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Original Research Article

Comparing the effect of zinc gluconate and placebo in the treatment of tachypnea, dyspnea and fever in children aged 2 to 23 months with acute bronchiolitis

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ABSTRACT

Background: Acute viral bronchiolitis is the most common infection of the lower respiratory tract in infants under 2 years and is one of the reasons for their admission all around the world. The aim of this study was comparing the effect of zinc gluconate and placebo in the treatment of tachypnea, dyspnea and fever in children aged 2 to 23 months with acute bronchiolitis.
Methods: This randomized clinical trial study has been done on 100 infants aged 2 to 32 months with the diagnosis of bronchiolitis who divided in two groups. 50 patients received zinc gluconate and 50 patients received placebo. The symptoms and sign of the disease at baseline and then at 24, 72, and 7 days after starting treatment and duration of hospitalization were compared between the two groups.
Results: The treatment and placebo groups were similar in respect to mean age and gender distribution. Two groups were similar in terms of clinical symptoms and signs at the time of admission. Bronchiolitis recovery was better in the treatment group than in the placebo group. This positive effect was statistically significant for vising (p=0.023) and rhinorrhea (p=0.027) at 72 hours after starting treatment. The mean duration of hospitalization was significantly less in the treatment group than in the placebo group (4.14±1.21 versus 4.64±1.2 days; p=0.016).
Conclusions: Results showed that the use of zinc gluconate as a zinc supplement in infants with acute bronchiolitis could improve their clinical symptoms and signs and decrease the duration of hospitalization.

Keywords: Acute bronchiolitis, Zinc gluconate, Infants

INTRODUCTION

Acute bronchiolitis is the most common cause of lower respiratory tract infection and the most common cause of hospitalization due to respiratory illness during infancy. About 50,000 to 80,000 per year hospitalizations occur in children under one years old groups in the United States are attributed to the acute bronchiolitis.[1] According to western statistics, 11.4 cases per 100 children under one years old and six per 100 children at 1-2 years old get bronchiolitis.[2] Acute bronchiolitis which most children are sensitive to is associated with symptoms such as fever, wheezing and cough. Most of the cause is respiratory syncytial virus (RSV) but mycoplasma and other viruses can also be risk factors. Acute bronchiolitis is often associated pathologically with bronchiectasis and in this fibroblasts and collagen do not appear in the biopsy and diseases often improve spontaneously.[3] The clinical signs of acute bronchiolitis are like viral pneumonia and the most important symptoms are fever and wheezing and

increase breathing rate.[4] In infants especially infants under six months, due to the small diameter of the airways, edema and inflammation of the bronchioles can lead to respiratory distress.[1] Therefore appropriate treatment is needed. Treatment is often supportive and includes fluid therapy, antipyretic drugs and oxygen.[5] Recently more studies have been done about treatments for bronchial dilators such as salbutamol and epinephrine as nebulizers.[4,5] There is no consensus on the use of bronchodilators and beta agonists.[6,7] Inhaled salbutamol (ventolin) is currently used in Iranian hospitals to treat patients with bronchiolitis but several studies have shown that it is not effective.[8] Need for zinc minerals in burns, liver cirrhosis, diabetes, gastrectomy anorexia, genetic disorders, premature infants, chronic infections, bowel diseases, pancreatic diseases, kidney disease, skin disorders, stress and trauma may increase. Zinc is essential for maintaining the structure of nucleic acids, proteins and cell membranes. In addition, normal growth and cell division, tissue repair, sexual maturation and reproductive system, wound healing, immune defense and possibly the dynamics of physiological zinc dependent actions.[9,10] Studies show a positive effect of zinc on the improvement of pneumonia.[10,11] There is no consensus on the positive effect of zinc sulfate on the recovery of bronchiolitis. The aim of this study was to compare the effect of Zinc gluconate and placebo in the treatment of tachypnea, dyspnea and fever in children aged 2 to 23 months with acute bronchiolitis.

METHODS

This clinical trial study was performed on 100 children aged 2 to 23 months who referred to emergency Department of Ardabil Pediatric Hospital with diagnosis of acute viral bronchiolitis at 2018. Children aged 2 to 23 months; first episode of wheezing following viral upper airway infection and clinical manifestations of acute bronchiolitis including wheezing, rhinorrhea, tachypnea (RR> 50/min at rest in infant under one year and RR >40/min at rest in infants over one year), cyanosis, subcostal and intercostal retraction, nasal flaring and fever (axillary temperature above 37.3 °C and oral temperature above 37.8 °C and rectal temperature above 38.3 °C) with or no apnea episodes and no consolidation in CXR were included in the study and children with a history of previous wheezing episodes, a history of asthma and allergies in their family, recent antibiotic use, chronic heart and lung disease, immunodeficiency, down syndrome, metabolic or neurological diseases, history of prematurity or the use of mechanical ventilation in neonates, zinc intake during the last month, severe malnutrition and eventually critically ill children who needed immediate hospitalization due to dehydration and decreased consciousness and lethargy or with respiratory failure symptoms were excluded from the study.

The children were randomly divided into two groups of 50 each. One group received 1% zinc gluconate orally (1 cc/kg in infants under 1 year of age and 10 cc (20 mg) in infants over one year of age) and the other group received placebo (sucrose 30 g, oral flavoring, dextrose serum 5% to 100%). Zinc gluconate and placebo syrups were similar in appearance and taste, smell and color. The study design was single blind and patients were not aware of the type of drug being administered. In this study, infants in both treatment and placebo groups in toward clinical manifestations including tachypnea, subcostal and intercostal retraction, wheezing, cyanosis, fever, rhinorrhea and nasal flaring at zero, 24, 72 hours and 7 days after starting the drug followed and researcher completed the relevant checklists. After completing the checklists for all patients, descriptive statistical methods were used to analyze data. chi-square and t-test were used for statistical analysis in SPSS version 19 and p value less than 0.05 was considered significant. The written consent form was completed for all samples and the study approved by the Ethics Committee of Ardabil university of medical sciences by code IR.ARUMS.REC.1397.097. Also, the study was registered with IRCT201603-18027097N12 at the Clinical Trial Registration Center of Iran.

RESULTS

Of all samples, 59% were male and 41% were female. The sex distribution of the treatment group was 31 males (62%) and 19 females (38%) and the placebo group was 28 males (56%) and 22 females (44%). The average age of the patients was 5.88±4.27 months (2-21 months) and the treatment group was 5.82±4.13 and the placebo group was 5.94±4.46. There was no significant difference between the two groups in terms of age and gender. Patients in the two treatment and control groups at baseline included clinical symptoms including wheezing (p=0.1), fever (p=0.305), rhinorrhea (p=0.313), tachypnea (p=0.556), nasal flaring (p=0.779), sub rib retraction (p=0.423), inter rib retraction (p=0.423), and cyanosis (p=0.505) were not statistically significant (Table 1).

Patients in the two treatment and control groups did not show any statistically significant difference in clinical symptoms at 24 hours after treatment but at 72 hours after treatment, the difference between the two groups was statistically significant in terms of the number of people with wheezing (p=0.023) and rhinorrhea (p=0.027) and the frequency of wheezing (16% vs. 36%) and rhinorrhea (zero vs. 12%) were significantly lower in the zinc treated group than in the placebo group. On the 7th day after treatment, the clinical symptoms of all patients in two groups were eliminated (Table 2).

Frequency of complete recovery at 24 hours in treatment group was 8% and 2% in placebo group (p=0.362) and frequency of complete recovery at 72 hours in treatment group was 74% and in placebo group was 46% (p=0.004). By the seventh day after treatment all patients in both groups had been recovered. The average length of stay in the treatment group was 4.04±1.21 days and in the placebo group was 4.64±1.23 days the difference between the two

groups was statistically significant (p=0.016) and length of stay among patients in the treatment group were significantly shorter than patients in the placebo group (Table 3).

Table 1: Clinical symptoms in patients in two groups.

Groups variables		Treatment (n=50)		Placebo (n=50)		P value
		N	%	N	%	
Whizzing	+	50	100	50	100	1
	-	0	0	0	0	
Fever	+	22	44	17	34	0.3
	-	28	56	33	66	
Rhinorrhea	+	26	52	31	62	0.3
	-	24	48	19	38	
Tachypnea	+	42	84	44	88	0.56
	-	8	16	6	12	
Nasal flaring	+	7	14	8	16	0.78
	-	43	86	42	84	
Sub-gear retraction	+	24	48	28	56	0.42
	-	26	52	22	44	
Inter-gear retraction	+	26	52	21	42	0.42
	-	24	48	29	58	
Cyanosis	+	6	12	4	8	0.51
	-	44	88	46	92	

Table 2: Clinical symptoms in patients in two groups by times.

Times Variables		24 hours later					72 hours later					7 days later				
		Treatment		Placebo		P value	Treatment		Placebo		P value	Treatment		Placebo		
		N	%	N	%		N	%	N	%		N	%	N	%	
Whizzing	+	38	76	43	86	0.2	8	16	18	36	0.02	0	0	0	0	
	-	12	24	7	14		42	84	32	64		50	100	50	100	
Fever	+	4	8	8	16	0.21	1	2	2	4	1	0	0	0	0	
	-	46	92	42	84		49	98	48	96		50	100	50	100	
Rhinorrhea	+	13	26	17	34	0.38	0	0	6	12	0.03	0	0	0	0	
	-	37	74	33	66		50	100	44	88		50	100	50	100	
Tachypnea	+	20	40	24	48	0.42	4	8	6	12	0.5	0	0	0	0	
	-	30	60	26	52		46	92	44	88		50	100	50	100	
Nasal Flaring	+	1	2	3	6	0.62	0	0	0	0	1	0	0	0	0	
	-	49	98	47	94		50	100	50	100		50	100	50	100	
Sub-gear retraction	+	7	14	11	22	0.3	0	0	3	6	0.2	0	0	0	0	
	-	43	86	39	78		50	100	47	94		50	100	50	100	
Inter-gear retraction	+	4	8	9	18	0.14	0	0	2	4	0.5	0	0	0	0	
	-	46	92	41	82		50	100	48	96		50	100	50	100	
Cyanosis	+	2	4	1	2	1	1	2	0	0	1	0	0	0	0	
	-	48	96	49	98		49	98	50	100		50	100	50	100	

Table 3: The frequency of completed recovery in patients in two groups.

Groups times		Treatment (n=50)		Placebo (n=50)		P value
		N	%	N	%	
24 hours	Yes	4	8	1	2	0.36
	No	46	92	49	98	
72 hours	Yes	37	74	23	46	0.004
	No	13	26	27	54	
In 7th day	Yes	50	100	50	100	1
	No	0	0	0	0	

DISCUSSION

The findings of the present study showed that in generally the process of healing of bronchiolitis in the treated infants with zinc was more favorable than the placebo group; this positive effect on wheezing and rhinorrhea was statistically significant at 72 hours after treatment. In addition, the majority of patients in the treatment group recovered from the disease within 72 hours of treatment (74% vs. 46%, p=0.004) and the average length of stay in the treatment group was significantly lower than the placebo group (4.4±1.21 versus 4.64±1.23 days and p=0.016). A study by Mahyar et al in Qazvin at 2017 which investigated the effect of zinc sulfate in the treatment of acute bronchiolitis in children showed that the process of clinical symptoms improvement in the zinc sulfate group compared to the placebo group was more favorable at 24, 48, 72, 96 and 120 hours after treatment, which was consistent with the findings of the present study.[12] Also, the improvement of wheezing at 48 and 72 hours and complete recovery within 72 hours after treatment was significantly greater in the zinc sulfate group and length of stay in hospital significantly longer than the placebo group which was similar to our study results. But in another study conducted by Heydarian et al in Mashhad, different findings were reported from our study. In their study zinc sulfate had no profit in improving clinical presentation or complete recovery or length of hospitalization. We could say that the design of our study and both of the above studies were a randomized placebo controlled clinical trial and all three infants were studied 2 to 23 months. However, the difference between our study and that of Heydarian et al was in the number of patients studied (100 patients versus 50 patients) this small sample size in their study, along with other factors such as intrinsic differences in the study participants, differences in disease characteristics such as differences in disease severity, differences in disease definition or differences in definition of recovery, can all result in different results two studies have been effective.[9] Studies investigating the effect of pediatric pneumonia have also been divided into two groups with some concurring with our finding that zink supplementation has a beneficial effect on the treatment of pneumonia but some link between zinc supplementation and pneumonia treatment have not been demonstrated. For example a study by Yuan et al in China showed that zinc deficiency is common in infants with severe pneumonia, but supplemental zinc normalization did not improve the clinical outcome of infants with pneumonia.[13] A study by Fataki et al in Tanzania showed no evidence of beneficial effects of zinc in the treatment of children with acute pneumonia.[14] In a study by Brant et al in Nepal zinc auxiliary treatment did not accelerate the recovery time of children with severe or non-severe pneumonia.[15] A study by Boze et al in India showed that zinc supplementation had no significant effect on length of stay or symptoms of severe pneumonia in children.[16] In a study in India at 2017 by Nayir et al, they investigated the effect of zinc in the treatment of acute respiratory infections in children aged 2 to 60 months and their study provided a significant advantage for zinc supplementation during the episode of acute respiratory infections did not show a decrease in the duration or complications of the disease.[17] But contrary to above studies and consistent with our findings a 2004 study by Brooks et al in Bangladesh showed that zinc supplementation in infants with severe pneumonia had a significant effect on decreasing the duration of breast compression, Tachypnea, has hypoxia thereby significantly reducing the duration of illness and length of stay.[10] A study by Valavi et al in Ahwaz in 2012 showed that the duration of fever and respiratory distress were significantly shorter in infants treated with zinc compared to placebo and patients required significantly shorter hospitalizations than controls.[18] A study by Besnet et al in India also found that zinc supplementation reduces the time of severe pneumonia and the risk of treatment failure in children but the decrease in their study was not statistically significant.[19] Other studies have also shown a positive effect of zinc on pneumonia in that it prevents pneumonia.[20-22]

The advantage of zinc in our study increased 72 hours after consumption; this delay in start of impact has also been reported in other studies and it may be essential in the mechanism of the zinc effect; for example in the Broks et al study advantage was increased over 100 hours after use and in the Mahyar et al study after 72 hours.[10,12] In the present study due to the lack of resources and credentials we unable to measure the serum level of patients at baseline and at release time because by this we could also examine the effectiveness of zinc supplementation by separating zinc deficient groups with suitable zinc levels. A number of studies have shown that irrespective of the status zinc in the child, zinc can enhance the acute phase response and the protective immune response in which case even children with enough zinc intake may also benefit from zinc supplementation benefit from illness time.[10] In the present study no significant effects of zinc supplementation were observed in the treatment group. Most of the previous studies have not reported a significant complication and only a few studies have reported vomiting after zinc supplementation in some patients.[14,15,19] Overall zinc supplements appear to be well tolerated and safe by infants. Like most studies this study had limitations including: lack of previous studies for comparison of the results of the present study with other studies. Unable to measure serum zinc levels at the time of study entry and discharge time due to a lack of resources.

CONCLUSION

The findings of the present study showed that zinc gluconate supplementation was effective in accelerating the improvement of clinical symptoms in infants aged 2 to 23 months with acute bronchiolitis and it reduces the length of hospital stay which was greater in the first 72 hours. Because of limited studies in this area, further research is needed to provide appropriate recommendations for the use of zinc in the treatment of bronchiolitis in other population.

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REFERENCES

1. Goodman D. Inflammatory disorder of the small. In:Behrman RE, Kliegman RM, Jenson HB, Editors. Nelson Textbook of Pediatrics. Philadelphia: WB Saunders; 2003.
2. Henderson FW, Clyde WA Jr, Collier AM. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr. 1979;95:183-90.
3. Smyth RL, Openshaw PJ. Bronchiolitis. Lancet. 2006;368:312-22.
4. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The tucson children respiratory study. II. Lower respiratory tract illness in thefirst year of life. Am J Epidemiol. 2009;129:1232-46.
5. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2000:Cd001266.
6. Scarfone RJ. Controversies in the treatment of bronchiolitis. Curr Opin Pediatr. 2005;17:62-6.
7. Sethi GR, Nagar G. Evidence based treatment of bronchiolitis. Indian J Pediatr. 2004;71:733-7.
8. Dawson-Caswell M, Muncie HL. Respiratory syncytial virus infection in children. Am Fam Physician. 2011;83(2) :141-6
9. Heydarian F, Behmanesh F, Daluee M, Kianifar H, Hematian M. The role of zinc sulfate in acute bronchiolitis in patients aged 2 to 23 months. Iranian J Pediatr. 2011;21(2):231-4.
10. Brooks WA, Yunus M, Santosham M. Zinc for severe pneumonia in very young children: doubleblind placebo-controlled trial. Lancet. 2004;363(9422):1683-8.
11. Mahalanabis D, Lahiri M, Paul D. 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. Am J Clin Nutr. 2004;79(3):40-6.
12. Mahyar A, Ayazi P, Ahmadi NK, Nikoo ST, Hamzehloo S, Taremiha A, et al. Zinc sulphate for acute bronchiolitis: A double-blind placebo-controlled trial. Infez Med. 2016;4:331-6.
13. Yuan X, Qian SY, Li Z, Zhang ZZ. Effect of zinc supplementation on infants with severe pneumonia. World J Pediatr. 2016;12(2):166-9.
14. Fataki MR, Kisenge RR, Sudfeld CR, Aboud S, Okuma J, Mehta S, Spiegelman D, Fawzi WW. Effect of zinc supplementation on duration of hospitalization in Tanzanian children presenting with acute pneumonia. J Trop Pediatr. 2013;60(2):104-11.
15. Valentiner-Branth P, Shrestha PS, Chandyo RK, Mathisen M, Basnet S, Bhandari N, et al. A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2-35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal. Am J Clin Nutr. 2010;91(6):1667-74.
16. 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. Am J Clin Nutr. 2006;83(5):1089-96.
17. Nair BT, Bhunia R, Sharma KK. Role of zinc supplementation in acute respiratory tract infections in children aged 2 to 60 months. International J Contemporary Pediatrics. 2017;4(5):1758-62.
18. 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. Indian J Pediatrics. 2011;78(9):1079-84.
19. Basnet S, Shrestha PS, Sharma A, Mathisen M, Prasai R, Bhandari N, Adhikari RK, Sommerfelt H, Valentiner-Branth P, Strand TA, Zinc Severe Pneumonia Study Group. A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children. Pediatrics. 2012:peds-2011.
20. Sazawal, S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. 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.
21. Bhutta ZA, Black RE, Borwn KH. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries:pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 1999;135:689-97.
22. Bhandari N, Bahl S, Taneja S. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. BMJ. 2002;324:1358.
23. Zorc JJ, Hall CB. Bronchiolitis:mRecent evidence on diagnosis and management. Pediatrics. 2010;125:342-9.

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