Research Article

The evaluation of effect of zinc sulfate supplement on pneumonia of 1 to 5 years old children

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ABSTRACT

Background: Pneumonia is one of the common causes in young children. Some studies have shown beneficial effect of zinc supplement on treatment of pneumonia. The aim of this study was to investigate the effect of zinc in treatment of children with pneumonia.
Methods and Materials: In this randomized clinical trial study, one hundred children with pneumonia (50 in case and 50 in control group) from pediatric ward of shahidbeheshti hospital of kashan university enrolled. Both groups received standard treatment. In addition to, zinc sulphate syrup was given to case group and placebo to control group. Respiratory rate, bed and cough and fever duration were compared between the case and control groups
Results: The mean duration of fever in the case group was 2.32 days and in the control group 2.44 days (p=0.55). The mean of bed duration in the case group was 5.30 days and in the control group 5.98 days (p=0.03). The mean of cough duration in the case and control groups was 4.7 and 5.22 days respectively (p=0.03) Respiratory rate in the case group was 3.10 and in the control 3.66 (p=0.008).
Conclusion: The study showed that zinc supplementation has a beneficial effect in decreasing the tachypnea duration , and cough and duration of hospitalization in children with pneumonia. But there was no significant effect on decreasing the fever duration.

Key words: Zinc, Supplement,Pneumonia,children

INTRODUCTION

The majority of pneumonia cases are caused by microorganisms, however, from noninfectious types of pneumonia, food or stomach acid aspiration, foreign bodies, hydrocarbons and lipoid substances, hypersensitivity reaction and pneumonitis caused by drug or radiation can be mentioned [1, 2]. Around 154 million of 185 million pneumonia cases are occurred in developing countries and pneumonia approximately leads to 3 million deaths annually which 29% of them are occurred in children under 5 years old [3]. The incidence rate of pneumonia is 10 folds higher in developing countries comparing to developed countries and the children mortality rate caused by pneumonia is also about 200 folds higher in developing countries and also total incidence of pneumonia in American infants is as: 30% in the first year, 20% in the second year and 10% in children older than 2 years old [4]. The most common etiology in children 1 to 5 years old is viral infections; also, bacterial infections include 10-30% of infants pneumonia. Microorganisms are transferred down by blood diffusion or local extension and arrive at lungs. 1 to 3 months infants often catch non-fever pneumonia which

most of cases are caused by maternal or environmental factors [5].

Tachypnea is the most common sign of pneumonia. Increasing of respiratory attempt along with contraction of intercostal muscles, subcostal muscles, suprasternal, tremor of nasal blades and the application of accessory respiratory muscles are other common manifestations of pneumonia. The severe form of disease might be accompany with cyanosis and breathing fatigue, especially in infants. Bacterial pneumonia in adults and children is typically begins along with sudden fever, cough and chest pain. Infiltration in graph of chest x-ray shows the existence of pneumonia [6].

Factors of hospitalization of children with pneumonia are a following: age under 6 months- tuberculosis cycle along with acute syndrome of chest- involvement of various lobes- immune suppress conditions- toxic and unwell appearance of patient- moderate to severe respiratory distress- need to supplementary oxygen- dehydration, vomiting or lack of resistance to drugs or oral fluids- lack of appropriate response to oral antibiotics and social conditions of patient (inability for application of drug and lack of supervision of patient's treatment at home or lack of possibility of patient's appropriate monitoring) [7]. Usually patients with acquisitive form of pneumonia response to treatment 48 to 96 hours after beginning of antibiotic therapy and clinical signs (fever, tachypnea, chest pain) of patients is recovered and radiographic findings are recovered with a little delay and after recovering of clinical signs [2, 7].

In a study conducted in USA, prescription of Zinc compounds was along with significant decrease of gastroenteritis incidence and pneumonia [8]. In another study in Bangladesh about Zinc serum concentrations in children with pneumonia and gastroenteritis it was found that serum concentrations of Zinc is lower in patients with pneumonia and gastroenteritis comparing with other people with the same age [9]. In another survey, in developing countries about therapeutic and preventive effects of Zinc prescription in relation with severe infectious diseases it was determined that Zinc deficiency leads to immune system defect, increasing of possibility of catching serious infectious diseases such as diarrhea, pneumonia and malaria, also, it was observed in this survey that Zinc prescription in acute diarrhea leads decreasing and shortening of disease period [10].

Various clinical practices have provided evidences about importance of Zinc deficiency in health of children. A merged analysis shows data harvested from 7 trials evaluating preventive effects of Zinc on pneumonia and diarrhea. In the mentioned evaluation, the incidences of diarrhea and pneumonia in patients under 5 years old receiving Zinc supplement were reduced by 18% and 41%, respectively [11]. While, diarrhea and pneumonia are two most common reasons of mortality between children under 5 years old, but on the other hand, in a study conducted in India, Zinc treatment in children with pneumonia did not show significant effect in clinical cycle and duration of hospitalization in these people [12, 13]. However, in study of AminiSani (2007) in Iran, it was showed that prescription of Zinc to low-weight infants in birth, has effect in incidence of diarrhea and acute respiratory infections in infants and also effects on weight gain of infants so that infants receiving Zinc catch diarrhea and pneumonia with lower frequencies and on the other hand weight gaining of these infants is better than control [14]. In another study by GholamrezaSoleimani and coworkers (2006) on 204 infants with diarrhea and pneumonia the researchers resulted that Zinc concentrations in these infants was lower comparing to children with no problems, therefore, they resulted that prescription of Zinc in these children can decrease the incidence of pneumonia and diarrhea between them [15].

With regards to the above notes and various results of studies on prescription of Zinc compounds in prevention or treatment of pneumonia in children and given that no research has been conducted about the effect of treatment with Zinc on children with pneumonia in Kashan and reminding of this note that we live in an area that annual incomes of families are low and they are at a low level for economical and health points, and this note

causes higher incidence of most infectious diseases and at top of them pneumonia and with regards to this note that in many cases it force families spending high costs , therefore the aim of this study is the evaluation of Zinc supplementary treatment effect in treatment of pneumonia between children.

METHOD:

This study was of interventional type. The patients including children 1 to 5 years old hospitalized in pediatric unit of KashanShahidBeheshti Hospital in 2014 and the diagnosis of pneumonia with pediatric specialists of KashanShahidBeheshti Hospital. After acception of patients and definition of survey purposes for patients and taking written permit from their parents, the patients were randomly categorized into two intervention and control group (placebo syrup). In intervention group the patients were received 1 mg/kg BW Zinc Sulfate syrup (Farabi Co- Iran) and in control group they were received placebo syrup (Farabi Co- Iran) with the same dose for 7 days. Also, for all patients, antibiotic therapy based on standard protocol of pneumonia standard according to last edition of Nelson book was prescribed except receiving Zinc Sulfate syrup or placebo syrup, in this way that injective cephalosporins of generation 3 were used as the first line of treatment for treatment of children. Implements for collection of study data are questionnaire which include demographic characteristics (age and gender of patient), body temperature during hospitalization time and also duration of hospitalization, rate of breathing per minute during hospitalization and duration of hospitalization and duration of hospitalization in days which were completed via referring to profile of hospitalization of patients and asking from the patient and his/her concomitant.

RESULTS

In this study, 100 children with pneumonia hospitalized in pediatric unit of Hospital were randomly divided into two groups (50 patients in intervention group and 50 patients in control group (placebo). The intervention group included 27 boys (54%) and 23 girls (46%) and the control group included 25 boys (50%) and 25 girls (50%).

The average age of intervention group was 2.99 ± 1.9 years old and the average age of control group (placebo syrup) was 3.28 ± 1.08 years old with standard deviation of 1.08 years, there was no significant difference between the two groups for gender and average age of patients (p›0.05).

Clinical signs:

The results showed that there was no significant difference between the two groups for average of temperature, rate of breathing during hospitalization and duration of fever (p›0.05), but there was a significant difference between the two groups for average of tachypnea duration, average of coughing duration and average of hospitalization duration (p‹0.05). The above results are shown separately in table 1.

Table 1: the comparison of clinical in control and intervention group.

Parameter	Intervention group	Control group	P value
Body temperature	39.14 ± 0.47	39.11 ± 0.45	0.47
Number of breathing	46.90 ± 5.15	47.96 ± 4.74	0.18
Average of fever duration	2.32 ± 1.23	2.44 ± 1.16	0.55
Tachypnea duration	3.10 ± 1.48	3.66 ± 1.22	0.008
Duration of coughing	4.70 ± 1.58	5.22 ± 1.46	0.03
Hospitalization duration	5.30 ± 1.64	5.98 ± 1.61	0.03

DISCUSSION

The effect of Zinc in neurotransmission, immunity function, growth and development, activity of some hormones, function of sense of taste and smell and wound healing is approved [16]. The main and important role of Zinc in biosynthesis of protein and acid nucleic is also approved. The role of Zinc in shortening of fever period and faster recovery process in infections of respiratory system in children are found [17]. Even, some studies, have considered the routine consumption of children 6 months to 3 years in decrease of pneumonia incidence. Maybe its reason is caused by improvement of immunity system function especially increasing of CD4 [11, 18]. It is showed in various studies

that serum levels of Zinc in children with pneumonia, has significant decrease comparing to the control group [19, 20]. The tendency to infection in children with food deficiency is higher because of reduction of cellular immunity[21]. It is possible that reduction of Zinc levels is one reason of immunity suppress in children with food deficiency [22]. The aim of the present study was evaluation of effect of Zinc sulfate supplement in children 1 to 5 years old, the results showed that the supplement of Zinc sulfate decreases the mean duration of tachypnea, mean duration of coughing and mean duration of hospitalization comparing to the control group significantly but do not effect significantly on mean of temperature, respiratory rate during hospitalization and duration of fever comparing to the control group. Qasemzadehand coworkers (2014), evaluated the effect of Zinc sulfate supplement on 3 to 60 months children with pneumonia and showed that this supplement decreases the duration of hospitalization that their study was not consistent with ours for this aspect. On the other hand they showed in their study that this supplement has not any effect on clinical signs (cough, fever, tachypnea and …) in patients, that was not consistent with our results. The reason of this difference in results might be variety of age of patients and dose of supplement consumed in their study comparing to ours [23].

In another study, Habibian and coworkers (2013) evaluated 124 patients with respiratory infections and showed that Zinc supplement do not posses any effect on respiratory rate and duration of hospitalization, but decreased the fever duration, these results were not parallel with our results [24]. It seems that difference in age of evaluated patients and also the type of respiratory infection from one way and consumption dose of supplement have been effective in these results. Also, supplement dose of Zinc in their study for all patients without consideration of patient weight was reported 10 mg, twice a day for 5 days.

Valaviet al (2011) evaluated the effect of Zinc supplement on 128 children with severe pneumonia. The results of their study showed that adding Zinc supplement to pneumonia treatment causes reduction of signs (fever and tachypnea) and reduction of hospitalization duration in intervention group that except decrease of fever duration that was in contrast with our results, other results were parallel and consistent with results of our study. These similar results are harvested while in volvi et al study, in contrast to our study, children with age of lower than one year are also present in study and also the amount of Zinc supplement consumed in this study is twofold higher than our study (2 mg/kg BW) [25].

In another study, Wadhwa N (2013) in India evaluated 550 patients with severe and very severe pneumonia with age of 2 to 24 months and resulted that Zinc supplement do not effect in severe and very severe pneumonia. In this study, only the effect of addition of Zinc supplement to pneumonia treatment on duration of hospitalization has been evaluated and the study on clinical signs (cough, tachypnea, fever and ...) has not been performed [26]. In another study in 2012 in Oganda, Srinivasan MG evaluated 352 patients with 6 to 59 month. They resulted that adding Zinc supplement to antibiotic therapy of severe pneumonia leads to difference in intervention and control group in improvement of clinical signs such as tachypnea, fever and oxygen need, but it was effective in reduction of case fatality [27]. The results of these two studies were not consistent with our study.

In two similar studies in 2012 and 2014, respectively in India by Shah Gh and Ecuador by Sempertegui F. it was shown that Zinc supplement did not effect on reduction of duration and sings of pneumonia in patients under 5 years old that these results were in contrast with results of our study [28, 29]. In thsese two studies also the harvested results were different with our results possibly because of the mentioned reasons such as presence of children under 0ne year old (younger than 12 months) and performing the study on patients with severe and very severe pneumonia.

CONCLUSIONS:
The most important findings of our study were the correlation of Zinc supplement with reduction of hospitalization duration, reduction of tachypnea duration and reduction of cough

duration in intervention group. Anyway, the contradictory harvested results in this study and other studies in Iran and other regions of the world might be explainable with supplement prescription (dose and duration of prescription), characteristics of patients (age, background disease and serum level of Zinc) and type of disease (severe or very severe pneumonia, other respiratory infections). The results of the present study and their comparison with other studies conducted in Iran and other regions of world showed that prescription of Zinc supplement can reduce pneumonia severity and the most important note about this study and other studies supports this issue that adding Zinc supplement to standard antibiotic therapy decreases hospitalization time.

REFERENCES

1. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Nelson textbook of pediatrics. *Philadelphia: Saunders Elsevier* 2007,**715**.

2. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization* 2008,**86**:408-416B.

3. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *The lancet* 2003,**361**:2226-2234.

4. Adegbola RA. Childhood pneumonia as a global health priority and the strategic interest of the Bill & Melinda Gates Foundation. *Clinical infectious diseases* 2012,**54**:S89-S92.

5. Selvaraj K, Chinnakali P, Majumdar A, Krishnan IS. Acute respiratory infections among under-5 children in India: A situational analysis. *Journal of Natural Science, Biology and Medicine* 2014,**5**:15.

6. Palafox M, Guiscafré H, Reyes H, Muñoz O, Martínez H. Diagnostic value of tachypnoea in pneumonia defined radiologically. *Archives of disease in childhood* 2000,**82**:41-45.

7. Tiewsoh K, Lodha R, Pandey RM, Broor S, Kalaivani M, Kabra SK. Factors determining the outcome of children hospitalized with severe pneumonia. *BMC pediatrics* 2009,**9**:15.

8. Yamey G. Zinc supplementation prevents diarrhoea and pneumonia. *BMJ: British Medical Journal* 1999,**319**:1521.

9. Shakur M, Malek M, Tarafder S. Zinc status of Bangladeshi children suffering from acute respiratory infection. *Orion* 2000,**5**.

10. Black RE. Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. *The American journal of clinical nutrition* 1998,**68**:476S-479S.

11. Bhutta Z, Black RE, Brown K, 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. *The Journal of pediatrics* 1999,**135**:689-697.

12. Mahalanabis D, Lahiri M, Paul D, Gupta S, Gupta A, Wahed MA, *et al.* Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. *The American journal of clinical nutrition* 2004,**79**:430-436.

13. Bose A, Coles CL, John H, Moses P, Raghupathy P, Kirubakaran C, *et al.* Efficacy of zinc in the treatment of severe pneumonia in hospitalized children< 2 y old. *The American journal of clinical nutrition* 2006,**83**:1089-1096.

14. Barak M, Shamshirgaran S, Amani F, Mohammadi S, Fazli B. Effect of Zinc Supplementation on the Growth of acute respiratory infections and diahrea in Low Birth Weight Infants. *Journal of Ardabil University of Medical Sciences* 2007,**7**:122-131.

15. SOLEYMANI GR, Abtahi S. Evaluation of serum Zinc status in hospitalized children aged 1-4 years with Pneumonia and gastroenteritis in Zahedan. 2006.

16. Salgueiro MaJ, Zubillaga MB, Lysionek AE, Caro RA, Weill R, Boccio JR. The role of zinc in the growth and development of children. *Nutrition* 2002,**18**:510-519.

17. Cetin I, Massari M, Parisi F. Role of micronutrients in the periconceptional period. In: *Handbook of diet and nutrition in*

the menstrual cycle, periconception and fertility: Wageningen Academic Publishers; 2014. pp. 998-1006.

18. 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. *The Lancet*,**363**:1683-1688.

19. Shakur MS, Malek M, Bano N, Islam K. Zinc status in well nourished Bangladeshi children suffering from acute lower respiratory infection. *Age (mo)* 2004,**32**:30-36.64.

20. Arıca S, Arıca V, Dag H, Kaya A, Hatipoglu S, Fenercioglu A*, et al.* Serum zinc levels in children of 0-24 months diagnosed with pneumonia admitted to our clinic. *Int J Clin Exp Med* 2011,**4**:227-233.

21. Haase H, Rink L. Zinc signals and immune function. *Biofactors* 2014,**40**:27-40.

22. Prasad AS. Zinc in human health: effect of zinc on immune cells. *MOLECULAR MEDICINE-CAMBRIDGE MA THEN NEW YORK-* 2008,**14**:353.

23. Qasemzadeh MJ, Fathi M, Tashvighi M, Gharehbeglou M, Yadollah-Damavandi S, Parsa Y*, et al.* The effect of adjuvant zinc therapy on recovery from pneumonia in hospitalized children: a double-blind randomized controlled trial. *Scientifica* 2014,**2014**.

24. Habibian R, Khoshdel A, Kheiri S, Torabi A. The Effect of Zinc Sulphate Syrup on Children's Respiratory Tract Infections. *Journal of Babol University of Medical Sciences* 2013,**15**:22-29.

25. Valavi E, Hakimzadeh M, Shamsizadeh A, Aminzadeh M, Alghasi A. The efficacy of zinc supplementation on outcome of children with severe pneumonia. A randomized double-blind placebo-controlled clinical trial. *The Indian Journal of Pediatrics* 2011,**78**:1079-1084.

26. Wadhwa N, Chandran A, Aneja S, Lodha R, Kabra SK, Chaturvedi MK*, et al.* Efficacy of zinc given as an adjunct in the treatment of severe and very severe pneumonia in hospitalized children 2–24 mo of age: a randomized, double-blind, placebo-

controlled trial. *The American journal of clinical nutrition* 2013,**97**:1387-1394.

27. Srinivasan MG, Ndeezi G, Mboijana CK, Kiguli S, Bimenya GS, Nankabirwa V*, et al.* Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial. *BMC medicine* 2012,**10**:14.

28. Shah GS, Dutta AK, Shah D, Mishra OP. Role of zinc in severe pneumonia: a randomized double bind placebo controlled study. *Italian journal of pediatrics* 2012,**38**:36.

29. Sempértegui F, Estrella B, Rodríguez O, Gómez D, Cabezas M, Salgado G*, et al.* Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. *The American journal of clinical nutrition* 2014,**99**:497-505.