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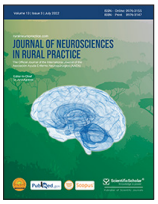

Original Article

Effectiveness of prophylactic iron supplementation in the reduction of recurrence of febrile seizures in children: A prospective study with comparison with historical controls

Indar Kumar Sharawat[1], Prateek Kumar Panda[1], Vinod Kumar[1], Aparna Ramachandran[2], Sanjot Bhardwaj[1], Vignesh Kaniyappan Murugan[1], Amit Kumar Pradhan[1], Rajkali Rajendiran[1], Nowneet Kumar Bhat[1]

[1]Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, [2]Department of Neurology, IQRAA International Hospital and Research Centre, Kozhikode, Kerala, India.

ABSTRACT

Objectives: The primary objective of the study was to compare the number of patients with febrile seizure recurrence within 1 year of presenting to our institute, among patients who received and didn't receive oral iron supplementation.

Materials and Methods: This prospective intervention study with historical controls was conducted to compare the number of patients with febrile seizure recurrence within 1 year, among patients who received and did not receive oral iron supplementation. The intervention group additionally received prophylactic iron supplementation of 20 mg biweekly for 1 year.

Results: A total of 53 patients each were enrolled in both the groups, with comparable baseline characteristics. Although there was a trend toward a lower rate of recurrence of febrile seizures in the interventional group, as compared to the control group, it did not reach the point of statistical significance (P = 0.35). Both in the worst-case scenario and best-case scenario, there was a trend toward less risk of recurrence of febrile seizure in the intervention group, but it did not reach the point of statistical significance (P = 0.43 and 0.52). For the original scenario, worst-case scenario, and best-case scenario, the absolute risk reduction was 6.5%, 7%, and 6%, respectively, with corresponding number needed to treat (NNT) being 15, 14, and 16, respectively. The trend for absolute risk reduction was more pronounced in those with complex febrile seizures with an NNT of 6.5, but it still did not reach the point of statistical significance (P = 0.16). Moderate/severe IDA was also found to be an independent risk factor for recurrence of febrile seizure in the intervention group (P = 0.03).

Conclusion: Oral serum iron supplementation does not significantly reduce the recurrence rate of febrile seizures in children aged 6–60 months. However, there is a trend toward reduction in the frequency of recurrence of febrile seizures, which is more pronounced in the subset with complex febrile seizures.

Keywords: Febrile seizures, Iron-deficiency anemia, Nutritional deficiency, Supplementation, Childhood epilepsy, Recurrence

INTRODUCTION

Febrile seizures are the most predominant type of seizures in children aged 6 months–5 years.[1] At least 2–5% of children in this age group have one or more febrile seizures.[2] A febrile seizure is usually defined as a seizure that occurs in a neurologically normal child aged 6 month–5 years, associated with a rectal temperature of at least 38 degrees, without any history of previous afebrile seizures and no evidence of intracranial infection as such.[3] While around 80% of febrile seizures are simple febrile seizures, the rest of the febrile seizures demonstrate one or more complex features.[4] While intermittent prophylaxis with benzodiazepines or continuous prophylaxis with valproate or other anti-seizure medications (ASMs) is usually not advised for every case of simple febrile seizure, these medications if properly administered reduce the probability of recurrence of febrile seizure.[5] However, they are associated with some adverse effects in a few cases.[6] Several studies have shown iron-deficiency anemia (IDA) as one of the risk factors for febrile seizure.[7,8] Iron-deficiency anemia is the most common nutritional disorder globally.[9] According to the National Family Health Survey-5 of India, IDA has a reported prevalence of 67% in 6–60-month-old children.[10] Under the aegis of the Government of India's (GOI) National Iron Plus Initiative (NIPI), oral iron supplementation biweekly needs to be administered to all children aged 6–60 months.[11]

Controlled studies to weigh the potency of prophylactic iron supplementation in preventing the recurrence of febrile

***Corresponding author:** Prateek Kumar Panda, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India. drprateekpanda@gmail.com

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seizures have not yet been performed. Thus, this study was planned to evaluate the effectiveness of prophylactic iron-folic acid supplementation in the reduction of recurrence of febrile seizures in children.

MATERIALS AND METHODS

This was a prospective interventional study, with historical controls as comparators, performed in a tertiary care teaching hospital in North India between August 2020 and May 2022. The primary objective of the study was to compare the number of patients with febrile seizure recurrence within 1 year of presenting to our institute, among patients who received and did not receive oral iron supplementation. The secondary objectives were to compare the number of patients with an average duration of febrile seizures and the number of febrile seizures, during follow-up, in patients who had a repeat episode of febrile seizure, the number of patients with febrile status epilepticus, and number of patients with failure of intermittent clobazam prophylaxis.

The patients aged 6 months–60 months presenting with febrile seizures to our institute between August 2020 and May 2021 were included in our study as an intervention arm. Similarly, the patients aged 6–60 months presenting with febrile seizures to our institute between August 2019 and July 2020 were included in the study as the control arm. Those patients already on an iron supplement, patients with the presence of central nervous system (CNS) infection, or new-onset persistent focal deficit were excluded from both arms. Those patients who were diagnosed to have anemia due to other causes such as Vitamin B12 deficiency and hemolytic anemia were also excluded from both groups. We included patients with both simple and complex febrile seizures, febrile seizures plus, and febrile status epilepticus patients, but we excluded patients with a definite diagnosis of epilepsy such as genetic epilepsy with febrile seizures plus, Dravet syndrome, or any other pre-existing epilepsy syndromes.

The definitions of febrile seizure, simple febrile seizure, complex febrile seizure, etc., planning neurodiagnostic evaluations such as magnetic resonance imaging (MRI) of the brain, electroencephalogram (EEG), and cerebrospinal fluid (CSF) examination, and starting intermittent and continuous prophylaxis with clobazam and valproate were as per American Academy of Pediatrics guidelines and Association of Child Neurology Consensus Statement on the Diagnosis and Management of Febrile Seizures.[12,13]

The randomized controlled trial (RCT) by Fallah *et al*.,[14] that compared the efficacy of zinc supplementation on recurrence of febrile seizures within 1-year follow-up and they found overall recurrence rate of 38%. At the time of initiation of our study, no other published study was available that explored the efficacy of prophylactic iron supplementation on the recurrence of febrile seizures (the study by Nandhini *et al*. was published in 2021). In absence of the previous studies directly comparing the efficacy of prophylactic iron supplementation, we anticipated the recurrence rate in the iron supplementation group and control group to be 18% and 38%, respectively. We also assumed an enrollment ratio of 1:1 between two groups, alpha error to be 0.1, and power to be 80%. We calculated a minimum sample size of 53 for each group. Hence, we decided to enroll the first 53 consecutive patients satisfying the inclusion criteria during the enrolment period of September 2020–May 2021. For historical controls also, we decided to enroll the first 53 consecutive patients presenting to our center with febrile seizures and satisfying inclusion criteria for the control group.

The intervention group additionally received prophylactic iron supplementation of 20 mg biweekly for 1 year as per NIPI introduced by GOI. Infants and children with normal values of hemoglobin (Hb) (≥11 mg/dl), mean corpuscular volume (MCV) (80–100 fl), mean corpuscular Hb (MCH) (27–31 pg), MCH concentration (MCHC) (32–36 g/dl), serum iron concentration (60–170 micrograms per deciliter), total iron-binding capacity (TIBC) (240–450 mcg/dL), transferrin saturation (20–50%), and serum ferritin (>20 ng/ml) were considered as being in normal iron status (NIS). Infants with normal Hb values but low MCV, MCH, MCHC, and/or serum ferritin or serum iron concentration or transferrin saturation or elevated TIBC were considered as having subclinical iron deficiency (SID). However, along with abnormalities in these parameters, if the Hb level is normal, then the child was considered to have IDA. According to the World Health Organization classification of anemia, children were classified into mild, moderate, and severe IDA based on their Hb values.[15] Children with Hb values of 10–10.9 g/dl were considered as having mild IDA, children with Hb values of 7–9.9 g/dl were considered as having moderate IDA, and children with Hb values of <7 g/dl were considered as having severe IDA. Children with NIS received biweekly 20 mg iron supplementation, administered in a syrup form given 1 h after a meal during the follow-up period of 1 year, along with biannual deworming with albendazole as advised in NIPI. For children in the SID group, therapeutic doses of iron (4 mg/kg/day of elemental iron, daily 1 h after the meal) were instituted for 3 months to correct the existing IDA. This was followed by supplementing them with oral iron supplementation biweekly for 1 full year along with biannual deworming. For all the infants with existing IDA, correction with therapeutic doses of iron (4 mg/kg/day of elemental iron, daily 1 h after a meal) was instituted. For patients with mild, moderate, and severe IDA, the therapy was instituted for a duration of 4, 5, and 6 months, respectively.[16] This was followed by instituting a prophylactic dose in these children with a regimen similar to that provided for the NIS group after blood test confirmation. Complete blood count with RBC indices was repeated in these children every

3 months, while complete serum iron profile was repeated every 3–6 months or as clinically indicated to determine the compliance to treatment, therapeutic response, and also to rule out any signs of iron overload or toxicity.

In the intervention group, at the time of initial presentation, we noted sociodemographic details, birth and development history, recent immunization, detailed clinical examination, especially for any evidence of focal deficit, CNS infections, signs of micronutrient deficiency, details of seizure episode including the type of febrile seizure, duration, frequency, how it got aborted, antipyretics, ASMs or other medications like antibiotics received by the child, and duration of post-ictal drowsiness. Although neurodiagnostic evaluations, random blood sugar, serum calcium, and other investigations were only performed as per standard recommendations when clinically indicated and not in all children, we noted the findings in complete blood count, serum electrolyte, neurodiagnostic tests such as computed tomography/MRI brain, EEG, and CSF examination findings. Intermittent or continuous prophylaxis was started as clinically indicated following the standard recommendations, along with antipyretics and advice for recovery position and midazolam nasal spray as emergency abortive medication. Throughout the follow-up period, the data of febrile episodes and the febrile seizure/unprovoked seizure episodes were documented in all children by 3 monthly periodic follow-up. At each visit, we also used to check for compliance with medications prescribed and whenever febrile seizures recurred during follow-up, we noted all the clinical details.

In the control group, we tried to collect all these information from a prospective registry of data, which contained baseline and clinical/diagnostic follow-up information of children presenting with neurological problems to our center. We compared baseline sociodemographic and clinical variables of both groups to note for any mismatching of key clinical variables and adjusted for those variables while determining primary/secondary outcomes. We included consecutive cases in both the intervention and control groups, irrespective of the fact whether they completed 12-month follow-up period or were lost to follow-up. We determined the primary outcome using both best-case scenario (assumed that all lost to follow-up patients did not have a recurrence of febrile seizure) and worst-case scenario (assumed that all lost to follow-up patients did not have a recurrence of febrile seizure) to account for the missing data arising from loss to follow-up.

Statistical analysis

Statistical analysis was performed using SPSS software version 29.0. Categorical variables were presented as the frequency with a 95% confidence interval and continuous variables were represented as mean and SD/median with IQR. Differences in the distribution of categorical variables were compared between two groups and were tested for statistical significance using Chi-square or Fisher's exact test. For the corresponding purpose for continuous variables, we used the Student's *t*-test or Wilcoxon rank-sum test, depending on whether parametric or non-parametric variables. Multivariate logistic regression was used to determine predictors for febrile seizure recurrence. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

A total of 53 patients each were included in the intervention and historical control group. For including 53 patients in the interventional arm, we had to screen 61 patients with febrile seizures (three patients were already receiving oral iron supplementation and five patients had clinical/laboratory evidence of Vitamin B12 deficiency for anemia). Similarly, we screened 65 patients with febrile seizures in the control group (seven patients had clinical/laboratory evidence of Vitamin B12 deficiency, four patients had inadequate clinical details at baseline, and one patient was already receiving oral iron supplementation). Baseline sociodemographic and clinical variables were comparable between both groups, ensuring comparability between the groups [Tables 1 and 2]. The number of patients who were lost to follow-up in the interventional and control groups was three and four patients, respectively ($P = 0.81$).

Hematological parameters were available only for 24 patients in the historical control group [Table 3], as a complete blood count was performed only in cases with clinical pallor or when there was some other clinical indication as per the treating team. Out of these 24 children, three had SID, 15 had mild, five had moderate, and one had severe iron-deficiency anemia. On the other hand, in the intervention group, 13 had NIS, 17 had SID, 13 had mild, six had moderate, and one had severe IDA. After treatment with oral iron supplementation, at 12 months, out of the 50 patients who were on regular follow-up, 13 had SID, and the rest had NIS. There was a significant improvement in serum ferritin, serum iron level, transferrin saturation, and TIBC at 12 months as compared to baseline ($P < 0.001$ for all). However, three out of 50 patients had significant gastrointestinal adverse effects requiring discontinuation of the medication/change in serum iron formulation (constipation, gastric upset as noted by the mother). Seven other parents also complained of minor gastrointestinal adverse effects, which were self-limiting and did not require discontinuation of the medication. There was a trend toward lower Hb level and other RBC indices like MCV in the historical control group, as CBC was performed in that group, only when there was pallor clinically or the treating clinician felt some other indication for ordering the test. In this historical control group, both SID group and IDA group received therapeutic doses of oral iron supplementation,

Table 1: Comparison of sociodemographic variables of the intervention and control group.

Variable	Control group (*n*=53)	Intervention group (*n*=53)	*P*-value
Age at presentation (months)	18.4±5.3	19.5±5.2	0.62
Gender			
Male	36	34	0.71
Female	17	19	
SES			
Lower	21	20	0.73
Middle	31	33	
Upper	1	0	
Residence			
Rural	46	45	0.65
Urban	7	8	
History of febrile seizures	15	17	0.69
Family history of febrile seizure in a first-degree relative	11	10	0.82

Table 2: Comparison of baseline clinical variables of the intervention and control group.

Variable	Control group (*n*=53)	Intervention group (*n*=53)	*P*-value
Type of febrile seizure			
Simple febrile seizure	31	30	0.76
Complex febrile seizure	22	23	
Temperature at the time of febrile seizure (in F)	101.4±0.3	101.7±0.5	0.67
Duration of fever before the onset of seizure (in hours)	7.6±5.2	8.3±5.9	0.46
Number of febrile seizures in past (median) (IQR)	0 (0-2)	0 (0-2)	0.69
Duration of seizure (minutes)	1.2±0.7	1.3±0.9	0.62
Febrile status epilepticus	2	2	1.00
Intermittent prophylaxis	23	23	1.00
Continuous prophylaxis	4	5	0.89
Post-ictal sedation/drowsiness (minutes)	8.4±5.7	9.3±6.8	0.31
Meningeal signs	0	0	
Focal deficit	0	0	
Presence of neurodevelopmental delay	7	6	0.67
Presence of clinical pallor	11	12	0.72
Cause of fever			
Respiratory infection	39	41	0.69
Gastrointestinal infection	10	10	
Others	4	2	
Completed 12-month clinical follow-up	49	50	0.81

but not all of them were specifically investigated for iron deficiency nor all of them receive oral iron supplementation.

EEG and MRI brain were performed in 41 and 17 in the control group and 49 and 23 in the interventional group. MRI brain showed subtle abnormalities in the mesial temporal lobe in three and four children in the historical control and interventional group. Most of them had febrile status epilepticus and the changes in the temporal lobe could also be due to postictal changes like edema causing T2/FLAIR hyperintensity. Initial EEG was performed within 48–72 h in all of these children and five and six children in the historical control group and the interventional group showed some epileptiform abnormalities (all of them had focal discharges from frontal or temporal electrodes with low spike-wave index). On follow-up EEG performed at 3–6 months, all of them had normal EEG, suggesting that these changes were probably transient abnormalities. None of them had unprovoked seizures on follow-up. However, it could be because in the historical control group, we excluded the children with febrile seizure plus or Generalized epilepsy with febrile seizure plus (GEPS+), who had unprovoked seizures and the interventional group was followed for 12 months only. The probability that these children will later evolve into febrile seizure plus or GEFS+ cannot be ruled out altogether.

Although there was a trend toward a lower rate of recurrence of febrile seizures in the interventional group, as compared

to the historical control group, it did not reach the point of statistical significance (P = 0.35). Both in the worst-case scenario and best-case scenario, there was a trend toward less risk of recurrence of febrile seizure in the intervention group, but it did not reach the point of statistical significance (P = 0.43 and 0.52) [Table 4]. For the original scenario, worst-case scenario, and best-case scenario, the absolute risk reduction was 6.5%, 7%, and 6%, respectively, with corresponding number needed- to treat (NNT) being 15, 14, and 16, respectively. It suggests that around 14–16 patients need to be provided with oral iron supplementation to prevent the recurrence of febrile seizures in one patient. In subgroup analysis, the trend for absolute risk reduction with iron supplementation was more pronounced in those with complex febrile seizures, but it still did not reach the point of statistical significance (P = 0.16). For this subgroup of patients with complex febrile seizure, the absolute risk reduction for febrile seizure recurrence was 15.5% and the number needed to treat was 6.5. None of the children in either group had a recurrence of febrile status epilepticus. Similarly, there was a trend toward more failure of intermittent prophylaxis with clobazam in the prevention of febrile seizure recurrence in the historical control group as compared to the intervention group, but it did not reach the point of statistical significance. In this case, the absolute risk reduction was 8.5% and NNT was 11.7.

Subsequently, we intended to determine the predictors for recurrence of febrile seizure individually in both groups and combined in both groups. Already described risk factors for recurrence of febrile seizure in the previous literature were also found to be independent risk factors for recurrence of febrile seizure, such as first febrile seizure at an age younger than 18 months, fever duration of <1 h before seizure onset, first-degree relative with a history of febrile seizures, and a temperature of less than 104°F (40°C) at the time of febrile seizure (P < 0.05 for all). Apart from that, moderate/severe IDA was also found to be an independent risk factor for recurrence of febrile seizure in the intervention group (P = 0.03). Three out of six children with moderate-to-severe IDA had a recurrence of febrile seizure, while one out of the rest of 44 children had a recurrence of febrile seizure. We could not include iron deficiency as an independent variable for the historical control group, as we did not have the required information for all children. However, none of the other risk factors were completely modifiable like iron deficiency.

DISCUSSION

Our study showed that oral iron supplementation may have some efficacy in the reduction of febrile seizure recurrence, although the primary endpoint for efficacy was not reached in our study. The efficacy of oral iron supplementation in preventing the recurrence of febrile seizures was more pronounced in the group with complex febrile seizures and those with moderate/severe IDA.

Table 3: Comparison of hematological parameters in the interventional and control groups.

Variable	Control group (*n*=24)	Intervention group (*n*=53)	*P*-value
Hemoglobin (gm/dl)	9.4±1.7	9.6±1.8	0.65
MCV (fl)	76.4±8.7	77.9±9.1	0.83
MCH (pg)	26.3±2.6	26.5±2.8	0.71
MCHC	30.7±2.7	31.1±2.9	0.63
RDW	16.5±2.6	15.4±2.2	0.52
Peripheral smear showing features suggestive of iron-deficiency anemia	17/24	23/50	0.04

MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration

Table 4: Recurrence of febrile seizure in the interventional and control groups.

Variable	Control group (*n*=53)	Intervention group (*n*=53)	*P*-value
Number of febrile episodes during 1-year follow-up (median and IQR)	5 (3–6)	5 (4–6)	0.72
Recurrence of febrile seizure (excluding loss to follow-up)	7/49	4/50	0.35
Recurrence of febrile seizure (worst case scenario)	11/53	7/53	0.43
Recurrence of febrile seizure (best case scenario)	7/53	4/53	0.52
Number of patients with recurrence of febrile status epilepticus	0	0	-
Number of patients with failure of intermittent prophylaxis	4/23	2/23	
Number of patients with poor compliance to intermittent prophylaxis	3/23	2/23	0.66
Number of patients with failure of continuous prophylaxis	0/4	0/5	-
Number of patients with poor compliance to continuous prophylaxis	0/4	0/5	-
Number of patients with unprovoked seizures	1	0	0.94

Most of the risk factors for recurrence of febrile seizures are non-modifiable, unlike iron deficiency. Moreover, patients with subclinical or clinical iron deficiency anyway need to be provided with therapeutic doses of oral iron supplementation. Taking into account, the high prevalence of subclinical and clinical iron deficiency in infancy and toddlers GOI has started NIPI.[17] Prophylactic doses of biweekly iron did not lead to serum iron levels beyond the therapeutic range in any of the children. Only those children receiving a therapeutic doses of iron had most of the gastrointestinal adverse effects. Hence, prophylactic doses of oral iron supplementation appear to be safe. While prophylactic biweekly oral iron supplementation is recommended for all children in the 6–60 months age group as per NIPI, it might not hold true for clinical settings in developed countries. Our country, especially the setting for the current study in Uttarakhand state, mostly harbors parents belonging to lower and middle socioeconomic status (SES).[18] Apart from SES, poor weaning practices, endemicity for worm infestation, and other cultural/social factors lead to a high prevalence of clinical/subclinical iron deficiency in our setting.

For this reason, completing a double-blind and placebo-controlled trial exploring the efficacy of oral iron supplementation in preventing febrile seizure recurrence may suffer from ethical problems in the Indian setting. The majority of children with febrile seizures in the control group are likely to have some evidence of iron deficiency and are likely to require oral iron supplementation and if we excluded these children from inclusion in both groups, the trial will suffer from selection bias, compromising the generalizability. However, in developed countries, where the prevalence of iron deficiency in toddlers is relatively low, such double-blind and placebo-controlled trials can be attempted.[19] Such a trial is likely to generate more robust evidence favoring or disfavoring the efficacy of iron supplementation.

Compliance with oral iron supplementation over the long term is another issue, which needs to be addressed before generalizing our study results. The majority of cases of simple febrile seizure may not have a second episode of febrile seizure, and for most of them, even intermittent clobazam prophylaxis is not recommended, unless there is undue parental anxiety.[20] In such cases, the risk-benefit of oral iron supplementation needs to be estimated in future studies exploring the same topic. The NNT for the whole of the febrile seizure group was between 14 and 16, while for the children with complex febrile seizures, it was six only. Hence, at least children with complex febrile seizures or with any other factor predicting a high risk of recurrence of febrile seizure should be provided with oral iron supplementation according to their serum iron profile status.

The only other prospective study performed in this regard by Nandhini *et al.*[21] had various shortcomings, including the fact that it included only patients with simple febrile seizure, there was no control group, and they relied on serum ferritin to determine serum iron status, which is an acute-phase reactant. There was almost no patient with severe anemia in that cohort, which could have probably confounded the result that they did not find any significant difference between the febrile seizure recurrence rates between the groups with NIS, mild, moderate, or severe iron-deficiency anemia. Moreover, the fact that they treated the iron deficiency could have reduced the rate of recurrence of febrile seizures. The fact that the control group in our study did not differ significantly from the intervention group in terms of febrile seizure recurrence might also be due to the fact that those with clinical pallor were treated with oral iron supplementation even in the control group. The high prevalence of iron deficiency precludes performing an RCT for the same objectives, as it is unethical to withhold iron supplementation for a child having iron deficiency.

Several case–control studies have shown a high prevalence of iron deficiency in patients with febrile seizures. A systematic review by Kwak *et al.*[7] included 17 studies and 2416 children with febrile seizures, along with 2387 controls, and found that iron-deficiency anemia was significantly associated with febrile seizures. They also found that iron-deficiency anemia diagnosed on the basis of low plasma ferritin or MCV was associated with febrile seizures, but iron-deficiency anemia diagnosed based on serum iron studies alone was not associated with febrile seizures. Vaswani *et al.*,[22] Jang *et al.*,[23] Khurram *et al.*,[24] and Derakhshanfar *et al.*,[25] in their studies, found that iron deficiency is an independent risk factor for febrile seizures. Only the study by Yousefichaijan *et al.*[26] had contradictory findings to suggest that iron deficiency was less prevalent in cases with febrile seizures as compared to controls.

Our study has several limitations. The absence of a prospective randomized controlled group and the lack of certain key variables pertaining to serum iron profile were the two most important limitations. Even in the control group, a significant subset of participants received oral iron supplementation. A large number of patients were also started on intermittent or continuous prophylaxis with ASM, which might have reduced the recurrence of febrile seizures. For subgroup analysis, the sample size was not sufficient, for example, for the subgroup with complex febrile seizures. We have not taken into account the dietary intake of iron in either group. In the intervention group, the parents might have changed their dietary habits after being enrolled in the study. Finally, the follow-up duration of 1 year may not be sufficient for events like febrile seizures, which may recur after a period of 2–3 years after the first episode of febrile seizure. Still, our study is the first in the literature to compare the efficacy of prophylactic serum iron supplementation in the reduction of febrile seizure recurrence.

CONCLUSION

Oral serum iron supplementation does not significantly reduce the recurrence rate of febrile seizures in children aged 6–60 months. However, there is a trend toward reduction in the frequency of recurrence of febrile seizures, which is more pronounced in the subset with complex febrile seizures.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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