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Investigating the Effect of Prescribing Zinc Sulfate on Improving the Clinical Symptoms of Pneumonia in 2-59-Month-Old Children

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Abstract

Background: Acute respiratory infections and especially pneumonia are considered as the most important infection-induced cause of child mortality in developing countries. We aimed to investigate the effect of prescribing zinc sulfate on improving the clinical symptoms of pneumonia in 2-59-month-old children.

Materials and Methods: This clinical trial study was performed on 108 children complaining of fever, coughs, and tachypnea referring to three educational hospitals of Mashhad (Ghaem, Imam Reza, and Dr. Sheikh). The patients were randomly assigned into control (n=54), and intervention (n=54). In the control group placebo was prescribed, while the intervention group received oral zinc sulfate 10 mg (1 ml/ kg in children younger than one year, and 20 mg/kg for children above one year every 12 hours. During hospitalization, every 12 hours the clinical symptoms of both groups including tachypnea, duration of fever, coughs, intercostal retraction, hypoxia, crackles-wheezing, and duration of hospitalization were recorded. At the beginning and end of the treatment, two blood samples were taken for determining the serum level of zinc.

Results: The findings indicated that the serum level of zinc sulfate after the intervention increased significantly in the intervention group ($p<0.001$). There was a significant difference in the duration of fever between the intervention and control groups 24 hours after hospitalization ($p=0.014$) and 36 hours post-hospitalization ($p=0.02$). Comparing the presence or absence of tachypnea in the intervention and control groups, there was a significant difference at 36 hours post-hospitalization ($p=0.02$).

Conclusion: Based on the results, zinc supplement was effective for patients with pneumonia in reducing the duration of fever and number of breaths, but it had no significant effect on the duration of coughs and hospitalization.

Key Words: Children, Cyanosis-Tachypnea, Pneumonia, Zinc sulfate.

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1- INTRODUCTION

According to WHO, annually 4.1 million deaths occur worldwide due to acute respiratory infections (ARIs), with 90% being due to acute pneumonia. Specifically, 1.9 million of them are children younger than five years old (1), mostly related to developing countries because of malnutrition (2). Meanwhile, lower respiratory tract infections and especially pneumonia constitute around 20% of the causes of pediatric mortality; per every 1000 live children born in developing countries, 12-20 children die before the age of five because of pneumonia (1, 3). By definition, lung inflammation is called pneumonitis, and if the cause of this inflammation is a microbial agent, it is called pneumonia. Microbial agents can include bacterial, viral, or parasitic. According to WHO, clinically, pneumonia involves acute cough attacks with or without fever associated with respiratory problems or tachypnea (5). According to this definition, fever and tachypnea have high sensitivity and low specificity, while auscultating pulmonary crackles or pleural pain have high specificity and low sensitivity in diagnosing pneumonia (6).

Zinc is a trace element playing a significant role in the metabolism of the body. It is an essential micronutrient required for proper functioning of the immune system. Zinc deficiency leads to vulnerability to microbial, viral, and fungal infections (7, 9). Also, children with vitamin A, zinc, and iron deficiency or those who are more susceptible to upper respiratory tract infections. In different studies, various zinc oral supplements have been used to prevent and treat upper respiratory infections, and their results have been discrepant and sometimes contradictory (10-22). The body cannot store zinc and requires constant intake of zinc through diet. Some studies have emphasized that in children who use zinc supplement the incidence of respiratory infections is less (23-25). Another study found that the healthy children who had low zinc concentration at the baseline showed more incidence of acute respiratory tract infections during the follow-up period compared to the children with normal zinc level (26). Prasad et al. indicated the useful effect of zinc for treating the common cold (27). In another study, zinc had no preventive or therapeutic effect for respiratory infections (28). Generally, there are sparse studies regarding the effect of zinc and pneumonia on 2 to 59-month-old children, with discrepant results. Considering these divergent and contradictory results, our aim in this research was to investigate the effect of zinc sulfate on improving the clinical symptoms of pneumonia in 2-59-month-old Iranian children.

2- MATERIALS AND METHODS

This double-blind clinical trial study with the clinical trial registration number of (TCTR20200512005) was performed on 108 2-59-month-old children with diagnosis of pneumonia referring to the pediatric ward of educational hospitals (Imam Reza, Ghaem, and Dr. Sheikh) affiliated with Mashhad University of Medical Sciences. The basis for determining the sample size was previous studies (30-32), and the number of children referring to the three educational hospitals with the diagnosis of pneumonia over one year.

2-1. Intervention

Any child 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=59), and control (n=59) 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 (similar to the zinc sulfate syrup in terms of color and taste, made by Farabi Pharmaceutical Company). On the other hand, the intervention group received zinc sulfate (made by Farabi Pharmaceutical Company) as 10 mg/day in children younger than one, and 20 mg/day in children above one year-old every 12 hours (during hospitalization). The rest of the standard and conventional treatments of pneumonia were performed according to the protocol and routine in the pediatric wards of Ghaem, Imam Reza, and Dr. Sheik hospitals equally for both groups.

The severity of disease of both groups was assessed based on clinical and para-clinical symptoms according to the pediatrician as well as response to treatment with improvement of clinical symptoms such as resolution of fever and overall well-being, increased appetite alongside resolution or mitigation of coughs and wheezing as well as normalization of the number of breaths and elimination of respiratory distress. 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 by a pediatric resident. In both groups, at the beginning and end of hospitalization, one blood sample was taken by an experienced nurse for the necessary tests and for determining the serum level of zinc through the brachial vein and sent to laboratory. The inclusion criteria were children 2-59-months-old with a diagnosis of pneumonia based on history and clinical examination, and if necessary, chest x-ray by a pediatrician.

2-2. Exclusion criteria

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. Chronic diarrhea was defined as diarrhea for more than 14 days. Malnutrition was characterized based on clinical symptoms of kwashiorkor or marasmus or FTT (29). Severe infection meant severe sepsis. Further, the patients suspected of foreign bodies and gastroesophageal reflux were also excluded.

2-3. Ethical considerations

Sampling and implementation of the proposal were performed after acquiring written permission from the parents of participating patients. Prescription of zinc sulfate the mentioned dose, even if the patient was not deficient, would not cause any side effects. Any patient who was intolerant of oral zinc supplement or desired to quit the study was excluded. The drug and placebo were provided at no charge for patients. Further, the tests at both times were also done free of charge for every patient.

2-4. 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.

3- RESULTS

3-1. Baseline characteristics

In this research, 54 patients were assigned to the intervention and 54 to the control groups. The gender distribution of the tested patients was 50.5% boys and 49.5% 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 12.77+0.706, with the minimum and maximum of 3 and 58 months-old, respectively. The mean age in the intervention group was 13.56+0.736 and in the control it was 11.97+0.712 (p>0.05). The mean age of hospitalization in the case and control groups was 13.56+0.781 and 11.97+0.793 months, respectively, which was not statistically significant (p=0.515). The mean duration of hospitalization was 5.34+0.643, with the minimum and maximum of 2 and 11 days respectively. The mean duration of hospitalization cases and control groups was 5.7+0.312 and 5.11+0.308 days respectively; based on the Mann-Whitney test, there was no significant difference between the two groups (p=0.174).

3-2. Comparing the serum level of zinc

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 70.61+11.5 and 92.8+11.6 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 70.9+10.7 and 71.6+9.8 mcg/dl at the beginning and end of hospitalization respectively (p=0.51) (**Table.1**).

Table-1: 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	70.61(11.5)	92.8(11.6)	<0.001
Control	70.9(10.7)	71.6(9.8)	0.51

3-3. Comparing tachypnea

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.2**, 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=0.02). 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-2: Comparison of tachypnea in two groups based on measurement time.

Time	Sub-group	Group		Total	P-value
		Intervention	Control		
During hospitalization	Yes	45(83.3)	49(90.6)	93(86.9)	0.267
	No	9(16.7)	5(9.4)	14(13.1)	
12 hours after hospitalization	Yes	42(77.8)	42(77.4)	83(77.6)	0.959
	No	12(22.2)	12(22.6)	24(22.4)	
24 hours after hospitalization	Yes	39(72.2)	32(58.5)	70(65.4)	0.135
	No	15(27.8)	22(41.5)	37(34.6)	
36 hours after hospitalization	Yes	18(33.3)	8(14.8)	26(24.1)	0.02
	No	36(66.7)	46(85.2)	82(75.7)	
48 hours after hospitalization	Yes	5(3.9)	4(7.4)	9(8.3)	0.7
	No	49(90.7)	50(92.6)	99(91.7)	

4- DISCUSSION

Considering the high prevalence of respiratory infections in children which is one of the major causes of mortality and occupation of hospital beds and regarding the staggering costs these infections incur to the healthcare system of the country, reduction of child mortality is one of the top priorities of the Ministry of Health. In this regard, prescription of supplements and drugs capable of reducing the duration of hospitalization as well as severity of symptoms and eventually mortality and morbidity can significantly help the healthcare system of the country. The aim of the present study was to examine the effect of zinc sulfate on improving the clinical symptoms of pneumonia in 2-59-month-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 are in line with the study 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 (31). 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 (33). 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 (34). 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 (35). In the study by Sandstead in India, it was found that zinc supplement had no useful effect on measles-associated pneumonia (36). Some studies have found that zinc supplement is effective in preventing acute respiratory infection (37), and pneumonia complications would diminish following proper nutrition for children (38). Meanwhile, the results of a study indicated that zinc supplement does not have any effect in severe and very severe pneumonia (39). 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 (40). 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 (41). In our study, no side effect of supplement was observed in patients. In some studies, digestive side effects have been reported (42). 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 (43). 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 this 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 (1). 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 (35).

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 (44). 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. It is possible that the patients with a higher zinc level become less ill and even if they do get sick, they do not need to be hospitalized, although this requires a wider and more comprehensive study.

5- CONCLUSION

Oral prescription of zinc sulfate 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. Based on this study, it is suggested that prescription of oral zinc sulfate supplement be considered for pediatric patients hospitalized due to

pneumonia, in addition to the standard and conventional pharmacotherapy of pneumonia.

6- CONFLICT OF INTEREST: None.

7- 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 Infect Dis 2002,2:25–32.

2. Zar HJ Pneumonia in HIV-infected and HIVuninfected children in developing countries: Epidemiology, clinical features, and management. Curr Opin Pulm Med 2004;10: 176–82.

3. UNICEF State of the World's Children New York: 2007, United Nations Children's Fund.

4. Karimi A , Kadivar MR , Fararoee M , Alborzi A Active case finding of communicable disease in the south of the Islamic republic of Iran Eastern Mediterranean Health Journal (2000) Vol 6 , Nos. 2&3 .

5. WHO Program for Control of Acute Respiratory Infections. 1990 Acute respiratory infections in children: case management in small hospitals in developing countries A manual for doctors and other senior health workers WHO Geneva, Switzerland.p. 74.

6. McIntosh K Community-acquired pneumonia in children N Engl J Med 2002; 346:4.

7. Hambidge M. Human zinc deficiency. J Nutr 2000; 130 (Suppl 5S):1344S-9S.

8. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr 1998; 68(Suppl 2):447S-63S.

9. Brown KH, Peerson JM, Rivera J, Allen LH. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta- analysis of randomised trials. Am J Clin Nutr 2002; 75(6):1062 -71.

10. Prasad A, Fitzgerald B, Bao F, Chandrasekar. Duration of symptoms and plasma cytokine levels in patients with the Common cold treated with zinc acetate. Ann Intern Med. 2000; 133: 245-52.

11. Sazawal S, Jalla S, Mazumdar A. zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double blind controlled trial. Pediatrics. 1998; 102: 1-5.

12. Bondestam M, Foucard T, Gebre – Medhin M. Susceptibility to infections. Annal otology Rhinology laryngology. 1983; 99: 566-7.

13. Nadim Arda, H, Tuncel u, Akdogin O, ozluoglu. The role of zinc in the treatment of tinnitus. Otol Neurotol. 2003; 24(1): 86-9.

14. Mossad SB, Macjnin ML, Madendrop SU, Mason P. Zinc gluconate lozenges for treating the Common Cold. Annals of internal Medicine. 1996; 125 (2): 81-8.

15. Fraker PJ, Gershwin ME, Good RA, Prasad A. Interrelationships between zinc and immune function. Fed proc. 1986; 45:1474-79.

16. Rick A. friedman, Anatomy and physiology. In: seiden AM, Tami TA, Pensak ML, Cotton RT, Glucman JL. Otolaryngology. The essentials. 2004

17. Van Wouwe JP, Van Gelderen HH, Bos JH. Subacute zinc deficiency in children with recurrent upper respiratory tract infection, Eur J Pediatr. 1987; 146 (3): 293-5.

18. Lee E, Woo JS, Hwang S, Lim HH, Suh H. Protective role of superoxide dismutase in rat Eustachian tubal mucosa against acute otitis media induced by upper respiratory tract infection. J. of Laryngology and otology. 2000; 114: 832-36.

19. Macknin ML, Peidmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate Lozenges for treating the Common cold in children. JAMA. 1998; 279 (24): 1962-67.

20. Kusunoki T, Nishida S, Murata K, Kobashi K, Nakatani H, Hiwasa T, et al. Cathepsin – L activity and its inhibitor in human otitis media. J Otolaryngology. 2001; 30 (3): 157-61.

21. Carr RR, Nahata MC. Complementary and alternative medicine for upper respiratory tract infection in children. American Journal of Health System Pharmacy. 2006; 63 (1): 33-9.

22. Ruggles RL, Abols I. Care of the ear Canal and mastoid. Ann Otol Rhinol Laryngol. 1983; 92: 566-7.

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 Clin Nutr 2002; 76(6):1401-8.

25. Baqui AH, Zaman K, Persson LA, et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. J Nutr 2003; 133(12):4150-57.

26. Bahl R, Bhandari N, Hambidge KM, Bhan MK. Plasma zinc as a predictor of diarrheal and respiratory morbidity in children in an urban slum setting. Am J Clin Nutr 1998; 68(Suppl 2):S414-S17.

27. Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. Ann Int Med 2000; 133(4):245-52.

28. Mathew JL. The role of zinc in prevention and treatment of childhood pneumonia: an examination and appraisal of current evidence. Indian J Pediatr 2011; 78(9):1136-39.

29. Watts KD, Goodman DS. Wheezing, bronchiolitis, bronchitis. Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier 2011; pp: 1456-9.

30. Izadi P, Yar Mohammadi ME, Kholdi N, Izadi B, Anari S, Yazdi N, et al. Effect of zinc sulfate supplementation on otitis media with effusion in children. DMed. 2009; 17 (5):27-34.

31. 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.

32. Abasi R, Asadi S H, Keshavarz K, Zoladl M, Kazeroono S, sharafieyan C et al . Lack of effect of zinc sulfate on wheezing after bronchiolitis in infants less than two years. Armaghane danesh. 2014; 19 (7):572-79.

33. 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.

34. 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 Clin Nutr. 2006;83: 1089–96.

35. 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 Clin Nutr. 2004;79:430-6.

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

37. 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.

38. 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 Clin Nurt 1999; 53(7):529-34.

39. 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.

40. 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 Clin Nutr 1996; 50(1):42-6.

41. 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 months to 5 years. Indian J Pediatr 2011; 78(9):1085-90.

42. 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 Popul Nutr 2005; 23(4):311-9.

43. Prasad AS, Beck FWJ, Bao B, et al. Zinc supplementation decreases incidence of infection in the elderly: Effect of zinc on the generation of cytokines and oxidative stress. Am J Clin Nutr 2007; 85(3):837-44.

44. Soleimani Gh, 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.