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Zinc sulphate for acute bronchiolitis: A double-blind placebo-controlled trial

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SUMMARY

The use of adjunctive therapies to achieve rapid recovery from clinical symptoms of acute bronchiolitis would appear necessary. This study was performed to determine the effect of zinc sulphate on treating acute bronchiolitis. In this study, 100 children affected with acute bronchiolitis were investigated. Fifty patients received oral zinc sulphate and 50 patients placebo. Signs and symptoms of the disease were compared between two groups at the time of admission and then 24, 48, 72, 96 and 120 hours after the beginning of treatment. The trend of recovery of clinical signs and symptoms was more favourable in the case group than in the control group in 24, 48, 72, 96 and 120 hours after beginning of the treatment. The significant differences were observed between the two groups in terms of improvements in coughing and wheezing 48 and 72 hours after the beginning of the treatment ($P<0.05$). Full recovery was observed in 49 (98%) patients receiving zinc sulphate within 72 hours of the beginning of treatment ($P=0.0001$). The present study showed that administration of zinc sulphate accelerates improvement from clinical signs and symptoms of acute bronchiolitis. Thus we recommend the use of zinc sulphate for the treatment of acute bronchiolitis.

Keywords: acute bronchiolitis, zinc sulphate, infants.

INTRODUCTION

Acute respiratory infection is the most common cause of disease and mortality in children under the age of 5 years particularly in developing countries. Acute bronchiolitis is also the most common disease of the lower respiratory tract in young infants [1-3]. The disease is primarily caused by invasive viral organisms, in particular but not exclusively respiratory syncytial virus (RSV). Acute inflammation, edema, necrosis of small airways epithelial cells, increased secretion of mucus, and bronchospasm are characteristics of acute bronchiolitis [4].

World Health Organization reported that 33.8 million children younger than 5 years of age developed acute infections of the lower respiratory tract by RSV across the world. Among these, 3.4 million young infants were hospitalized due to severity of the disease. The mortality rate due to acute bronchiolitis in children younger than 5 years of age was estimated 66,000 to 199,000 in 2005 [5]. Treatment of acute bronchiolitis is primarily based on maintenance of adequate hydration and oxygen therapy. The use of other methods such as saline, hypertonic saline, bronchodilators, inhaled adrenaline and corticosteroid are controversial. There are inadequate information to support the use of antibiotics in bronchiolitis, but it can be justified in the case of concomitant bacterial infections in infants with severe disease, especially in those who require mechanical ventilation [6-8].

Given reports on the effects of zinc sulphate on treating pneumonia, we've questioned whether zinc sulphate can be effective in treating acute bronchiolitis [9, 10]. Does the administration of

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zinc sulphate avert disease progression and accelerate healing in infants? Zinc is a vital micronutrient. It contributes to healing of mucous membranes of body organs such as the respiratory and the digestive systems and maintaining their health. In addition, zinc has antioxidant properties and boosting immune system performance [12-15]. One study showed the ineffectiveness of zinc sulphate on treating acute bronchiolitis [16]. Considering that only a few studies have been conducted on this topic, and also given the high prevalence and mortality rates of the disease in young infants, the present study was conducted to investigate the effects of zinc sulphate on treating acute bronchiolitis in children younger than 2 years of age.

PATIENTS AND METHODS

The present randomized, double-blind, controlled clinical trial was conducted on 100 infants aged 2 to 24 months affected with acute bronchiolitis. The primary outcome of this study was the improvement of clinical signs and symptoms of acute bronchiolitis after zinc therapy. This study was conducted in Qazvin children hospital (Qazvin, Iran) from November 2013 to March 2014. Qazvin children hospital is the only paediatrics teaching and referral hospital in Qazvin province which is located 140 km North West of Tehran, Iran. This hospital is affiliated to Qazvin University of Medical Sciences (Qazvin, Iran). Sample size was calculated based on $Z_{0.1}$=1.28, $Z_{0.05}$=2, d=0.3, P1=0.5 and P2=0.2 (the ratios of symptoms improvement in case and control groups) to provide 80% power in statistical analysis [10]. Inclusion criteria were:

1) aged between 2 to 24 months;
2) first episode of wheezing following the viral infection of the upper respiratory tract; *iii)* presence of clinical manifestations of acute bronchiolitis (expiratory wheezing ± crackles ± increased respiratory effort, including tachypnea, nasal flaring, intercostals, subcostal retractions and ± apnoeic episodes);
3) lack of consolidation on a chest x-ray [4,16-19]. All children admitted to emergency department, with mentioned criteria were included with the diagnosis of acute bronchiolitis.

Patients with history of more than one episode of wheezing, history of asthma and allergies in the patient and their family, presence of other diseases such as congenital heart disease, malnutrition and pneumonia, history of prematurity, low birth weight and intrauterine growth retardation, zinc sulphate administration in the last month prior to admission and previous antibiotic therapy were excluded. Patients were divided into two groups using simple randomization method (50 cases and 50 controls). In addition to routine and maintenance treatments (such as steam inhalation and bronchodilators) shared between the two groups, the case group was administered zinc sulphate syrup and the control group a placebo solution. Children younger than 1 year of age received 10 mg zinc sulphate in two divided doses and those over the age of 1 year received 20 mg in two divided doses and administered for 5 days [9].

The zinc sulphate solution bottles and placebo were similar in shape and size. In addition, placebo solution resembled the zinc sulphate in color, odor and taste. Types of administered treatments were identified by numbers 1 and 2 as selected by a different study group which not included the researchers. The numbers were presented to the personnel in sealed envelopes. The personnel were blinded to the type of treatment associated with each number. Based on the random numbers presented on the coverage, they selected one of the two treatment packages for every infant and gave it to their mothers. In this double-blind study, neither the mothers of participants nor the researchers knew which participants belonged to the control group, or presented on the case. Only after all data had been recorded and analyzed, the researchers taught which group each participant belonged to. Data analysis was done by a blind researcher too.

The two groups were matched regarding underlying and confounding variables such as age, gender, weight, height, head circumference, type of feeding, etc. Prior the enrollment, the study subject was explained to the parents and then the informed consent was obtained. At the time of admission, personal information's, clinical signs and symptoms and laboratory findings of the patients were recorded in prearranged forms at the time of admission. Clinical signs and symptoms of patients such as coryza, coughing, fever, tachypnea, etc were recorded at 24, 48, 72, 96 and 120 hours after the beginning of the treatment. Axillary temperature above 37.2°C and rectal tem-

perature more than 38ºC were considered fever. Respiratory rate more than 50/minute between 2 -12 months and over 40/minute between 12-24 months were considered tachypnea. All measurements such as weight, height, head circumference, temperature, etc were performed by standardized methods [20].

All the laboratory tests were performed in the laboratory department of Qazvin children's hospital using the standard method. A single investigator was responsible for performing clinical assessments. During the course of the study, the patients' parents or the physician recording the signs and symptoms were not aware about the type of treatment each group was receiving. Clinical recovery was considered when all of clinical features were disappeared. The zinc sulphate syrup used (each 5 cc equal to 5 mg) was produced by Razak Laboratories Company under the license No. 11/10198 in Tehran, Iran. Data obtained were analyzed in SPSS software (version 16) using the statistical Chi-squared test, the Mann-Whitney test , t-test and Kaplan-Meier survival curve. P<0.05 was considered significant.

Ethical considerations

The ethics committee of the Research Department in the Qazvin University of Medical Sciences Qazvin, Iran approved the study (Registration number of medical ethics: 28/20/8103).

All parents were provided information regarding the research method in simple language. The children were included in the study after their parents agreed and signed the informed consent form.

RESULTS

In the case group, 29 (58%) children were male and 21 (42%) were female. Where as in the control group there were 26 male (52%) and 24 female (48%) children, respectively (P=0.68). The minimum, maximum and median±IQR of age in the case group were 2, 24 and 7±10 months, respectively. These values in the control group were 2, 24 and 7±13.6 months, respectively (P=0.21). No significant difference was observed between the two groups in terms of age, gender, weight, height, head circumference and other variables (P>0.05) (Tables 1 and 2). The clinical signs and symptoms of disease such as rhinorrhea, cough, fever, tachypnea, wheezing and crackle were described in two groups in Table 2 (P>0.05). The laboratory findings of patients such as white blood cell count, C-reactive protein and sedimentation rate were in normal limits. The chest radiogra-

Table 1 - Comparison of variables between case and control groups before starting treatment.

Variables	*Case*	*Control*	*P*
Gender (male/female)[1]	29/21	26/24	0.68
Age (months)[2]	7±10	7±13.6	0.21
Weight (kg)[3]	8.1±2.1	7.3±2	0.08
Height (cm)[3]	66.2±8.3	65.1±10	0.56
Head circumference (cm)[3]	43.8±3.3	42.8±3.8	0.21
Breast feeding ± food/formula±food[1]	35/15	34/16	0.54
Exposure to smokers at house (yes/not)[1]	26/24	26/26	0.68
Duration of disease (days)[2]	3±1	2±1	0.13
Duration of cough (days)[2]	2±1.5	2±1.25	0.65
Duration of respiratory difficulty (hours)[2]	12±28	24±14	0.65
Dehydratation (yes/not)[1]	50/0	49/1	0.31
Pulse rate (per minute)[3]	122±11	120±10	0.28
Haemoglobin (g/dl)[3]	11.3±0.9	11.3±0.8	0.99
Oxygen saturation (%)[2]	98±3	98±2	0.58
PO2 (mm Hg)[2]	74±6	73.5±1	0.62
PCO2 (mm Hg)[2]	41±8.5	41±4.7	0.83
pH[2]	7.3±0.04	7.3±0.04	0.1

[1]frequency (chi square test); [2]median± IQR (Mann-Whitney test); [3]Mean± SD (T test).

Table 2 - Comparison of clinical manifestation between case and control groups before starting treatment.

Signs and symptoms	*Case*	*Control*	*P*
Rhinorrhea (yes/not)[1]	18/32	21/29	0.68
Cough (yes/not)[1]	47/3	45/5	0.46
Fever (yes/not)[1]	12/38	10/40	0.81
Tachipnea (yes/not)[1]	54/6	47/3	0.48
Dyspnea (yes/not)[1]	2/48	1/49	1
Nasal flaring (yes/not)[1]	0/50	2/48	0.49
Subcostal retraction (yes/not)[1]	23/27	17/33	0.3
Intercostal retraction (yes/not)[1]	27/23	23/27	0.54
Cyanosis (yes/not)[1]	2/48	0/50	0.49
Wheezing (yes/not)	50/0	50/0	1
Fine crackles (yes/not)[1]	8/42	9/42	1

[1]frequency (chi square test).

phy of patients revealed hyperinflated lungs with patchy atelectasis without any consolidation.

The improvement process of the clinical signs and symptoms in the two groups is presented in Table 3. A significant difference was observed between the two groups in terms of relief from coughing and wheezing 48 and 72 hours after the beginning of the treatment (P<0.05) (Table 3). The majority of the cases of full recovery in the group receiving zinc sulphate were observed 48 and 72 hours after the beginning of the treatment (Figure 1). Forty-nine patients fully recovered 72 hours after starting the treatment with zinc sulphate. Meanwhile, in the placebo group, only 26 patients fully recovered (P<0.0001) (Figure 1) (Kaplan-Meier analysis).

The mean duration of hospital stay was significantly shorter in the group receiving zinc sulphate than in the placebo group (4.6±1.7 vs. 5.4±2 days), (P=0.023) (t-test). No side-effects such as nausea and vomiting were observed as a result of the administration of zinc sulphate in the case group. In the present study we did not observe any side-effects such as nausea and vomiting following administration of zinc sulphate in our case group.

Table 3 - Comparison of clinical manifestations between case and control groups after starting treatment.

Signs and symptoms	*24 hours*			*48 hours*			*72 hours*			*96 hours*			*120 hours*		
	Case	*Control*	*P**	*Case*	*Control*	*P**	*Case*	*Control*	*P**	*Case*	*Control*	*P**	*Case*	*Control*	*P**
Rhinorrhea	6	7	0.76	0	1	0.31	0	0	1						
Cough	30	41	0.15	15	31	0.01	2	15	0.001	0	1	0.3	0	0	1
Fever	1	1	1	0	0	1									
Tachipnea	16	17	0.8	1	1	1	0	0	1						
Dyspnea	0	0	1												
Nasal flaring	0	0	1												
Subcostal retraction	5	4	0.7	0	0	1									
Intercostal retraction	7	5	0.53	1	0	0.31	0	0	1						
Cyanosis	1	0	0.31	0	0	1									
Wheezing	38	44	0.11	14	26	0.24	0	16	0.0001	0	0	1			
Fine crackles	4	4	1	2	0	0.15	0	0	1						

*Chi square test.

DISCUSSION

The present study demonstrated that the administration of zinc sulphate accelerates the improvement of clinical signs and symptoms in patients with acute bronchiolitis. As soon as our knowledge and literature review is concerned, few studies have been conducted on the effects of zinc on treating acute bronchiolitis. A study conducted by Heydarian et al. on 50 patients of 2 to 23 months old afflicted with acute bronchiolitis. Clinical symptoms in these patients did not improve following administration of zinc sulphate [16]. However, in the present study, 49 of the 50 patients belonging to the case group fully recovered 72 hours after the beginning of zinc sulphate. By contrast, in the placebo group, only 26 patients had fully recovered. In addition, the group receiving zinc sulphate had shorter hospital stay comparing to the placebo group.

The number of zinc sulphate doses administered and the number of patients enrolled in the present study could explain the discordance in the results observed in our study compared to those of the Heydarian's study. In the present study, all infants younger than 1 year of age received 10 mg of zinc sulphate orally, comparing the Heydarian's study whose patients received 1cc/kg equal to 1mg/kg orally. The administered dose of zinc sulphate in our study was higher than Heydarian's study. In addition, Heydarian study was a pilot study on 50 patients, while our study was performed on 100 patients. These differences could explain different results. Studies conducted on the effects of zinc on pneumonia have yielded contradictory results [9,11,21,22]. In a study conducted by Valavi et al. on 128 infants of 3 to 6 months afflicted with severe pneumonia, the administration of zinc was shown to accelerate the improvement of symptoms and reduced hospital stay. These findings were confirmed by studies conducted by Basnet and Brooks [9-11]. On the other hand, other studies did not confirm positive effects of zinc on treating pneumonia [21, 22]. Results of the present study are in accordance with research by Basnet, Brooks and Valavi [9, 11].

Study by Suara and Crowe showed the inhibitory effect of zinc on proliferation of RSV *in vitro*. They believed that sedimentation of zinc in or on the monolayer cell prevents the absorption of the virus and plaque formation [23].

Zinc is an essential trace element in humans and performs three main biological roles, namely, catalytic, structural and regulatory roles. The vital role of zinc has been confirmed in homeostasis, immune function, oxidative stress, apoptosis and tissue growth, development, repair and regeneration [14, 20, 24]. Airway epithelium protection is one of the main characteristics of zinc [14]. As an antioxidant element, an organelle stabilizer, an anti-apoptotic agent, a major co-factor of DNA synthesis, a crucial component of tissue repair and an anti-inflammatory agent, zinc protects the airway epithelium against oxy radicals and other noxious agents [14].

Based on results obtained, zinc sulphate is suggested as a complementary treatment to be used alongside maintenance treatments for acute bronchiolitis. This additional measure also reduces hospital stay. As far as our knowledge and literature review is concerned, there is no serious side effect of zinc sulphate, so it could be use safely in pediatric group. The results of this study could not be generalized to involve ICU patients. So, we recommend a different study to compare the effect of zinc sulphate in ICU patients. Limitations of this study were: failure to measure serum zinc levels in the two groups before and after treatments; lack of viral investigation. Further studies are suggested to be conducted on this topic with larger sample sizes, serum zinc levels measurement, and not only viral testing but also Bordetella species or Mycoplasma evaluations [25].

Conflict of Interest: No conflict of interest

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