

Study of zinc supplementation in prevention of recurrence of febrile seizures in children at a tertiary care center

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Abstract

Background: Febrile seizure is the most common form of seizures among all children's neurological problems; commonly affect children under 5 years of age. Studies carried out by different researchers; with noticeable prevalence of febrile seizures, stated low zinc levels in febrile seizures. Also, other studies noted crucial role of zinc in central nervous system. Present study was conducted at a tertiary care hospital to assess whether zinc supplementation can prevent recurrence of febrile seizures in children. **Material and Methods:** Present study was a randomized, placebo-controlled trial conducted in Department of paediatrics, BKL Walawalkar Trust Rural Medical College. Total 70 children (35 in the case group and 35 in the control group) who were admitted in our department with simple febrile seizure were considered for present study. **Results:** Mean age of children in present study was 1.88 ± 1.10 years. No statistically significant differences in age and gender noted in present study. Significant difference ($p = 0.003$) was noted after zinc supplementation in between these two groups. No significant difference was noted in recurrence after zinc supplementation in our study. **Conclusion:** Considering role of genetic factors, family history and infections in the etiology of febrile seizures, role of zinc in prevention of recurrence of febrile seizures should be investigated with further larger studies.

Key Words: zinc supplementation, febrile seizures, recurrence prevention.

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INTRODUCTION

Febrile seizure is the most common form of seizures among all children's neurological problems; commonly affect children under 5 years of age. Worldwide its incidence is 2–5%. Risk factors for febrile seizures are male sex; family history of febrile seizures; a body temperature of 38°C or higher; underlying cause of fever; antenatal complications; low serum calcium (Ca), sodium (Na), and blood sugar; microcytic hypochromic anaemia,

maternal smoking and alcohol consumption during pregnancy². The etiology and pathogenesis of febrile seizure remain unknown. However, several factors such as vitamin B6 deficiency, electrolyte disturbances, reduction in serum and cerebrospinal fluid (CSF) zinc levels, and low gamma-aminobutyric acid (GABA) levels are thought to play a role in the pathogenesis of febrile seizure.^{3,4} Febrile seizures should also be distinguished from epilepsy, which is characterized by recurrent non-febrile seizures. In brain, zinc is present in large quantities in the hippocampus. Gamma aminobutyric acid (GABA) is an important inhibitory neurotransmitter. Zinc has a regulatory effect on glutamic acid decarboxylase and the synthesis of GABA. Zinc regulates glutamic acid decarboxylase activity which is an important enzyme in production of γ - amino butyric acid. It also regulates the neurotransmitter affinity. It mediates inhibition of calcium on N-methyl-D-aspartate receptors there by reducing excitatory discharge of neurons. In deficiency of zinc, these receptors get stimulated which may produce epileptiform discharges in children with fever⁵. Studies

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carried out by different researchers; with noticeable prevalence of febrile seizures, stated low zinc levels in febrile seizures. Also, other studies noted crucial role of zinc in central nervous system. It is interesting to know at what extent the zinc plays a role in the pathophysiology of febrile seizures and how much the prophylactic prescription of zinc could be capable of preventing febrile seizure^{6,7}. Present study was conducted at a tertiary care hospital to assess whether zinc supplementation can prevent recurrence of febrile seizures in children.

MATERIAL AND METHODS

Present study was a randomized, placebo-controlled trial conducted in Department of paediatrics, BKL Walawalkar Trust Rural Medical College. Study duration was Sept 2018 to Aug 2019. Institutional ethical committee approval was taken for present study.

We recruited total 70 children (35 in the case group and 35 in the control group) who were admitted in our department with simple febrile seizure. febrile seizure was defined as seizures that occur between the age of 6 and 60 months with a temperature of 38°C or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. Simple febrile seizure

RESULTS

After applying inclusion and exclusion criteria, total 70 children randomly divided in two groups of 35 each. The case group consisted of, 19 boys (54.28 %) and 16 girls (45.7%) with a mean age of 1.97 ± 1.01 years and the control group consisted of 20 boys (57.14%) and 15 girls (42.86%) with a mean age of 1.79 ± 1.14 years. . Mean age of children in present study was 1.88 ± 1.10 years. No statistically significant differences in age and gender noted in present study.

Table 1: Comparison of cases and controls with respect to age and gender

Characteristic	Groups		P value
	Cases (n=35)	Control (n=35)	
	Gender		
Boys	19 (54.28 %)	20 (57.14%)	Not significant
Girls	16 (45.7%)	15 (42.86%)	
Age (mean ± SD years)	1.97 ± 1.01	1.79 ± 1.14	Not significant

No relationship was found between the serum zinc levels and temperature, weight, or family history of febrile seizure among two groups. Serum zinc levels in the case (65.37 ± 12.21 µg/dL) and control (67.32 ± 9.85 µg/dL) groups was noted at the beginning of present study. Serum zinc levels at the beginning of study were non-significant when compared. After completion of study, serum zinc levels in the case group was 87.13 ± 8.76 µg/dL and in control group was 74.21 ± 10.19 µg/dL. Significant difference (p - 0.003) was noted after zinc supplementation in between these two groups. We noted 5 (14.28 %) patients with recurrence in case groups while 4 (11.42 %) patients with recurrence in control groups was noted during study period. No significant difference was noted in recurrence after zinc supplementation in our study.

Table 2: Comparison of Serum Zinc Levels and the Recurrence of Febrile Seizures in the Case and Control Groups

Serum Zinc Levels (µg/dL)	Groups		P value
	Cases (n=35)	Control (n=35)	
At the beginning of the study	65.37 ± 12.21	67.32 ± 9.85	0.461
At the end of the study	87.13 ± 8.76	74.21 ± 10.19	0.003
Recurrence of febrile seizure (percentage)	5 (14.28 %)	4 (11.42 %)	1.000

Values are expressed as mean ± SD

is a primary generalized, usually tonic-clonic attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-h period.

Inclusion criteria

Inclusion criteria were age from 6 to 60 months, both sexes, patients with simple febrile seizures, and normal anthropometric measurements.

Exclusion criteria

We excluded patients on zinc supplement, patients with apparent neurological disturbance other than febrile seizures, and patients with failure to thrive. Written informed consent was obtained from the parents, and fasting blood samples were obtained at 8 AM in order to measure serum zinc levels. The case group received 1mg/kg/day of zinc in the form of syrup of zinc sulphate, and the control group received placebo. Monthly follow-up for 1 year was provided to both groups. Episodes of febrile illnesses, any recurrence of febrile seizures, other illnesses were noted during study period. At the end of the study, serum zinc levels were measured. Quantitative variables were presented as mean ± SD values, and qualitative variables were presented as percentage values. The differences between the groups were considered significant when p-values were less than 0.05.

DISCUSSION

Febrile seizure is an age-dependent response of the immature brain to fever. The etiology of febrile seizure is unknown but genetic factors or electrolyte disturbances may have a role in its occurrence or recurrence. Zinc is also an essential element in brain function. It can directly elevate the threshold of the seizure level by inhibiting N-methyl-D-aspartate (NMDA) receptors or through improving calcium inhibitory function⁸. Zinc also activates pyridoxal kinase, which in turn helps in the pyridoxal phosphate synthesis from pyridoxal. Pyridoxal phosphate in turn activates glutamic acid decarboxylase which involved in synthesis of GABA. Post synaptic receptors in interaction with zinc assists in GABA action. Hence hypozincemia leads to decrease in GABA level which leads to development of seizures^{9,10}. However, several factors such as vitamin B6 deficiency, electrolyte disturbances, reduction in serum and cerebrospinal fluid (CSF) zinc levels, and low gamma-aminobutyric acid (GABA) levels are thought to play a role in the pathogenesis of febrile seizure^{9,10}. Various studies done to assess role of zinc in febrile seizures. Lee *et al*¹¹. reported that there is an association between serum zinc level and febrile seizure. They measured the serum zinc levels in 288 children with febrile seizure and 40 patients with afebrile seizure. Zinc levels in children with febrile seizure were significantly lower than those in children with afebrile seizure. Ganesh *et al.* from India reported that serum zinc levels are lower in children with febrile seizure than in those with epileptic seizures and normal children¹². Gündüz *et al.*¹³ compared serum and CSF zinc levels in patients with febrile and afebrile convulsions and healthy controls; they concluded that compared to patients with afebrile convulsions and healthy controls, patients with febrile convulsions had lower serum zinc levels. In a study by Mishra *et al.*¹⁴ they reported that the serum zinc level in children afflicted with febrile seizure was lower than those in control group, and the difference was significant. However, Kafdar *et al.*¹⁵ reported that their findings did not support the hypothesis that febrile seizures are related to reduced serum zinc concentration. Very few studies were done on whether zinc supplementation can prevent recurrence of febrile seizures in children. Only one study was noted in Cochrane review¹⁶ on this topic. Cochrane review concluded that, neither continuous nor intermittent treatment with zinc, antiepileptic or antipyretic drugs can be recommended for children with febrile seizures. Febrile seizures can be frightening to witness. Parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management and, most importantly, the benign nature of the phenomenon. Fallah *et al.*¹⁷ offered a novel

approach by evaluating the effect of zinc supplementation on febrile seizure recurrence risk. It was a randomised single-blind clinical study comparing zinc sulfate with placebo. One hundred children, aged 1½ to 5 years, with a first simple febrile seizure, with weight and height above the third percentile and with normal serum zinc levels, were randomised to either daily zinc sulfate 2 mg/kg (maximum 50 mg) for six consecutive months or to placebo. Authors assessed seizure recurrence at 12 months and unwanted effects. Although it was hypothesised that decreased zinc levels might play a role in the pathogenesis of febrile seizures supplementation in this study, it conferred no significant benefit over placebo (RR 0.58, 95% CI 0.31 to 1.09). Shiva S *et al*¹⁸ studied whether zinc supplementation prevents recurrence of febrile seizures. They also concluded that zinc therapy with supplemental doses (1mg/kg/day) reduced the rate of occurrence of febrile illnesses but did not prevent the recurrence of febrile seizures. A systematic review for comparison of serum zinc levels among children with simple febrile seizure and control group was done. They concluded that zinc is a predictor of febrile seizures. A low level of this element among children can be regarded as a contributing factor for febrile seizures, a conclusion with a high consensus among different studies carried out in different parts of the world¹⁹.


CONCLUSION

Zinc is an essential element with a definite role in febrile seizures, it is recommended that zinc be prescribed for high-risk children. But considering role of genetic factors, family history and infections in the etiology of febrile seizures, role of zinc in prevention of recurrence of febrile seizures should be investigated with further larger studies.

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