The Effect of Oral Zinc Sulfate on Hepatitis B Vaccine immunogenicity in Premature Infants

Hemmati Mitra[1],Ahmadipour Shokoufeh[1],Babaei Homa[1],Mohsenzadeh Azam[2]

1-Department of Pediatrics, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
2--Department of Pediatrics, Madani Hospital, Lorestan University of Medical Sciences, Khorramabad, Iran
(Corresponding Author: Ahmadipour Shokoufeh , Email:shokofe57@yahoo.com)

Abstract: The immune system in premature neonates is weaker compared to mature ones. Zinc is a micro-nutritive, which plays an important role in the immune system .It can function as an adjuvant to improve the effectiveness of some vaccines. Neonate receive zinc in the third trimester of pregnancy, so the preterm neonate cannot receive it adequately and they have less storage for zinc. This study was conducted on 106 premature neonates. They were divided randomly into two groups of zinc taking and control group (n=53,each group). The first group received 3mg zinc sulfate for 6 months. Hepatitis B vaccination was performed for both groups. One month after the last vaccination for hepatitis B, the antibody titer for both groups was examined. In the zinc taking group, the response level(Antibody titer > 0.1µu/ml) to hepatitis B vaccine was 100% with the mean antibody of 236±443.5 µu/ml, but in control group the response level was 86.8% with the mean antibody of 170±205 µu/ml. There was a significant difference between the response level of intervention and control group (P=0.006); but there was not any significant difference in the average of antibody titer (P=0.328). Zinc can be used in premature infants to increase their response to hepatitis B vaccination. **The Effect of Oral Zinc Sulfate on Hepatitis B Vaccine immunogenicity in Premature Infants** *Life Sci J* 2012;9(4):3359-3361] (ISSN:1097-8135). http://www.lifesciencesite.com. 496

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Introduction

Premature infants are subject to higher risk of mortality and infectious diseases more than mature ones. 13 million premature infants are born annually, most of which are in Asia (54%) and Africa (31%) [1]. Premature infants and infants with low birth weight (LBW) are zinc deficient because of low body storage, and this is because of the fact that 60% of zinc enters the infants' body during the last three months of pregnancy [2]. On the other hand, zinc is a microelement with a great impact of the growth and strength of the immune system in the body. In addition to weakening the immune system, zinc deficiency causes hormone and endocrine disorder and as a result, it causes physical and mental growth retardation [2, 3, 4]. In addition, zinc functions in producing 100 different enzymes in the body[5]. All kinds of immune cells show decreased function after zinc depletion. In such situation, all functions related to monocytes and T cells are impaired, in natural killer cells and neutrophils cytotoxicity activity and phagocytosis is reduced, respectively. However, auto-reactivity and all reactivity will increase [6]. The immune system in premature infants does not evolve adequately, so these infants are subject to different viral and bacterial infections and mortality resulted from them. Besides, the ability to respond the vaccination in premature infants is less than mature ones [7,8]. The premature infants less than 2000g birth weight do not respond adequately to hepatitis B vaccine, so 4 doses of vaccine at the time of birth, 1st month, 2 months and 6 months old is injected [9,10]. Hepatitis B vaccine immunogenicity in premature infants is variant depending fetus birth age and weight**. In order to improve the immunogenicity of vaccination, different methods such as changes in vaccination method and adding supplements such as, levamisole, cimetidine, zinc sulfate and some other drugs have been investigated** [11]. There are large number of studies investigating the different methods for increasing the immune response after vaccination such as use of different adjuvants (such as Levamisole, Cimetedine and Zinc sulfate), different methods of vaccination (whether intradermal or intramuscular as well as rapid or conventional methods). For example, vaccination via the intradermal route (ID) is considered as a method that may be more effective than the conventional intramuscular (IM) route [12] However, such general belief is not supported by findings from all studies [13]. Different groups of people are subject to zinc deficiency like premature infants, the elderly, vegetarians and nephropathies (renal patients) (6). By considering the fact that the immune system in premature infants does not evolved completely, so in this paper the effect of zinc sulfate on antibody value and response after injecting hepatitis B vaccine studied in premature infants.

Methods and materials

This study is a clinical experience conducted in the hospitals related to Kermanshah medical school (Imam Reza and Mo'tazedi hospitals). First 146 premature neonates with the gestational age of 28-36 week and birth weight between1000-2500 gram

investigated, and finally because of the lack of parents' cooperation, 106 infants investigated to the end of the study. The criteria to enter the study include HBSAg of the mother being negative (based on the tests done in pregnancy care), no congenital sepsis or anomaly in the infants not affected by any diseases during the study period, and only breast feeding of the infants.

The gestational age of each infant was determined according to mother's LMP and Ballard scoring system. The socio-Economical conditions of the families in both groups were the same. An information form, in which the sex, weight, height, head circumference at the time of birth and parent's phone number were included, was supplied for each infant. In the case of parents' satisfaction to conduct the study and cooperation to the end of the research, the infants were divided into 2 groups of zinc-takers and control group (n=53 each group) randomly. A written consent was taken separately from the parents .If an infant did not take the zinc sulfate syrup regularly each day, they were excluded from the study. The zinc-taking group received 3mg equal to 3cc zinc sulfate syrup (Made in Iran,Razak Company,5mg/5cc) daily.

Both zinc taking and control groups were evaluated and examined monthly, to the end of 7 months old. Hepatitis B vaccine (Hepavax, Korea) was injected deep intra-muscular for both groups based on national routine for about 0.5cc on the upper-anterior part of the thigh. For both groups, the infants less than 2kg weight received an extra hepatitis B vaccination in one month old. During the study, if an infant suffered from a disease which needed hospitalization, or he/she did not take the syrup daily and regularly, they were excluded from the study. One month after the last hepatitis B vaccination, 1cc blood clot was taken from the infants and hepatitis B antibody titer was calculated using competitive Eliza method (Biomerieux, USA) in Imam Reza hospital laboratory, and the data collected was analyzed statistically using SPSS17 software. To compare the antibody titer and other variables in both groups, t-test and levene's test were used.

Results

First, 146 premature infants entered the study, but because of the lack of parent's cooperation to the end of the study, dispensing with bloodletting, 3 diarrhea and 4 pneumonic cases resulted in hospitalization of the control group and also irregular zinc taking, 53 infants in each group were investigated to the end of 7 months old. In zinc-taking group, there were 30 boys and 23 girls and in control group, there were 28 boys and 25 girls. There was not any significant difference between the fetus age, birth weight and sex of both groups. The average age and weight of birth for both groups is summarized in Table 1. Both groups were investigated for their response to hepatitis B vaccine and antibody titer and the results are shown in Table 2.

Table 1. Comparison of age and weight of birth among the two groups

Variable	With Zinc(n=53)	Without Zinc(n=53)	P- value
Age (weeks)	32.9±2.2	32.7±2.1	0.594
Weight (grams)	1867.9±358.7	1765.1±313.9	0.119

Table 2. Comparison of Antibody Titer to the end of 7 month: after hepatitis B vaccine prescription among the two groups

variable	With Zinc(n=53)	Without Zinc(n=53)	P- value
Average of Hepatitis B Antibody Titer	236±443.5	170±205	0.328
Immunity(%) (Antibody Titer > 0.1µu/ml)	100%	86.8%	0.006

During the study, there were four nausea and vomiting cases after taking zinc, rectified after it was recommended taking it with mother's milk, and no serious complication was observed because of taking zinc.

Discussion

In this study, 106 premature infants were investigated and there was not any significant difference between their age, sex and birth weight. The group under study received 3mg zinc sulfate syrup daily for 6 months but the control group did not take zinc. One month after the last hepatitis B vaccination, the antibody titer was evaluated and all of the infants taking zinc for 6 months, had acceptable antibody titer of over 0.1µu/ml and responded well to hepatitis B vaccination and didn't required to repeat vaccination; while only 86.8% of the infants who didn't receive zinc sulfate had an acceptable antibody titer, and there was a significant difference between two groups according to their response to vaccine (p=0.006).

In one study in Bangladish, 242 infant with the age of 33-40 weeks were investigated and they received 5mg zinc daily for 4 weeks alongside

pneumococcus heptavalent vaccine and after wards antibody titer was evaluated and showed that in the group under study. The 9-serotype antibody increased more than the control group [14]. Another study was done in India, CD_4 value increased in 5-7 years old children who received 10mg zinc daily for one month [15]. According to the results of one study the CD_4 value after DPT vaccination and polio injection in premature infants was lower than mature ones [16]. Several studies were conducted on hemodialysis patients and the HBS-AB level was evaluated after zinc prescription and hepatitis B vaccination. In a clinical experience, 50 people of over 40 years old ages who were HBC-Ab negative received 200mg zinc sulfate capsules for 30 days and after 3 hepatitis B vaccination, hepatitis B antibody titer was measured and it showed no difference with the control group [17]. In a study conducted on rats, the antibody response to hepatitis B vaccine was weaker in the group who had low zinc diet [18]. In one study the suppressive effect of zinc on antibody response to cholera toxin in children given the killed oral cholera vaccine was reported [19].

In another study a group of teenagers received 400mg zinc daily for 2 months before influenza vaccination, then influenza CD_3,CD_4 and CD_8 antibody titer was measured and there was no difference between them and control group [20].

Based on the findings in this study and the above researchers, studies it can be concluded that sulfate syrup prescription does not have any serious complications and on the other hand, it has a well-deserved effect on responding to hepatitis B vaccine in premature infants. Therefore, it is better to use zinc to increase immunogenicity and response to hepatitis B vaccine, especially in developing countries with the high rate of hepatitis B, in addition to the vitamins and the elements that the premature infants take routinely.

It is suggested that in later studies the serum level of zinc in premature infants and also the effect of zinc sulfate on immunogenicity of other vaccines and its long-term prescription effect on growth and evolutional-neural criteria in premature infants, to be evaluated.

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