Study of zinc sulphate in pneumonia

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Abstract

Aim: The aim of the present study was to examine the effect of zinc sulphate on improving the clinical symptoms of pneumonia in 2-59- month-old children. **Materials and methods:** A clinical study was conducted in the Department of Paediatrics Darbhanga Medical College and Hospital,Darbhanga, Bihar,India . The children with pneumonia were randomly assigned into intervention (n=70), and control (n=70) groups. The control group received placebo. The intervention group received zinc sulphate as 10 mg/day in children younger than one, and 20 mg/day in children above one yearold every 12 hours (during hospitalization). During hospitalization, every 12 hours the clinical symptoms of both groups including tachypnoea (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, Blood sample was taken for the necessary tests and for determining the serum level of zinc through the brachial vein and sent to laboratory. **Results:**In this study 140 patients were included. Out of 140, 70 patients were included to the intervention and 70 to the control groups. The gender distribution of the tested patients was 57.14% boys and 42.86% girls. There was no significant difference between the two groups in terms of age, gender, and weight. The mean age of the hospitalized patients was12.83±0.705, with the minimum andmaximum of 2 and 59 months-old, respectively. The mean age in the intervention group was 13.91±0.812 and in the control it was 11.78±0.754 (p>0.05). The mean age of hospitalization in the case and control groups was 13.85±0.805 and 13.04±0.784 months, respectively, which was not statistically significant (p=0.511). The mean duration of hospitalization was 6.11±0.625, with the minimum and maximum of 2 and 12 days respectively. The mean duration of hospitalization cases and control groups was 6.2±0.316 and 4.85±0.328 days respectively; based on the Mann-Whitney test, there was no significant difference between the two groups (p=0.118).
Conclusion: Zinc sulphate in children referring with pneumonia symptoms had a useful effect on reducing the duration of fever and improving the respiratory status (tachypnea) in 2 to 59- month-old children.
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.

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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 and iron deficiency is one of the most common nutritional problems in Iran and many developed countries. According to statistics, about 50% of the common nutritional problems are due to a combined deficiency of the two elements, though the beneficial role of zinc compared to iron has been forgotten in Iran.[6] Zinc is an essential nutritional element, with a broad spectrum of biological activities

in humans. 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.[1,7] Numerous studies on therapeutic and prophylactic effects of zinc administration in infectious diseases indicate that administration of zinc compounds significantly reduces the incidence of gastroenteritis and pneumonia, and its deficiency could cause immune system deficiencies and increase the risk of serious infectious diseases such as diarrhoea and malaria.[1,8-10] Another study showed that serum zinc level in children with pneumonia and gastroenteritis was lower than in those of the same age.[11] It should be noted that inadequate intakes of zinc in the diet were the main cause of zinc deficiency. The annual report of the World Health Organization in 2003 has emphasized on the importance of adding zinc as a food supplement to the diet. The clinical symptoms of zinc deficiency during early childhood include acute or chronic diarrhoea accompanied by malnutrition, psychiatric disorders, and behavioural problems. A chronic zinc deficiency could cause alopecia, stunted growth, skin lesions, and common childhood infections such as pneumonia.[12] Zinc supplements can prevent and decrease the incidence of pneumonia. It can also shorten diarrhoea episodes and resolve them.[13] The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend that the children living in developing countries should take zinc supplement for 10 to 12 days as follows: 10 mg daily for infants younger than 6 months and 20 mg daily for infants older than 6 months. The purpose of this treatment is to reduce the severity of acute diarrhea episodes and hasten recovery from severe pneumonia in developing countries.[7]

Materials and Methods

A clinical study was conducted in the Department of Paediatrics Darbhanga Medical College and Hospital, Darbhanga Bihar, India.

Methodology

140 children 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 paediatrician 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=70), and control (n=70) 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 oneyearold 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 2-59-months-old 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, Chi-square were applied; $p< 0.05$ was considered statistically significant.

Results

In this study 140 patients were included. Out of 140,70 patients were including to the intervention and 70 to the control groups. The gender distribution of the tested patients was 57.14% boys and 42.86% girls. There was no significant difference between the two groups in terms of age, gender, and weight. The mean age of the hospitalized patients was12.83±0.705, with the minimum andmaximum of 2 and 59 months-old, respectively. The mean age in the intervention group was 13.91±0.812 and in the control it was 11.78±0.754 (p>0.05). The mean age of hospitalization in the case and control groups was 13.85±0.805 and 13.04±0.784 months, respectively, which was not statistically significant (p=0.511). The mean duration of

hospitalization was 6.11±0.625, with the minimum and maximum of 2 and 12 days respectively.The mean duration of hospitalization cases and control groups was 6.2±0.316 and 4.85±0.328 days respectively; based on the Mann-Whitney test, there was no significant difference between the two groups (p=0.118).

Table 1: Gender distribution of children's

Gender	N=140	%
Male	80	57.14%
Female	40	42.86%

Table 2: Basic character

Group	Intervention	Control	P-value
	Mean (SD)	Mean (SD)	
Age	13.91±0.812	11.78±0.754	p>0.05
Hospitalization age	13.85±0.805	13.04±0.784	(p=0.511)
duration of hospitalization	6.2±0.316	4.85±0.328	(p=0.118)

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 sulphate syrup) was 70.58±12.25 mcg/dl and 95.33±12.9 mcg/dl 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 72.58±11.05 mcg/dl and 72.56±9.69 mcg/dl at the beginning and end of hospitalization respectively (p=0.44) (**Table.3**).

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

Group	Zinclevel during hospitalization	Zinc level during discharge	P-value
	Mean (SD)	Mean (SD)	
Intervention	70.58±12.25 mcg/dl	95.33±12.9 mcg/dl	<0.001
Control	72.58±11.05 mcg/dl	72.56±9.69 mcg/dl	0.44

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 wasa significant difference (p=0.02). The peripheral capillary blood oxygen saturation was calculated andrecorded from the beginning of hospitalization every 12 hours until discharge for both control and intervention groups. 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 hospitalizationand every 12 hours thereafter until complete recovery, presence or absence of intercostal and subcostal retraction wasrecorded. 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. 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	58(82.86)	64(91.43)	122(87.14)	0.278
	No	12(17.14)	6(8.57)	18(12.86)	
12 hours after hospitalization	Yes	55(78.57)	57(81.43)	112(80)	0.785
	No	15(21.14)	13(18.57)	28(20)	
24 hours after hospitalization	Yes	50(71.42)	43(61.43)	83(59.29)	0.125
	No	20(28.57)	27(38.57)	47(40.71)	
36 hours after hospitalization	Yes	23(32.86)	13(18.57)	36(25.71)	0.02
	No	47(67.14)	57(81.43)	104(74.29)	
48 hours after hospitalization	Yes	6(8.57)	4(5.71)	10(7.14)	0.8
	No	64(91.43)	66(94.29)	130(92.86)	

Discussion

The present study aimed to evaluate the effect of zinc on the clinical course of pneumonia in 2 to 59-month-old children hospitalized in paediatric wards. Implementation of a random allocation might be a possible reason for the fact that in this trial, there was no statistically significant difference between the two groups in terms of some factors affecting the disease such as age, sex, family history of respiratory infections, and infections leading to hospitalization. Similar symptoms such as cough, fever, tachypnea, tachycardia, and respiratory distress in the abovementioned groups at admittance and before the intervention indicate that the severity of the disease has been almost the same. Therefore, the major difference between the children in the treatment group can be found in the element of zinc which is administered along with the standard antimicrobial therapy for pneumonia. In this study and compared to the comparison group, a significant decrease was found in the duration of hospitalization and recovery from pneumonia symptoms in zincreceiving children. This indicates the effect of zinc therapy and a change in the clinical course of pneumonia among the children under investigation. This finding is consistent with the results of most studies in this field.[5,14] some of which are mentioned below.

The results showed that sink supplement in patientswith 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.[15] 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.[16] Ina study, Mahalanabis et al. used zincsupplement in the treatment regimen of children with pneumonia and concluded that the treatment group showed diminished fever, but it had no effect on tachypnea.[17] In the study by Sandsteadin India, it was found that zinc supplement had no useful effect on measles-associated pneumonia.[18] Some studies have found that zinc supplement is effective in preventing acute respiratory infection[19] , and pneumonia complications would diminish following proper nutrition for children.[20] Meanwhile, the results of a study indicated that zinc supplement does not have any effect in severe and very severe pneumonia.[21] 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.[22] Also, the results of other studies indicated that incidence of respiratory infections was lower in the children receiving zinc supplements.[23,24]

In other studies, it was found that zinc supplement had no effect on reducing the duration of pneumonia symptoms in children below five.[25] In our study, no side effect of supplement was observed in patients. In some studies, digestive side effects have been reported.[26] 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.[27] 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 caseand 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.[17]Research findings in Zahedan showed that zinc deficiency is associated with increased susceptibility to pneumonia andgastroenteritis in children younger thanfive. Investigation of the effect of prescribing zinc compounds or fortifying the food with zinc in regions with zinc deficiency have been recommended forreducing incidence of pneumonia and gastroenteritis in this age group in future studies.[28] In this study, no significant change was observed in the duration of hospitalization, but the mean zinc level in both intervention and control groups was at the minimum level against the normal value.

Conclusion

Improve the clinical course and duration of symptoms, it is recommended to administer zinc supplementation to the children with suspected respiratory symptoms on their arrival at the hospital. Zinc sulphate in children referring with pneumonia symptoms had a useful effect on reducing the duration of fever and improving the respiratory status (tachypnea) in 2 to 59- month-old children.

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 immunodeficiency," 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. Emamghorashi F and Heidari T. "Iron status of babies born to iron-deficient anaemic mothers in an Iranian hospital," Eastern Mediterranean Health Journal.2004;10(6):8–814.
7. Kliegman R M, Bonita F, GemeM D J, Nina F, and Richard E, Nelson Textbook of Pediatrics, Elsevier Saunders, 19 edition, 2011.
8. Dıaz-Gomez N M, Domenech E, Barroso F, Castells S, Cortabarria C, and Jimenez A, "The effect of zinc supplementation on linear growth, body composition, and growth factors in preterm infants," Pediatrics.2003;111(5):1002–1009.
9. Hall S L, Dimai H P, and Farley J R, "Effects of zinc on human skeletal alkaline phosphatase activity in vitro," Calcified Tissue International.1999;64(2):163–172.
10. Yakoob M Y, Theodoratou E, Jabeen A et al. "Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria," BMC Public Health.2011;11(3).
11. Shils M E and Shike M, Modern Nutrition in Health and Disease, Lippincott Williams & Wilkins, 2006.
12. Laitinen R, Vuori E, Dahlstrom S, and Akerblom H K, "Zinc, copper, and growth status in children and adolescents," Pediatric Research.1989;25(4):323–326.
13. Black R E, "Zinc deficiency, infectious disease and mortality in the developing world," The Journal of Nutrition.2003;133(5):1485S–1489S.
14. Bhandari N, Bahl R, Taneja S. "Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum," British Medical Journal.2002;324:(7350):1358–1361.
15. 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.
16. 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.

17. 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.

18. Sandstead HH. Zinc deficiency. A public health problem? Am J Dis Child 1991; 145(8):853-9.

19. 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 Pediatr1999; 135(6):689-97.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. Ganguly A, Chakraborty S, Datta K, HazraA, DattaS, ChakrabortyJ.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.

26. 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.

27. Prasad AS, Beck FWJ, Bao B, et al. Zinc supplementation decreases incidenceof months to 5 years. Indian J Pediatr 2011; 78(9):1085-90.

28. SoleimaniGh, Abtahi S. Evaluation of serum zinc level in children hospitalized due to pneumonia and gastroenteritis in Zahedan. Zahedan journal of research in medicalscience. 2005; 7(4):251-7.

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