of stool frequency and also no trial subject had watery stool consistency at day 5. Also there was no serious or unexpected adverse event and the investigational product was found to be safe. Below we have also discussed some of the similar kind of studies whose conclusion was supportive to this post marketing surveillance study.

P. Dutta et al. conducted a double-blind, randomised and controlled clinical trial on 80 malnourished children aged 3 to 24 months with diarrhoea to assess the efficacy of Zinc supplementation (Zinc Sulphate) when combined with ORS. This clinical trial was conducted in Calcutta,

India. Out of 80 patients recruited for the clinical trial, 44 children were randomized to the Zinc supplementation group, while 36 were assigned to the placebo group. In 5 days, 100% of children in the Zinc supplement group and 89 percent of children in the placebo group recovered from diarrhoea within 5 days of hospitalization ($p=0.04$). Children who obtained zinc supplementation had shorter diarrhoea length ($P= 0.0001$), passed less liquid stools ($P= 0.0001$) as compared to the placebo group. So, it was concluded that the Zinc supplementation in combination to ORS was efficacious for the treatment of diarrhoea.^[16]

Kiran et. al conducted a, randomised, double-blind clinical trial to evaluate the efficacy and safety for Zinc in diarrhoeal patients. The stool frequency and consistency were the efficacy parameters of the study. Total 200 patients were recruited for the clinical trial out of which 182 completed the study. The study duration was of 5 days. The average stool frequency was 7.07 which was reduced to 4.68 at day 3 and was further reduced to 3.5 at day 5. Also, in the clinical trial duration of 5 days, there was improvement in stool consistency. It was concluded that the Zinc gluconate with ORS therapy was safe and efficacious for the treatment of diarrhoea in Indian paediatric patients.^[17]

S Bhatnagar et al conducted a double-blind, randomized, multicentric, controlled trial in India. The study was conducted on total 287 patients of age 3 to 36 months having diarrhoea for more than 72 hrs. Patients recruited were either randomized to Zinc or placebo. Patients randomized to Zinc either received 15 mg (of age less than 12 months) or 30 mg (of age more than 12 months). The main outcome measures were stool output and diarrheal duration. Zinc treatment reduced total stool output (ratio of geometric means, 0.69; 95% confidence interval [CI]: 0.48, 0.99) and stool output per day of diarrhoea (ratio of geometric means, 0.76; 95% CI: 0.59, 0.98). The risk of continued diarrhoea was lowered (relative hazards, 0.76; 95% CI: 0.59, 0.97) and the proportion of diarrheal episodes lasting ≥ 5 days (odds ratio, 0.49; 95% CI: 0.25, 0.97) or ≥ 7 days was less (odds ratio, 0.09; 95% CI: 0.01, 0.73) in the zinc group. So it was concluded that Zinc was efficacious for the treatment of diarrhoea.^[18]

CONCLUSION

Investigational product (Zinc Gluconate equivalent to elemental Zinc 20 mg per 5ml) with ORS therapy was found to be efficacious as well as safe for the treatment of diarrhoea in Indian paediatric population.

ACKNOWLEDGEMENT

We would like to acknowledge Dr. Vikas Verma (Chhattisgarh), Dr. Swagat Das (Odisha), Dr. Naresh Acharya (Odisha), Dr. Suvarnshu Narayan Malik (Odisha), Dr. Raghavendra Singh Lacchawaha (Chhattisgarh), Dr. Suresh Honmane (Maharashtra), Dr. Kailas Umbarkar (Maharashtra), Dr. Rahul Kulkarni (Maharashtra), Dr. Pradeep Agarwal (Chhattisgarh), Dr.

Ashwinkumar Waghmode (Maharashtra), Dr. Ashish Gujar (Maharashtra), Dr. Sadanand Shetye (Maharashtra) who were the investigators in this study.

DISCLOSURE

This post marketing surveillance study was conducted as a part of Pharmacovigilance activity for Zincogut Syrup (Zinc Gluconate equivalent to elemental Zinc 20 mg per 5ml) by Centaur Pharmaceuticals Pvt Ltd.

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