Original Research Article

The effect of zinc sulphate on improving the clinical symptoms of pneumonia in children: A Double blind clinical trial

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Abstract

Aim: The aim of the present study was to examine the effect of zinc sulfate on improving the clinical symptoms of pneumonia children. **Materials and methods:** A clinical study was conducted in the Department of PaediatricsKalawati Saran Children Hospital, New Delhi, India for 16 months. The children with pneumonia were randomly assigned into intervention (n=60), and control (n=60) groups. The control group received placebo. On the other hand, the intervention group received zinc sulphate as 10 mg/day in children younger than one, and 20 mg/day in children above one year-old every 12 hours (during hospitalization). During hospitalization, every 12 hours the clinical symptoms of both groups including tachypnea (number of breaths), coughs, fever, intercostal retraction, hypoxia, crackles, wheezing, lethargy, and duration of hospitalization were evaluated. **Results:** Out of 120, 60 patients were included to the intervention and 60 to the control groups. The gender distribution of the tested patients was 58.33% boys and 41.67% girls. There was no significant difference between the two groups in terms of age, gender, and weight. The mean age in the intervention group was 13.86+0.779 and in the control it was 12.06+0.689 ($p>0.05$). The mean age of hospitalization in the case and control groups was 14.11+0.787 and 12.65+0.853 months, respectively, which was not statistically significant ($p=0.487$). The mean duration of hospitalization cases and control groups was 5.2+0.278 and 5.22+0.287 days respectively; based on the Mann-Whitney test, there was no significant difference between the two groups ($p=0.185$). The mean serum level of zinc in the intervention group (receiving zinc sulfate syrup) was 70.19(11.5) and 93.7(12.7) mcg/dl at the baseline and at the end of hospitalization respectively ($p<0.001$); while the mean serum level of zinc in the control group (receiving placebo) was 70.7(10.4) and 71.4(10.3)mcg/dl at the beginning and end of hospitalization respectively ($p=0.45$). According to Chi-square test, there was no significant difference between the two groups when comparing the presence or absence of tachypnea during hospitalization, as well as 12 and 24 hours post-hospitalization. However, at 36 hours post-hospitalization, there was a significant difference ($p=0.01$). **Conclusion:** we conclude that oral zinc sulfate supplement be considered for pediatric patients hospitalized due to pneumonia, in addition to the standard and conventional pharmacotherapy of pneumonia.

Keywords: Pneumonia, zinc, supplementation, treatment.

Introduction

Acute lower respiratory tract infection is one of the most important and common diseases among children, which is accompanied by high mortality rate, especially in young children. This infection is the most important cause of mortality among children under 5 in developing countries, accounting for nearly one-third of the cases[1-4]. Pneumonia is one of the most common implications of lower respiratory tract involvement. The World Health Organization estimates that of approximately 4 million annual deaths due to pneumonia, half of the cases occur in children less than 1 year of age[2,3,5]. On the other hand, malnutrition plays a significant role in the increased prevalence, severity, and prognosis of pneumonia, especially among children[3]. Zinc is an essential trace element required for maintaining intestinal cells, bone growth, and immune function. Children who are living in low-income settings are often undernourished and zinc deficient. This element plays an important and vital role in the physical development of digestive and immune systems. Zinc deficiency in children can cause stunted growth and increased incidence of infections (pneumonia, gastroenteritis) through weakening the immune system and changing neural and behavioral actions[6,7].

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Severe zinc deficiency has been associated with stunting of growth, impaired immunity, skin disorders, learning disabilities and anorexia[3]. Deficiencies may arise from the insufficient intake of foods containing zinc or insufficient absorption. Most foods high in zinc are of animal origin, such as meats, fish and dairy products. These foods may be more difficult to access for low-income populations. Dietary fibre and compounds called phytates, which are often found in foods such as cereals, nuts and legumes, bind to zinc and result in poor absorption[8].Frequent diarrhoea, that is also associated with chronic under nutrition, may further deplete body stores of zinc[9,10].

Zinc deficient children are at increased risk of restricted growth and developing diarrhoeal diseases, as well as respiratory tract infections such as acute lower respiratory tract infections[11].Diarrhoeal disorders and acute lower respiratory tract infections, especially pneumonia are the two most common causes of infant and child death in low-income countries[12].

Materials and Methods

A clinical study was conducted in the Department of Paediatrics, Kalawati Saran Children Hospital, New Delhi, India for 16 months, after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

120 children's with the symptoms of cough and fever as well as tachypnea plus respiratory distress and pulmonary infiltration as pneumonia was included. Then, based on clinical examination by a

pediatrician and the chest x-ray pattern which was reticular, lobar, or bronchoalveolar, they were categorized as viral and bacterial pneumonia. The children with pneumonia were randomly assigned into intervention (n=60), and control (n=60) groups. This research was performed as double-blind clinical trial, and only the physician was aware of the contents of the two drugs. The control group received placebo. On the other hand, the intervention group received zinc sulphate as 10 mg/day in children younger than one, and 20 mg/day in children above one year-old every 12 hours (during hospitalization). During hospitalization, every 12 hours the clinical symptoms of both groups including tachypnea (number of breaths), coughs, fever, intercostal retraction, hypoxia, crackles, wheezing, lethargy, and duration of hospitalization were evaluated. In both groups, at the beginning and end of hospitalization, one blood sample was taken for the necessary tests and for determining the serum level of zinc through the brachial vein and sent to laboratory. The children below 6 year with a diagnosis of pneumonia based on history and clinical examination, were include in this study. Children with chronic diseases such as immunodeficiency, cystic fibrosis, renal diseases, chronic pulmonary diseases, malnutrition and chronic diarrhea, acute severe infection, history of hospitalization over the past three months, use of immunosuppressive drugs, and history of taking zinc supplements over the past two weeks were excluded from the study.

Statistical analysis

Data analysis after coding, the data were analyzed by SPSS software version 16.0. In descriptive statistics, central indices (mean, standard deviation, frequency, and percentage) were used. Normality of distribution of quantitative variables was determined based on Kolmogorov-Smirnov test. To analyze and compare the quantitative and normal variables, t-test, and for qualitative and abnormal variables, Mann-Whitney test were used. For the qualitative and ranked variables, Mann-Whitney test, and for qualitative and nominal variables, Chisquare were applied; $p < 0.05$ was considered statistically significant.

Results

In this study 120 patients were include. Out of 120, 60 patients were include to the intervention and 60 to the control groups. The gender distribution of the tested patients was 58.33% boys and 41.67% girls. There was no significant difference between the two groups in terms of age, gender, and weight. The mean age of the hospitalized patients was 14.02+0.625, with below 6 year old, respectively. The mean age in the intervention group was 13.86+0.779 and in the control it was 12.06+0.689 (p>0.05). The mean age of hospitalization in the case and control groups was 14.11+0.787 and 12.65+0.853 months, respectively, which was not statistically significant (p=0.487). The mean duration of hospitalization was 5.78+0.551, with the minimum and maximum of 2 and 12 days respectively. The mean duration of hospitalization cases and control groups was 5.2+0.278 and 5.22+0.287 days respectively; based on the Mann-Whitney test, there was no significant difference between the two groups (p=0.185).

Table 1 Gender distribution of children's

Gender	N=120	%
Male	70	58.33%
Female	50	41.67%

Table 2. Basic character of children's

Group	Intervention	Control	P-value
	Mean (SD)	Mean (SD)	
Age	13.86+0.779	12.06+0.689	p>0.05
Hospitalization age	14.11+0.787	12.65+0.853	(p=0.487).
Duration of hospitalization	5.2+0.278	5.22+0.287	(p=0.185).

The serum level of zinc was calculated at the beginning of hospitalization and at the time of discharge for both intervention and control groups. The mean serum level of zinc in the intervention group (receiving zinc sulfate syrup) was 70.19(11.5) and 93.7(12.7) mcg/dl at the baseline and at the end of hospitalization respectively (p<0.001); while the mean serum level of zinc in the control group (receiving placebo) was 70.7(10.4)and 71.4(10.3)mcg/dl at the beginning and end of hospitalization respectively (p=0.45) (**Table.3**).

Table-3: Comparison of serum zinc levels in two groups of intervention and control before hospitalization and during discharge.

Group	Zinc level during hospitalization	Zinc level during discharge	P-value
	Mean (SD)	Mean (SD)	
Intervention	70.19(11.5) mcg/dl	93.7(12.7) mcg/dl	<0.001
Control	70.7(10.4) mcg/dl	71.4(10.3) mcg/dl	0.45

The number of breaths of all patients (control and intervention) was registered from the beginning of hospitalization and every 12 hours until the end of hospitalization. As observed in Table 4, according to Chi-square test, there was no significant difference between the two groups when comparing the presence or absence of tachypnea during hospitalization, as well as 12 and 24 hours post-hospitalization. However, at 36 hours post-hospitalization, there was a significant difference (p=0.01). The peripheral capillary blood oxygen saturation was calculated and recorded from the beginning of hospitalization every 12 hours until discharge for both control and intervention groups. According to Chi-square and Fisher exact test, there was no significant difference between the two groups regarding presence or absence of cyanosis during hospitalization and some hours post-hospitalization. Presence or absence of coughs in the study patients was recorded from the hospitalization every 12 hours. Regarding cough improvement in the intervention and control groups in terms of age, no significant improvement was observed in the study groups. In all of the patients studied (both intervention and control), from the beginning of hospitalization and every 12 hours thereafter until complete recovery, presence or absence of intercostal and subcostal retraction was recorded. According to Chi-square and Fisher exact test, there was no significant difference between the two groups regarding presence or absence of retraction at the time of hospitalization and hours after hospitalization. The severity of wheezing was calculated and recorded in both intervention and control groups at the beginning of hospitalization and thereafter every 12 hours. According to Chi-square and Fisher exact test, there was no significant difference between the two groups regarding

presence or absence of wheezing during hospitalization and hours post-hospitalization. The findings also indicated that based on Chi-square and Fisher exact test, there was no significant difference between the intervention and control groups when comparing presence or absence of lethargy during hospitalization as well as 12 and 24 hours post-hospitalization.

Table-4: Comparison of tachypnea in two groups based on measurement time

Time	Sub-group	Group		Total	P-value
		Intervention	Control		
During hospitalization	Yes	50(83.33)	53(88.33)	103(85.83)	0.227
	No	10(16.67)	7(11.67)	17(14.17)	
12 hours after hospitalization	Yes	46(76.67)	46(76.67)	92(76.67)	0.815
	No	14(13.33)	14(13.33)	28(23.33)	
24 hours after hospitalization	Yes	43(71.67)	33(55)	76(63.33)	0.105
	No	17(28.33)	27(45)	44(36.37)	
36 hours after hospitalization	Yes	18(30)	11(18.33)	29(24.17)	0.01
	No	42(70)	49(81.67)	91(75.83)	
48 hours after hospitalization	Yes	4(6.67)	3(5)	7(5.83)	0.7
	No	56(93.33)	57(95)	113(94.17)	

Discussion

The aim of the present study was to examine the effect of zinc sulfate on improving the clinical symptoms of pneumonia in below 6 year old children. The results showed that sink supplement in patients with pneumonia had a useful effect in reducing the duration of fever and number of breaths, but it had no significant effect on the cough and duration of hospitalization. The results of this study was similar by Habibian et al., reported that prescription of zinc supplement had no effect on number of breaths and duration of hospitalization, but it could reduce the fever[13].Brooks et al. in their study on 270 2-23-month-old children with severe pneumonia concluded that addition of zinc by 20 ml/day resulted in facilitation of pneumonia improvement in the children and reduced the pneumonia complications[5].In another study, the effect of zinc was examined on treating severe pneumonia in children younger than two. The researchers did not report any considerable impact on improving the pneumonia symptoms in children[14]. In a study, Mahalanabis et al. used zinc supplement in the treatment regimen of children with pneumonia and concluded that the treatment group showed diminished fever, but it had no effect on tachypnea[15].In the study by Sandstead in India, it was found that zinc supplement had no useful effect on measles-associated pneumonia[16].Some studies have found that zinc supplement is effective in preventing acute respiratory infection[17], and pneumonia complications would diminish following proper nutrition for children[18].Meanwhile, the results of a study indicated that zinc supplement does not have any effect in severe and very severe pneumonia[19].Possibly, the effect of zinc on reducing the duration of fever in children in the present study has been due to the fact that we eliminated the severe cases of infection. The results of another study showed that children with malnutrition who received zinc supplement for 60 days reported lower incidence of coughs, fever, and upper respiratory infections compared to the control group[20]. Also, the results of other studies indicated that incidence of respiratory infections was lower in the children receiving zinc supplements[21,22].

In other studies, it was found that zinc supplement had no effect on reducing the duration of pneumonia symptoms in children below five[23].In our study, no side effect of supplement was observed in patients. In some studies, digestive side effects have been reported[24].The most important finding in the present study was the relationship between zinc supplement and reduction of fever duration in both study groups. Possibly, reduction of inflammatory cytokines in the group receiving the zinc supplement is one of the reasons for this reduction in fever duration[25]. It is suggested that this study be conducted with a larger sample size and on a wider scale with different doses and treatment duration and the results then be compared to each other. In another study, performed as double-blind in Nepal on 122 children with severe pneumonia, no change was observed in the duration of hospitalization in the case and control groups who had received zinc and placebo. In our study, variables including the number of breaths, chest wall retraction, cyanosis, nasal flaring, fever, wheezing, alteration of antibiotic, and duration of hospitalization were recorded in both case and control groups and no significant difference was found. In another study performed in Australia, prescription of zinc supplement or vitamins had no effect on children with lower respiratory tract infection hospitalized in hospital[15].

Research findings in Zahedan showed that zinc deficiency is associated with increased susceptibility to pneumonia and gastroenteritis in children younger than five. Investigation of the effect of prescribing zinc compounds or fortifying the food with zinc in regions with zinc deficiency have been recommended for reducing incidence of pneumonia and gastroenteritis in this age group in future studies[26].

Conclusion

This study concluded that oral zinc sulfate supplement be considered for pediatric patients hospitalized due to pneumonia, in addition to the standard and conventional pharmacotherapy of pneumonia.

References

1. Williams B G, Gouws E, Boschi-Pinto C, Bryce J, and Dye C, “Estimates of world-wide distribution of child deaths from acute respiratory infections,” Lancet Infectious Diseases. 2002;2(1):25–32.
2. Pourpak Z, Aghamohammadi A, Sedighipour L et al. “Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immune deficiency,” Journal of Microbiology, Immunology and Infection.2006;39(2):114–120.
3. Faghihi N J, Hashemi P M, and Rahimi H H, “Pneumonia in children: is it related to Zinc deficiency,” Journal of Research in Medical Sciences. 2001;6(3):219–223.
4. Ramezani M, Ahmadi F, and KermanshahiS.“The effect of designed care plan on the duration and rate of pneumonia in infants in children medical center in Tehran,” Koomesh. 2006;7(1):27–34.
5. Brooks WA, Yunus M, Santosham M,Wahed MA, Nahar K, Yeasmin S et al. Zinc for severe pneumonia in very young children: double –blind placebo-controlled trial. Lancet. 2004; 363:1683–88.
6. Gibson RS, Ferguson EL. Assessment of dietary zinc in a population. American Journal of Clinical Nutrition. 1998; 68:430S–434S.
7. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled

analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. Journal of Pediatrics. 1999; 135(6):689–697.
8. Ruel MT, Rivera JA, Santizo MC, Lönnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. Pediatrics. 1997; 99(6):808–813.
9. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhoea in infants. Journal of Pediatrics. 1988; 113:452–457.
10. Naveh Y, Lightman A, Zinder O. Effect of diarrhea on serum zinc concentrations in infants and children. Journal of Pediatrics. 1982; 101:730–733.
11. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. Pediatrics. 2007; 119(6):1120–1130.
12. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children. Lancet 2005;365:1147–52.
13. Habibian R, Khoshdel A, Kheiri S, Torabi A. The Effect of Zinc Sulphate Syrup on Children's Respiratory Tract Infections. JBUMS. 2013; 15(4):22-9.
14. Bose A,Coles CL,Gunavathi,John H, Moses P, Raghupathy P, et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 yr old. Am J ClinNutr. 2006;83:1089–96.
15. Mahalanabis D,Lahiri M,Paul D,Gupta S,Gupta A,Wahed MA, et al. Randomised double-blind, placebo-controlled trialof the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. Am J ClinNutr. 2004;79:430-6.
16. Sandstead HH. Zinc deficiency. A public health problem? Am J Dis Child 1991; 145(8):853-9.
17. Bhutt Z, Black R, Brown KH, et al. Prevention of diarrhoea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 1999; 135(6):689-97.
18. Roy SK, Tomkins AM, Haider R, et al. Impact of zinc supplementation on subsequent growth and morbidity in Bangladesh children with acute diarrhoea. Eur J ClinNurt 1999; 53(7):529-34.
19. Bansal A, Parmar VR, Basu S, et al. Zinc supplementation in severe acute lower respiratory tract infection in children: a tripleblind randomized placebo controlled trial. Indian J Pediatr 2011; 78(1):33-7.
20. Sempertegui F, Estrella B, Correa E, et al. Effects of short-term zinc supplementation on cellular immunity, respiratory symptoms, and growth of malnourished Equadorian children. Eur J ClinNutr 1996; 50(1):42-6.
21. Bagui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002; 325(7372):1059.
22. Osendarp SJ, Santosham M, Black RE, Wahed MA, Van Raaij JM, Fuchs GJ. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J ClinNutr 2002; 76(6):1401-8.
23. Ganguly A, Chakraborty S, Datta K, Hazra A, Datta S, Chakraborty J. A randomized controlled trial of oral zinc in acute pneumonia in children aged between 2 infections in the elderly: Effect of zinc on the generation of cytokines and oxidative stress. Am J ClinNutr 2007; 85(3):837-44.
24. Larson CP, Hoque AB, Larson CP, Khan AM, Saha UR. Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial. J Health PopulNutr 2005; 23(4):311-9.
25. Prasad AS, Beck FWJ, Bao B, et al. Zinc supplementation decreases incidence of months to 5 years. Indian J Pediatr 2011; 78(9):1085-90.
26. SoleimaniGh, Abtahi S. Evaluation of serum zinc level in children hospitalized due to pneumonia and gastroenteritis in Zahedan. Zahedan journal of research in medical science. 2005; 7(4):251-7.

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