ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Comparison of Mean Duration of Rota Virus Diarrhea After Administration of Zinc Sulphate Versus Control

Sobia Khaliq[1]*, Amna Khalid[2] and Muhammad Khalid Masood[3]

[1]Consultant Paediatrician, Punjab Employee, Social Security Hospital, Jhang, Pakistan

[2]Final Year MBBS Student KEMU, Pakistan

[3]Professor of Paediatrics, Children's Hospital and UCHS, Pakistan

***Corresponding Author:** Sobia Khaliq, Consultant Paediatrician, Punjab Employee, Social Security Hospital, Jhang, Pakistan.

Received: November 07, 2024; **Published:** December 13, 2024

Abstract

Objective: To compare the mean duration of diarrhoea with zinc sulphate versus control in children presenting with acute watery diarrhoea due to rota virus.

Materials and Methods: This randomized controlled trial was conducted over a period of 6 months at emergency department of Paediatrics in Mayo Hospital Lahore. Total 560 cases; 280 cases in each group were included. Patients were selected on the basis of predefined inclusion and exclusion criteria. 280 patients received zinc sulfate 10 mg/day to children < 1 yr. and 20 mg/day > 1 yr. for 7 days and the 280 patients in control group received placebo (Distilled water). Patients were observed in ambulatory through their contact numbers till the resolution of symptoms i.e. reduction in number of stool (< 3/days) and/or normal stool consistency. Duration of resolution of symptoms were noted. All the information was collected on a pre-designed performa. Data entry and analysis was done by using SPSS 19.

Results: Average age of children in Group-A and in Group-B was 21.60 ± 7.27 and 22.42 ± 7.38 weeks. Gender distribution showed that there were 145 (51.78%) male and 135 (48.22%) female children in Group-A and in Group-B there were 143 (51.07%) male and 137 (48.93%) female children. In Group-A mean days of resolution of symptoms was 4.54 ± 0.77 days and in Group-B mean days of resolution of symptoms was 5.40 ± 0.68 days. Minimum and maximum days of resolution in Group-A was 3 and 6 days respectively. While in Group-B minimum and maximum days of resolution of symptoms was 4 and 7 days respectively. In terms of p-value significant difference was seen in both treatment groups for resolution of symptoms. In Group-A symptoms resolve early as compared to that of Group-B children. i.e. (p-value = 0.000)

Conclusion: Zinc supplementation is effective for early resolution of symptoms and reducing frequency of stools in treatment of Rota virus diarrhoea in children.

Keywords: *Rota Virus; Duration of Diarrhoea; Zinc Sulphate; Acute Watery Diarrhoea*

Introduction

Diarrhea in children and babies is the passage of loose stool [1]. Acute gastroenteritis (AGE) is among the leading causes of childhood morbidity and mortality worldwide, accounting for an estimated 1.3 million deaths in children under 5 years of age [2]. Rotavirus is well-known causative agent in developing nations [3]. By the age of five, nearly every child in the world has been infected with rotavirus at least once [4].

In the United States, in 2006, rotavirus caused an estimated 20 to 60 deaths, 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 outpatient visit [5]. In emerging nation like Thailand, childhood acute diarrhea has shown increasing trend and one million cases have been reported in year 2007 [6]. According to a study conducted by Jane S Nakawesi., *et al*. in Uganda the prevalence of rotavirus infection was 45.4% [7], while a study conducted by Afzal A., *et al*. showed 28.9% prevalence of rotavirus diarrhea in Pakistan [8].

A study conducted by Rodak L., *et al*. illustrates the high sensitivity of ELISA in rotavirus detection [9]. In 2004, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) took two significant steps to reduce this burden by recommending the use of low-osmolarity oral rehydration solution (ORS), and supplementation with zinc for up to two weeks as part of the case management of acute diarrhea [10].

However, there exists significant heterogeneity in the effects of zinc in reducing the mean duration of diarrhoea observed across published randomized controlled trials. According to studies conducted by Lukacik M., *et al*. mean duration of acute diarrhea was significantly lower for zinc compared with placebo. Overall, children who received zinc reported an 18.8% reduction in average stool frequency, 15.0% shortening of diarrhea duration, and a 17.9% probability of reducing diarrhea over placebo in acute diarrhea trials [11].

In contrast a study conducted by Boran P., *et al*. showed that the mean duration of diarrhoea after starting supplementation was 3.02 ± 2 days in the zinc group and 3.673 ± 3.2 days in the control group. There was no significant difference in diarrhoea duration by treatment group (p.0.05) [12].

While in one study Christa L., *et al*. showed that young infants do not appear to benefit from zinc supplementation for the treatment of diarrhea. Infants who received zinc had more days of diarrhea (rate ratio = 1.20) than did the infants who received placebo [13].

As there are discrepancies in different studies, we are confused whether to use zinc sulphate in acute watery diarrhea caused by rota virus or not. If it is useful then we should continue its usage, and if not useful we should stop giving zinc in acute diarrhea because of rota virus.

Objective of the Study

To compare the mean duration of diarrhea with zinc sulphate versus control in children presenting with acute watery diarrhea due to rota virus.

Operational definition

Three or more loose or liquid stools per day, or having more stools than is normal for that person, in which Rota virus is isolated by ELISA. Response was noted in terms of reduction in number of stool (< 3/days) and/or normal stool consistency, after administration of drug in days.

Hypothesis

There is some difference between mean duration of diarrhea after zinc sulphate versus control in acute watery diarrhea due to rota virus.

Materials and Methods

This randomized controlled trial was conducted from September 2019 to April 2020 in emergency department of Paediatrics medicine Mayo Hospital Lahore. Sample size of 560 cases; 280 cases in each group is calculated with 95% confidence interval, 80% power of study

and taking magnitude of mean duration of diarrhea i.e. 3.02 ± 2 days in zinc sulphate group and 3.67 ± 3.2 days in control group in children presenting with acute watery diarrhea [12]. Non-probability, purposive sampling technique was used.

Children of age 1-36 months of both genders presenting with acute diarrhea as per operational definition were included in study after taking informed consent from their parents. Children with history of diarrhoea > 14 days, severe dehydration, coexisting severe infection e.g. sepsis (clinical examination and CBC, blood culture and sensitivity), pneumonia (clinical examination and chest X-RAY), meningitis (clinical examination and CSF examination), immune deficiency (malnourished), on antibiotic therapy (checking medical record) were excluded from study.

560 children fulfilling the inclusion criteria were selected from emergency section of Paediatric Medicine KEMU/Mayo hospital Lahore. Demographic profile i.e. name, age, sex, their contact number and address was recorded. History of total duration of illness, number of stools, consistency of stool and stool colour was recorded. 560 patients, who fulfil the inclusion criteria, were included in the study. They were randomly divided into 2 groups (case group and control group) by lottery method. All patients (whether in case group or control group) if need intravenous rehydration for dehydration at the time of hospital arrival, were given according to weight and degree of dehydration.

Both groups were advised to take ORS (oral rehydration therapy) after every loose stool. No antibiotic was prescribed to any group. 280 Patients (case group) received zinc sulfate 10 mg/day to children < 1 yr. and 20 mg/day > 1 yr. for 7 days. 280 patient (control group) received placebo (Distilled water). Patients were observed in ambulatory through their contact numbers till the resolution of symptoms i.e. reduction in number of loose stools (< 3/days) and/or normal stool consistency. Duration of resolution of symptom were noted. All the information was collected on a pre-designed proforma.

Data was entered and analysed in SPSS version. Quantitative variables like age and duration of diarrhea was calculated as mean and standard deviation. Qualitative variables like gender were calculated as frequency and percentage. T-test was used to compare mean duration of diarrhea in both groups. p-value ≤ 0.05 was considered as significant.

Results

Average age of children in Group-A and in Group-B was 21.60 ± 7.27 and 22.42 ± 7.38 weeks. In both groups minimum and maximum age of children was 10 and 36 weeks respectively.

Gender distribution showed that there were 145 (51.78%) male and 135 (48.22%) female children in Group-A and in Group-B there were 143 (51.07%) male and 137 (48.93%) female children.

Mean height of children in Group-A and in Group-B was 72.18 ± 9.78 and 74.22 ± 11.68 cm. Minimum height in Group-A and in Group-B was 45 and 50 cm and maximum height was 95 cm.

Mean weight of children in Group-A and in Group-B was 7.18 ± 0.87 Kg and in Group-B it was 7.30 ± 0.92 Kg. Minimum and maximum weight in both treatment groups was 5.75 and 9 Kg respectively.

In Group-A 243 (86.78%) children and 217 (77.5%) children in Group-B had normal stool consistency. Stool consistency was high in Group-A as compared to Group-B (Table 1).

	Group-A	Group-B
Yes	243 (86.78%)	217 (77.5%)
No	37 (13.22%)	63 (22.5%)
Total	280	280

Table 1: *Normal stool consistency in relation to study groups.*

Group-A = Zinc Sulfate; Group-B = Placebo (Distil Water).

There were 65 (23.21%) children in Group-A and 90 (32.14%) children in Group-B had > 3 stools per day (Table 2).

	Group-A	Group-B
Yes	65 (23.21%)	90 (32.14%)
No	215 (76.79%)	190 (67.86%)
Total	280	280

Table 2: *Stool > 3 days in relation to study groups.*

Group-A = Zinc Sulfate; Group-B = Placebo (Distil Water).

In Group-A mean days of resolution of symptoms was 4.54 ± 0.77 days and in Group-B mean days of resolution of symptoms was 5.40 ± 0.68 days. Minimum and maximum days of resolution in Group-A was 3 and 6 days respectively. While in Group-B minimum and maximum days of resolution of symptoms was 4 and 7 days respectively. In terms of p-value significant difference was seen in both treatment groups for resolution of symptoms. In Group-A symptoms resolve early as compared to that of Group-B children. i.e. (p-value = 0.000) (Table 3).

	Group-A	Group-B
N	280	280
Mean	4.54	5.40
SD	0.77	0.68
Minimum	3	4
Maximum	6	7

Table 3: *Days of resolution of symptoms in relation to study groups.*

Group-A = Zinc Sulfate; Group-B = Placebo (Distil Water).

p-value = 0.000 (Significant: p-value < 0.05).

Discussion

Since their discovery in the 1970s, the human rotaviruses have been recognized as the most common infectious agents associated with diarrhea in the pediatric age group worldwide [14]. Virtually all children throughout the world are infected with rotavirus by the time they are 3-5 years old. Every year, rotavirus causes between 352 000 and 592 000 deaths globally among children < 5 years old, mostly in developing countries [15].

The treatment of rotavirus diarrhea has remained relatively unchanged over the last 35 years. Oral rehydration, breastfeeding, and early refeeding are still the most important tools in the management of children and infants with acute gastroenteritis and rotavirus diarrhea [14].

Oral rehydration is inexpensive, accessible, and it significantly reduces morbidity and mortality [16,17]. Oral rehydration, however, does not reduce the volume or duration of diarrhea. Other preparations used for treatment of diarrhea include probiotics, anti-peristaltic and anti-secretory agents [18].

Diarrheal diseases are a leading cause of childhood mortality and morbidity in developing countries and an important cause of malnutrition [19]. The majority of diarrheal deaths are caused by dehydration that can be treated with ORS or parenteral rehydration. ORS or parenteral rehydration, however, cannot reduce the volume, frequency, and duration of diarrhea [20]. Available antiperistaltic or anti-secretory drugs to reduce the severity of diarrhea can cause serious side-effects in children [18]. Various auxiliary treatments aimed at shortening the diarrheal episodes are optional.

Zinc supplementation during diarrhea is recommended in developing countries by the WHO and the United Nations Children's Fund (UNICEF) based on several trials demonstrating a significant effect of zinc in reducing the duration, severity, and recurrence of diarrhea in immunocompetent and in severely malnourished or immune-deficient children [21-23].

Studies linking diarrheal diseases with zinc deficiency were first described in reports of low plasma zinc levels in children with diarrhea [24]. Several studies showed that zinc reduced stool output and diarrheal duration when administered as an adjunct to oral rehydration solution (ORS) in hospitalized children aged 3-36 months with acute diarrhea and dehydration [25]. In a pooled analysis of nine randomized trials, zinc supplementation was reported to decrease the incidence of diarrhea by 18% [26]. The World Health Organization (WHO) recommends 14 days of zinc supplementation for all children who have acute diarrhea: 10 mg daily for infants younger than 6 months of age and 20 mg daily for all older infants and children [27].

In recent years, several studies have reported the therapeutic effect of zinc supplementation on diarrheal diseases that was beneficial on decreased episode duration, stool output, stool frequency, hospitalization duration. In some countries in West Asia such as Lebanon, Israel, Saudi Arabia and Iran in clinical trials showed a faster improvement in acute gastroenteritis in children less than five years. But in some countries, such as Turkey, this effect was not significant.

In this study it was observed that children who were given zinc sulfate among them stool > 3 was observed in only 65 (23.21%) children while in placebo group 90 (32.14%) of the children had stool > 3. This shows a wide difference in both groups regarding number of stools. However, it was observed that children on zinc therapy had short time period for resolution of symptoms as compared to that of placebo. i.e. (Zinc) 4.54 days and (Placebo) 5.40 days.

NazanDalgic from Turkey evaluated the effectiveness of zinc, probiotic bacteria, and lactose-free formula and their different combinations in the treatment of rotavirus diarrhea in young children. The patients were randomly divided into 8 different treatment groups. Group-1 (*S. boulardii*), Group-2 (Zinc), Group-3 (Lactose free formula), Group-4 (*S. Boulardii*+ Znc), Group-5 (*S. boulardii*+ lactose-free formula), Group-6 (Zinc+ lactose-free formula), Group-7 (*S. boulardii*+ Zinc+ lactose-free formula), Group-8 (Oral and/or parenteral rehydration solutions). Results of the study showed that the duration of diarrhea was significantly reduced in groups 2 (Zinc) and 4 (*S. Boulardii* + Zinc) compared to control. i.e. [3. 41 ± 1.38 and 3.11 ± 1.81] Days A statistically significant difference in the duration of hospitalization was observed for the groups 2 and 4 in comparison to the control group. [4.33 ± 1.38 and 4.11 ± 1.64] days [28]. Results of this study is consistent with the results reported by NazanDalgic confirming the effectiveness of zinc in children for treating rotavirus diarrhea.

A recently published study from Iran by Mohammad Karamyyar assessed the therapeutic effects of oral zinc supplementation on acute watery diarrhea of children with moderate dehydration. In his findings he reported that the mean diarrhea frequency (4.5 ± 2.3 vs. 5.3 ± 2.1; P = 0.004) was lower in the group receiving zinc +ORS. Stool consistency also confirmed earlier improvement in the treatment group

in the first three days of hospitalization (p-value < 0.05). The mean duration of hospitalization was significantly lower in the patients receiving zinc supplements (2.5 ± 0.7 vs. 3.3 ± 0.8 days; p-value = 0.001) [29]. Results of this study on terms of resolution of symptoms and number of stools was consistent with the results reported by Mohammad Karamyyar who also reported beneficial and significant effect of zinc in treating rotavirus diarrhea in children.

P Boran in his study evaluated the effect of daily zinc supplementation for 14 days on diarrhoea duration, severity, and morbidity in children. His results showed that the mean duration of diarrhoea after starting supplementation was 3.02 ± 2 days in the zinc group and 3.67 ± 3.2 days in the control group. The number of stools after starting supplementation was 5.8 ± 3.7 and 5.1 ± 3.9 on day 1, 2.9 ± 1.6 and 3.0 ± 2.2 on day 2, and 1.8 ± 1.1 and 1.6 ± 0.9 on day 3 in the zinc and control groups, respectively. No significant effect was found on the incidence and prevalence of diarrhoea in the zinc compared with the control group [30].

Boran did not reported significant results for the use of zinc which is contradicting to the results of this study which may be due to certain confounding geographical factors or difference on sample size or other relevant related factors with mothers hygiene and dosage issue of zinc. Germana V. Gregorio in his study determined whether zinc with oral rehydration solution (ORS) is more cost effective than ORS alone in the treatment of acute diarrhea. As per his findings mean duration of diarrhea was 17 hours shorter and mean total cost of treatment was 5% cheaper in the zinc than ORS group. Use of zinc with ORS reduced the total cost and duration of acute diarrhea [20].

Results of a local study from Pakistan Rawalpindi showed that the zinc supplementation had no effect on the outcome of acute diarrhoea in children. There was no significant reduction in the severity of acute diarrhoea in the children who were given the zinc supplements, in comparison to those who were managed with the standard treatment protocol [31].

Results of local study is also not in line the results of this study showing no beneficial effect of zinc in treating diarrhea in children however the author of the local study concluded that zinc supplements may offer promising results in reducing the diarrhoea associated morbidity, without the risk of any serious adverse effects.

BernadetaPatro in his study evaluated the efficacy and safety of zinc in the treatment of acute gastroenteritis in children in Poland. In his findings he reported that there was no significant difference in the duration of diarrhea (p-value > 0.05). Similarly, there was no significant difference in the groups in secondary outcome measures such as stool frequency on days 1, 2, and 3, vomiting frequency, intravenous fluid intake, and the number of children with diarrhea lasting >7 days [32].

In another study from India reported that supplementation with a combination of micronutrients and vitamins was not superior to zinc alone, confirming the clinical benefit of zinc in children with diarrhea [33].

Although the benefits of zinc supplementation in the management of diarrhoea have been established, there remain a number of barriers to the widespread implementation of this treatment strategy. Currently, zinc is not used to treat most cases of diarrhoea because the known benefits of zinc supplementation are still not widely appreciated by physicians and health-care workers in developing countries. There is a need to establish the optimal dosage and to investigate whether the same benefits of zinc supplementation are also applicable to children in middle- or high-income nations [34].

Despite the growing number of studies evaluating zinc supplementation for the treatment of AGE in children, there are still some questions to be answered in the areas of basic and applied research. The results of our study confirm that zinc supplementation is effective in the treatment of AGE. However, the recommendations of UNICEF and WHO on zinc supplementation as a universal treatment for diarrhea in these populations cannot be simply extrapolated to all children from developed countries; rather, in line with the ESPGHAN/ESPID recommendations, the UNICEF and WHO recommendations should apply to any malnourished child.

Conclusion

Results of this study confirmed that zinc supplementation is effective for early resolution of symptoms and less frequency of stools in treatment of Rota virus diarrhoea in children.i.e. Stool >3 [Zinc Group = 65 (23.21%), Placebo = 90 (32.14%)] and Resolution of symptoms [Zinc Group = 4.54 days, Placebo = 5.40 days] These results cleared the disparity regarding the role of therapeutic role of Zinc in treating Rota virus diarrhoea in children.

Bibliography

1. Bhutta ZZ. "Acute gastroenteritis in children". In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 18th edition. Philadelphia, Pa: Saunders Elsevier: chapter 337 (2007).

2. Black RE., *et al*. "Global, regional, and national causes of child mortality in 2008: a systematic analysis". *Lancet* 375.9730 (2010): 1969-1987.

3. Parashar UD., *et al*. "Rotavirus and severe childhood diarrhea". *Emerging Infectious Diseases* 12.2 (2006): 304-306.

4. Pongsuwannna Y., *et al*. "A long-term survey on the distribution of the human rotavirus G type in Thailand". *Journal of Medical Virology* 82.1 (2010): 157-163.

5. Umesh D., *et al*. "Prevention of rotavirus gastroenteritis among infants and children: Recommendations of the Advisory Committee on Immunization Practices (ACIP)". *Morbidity and Mortality Weekly Report* 58 (No. RR-2) (2009): 1-25.

6. Intusoma U., *et al*. "Epidemiology, clinical presentations and burden of rotavirus diarrhea in children under five seen at Ramathibodi Hospital, Thailand". *Journal of the Medical Association of Thailand* 91.9 (2008): 1350-1355.

7. Nakawesi JS., *et al*. "Prevalence and factors associated with rotavirus infection among children admitted with acute diarrhea in Uganda". *BMC Pediatrics* 24 (2010): 358.

8. Afzal A., *et al*. "Rota virus gastroenteritis in children upto five years of age". *Journal of Rawalpindi Medical College* 14.1 (2010): 33-35.

9. Rodak L., *et al*. "Comparing electron microscopy and a competitive blocking ELISA in the detection of rotaviruses in porcine faeces". *The Veterinary Journal* 187.2 (2011): 279-281.

10. Winch PJ., *et al*. "Effect of HIV/AIDS and malaria on the context for introduction of zinc treatment and low-osmolarity ORS for childhood diarrhoea". *Journal of Health, Population and Nutrition* 26.1 (2008): 1-11.

11. Lukacik M., *et al*. "A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea". *Pediatrics* 121.2 (2008): 326-336.

12. Boran P., *et al*. "Impact of zinc supplementation in children with acute diarrhoea in Turkey". *Archives of Disease in Childhood* 91.4 (2006): 296-299.

13. Christa L., *et al*. "Zinc Supplementation for the Treatment of Diarrhea in Infants in Pakistan, India and Ethiopia". *Journal of Pediatric Gastroenterology and Nutrition* 43.3 (2006): 357-363.

14. Teran CG., *et al*. "Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children". *International Journal of Infectious Diseases* 13.4 (2009): 518-523.

15. Jayashree S., *et al*. "Serum and salivary antibodies as indicators of rotavirus infection in neonates". *The Journal of Infectious Diseases* 158.5 (1988): 1117-1120.

16. Rhoads M. "Management of acute diarrhea in infants". *Journal of Parenteral and Enteral Nutrition* 23.5 (1999): S18-S19.

17. Nappert G., *et al*. "Oral rehydration solution therapy in the management of children with rotavirus diarrhea". *Nutrition Reviews* 58.3 (2000): 80-87.

18. Subbotina MD., *et al*. "Effect of oral administration of tormentil root extract (*Potentilla tormentilla*) on rotavirus diarrhea in children: a randomized, double blind, controlled trial". *The Pediatric Infectious Disease Journal* 22.8 (2003): 706-711.

19. Kosek M., *et al*. "The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000". *Bulletin of the World Health Organization* 81.3 (2003): 197-204.

20. Gregorio GV., *et al*. "Zinc supplementation reduced cost and duration of acute diarrhea in children". *Journal of Clinical Epidemiology* 60.6 (2007): 560-566.

21. Bhutta ZA., *et al*. "Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials". *The American Journal of Clinical Nutrition* 72.6 (2000): 1516-1522.

22. Canani RB and Ruotolo S. "The dawning of the" zinc era" in the treatment of pediatric acute gastroenteritis worldwide?" *Journal of Pediatric Gastroenterology and Nutrition* 42.3 (2006): 253-255.

23. Bobat R., *et al*. "Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial". *The Lancet* 366.9500 (2005): 1862-1867.

24. Bhatnagar S., *et al*. "Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial". *Journal of Pediatric Gastroenterology and Nutrition* 38.1 (2004): 34-40.

25. Bhutta Z., *et al*. "Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials". *The Journal of Pediatrics* 135.6 (1999): 689-697.

26. Bass ES., *et al*. "Rotavirus". *Pediatrics in Review* 28.5 (2007): 183-191.

27. Alam NH and Ashraf H. "Treatment of infectious diarrhea in children". *Pediatric Drugs* 5.3 (2003): 151-165.

28. Dalgic N., *et al*. "Probiotic, zinc and lactose-free formula in children with rotavirus diarrhea: Are they effective?" *Pediatrics International* 53.5 (2011): 677-682.

29. Karamyyar M., *et al*. "Therapeutic effects of oral zinc supplementation on acute watery diarrhea with moderate dehydration: a double-blind randomized clinical trial". *Iranian Journal of Medical Sciences* 38.2 (2013): 93-99.

30. Boran P., *et al*. "Impact of zinc supplementation in children with acute diarrhoea in Turkey". *Archives of Disease in Childhood* 91.4 (2006): 296-299.

31. Choudhry S., *et al*. "Zinc supplementation in children with acute diarrhea". *Journal of Rawalpindi Medical College (JRMC)* 13.2 (2009): 66-69.

32. Patro B., *et al*. "Oral zinc for the treatment of acute gastroenteritis in Polish children: a randomized, double-blind, placebo-controlled trial". *The Journal of Pediatrics* 157.6 (2010): 984-988.e1.

33. Dutta P., *et al*. "Zinc, vitamin A, and micronutrient supplementation in children with diarrhea: a randomized controlled clinical trial of combination therapy versus monotherapy". *The Journal of Pediatrics* 159.4 (2011): 633-637.

34. Aggarwal R., *et al*. "Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis". *Pediatrics* 119.6 (2007): 1120-1130.

Volume 14 Issue 1 January 2025