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Original Research Article

Randomized Clinical Assessment of Synbiotic or Zinc Supplementation in the Treatment of Children with Bacterial Pneumonia

Md Khalil Ahmad[1], Krishna Murari[2], Rajeev Ranjan[3]

[1]Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India.
[2]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India
[3]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India

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Corresponding author: Dr. Krishna Murari
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Abstract

Aim: The aim of this study was to evaluate the interventional effects of synbiotic and zinc sulphate on reducing clinical symptoms and the average duration of treatment in children with bacterial pneumonia.

Methods: The randomized clinical trial with a parallel-group in which infants and children with emergency or elective hospitalization in Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India were diagnosed with pneumonia. A total of 200 people were randomly assigned to the two study groups.

Results: The mean ± SE age in the zinc group was 22 ± 2.4 months compared to 17 ± 2.6 months in the placebo group (p = 0.08). The children in the placebo group had a lower weight and height compared to the zinc group (9.6 ± 0.5 vs. 11.19 ± 0.7, p = 0.01, and 70.5 ± 2.2 vs. 80.4 ± 2.4, p = 0.04, respectively), and there were more males in the placebo group compared to the zinc group (65 vs. 40%, p = 0.04, respectively). The baseline clinical symptoms were comparable (according to the WHO pneumonia classification)—pneumonia (65 vs. 60%), severe pneumonia (30 vs. 35%, p = 0.93), oxygen saturation (84 ± 0.6 vs. 84 ± 0.8, p = 0.36), and respiratory rate (mean ± SE, 45 ± 1.5 vs. 46 ± 1.4, p = 0.55)—between the zinc and the placebo group, respectively. The predominant radiographic pattern was interstitial (84 vs. 70%), followed by alveolar (8 vs. 15%) and mixed (2 vs. 10%) (p = 0.25), in the zinc and the placebo group. Also comparable was the percentage of children with rales, fever, cough, respiratory distress, rhinorrhea, vomit, nasal flare, and costal retraction by group.

Conclusion: The results of this study could not show any clinical benefit for prescribing zinc or synbiotics in combination with standard antibiotic therapy in the treatment of children and infants, and they could not reduce the side effects of this treatment.

Keywords: Children, Infants, Pneumonia, Prebiotics, Probiotics, Zinc

Introduction

Pneumonia in children is caused by viral or bacterial pathogens.1 The incidence of childhood pneumonia is higher in low- and middle-income countries, with 0.22 episodes per child-year2 compared with an incidence of 0.05 episodes per child-year in high-income countries.2 Pneumonia was the cause of death for 920 000 children younger than 5 years of age globally in 2015, accounting for 16% of childhood deaths. [1,3]

Community-acquired pneumonia is a major cause of morbidity and mortality in children in resource-limited countries and is responsible for w18% of deaths in children 5 years of age (1.4 million deaths/y). [4,5] Zinc, critical for healthy growth and immune function and commonly deficient in low-income countries, can improve growth and reduce the frequency and severity of diarrhea and acute lower respiratory tract infections (ALRIs), including pneumonia in children. [6,7] Whereas zinc is an important adjunct to diarrhea treatment, reducing time to recovery among children aged 6 months to 5 years, trials of zinc in children hospitalized with severe pneumonia have yielded mixed results. [8-10]

In a trial conducted in children aged 2–23 months in Bangladesh, zinc reduced the duration of clinical manifestations of severe pneumonia, including chest in drawing, tachypnea, hypoxia, and length of hospitalization. [9] Another study in Kolkata, India, found that short-course zinc supplementation given to children with severe ALRI significantly reduced fever duration and very ill status in boys but not girls. [11] However, studies in India and Nepal found no benefits of zinc supplementation in children with pneumonia.10 Inadequate statistical power, variations in pneumonia case definitions, methodologic differences, and regional differences in under nutrition and zinc deficiency may explain these conflicting results.

Respiratory infections, especially lower respiratory tract infections such as bronchitis and pneumonia, have multiple and sometimes irreversible effects on the health system; and the economic and social effects of these infections are among the most important challenges of public health because it causes high costs of treatment 2021and hospitalization, absenteeism from school, and loss of working days on the side of the parents.

A wide range of etiological factors, widespread inappropriate use of antibiotics, increased bacterial resistance, lack of access to vaccines for many viruses and bacteria challenge the effective and appropriate treatment of this disease. [12,13] This has reduced the sensitivity to common antibiotics and created multidrug resistance in children. [14]

Since the introduction of probiotics by Metchnikoff in the early 1990s, these compounds have been increasingly considered in improving the function of various body systems. According to the World Health Organization (WHO), and the Food and Agriculture Organization of the United Nations (FAO), probiotics are living microorganisms that when consumed in sufficient quantities as part of the food, have beneficial effects through the intestinal flora on the health of the host.

The aim of this study was to evaluate the interventional effects of synbiotics and zinc sulphate on reducing clinical symptoms and the average duration of treatment in children with bacterial pneumonia.

Methods

The randomized clinical trial with a parallel-group in which infants and children with emergency or elective

hospitalization in Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India were diagnosed with pneumonia. A total of 200 people were randomly assigned to the two study groups. Infants and children between the ages of one month and 18 years, based on clinical, radiographic, and laboratory findings, including left shift leukocytosis or high ESR3 and CRP4or lung involvement on radiography, with a diagnosis of moderate up to very severe bacterial pneumonia, isolated from patients with atypical and viral pneumonia were included in the study. The exclusion criteria were having a history of underlying diseases such as cystic fibrosis, immunodeficiency, chronic heart disease, developmental disorders, failure to thrive, and legal guardianship dissatisfaction. Furthermore, if the patient refused to complete the treatment and any side effects occurred during the study, he/she was excluded from the study.

Zinc and placebo contained in identical paper containers marked as A or B were diluted in 1ml of distilled water and administered every day orally throughout the duration of hospitalization.

Both substances looked like white powder inside the envelopes, and when they were diluted in distilled water, they also looked the same. At the inclusion of the child demographic, clinical characteristics, laboratory workup, a chest x-ray, and risk factors for pneumonia were obtained, and during the follow-up, clinical records including heart rate, oxygen saturation, respiratory distress, temperature, cough, rales, wheezing, and feeding capacity were recorded periodically six times a day until the discharge of the patient in a special format designed for this study. The nurses record the vital signs two times per shift in a hospital sheet, and there are three shifts per day. The clinical records were taken from those records and verified by the pediatricians. All the patients received the standard treatment protocol for children with pneumonia, which includes oxygen supplementation and intravenous fluid, and according to the criteria of the consultant physician, penicillin or ampicillin was administered or oseltamivir if influenza was suspected. Two blood draws were obtained, one when the child was admitted to the hospital and another one the day of discharge to perform lymphoproliferation and cytokine assays and to obtain sera, which was frozen at −70◦C until processing to determine serum zinc levels.

Nasal washes were also obtained the day of hospitalization by instilling 1ml of physiological saline solution through a sterile feeding tube connected to a syringe and aspirating the solution from each nostril, placing the content into viral medium, and storing at −70◦C until processing to detect viral or bacterial genetic material. The nasal washes and blood samples were processed.

Statistical Analysis

Mean (standard deviation) was used to describe quantitative variables in terms of conditions, and frequency report (percentage) was used for qualitative variables. Chi-square test or Fisher's exact test was used to compare qualitative factors between the study groups. Then, if normal, to compare the mean of the quantitative outcomes among the three groups, analysis of variance was used and if the data were not normal, its nonparametric equivalent, Kruskal-Wallis, was performed. For data analysis, SPSS software version 14 was implemented, and the value of P-value <0.05 was considered statistically significant.

Results

Table 1: Baseline demographic and clinical characteristics of children with pneumonia who received zinc supplementation and placebo

	Zinc n =100	Placebo n = 100	P
	mean ± SE	mean ± SE	
Age (Months)	22 ± 2.4	17 ± 2.6	0.08
Weight	11.19 ± 0.7	9.6 ± 0.5	0.01
Height	80.4 ± 2.4	70.5 ± 2.2	0.04
BMI	16.4 ± 0.5	14.6 ± 0.5	0.45
Female n (%)	60 (60%)	35 (35%)	0.07
Male n (%)	40 (40%)	65 (65%)	
Pneumonia n (%)	65 (65%)	60 (60%)	
Severe pneumonia n (%)	30 (30%)	35 (35%)	0.93
Very severe disease n (%)	5 (5%)	5 (5%)	
O2 saturation	84 ± 0.6	84 ± 0.8	0.36
Respiratory rate	45 ± 1.5	46 ± 1.4	0.55
Respiratory distress, %	60	64	0.45
Rales, %	95	90	0.50
Fever, %	35	40	0.46
Cough, %	60	75	0.4
Rhinorrhea, %	48	52	0.45
Vomit, %	12	10	0.65
Nasal flare, %	4	2	0.49
Costal retraction, %	6	0	0.11
X-ray normal pattern, %	6	5	
Alveolar pattern, %	8	15	0.25
Interstitial pattern, %	84	70	
Mixed pattern, %	2	10	
Symptomatic treatment+, n (%)	10 (10)	15 (15)	
Antibiotics++, n (%)	88 (88)	85 (85)	0.80
Antibiotics and antivirals, n (%)	2 (2)	5 (5)	
Zinc pre-treatment, mcg/dl	23 ± 1.8	21 ± 1.9	0.34
Zinc post-treatment, mcg/dl	33 ± 4	29 ± 2.8	0.45

The mean ± SE age in the zinc group was 22 ± 2.4 months compared to 17 ± 2.6 months in the placebo group (p = 0.08). The children in the placebo group had a lower weight and height compared to the zinc group (9.6 ± 0.5 vs. 11.19 ± 0.7, p = 0.01, and 70.5 ± 2.2 vs. 80.4 ± 2.4, p = 0.04, respectively), and there were more males in the placebo group compared to the zinc group (65 vs. 40%, p = 0.04, respectively). The baseline clinical symptoms were comparable (according to the WHO pneumonia classification)—pneumonia (65 vs. 60%), severe pneumonia (30 vs. 35%, p = 0.93), oxygen saturation (84 ± 0.6 vs. 84 ± 0.8, p = 0.36), and respiratory rate (mean ± SE, 45 ± 1.5 vs. 46 ± 1.4, p = 0.55)—between the zinc and the placebo group, respectively. The predominant radiographic pattern was interstitial (84 vs. 70%), followed by alveolar (8 vs. 15%) and mixed (2 vs. 10%) (p = 0.25), in the zinc and the placebo group. Also comparable was the percentage of children with rales, fever, cough, respiratory distress, rhinorrhea, vomit, nasal flare, and costal retraction by group. No differences in the percentage of symptomatic, antibiotic, or antiviral treatment between groups were observed. Penicillin is used as empiric treatment for CAP in children at

the Hospital based on sensitivity patterns (Table 1).

Table 2: Comparison of the time for improvement of clinical symptoms

	Zinc n =100	Placebo n = 100	p
	mean ± SE	mean ± SE	
Clinical improvement (hours)	75 ± 5	106 ± 6	0.01
Normalization of respiratory rate (hours)	36 ± 6	55 + 5	0.03
Normalization of O_2 saturation (hours)	55 ± 7	87 ± 9	0.07
Normalization of respiratory distress (hours)	45 ± 5	58 ± 4	0.25
Normalization of temperature (hours)	6 ± 1	7 ± 2	0.80
Days of hospitalization	4 ± 0.4	4.8 ± 0.2	0.90

The clinical improvement (mean in hours of the combination of all the clinical variables) (75 ± 5 vs. 106 ± 6, p = 0.01), the normalization of the respiratory rate (36 ± 6 vs. 55 ± 5, p = 0.03), and the normalization of oxygen saturation (55 ± 7 vs. 87 ± 9, p = 0.007) measured in hours was faster in the zinc group compared to the placebo group and statistically significant. In the analysis of covariance adjusting the effect of zinc for age (because the placebo group were younger), a p of 0.01 was found for time for clinical improvement, 0.07 for respiratory rate, and 0.009 for oxygen saturation, meaning that the younger age in the placebo group was not a bias and had no effect for the better response in the zinc group. Also, weight, height, BMI, gender, vaccination status, and nutrition status had no effect in the covariance analysis on the dependent variables. There were no statistically significant differences in the normalization of respiratory distress (45 ± 5 vs. 58 ± 4, p = 0.25), normalization of temperature (6 ± 1 vs. 7 ± 2, p = 0.80) in hours, and days of hospitalization (4 ± 0.4 vs. 4.8 ± 0.2, p = 0.90) between the zinc and the placebo group, respectively, although a tendency was observed (Table 3). No deaths were reported in any of the participants of the study. No side effects were reported in children who received zinc or placebo.

Discussion

Zinc deficiency alters innate and adaptive immunity. [18] Zinc supplementation improves immunity, ameliorates chronic dysfunctional inflammatory responses [17], and has been shown to shorten the duration and decrease severity in children with diarrhea, and since 2004, WHO and Unicef recommend zinc supplementation along with oral rehydration. [19]

In a clinical trial, Bagri et al. (2017) examined 476 children aged 2-24 months with pneumonia in one of the groups of antibiotic treatment alone or antibiotics in combination with zinc. In this study, as in the present study, the researchers did not report any significant clinical benefit for adding zinc to the antibiotic regimen of children with pneumonia, although they reported a non-significant tendency to early recovery for patients receiving zinc. [20]

We conducted a randomized triple-blinded controlled clinical trial, using the recommended WHO dose of zinc for children with diarrhea in children with pneumonia; measuring the clinical symptoms as previously reported in many RCTs but with a translational approach where we measured cytokines, the lymphoproliferative capacity after zinc supplementation, and serum zinc levels; and detecting the etiological agents by multiplex PCR, trying to find a correlation of the pathogen, the clinical development, and the immune response.

We found that zinc improves oxygen saturation, tachypnea and clinical status in fewer hours than the placebo group, independently of age, weight, height, BMI,

nutritional, or vaccination status according to the covariance analysis, and this correlates with an increase in Th1 cytokines IFNg and IL-2 in the zinc group at discharge of the patient (after zinc supplementation). Although there was no difference in hospital stay, the respiratory symptoms improved faster. Both hospitals attend to a very-low-income population, and the discharge of a patient depends on many factors; for example, some patients improved but stayed hospitalized to finish the antibiotic treatment due to the lack of resources to buy the antibiotic, or for administrative reasons like payment of the hospitalization and lack of money of the parents.

The children in the placebo group had a lower weight and height, which could be a confounding variable, although they were 5 months younger, and that would explain the differences; and it is noteworthy that malnutrition showed no differences between groups. Because of this difference in age, adjusting by age, weight, height, and BMI, the effect of zinc on the respiratory parameters with a covariance analysis did not show an effect, which means the younger age is not a bias in the better response of the zinc group.

Nonetheless, there have been studies that show the role of taking zinc with antibiotics in speeding up the treatment process and reducing the length of hospitalization in children with pneumonia. Among them, we can mention the study of Qasemzadeh et al. and Sazaval et al. [21,22] However, this study is relatively older than the recent studies that have not reported positive results of zinc therapy in the treatment of pneumonia in children. It should be noted that one of the main underlying factors in the worsening of pneumonia in children and the failure of treatment is serum zinc deficiency. [23]

Zinc levels increased in the treatment group compared to the placebo, but they were below normal levels at admission to the hospital for pneumonia and also at discharge despite the supplementation. It is possible that zinc was depleted by consumption by PBMCs or neutrophils because of the inflammatory response [24], or by the use of bacteria to drive key cellular processes during infection [25], but it is also possible that the children who attended both hospitals are from a very-low income population, and zinc deficiencies due to malnutrition (in our group, up to 30%) could be the basal state of the children; a control of healthy subjects would have been suitable to answer these questions. [26]

Conclusion

Although the beneficial effects of probiotics in modifying the microbial flora of the gastrointestinal tract has been proven, according to the results of the present study, adding zinc or probiotics to the treatment regimen of infants and children with bacterial pneumonia is not useful and their routine prescription in combination with antibiotics do not seem to have an effect on the treatment of bacterial pneumonia.

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