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Serum Vitamin C Levels in Children with Simple Febrile Seizures and the Effects of its Supplementation

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KEYWORDS

Febrile seizures, Antioxidant therapy, Vitamin C.

ABSTRACT:

Introduction: Febrile seizures are seizures that occur in children aged 6 to 60 months with a fever of 38°C (100.4°F) or higher, not caused by CNS infection or metabolic imbalance, and without a history of prior afebrile seizures. These seizures are generally short, lasting less than fifteen minutes, and do not recur within 24 hours. They affect 2-5% of normal infants and children with no neurological anomalies. The onset of febrile seizures has been linked to increased brain temperature, temperature-sensitive ion channels, interleukin-1β, and hyperventilation associated with fever. Oxidative stress is also implicated, with studies indicating higher levels of nitric oxide and reactive oxygen species in children with febrile seizures. Antioxidants like vitamin C, which regulate ROS and protect against oxidative damage, show promise in treating neurological conditions, and this study aims to explore the impact of vitamin C on the recurrence of febrile seizures.

Methods: The study was conducted in two phases at Saveetha Medical College and Hospital from February to February 2024. In the first phase, a case-control study included 50 healthy children and 50 children with febrile seizures, aged 6 months to 5 years. The second phase was a double-blind randomized control trial where children with febrile seizures were divided into two groups: one received daily vitamin C supplementation, and the other received a placebo. Participants and outcome assessors were blinded to the treatment groups. Serum vitamin C levels were measured using the Evelyn and Molly method, and statistical analysis included independent t-tests, chi-square tests, and odds ratios to compare vitamin C levels and assess the impact of supplementation on seizure recurrence.

Results: The study involved 50 children with febrile seizures and 50 age-matched children with fever, with mean ages of 2.66 and 2.91 years, respectively. The mean serum vitamin C level was significantly lower in children with febrile seizures (0.61 mcg/dL) compared to the controls (1.25 mcg/dL). Vitamin C supplementation significantly reduced the recurrence of febrile seizures over a 6-month period (84% reduction, $p = .004$). Children who received vitamin C had significantly lower odds of developing seizures (OR: 6, 95% CI [0.047, 0.591]).

Conclusion: Oxidative stress and an imbalance in the oxidant-antioxidant system are key factors in neuronal damage and febrile seizures. Vitamin C shows potential in preventing febrile seizures by mitigating oxidative stress, suggesting that continued intake after symptoms subside is beneficial. However, the study's small sample size and observational nature highlight the need for further randomized controlled trials to confirm these findings and understand the mechanisms of vitamin C's protective effects. Larger, multicentric studies are necessary to evaluate the effectiveness of vitamin C prophylaxis in preventing febrile seizures and reducing associated cell damage.

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Introduction

Febrile seizures are seizures that occur between the ages of 6 and 60 months with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A simple febrile seizure is a short, generalized seizure, lasting for less than fifteen minutes, occurring during a febrile episode not caused by an acute condition affecting the nervous system with no pre or post-ictal neurological deficits, that does not recur within 24 hours.(1) Between 2% and 5% of normal infants and children with no neurological anomalies experience at least one febrile seizure.(2) Incidence rates in India are comparable to those in developed countries, usually varying between 3.28 - 5.71 / 1000 population.(3)

The onset of febrile seizures has been linked to various processes. One of the factors is an increase in brain temperature, as evidenced by seizures occurring in children who take hot baths. Additionally, alterations in temperature-sensitive ion channels can influence neuronal firing, leading to aberrant and synchronized excitation of neuronal populations. The production of interleukin-1β also plays a role by enhancing neuronal excitability through its action on glutamate and GABA during fever. Furthermore, hyperventilation associated with hyperpyrexia can contribute to the onset of febrile seizures.(4)

The role of oxidative stress in the development of febrile seizures is well documented. For example, a study by Haspolat et al.(5) found that children's CSF fluid had higher amounts of nitric oxide six hours after they began having FS. There are also many indicating the formation of reactive oxygen species (ROS) and the resultant oxidative stress playing a role during seizure activity.(6) Oxidative stress is created when there is an imbalance in the production and subsequent clearance of ROS, ultimately leading to potential damage to the intracellular structures and components through various processes such as lipid peroxidation as well as protein oxidation. Hence the use of antioxidants to treat neurological conditions such as epilepsy have shown some promise, either alone or in combination with other anti-epileptic drugs.

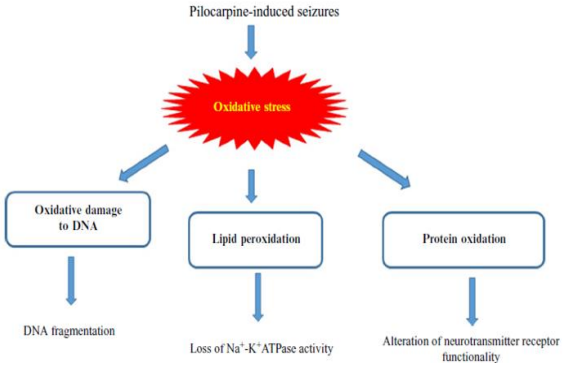

Figure 1: Biological consequences of febrile seizures-induced oxidative stress(7)

Ascorbic acid (Vitamin C), a compound belonging to the group of unsaturated polyhydroxy alcohols, is one of the basic antioxidants necessary for the functioning of the human body. Ascorbic acid regulates the level of ROS as early as at the stage of their formation. Common pathways of action antioxidant action of Vitamin C include free radical regulation, enhancing the functioning of other antioxidant enzymes, protection against lipid peroxidation, repairing existing oxidative damage and modulating the inflammatory and apoptotic pathways. By evaluating serum vitamin C levels and comparing them to those of healthy children, the current study aims to explore the possibility of free radical-mediated harm in children experiencing febrile seizures. It also aims to ascertain the impact of vitamin C supplementation on the recurrence of febrile seizures.

Materials and Methods

The first phase of this study was a case control study performed in the Paediatric department of Saveetha Medical College and Hospital from February 2023 to August 2023. During this phase, 50 healthy children and 50 children with febrile seizures were enrolled into the study after taking informed consent from their parents / guardians.

Inclusion criteria: Children between 6 months to 5 years with an episode simple febrile seizure and age matched children with fever

Exclusion criteria: Children outside of the age cutoffs with febrile seizures, those with underlying CNS malformations, those with a history of afebrile seizures, and CNS infections were not included.

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The second phase of the study, conducted from September 2023 to February 2024 was a double blinded randomised control trial where the children with febrile seizures were divided into 2 groups of 25 children each. One group were started on daily supplementation of vitamin C (0.5 to 3 years: 15mg, 4-5 years: 25 mg) and the other group was given a placebo

Randomization and Allocation concealment: Participants were randomly assigned to either the treatment group (receiving daily supplementation of Vitamin C) or the control group (receiving a placebo) using a computer-generated randomization sequence. The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes, which were opened only after participant enrolment and consent.

Blinding of Participants: Both the daily supplementation of Vitamin C and placebo were designed to be identical in appearance, taste, and packaging. Instructions for use and the administration schedule were the same for both groups, making it impossible for participants to distinguish between the treatments.

Blinding of Outcome Assessors: Outcome assessors, responsible for evaluating the study endpoints, were blinded to the treatment groups. They conducted clinical evaluations and collected data using neutral identifiers (e.g., Group A and Group B) to prevent any bias during the assessment process.

Data and Sample collection: Blood samples required were collected under aseptic precautions. Serum Vitamin C levels were estimated using the Evelyn and Molly method.

Estimation of Serum Vitamin C: Reduced 2,6-dichlorophenol indophenol is a colourless product of the reaction between 2,6-dichlorophenol indophenol and ascorbic acid. The amount of ascorbic acid in the solution determines the colour that is produced. Reduced colour signifies a low ascorbic acid content. At 520 nm, the optical density was determined with a spectrophotometer.

Statistical Analysis: All the collected data was entered into an MS Excel spreadsheet. Serum vitamin C levels in children with and without febrile seizures were compared using independent t - test. Chi – square test and odd's ratio were used to determine the effect of vitamin C supplementation on the recurrence of febrile seizures.

Results

Our study included 50 children with febrile seizures and 50 age matched children with fever, who came to the ER and Paediatric OPD for Saveetha Medical College and Hospital, with a mean age of 2.66 ± 1.17 among cases and 2.91 ± 1.38 among controls (p = .174). Out of the hundred children, 55 were male and 45 were female.

Table 1: Age distribution among cases and controls

	Age (yrs)		
	Mean	SD	p-value
Cases (n = 50)	2.66	1.17	0.174
Controls (n = 50)	2.91	1.38	

A comparative analysis was conducted to examine the serum vitamin C levels between cases and controls. The mean serum vitamin C level for cases was 0.61 mcg/dL (SD = 0.27), whereas for controls, the mean level was 1.25 mcg/dL (SD = 0.38). The difference in serum vitamin C levels between the two groups was statistically significant, p < .001. These results indicate a significantly lower serum vitamin C level in cases compared to controls.

Table 2: Serum Vitamin C concentration between cases and controls

	Serum Vitamin C (mcg/dL)		
	Mean	SD	p-value
Cases	0.61	0.27	< .001
Controls	1.25	0.38	

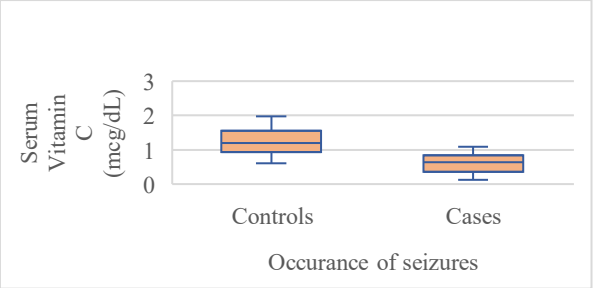

Figure 2: Serum Vitamin C concentration between cases and controls

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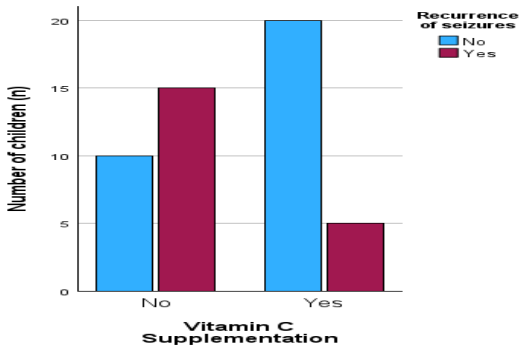

Figure 3: Recurrence of seizures between cases and controls

Among the children with febrile seizures who were supplemented with Vitamin C, significantly fewer children had recurrence of febrile seizures in the 6-month period after the presenting episode (84%). Chi-square = 8.333, df = 1, p = .004. There is a significant difference in the odds of developing seizures, by supplementing Vitamin C (OR: 6, 95% CI [0.047, 0.591]).

Discussion

The term 'oxidative stress' refers to a change in the equilibrium that favours reactive oxygen species over antioxidant defence systems. Neurological disorders include epileptic seizures, stroke, neurodegenerative diseases, and neurotrauma are associated with oxidative stress as a pathophysiological factor.

Our brain is vulnerable to oxidative damage due to its high metabolic demand, high polyunsaturated fatty acid content, low capacity for repair, and high iron burden (Reactive Oxygen species). Cell membranes and certain organelles, such as the mitochondria and endoplasmic reticulum, depend on polyunsaturated fatty acids for their proper functioning. The impact of febrile seizures on oxidative equilibrium is unclear, despite the fact that it is commonly known that epileptic convulsions lead to oxidative stress.(8) Reduced GABA-mediated inhibitory responses in conjunction with enhanced glutamatergic tonus (by NMDA currents and/or dysfunctional astrocyte clearance) result in elevated intracellular calcium concentration, the primary cause of OS-associated feedback and hyperexcitability. Additionally, in both human and animal epilepsy models, there has been a decrease in the expression of antioxidant defence proteins (e.g., GPx, SOD, and Nrf2). Increased ROS production and the ensuing mitochondrial dysfunction work in concert with OS to cause synaptic dysfunction and cell death. Neuroinflammation, which is further evidenced by increased cytokine expression, amplifies OS and causes astrogliosis, which impairs NMDA function and results in cell death.(6) Many antioxidants like vitamin C, vitamin E, vitamin A, uric acid, bilirubin, etc., contribute greatly to the body's defensive system.

The findings of our study reveal significant differences in serum vitamin C levels between children with febrile seizures and age-matched controls with fever. Specifically, children with febrile seizures exhibited markedly lower serum vitamin C levels (mean = 0.61 mcg/dL, SD = 0.27) compared to the control group (mean = 1.25 mcg/dL, SD = 0.38), with a highly significant p-value of < .001. These results align with existing literature suggesting that oxidative stress and the resultant depletion of antioxidants, such as vitamin C, may play a role in the pathophysiology of febrile seizures. Similar result were also seen in the study done by Kumar IU et al.(9)

Vitamin C is a potent antioxidant that neutralizes free radicals and reduces oxidative stress, which is implicated in neuronal excitability and seizure activity.(10) The observed lower levels of serum vitamin C in febrile seizure cases could indicate an increased oxidative burden in these children. Previous studies have similarly documented reduced levels of antioxidants in children with febrile seizures, underscoring the potential role of oxidative stress in the genesis of these seizures.(11) Other markers of oxidative stress are also seen to be lower among children with febrile seizures as evidenced by studies done by El-Marsy HMA et al. and Günesx S et al.(12,13)

Our study further demonstrated that vitamin C supplementation significantly reduced the recurrence of febrile seizures within a six-month period following the initial episode. Among children who received vitamin C supplementation, 84% experienced a reduction in seizure recurrence, a statistically significant finding (Chi-square = 8.333, df = 1, p = .004). This finding is consistent with research indicating that antioxidant supplementation can mitigate oxidative stress and potentially prevent seizure recurrence.(14)

The odds of developing recurrent seizures were significantly lower in the vitamin C supplemented group, with an odds ratio of 6 (95% CI [0.047, 0.591]). This

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suggests that vitamin C supplementation could serve as a protective factor against seizure recurrence, highlighting its therapeutic potential in managing febrile seizures. The mechanisms underlying this protective effect may involve the stabilization of neuronal membranes, reduction of excitotoxicity, and modulation of inflammatory pathways.(15)

Conclusion

The oxidant-antioxidant systems of the children experiencing febrile seizures are out of equilibrium. Oxidative stress is thought to be one of the processes that underpins neuronal damage and may also act as a standalone mechanism in the course of the disease. Additionally, it may result in cell damage, mitochondrial malfunction, and seizures. A dysregulation of the oxidants and antioxidants system leads to lipid peroxidation and ultimately neuronal injury, which is the cause of febrile seizures.

It appears that vitamin C can help avoid febrile seizures. Giving it prophylactically is preferable. The invasive particles have the potential to become an oxidized particle inside the body when exposed to vitamin C. Therefore, in order to get rid of these damaged particles, vitamin C intake must be continued even after the symptoms go away. The degree of oxidation and infection determines the necessary amount of vitamin C.

However, it is important to note that our study is limited by its sample size and observational nature, necessitating further randomized controlled trials to confirm these findings and elucidate the precise mechanisms by which vitamin C exerts its protective effects. Additionally, while our results are promising, they should be interpreted with caution until corroborated by larger, multicentric studies.

To assess the effectiveness of vitamin C prophylaxis in preventing febrile seizures and in reducing the number of episodes and subsequent cell damage brought on by febrile seizures, more extensive trials are needed.

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