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Efficacy of zinc sulfate supplement on febrile seizure recurrence prevention in children with normal serum zinc level: A randomised clinical trial

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ABSTRACT

Objective: Serum zinc level might be related to pathogenesis of febrile seizure (FS). The purpose of this study was to evaluate efficacy and safety of oral zinc supplementation on FS recurrence prevention in non-zinc-deficient children.
Materials and Methods: In a randomized clinical study, one hundred 18 to 60 mo old children with normal zinc level with first simple FS were referred to Shahid Sadoughi Hospital, Yazd, Iran from May 2012 to June 2013, were randomly assigned to two groups to receive 2 mg/kg/d zinc sulfate for six consecutive months or placebo as control group and were followed up for 1 y for FS recurrence.
Results: 41 girls and 59 boys with mean age of 2.47 ± 1.01 y were evaluated. Race, mean weight, height and body fat were similar in both groups. FS recurrence occurred in 19 children (38%) in the control group [95% confidence interval (CI): 19.45%–53.95%] and in 11 children (22%) in the zinc sulfate (95% CI: 57.47%–89.13%) groups, respectively; and the zinc group had lower FS recurrence ($P = 0.03$). The mean serum zinc level before intervention was lower in children with FS recurrence (72.43 ± 14.58 μg/dL versus 96.33 ± 12.69 μg/dL, $P = 0.04$).
Gastrointestinal side effects (vomiting in five children, heartburn in two children and abdominal pain in one child) were seen in 16% of the zinc group and vomiting occurred in two children (4%) in control group and frequency of adverse events was similar in the two groups ($P = 0.1$).
Conclusion: Zinc supplementation should be considered as effective and safe in prevention of FS recurrence.

Introduction

Febrile seizure (FS) is defined as a seizure associated with a febrile illness in the absence of central nervous system infections or acute electrolyte abnormalities in 6 to 60 mo old children without previous afebrile seizures, and is the most common type of seizures in children, occurring in 2 to 5% of them. FS is divided into simple (benign) and complex types. Complex FS is defined as a seizure lasting longer than 15 min, recurring within 24 h. One major concern of parents of children with first FS is the risk of recurrence and the most important factor which increases febrile convulsion recurrence rate is occurrence of first FS at an age of less than 1 year. Other major risk factors for recurrence of FS are duration of fever in less than 24 h and 38 to 39°C fever. Minor risk factors for recurrence of FS are positive family history of FS, family history of epilepsy, Complex FS, day care, male sex, and lower serum sodium [1].

The pathogenesis of febrile convulsion is undetermined and factors such as genetic predisposition, fever-associated synchronized neuronal activity of brain ion channels changes, neurotransmitters imbalance, reduction in inhibitory neurotransmitter

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of gamma-amino butyric acid (GABA) and change in trace elements level might be contributing factors [2,3].

"Zinc is a trace element that has a critical role in cell division, protein synthesis, wound healing and immune function and it is estimated that 25% of the world population is at risk of zinc deficiency [4]."

Based on results of some studies, blood and cerebrospinal fluid zinc level of children with febrile seizure was significantly lower than in children with afebrile seizure. Zinc level has an important role in level of gamma-amino-butyric acid (GABA) as the main inhibitory neurotransmitter of brain. Zinc stimulates pyridoxal kinase enzyme activity and decarboxylation of glutamic acid and increases brain GABA level and also prevents the excitatory neuronal discharge. Therefore, decrease of serum zinc level and GABA levels might play a role in the pathogenesis of FS [5–9].

Theory/calculation

It is hypothesized that zinc supplementation in children with febrile convulsion might decrease recurrence of febrile seizure and the purpose of present research was to evaluate efficacy and safety of oral zinc supplementation on febrile seizure recurrence in non-zinc-deficient children in Yazd, Iran.

Materials and methods

In a randomized single-blind clinical, parallel group study, all consecutive 18 to 60 mo old referred children with first febrile seizure to Shahid Sadoughi Hospital, Yazd, Iran from May 2012 to June 2013 were enrolled in the study.

Sample size was assessed to be 50 children in each group based on Z formula and a CI of 95% with 80% power to detect a 25% difference in febrile seizure recurrence between the two groups with type one error (alpha) of 0.05.

Eligible participants included children ages 18 to 60 mo, with first simple FS, their weight and height were above the third percentile on a standard growth curves of National Health and Nutrition Examination Survey III (NHANES III) curves [10] and with normal serum zinc level (plasma level of 70-158 μg/dL) [11] were measured by coupled plasma mass spectrometry within the first 2 h after the first FS attack.

Exclusion criteria consisted of receiving a zinc combination or supplementation within the past 2 mo, central nervous system infections, history of previous febrile or afebrile seizure, neurodevelopmental delay, presence of any chronic systemic diseases (endocrine, cardiac, renal, metabolic, malignancy, rheumatologic, etc), iron deficiency, and iron deficiency anemia (anemia was defined as hemoglobin level of less than 10.5 g/dL in 18 mo to 2 y and less than 11.5 g/dL in 2 to 6 y and iron deficiency was defined as serum ferritin level of less than 12 ng/mL if CRP was negative or 1+, ferritin level of less than 30 ng/mL if CRP was ≥2+, or serum iron levels of less than 22 μg/dL) [12].

Children who were underweight (weight below the third percentile on a standard growth curve), short stature (height of less than two standard deviation from height) based on NHANES III [10] zinc deficient (plasma level less than 70 μg/dL) [11], or had severe malnutrition, were excluded.

Developmental status of children was assessed using the Denver II Developmental Screening Test by the pediatric neurologist of research.

The patients were weighed using a digital scale with a sensitivity of 100 grams while wearing little or no outer clothing. The crown-heel height was measured by stadiometer to the nearest millimeter. The weighing scale and stadiometer were products of Seca (Hamburg, Germany) and all measurements were done by one researcher.

Children in both groups were from Yazd, Iran and their race/ethnicity, socioeconomic status, diet, and the consumption of zinc-rich foods were similar.

The trial used computer generated equal simple randomization by random numbers and allocation ratio was 1:1 for the two groups.

Randomization and blinding was done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors and data analysts were all kept blinded to the allocation.

The children were randomized to receive daily supplementation of single dose of 2 mg/kg (maximum 50 mg) zinc sulfate for six consecutive months (Group I) or placebo as control group (Group II). Appearance and taste of zinc and placebo syrups were identical and the bottles were coded, known only to the pediatric ward nurse.

In both groups, children were followed up every 3 mo for 1 year for the recurrence of FS, timing of recurrence and side effects. The intervention was delivered by mothers and primary and secondary outcomes were assessed by the intern of research who was not informed of the drug group assignment.

The primary endpoint was FS recurrence and secondary endpoint was clinical side effects.

The data were analyzed using Statistical Package for the Social Sciences version 17 (IBM SPSS Statistics, Armonk, NY, USA) statistical software. Chi-square test was used for data analysis of qualitative variables and mean values were compared using independent Student's *t* test. The Kaplan-Meier method was used to calculate the probability of recurrence of FS during follow-up. Differences were considered significant at *P* values of less than 0.05.

Informed consent was taken from the children's parents before the administration of the drugs and the study approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

This study is registered in Iranian clinical trials with registration number: IRCT201211262639 N9 and the researchers got no support from the drug company.

Results

The design and conduct of this trial was straightforward, and we did not have any losses during follow-up, nor exclusions. 41 girls and 59 boys with mean age of 2.47 ± 1.01 y were followed up in two groups.

Comparison of some characteristics of the children is shown in Table 1, which indicates no statistically significant differences were seen from viewpoints of sex, family history of FS, family history of epilepsy, mean age, mean height, weight, body mass index (BMI), weigh in kg/height in m^2, temperature at admission, duration of fever before FS, duration of seizure, serum sodium, hemoglobin, ferritin, and zinc levels at the start of the study in both groups.

Thirty-two children had febrile seizure recurrence, with a mean occurrence time of 6.3 ± 3.7 mo. The cumulative percentage of FS recurrence, according to the Kaplan-Meier method, was 15.6% at 1 mo, 56.3% at 6 mo, and 90.6% at 1 year.

Recurrence of febrile seizure occurred in 19 children (38%) in the control group (95% CI: 19.45% to 53.95%) and in 11 children

Table 1
Comparison of selected characteristics of children in both groups

Data	Placebo	Zinc sulfate	*P* value
Sex			
Girl	19	22	0.5
Boy	31	28	
Family history of febrile seizure			
Yes	10	12	0.6
No	40	38	
Family history of epilepsy			
Yes	7	6	0.9
No	43	44	
Age in year (mean ± SD)	2.37 ± 0.93	2.58 ± 1.07	0.3
Weight in kg (mean ± SD)	12.89 ± 2.12	13.11 ± 1.43	0.9
Height in centimeter (mean ± SD)	87.14 ± 7.68	86.12 ± 9.71	0.7
Body mass index (mean ± SD)	18.54 ± 7.61	19.43 ± 8.97	0.4
Temperature at admission in centigrade (mean ± SD)	38.66 ± 0.68	38.54 ± 0.61	0.4
Duration of fever before FS in hour (mean ± SD)	17.34 ± 3.89	13.83 ± 2.07	0.3
Seizure duration in minutes (mean ± SD)	7.24 ± 4.8	6.78 ± 4.5	0.6
Serum sodium level in meq/lit (mean ± SD)	139.1 ± 9.48	141.2 ± 10.69	0.7
Hemoglobin level in g/dL (mean ± SD)	11.44 ± 1.21	11.34 ± 1.56	0.9
Serum ferritin in ng/mL (mean ± SD)	54.51 ± 11.33	55.32 ± 10.26	0.8
Zinc level at the start of the study in μg/dL (mean ± SD)	84.67 ± 12.34	81.73 ± 13.35	0.5