

Role of prophylactic iron supplements in preventing recurrences of simple febrile seizures in infants: A prospective study

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Abstract

Background: An important risk factor for simple febrile seizures (SFS) could be iron deficiency anaemia (IDA). Though SFS are benign, a history of seizures amongst children in their infancy is often associated with increased chances of recurrence.

Objectives: To gauge the effectiveness of prophylactic iron and folic acid (IFA) supplementation in maintaining normal iron status (NIS) and to reduce the recurrences of SFS in children aged 6-12 months over 1 year of follow up.

Method: This study recruited 101 children with SFS. Baseline clinical and laboratory investigations were conducted for all the children. Children with NIS were prescribed biweekly IFA supplementation. Mild, moderate and severe IDA were managed using iron therapy, following which, prophylactic IFA supplementation with biannual deworming was piloted for one year. At the end of one year, serum ferritin levels and complete blood counts were assessed and the frequency of SFS episodes were documented. Data analysis was done using Chi-Square test.

Results: Frequency of IDA in the study was 93.1%. After intervention, 63.4% showed NIS and increased serum ferritin levels. Thus, the iron status improved after supplementing IFA for one year. After one year of IFA supplementation it was noted that 81.2% of children were void of SFS.

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Conclusions: Reduced ferritin levels in infants with FS showed significant improvement after bi-weekly IFA supplementation. Although a reduction in the recurrence of SFS in IDA infants was noted after therapeutic dose supplementation of iron, this reduction was not statistically significant.

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(Key words: Febrile seizures, infant, iron-deficiency anaemia).

Introduction

Simple febrile seizures (SFS) have a global prevalence of 2–5% in 6 month to 5 year old children and are usually benign¹⁻³. The occurrence of SFS in the first year of life escalates the chances of recurrence by 50%⁴. SFS affects 5-10% of Indian children⁵. Although SFS do not have any lasting effects, they can lead to complications like aspiration⁶. The episodes by themselves can be agonizing to both parents and the child⁷.

Iron deficiency anaemia (IDA) is considered to be one of the risk factors for FS⁸⁻¹⁰. It is the commonest nutritional disorder globally¹¹. According to the National Family Health Survey-4 of India, IDA has a reported prevalence of 58.4% in 6-59 month old children⁹. Studies to weigh the potency of prophylactic iron and folic acid (IFA) supplementation in preventing the recurrence of SFS have not yet been documented. Thus, this is a pioneer study to evaluate the effectiveness of prophylactic IFA supplementation in the reduction of recurrence of SFS in children. This prospective study was conducted in children with SFS, under the aegis of Government of India's National Iron Plus Initiative (NIPI).

Method

This prospective study was carried out at a tertiary health care centre, from December 2017 to August 2019. This study recruited 101 infants with SFS from 6 to 12 months of age. There were no dropouts. Infants with atypical or complex FS at presentation and those diagnosed with anaemia due to other aetiologies like haemolytic anaemia were not considered for the study. Additionally, children whose parents refused to provide consent were also excluded from the study.

A comprehensive case history was recorded in all the recruited children with pertinent questions such as age at the first episode of SFS and a history of SFS in parents, siblings or first-degree relatives. Blood investigations such as complete blood count (CBC) and serum ferritin levels were done two weeks after the acute febrile illness settled. CBC was analysed using automated cell analyser and serum ferritin by fully automated bi-directionally interfaced chemiluminescent immunoassay.

Infants with normal values of haemoglobin (Hb) (≥ 11 mg/dl), mean corpuscular volume (MCV) (< 87 fl), mean corpuscular haemoglobin (MCH) (< 29 pg), mean corpuscular haemoglobin concentration (MCHC) (< 34 g/dl) and serum ferritin (< 12 ng/ml for males and < 30 ng/ml for females) were considered as being in normal iron status (NIS)¹². Infants with normal Hb values but low MCV, MCH, MCHC and/or serum ferritin were considered as having sub-clinical iron deficiency (SID). Infants with low Hb, MCV, MCH, MCHC and serum ferritin were considered to have IDA. According to the World Health Organisation (WHO) classification of anaemia, infants were classified into mild, moderate and severe IDA based on their Hb values. Infants with Hb values of 10-10.9 g/dl were considered as having mild IDA, infants with Hb values of 7-9.9 g/dl were considered as having moderate IDA and infants with Hb values of < 7 g/dl were considered as having severe IDA¹¹.

For infants in the NIS group, bi-weekly IFA (supplied in 100 ml bottle, 1 ml containing 20 mg of elemental iron and 100 mcg of folic acid in syrup form given 1 hour after meal) was instituted for one full year as per the NIPI. Biannual deworming was done. For infants in the SID group, therapeutic doses of iron (4mg/kg/day of elemental iron, daily 1 hour after the meal) was instituted for 3 months to correct the existing IDA. This was followed by supplementing them with

IFA bi-weekly for one full year along with bi-annual deworming. For all the infants with existing IDA, correction with therapeutic doses of iron (4mg/kg/day of elemental iron, daily 1 hour after 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. This was followed by instituting a therapeutic dose in these infants with the regimen similar to that provided for the NIS group after blood test confirmation.

Throughout the study period, the sum of febrile episodes and the SFS episodes was documented in all children by periodic follow up. CBC and serum ferritin were done at the end of one year of iron prophylaxis.

Ethical issues: Ethical clearance was obtained from the Institutional Ethics Committee of Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth (Deemed-to-be University), Puducherry, India (No. PG Dissertation/ 12/ 2017/ 97). Informed written consent was obtained from the parents

Statistical analysis: Data was analysed using SPSS version 22. The distribution of infants based on the grades of anaemia and recurrence of SFS with respect to the grades of anaemia were analysed using Chi-square test. Variables such as gender distribution, level of Hb, level of ferritin before and after treatment, mean values of the RBC indices of the study population before and after the intervention were compared using the independent t-test. Differences were considered significant at $p < 0.05$.

Results

Among the 101 eligible participants of the study, 67.3% were males and 32.7% were females. Figure 1 shows the anaemia grade distribution in the study population before and after intervention.

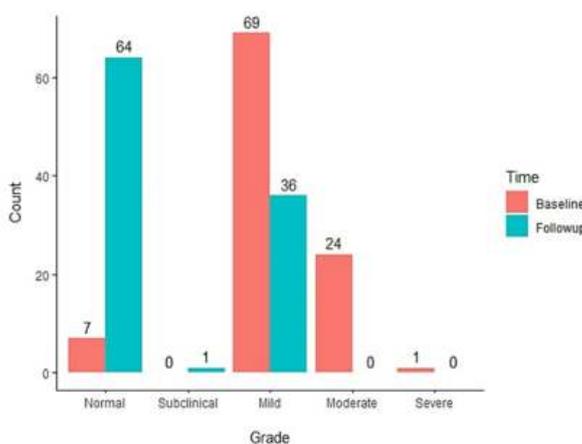


Figure 1: Comparing different grades of anaemia in the study population before and after intervention

A majority of the population showed normal iron status (NIS), indicating the improvement in anaemia status after intervention. In the study group, 7 (6.9%) children had NIS, 69 (68.3%) had mild IDA, 24 (23.8%) had moderate IDA and 1 (1%) had severe IDA, with an overall prevalence of IDA at 93.1%.

Following prophylactic iron supplementation, a majority of the infants (63.4%) showed NIS with a marked upsurge in serum ferritin and Hb values on one year of follow-up. A majority of children (81.2%) had no recurrence of seizure, 12.9% had recurrence of SFS and 5.9% had recurrences as complex FS or epilepsy was also observed. It was also noted that there was no recurrence in the group

with NIS and 33% and 75% of the recurrences were noted in children in the mild and moderate IDA group respectively.

The serum ferritin level and red blood cell (RBC) indices before and after intervention were also noted in this study. Figure 2 shows a strip chart of the distribution of these parameters before and after intervention. It demonstrates a marked increase in serum ferritin levels and Hb values indicating the improvement in anaemia status. The differences in the RBC indices before and after intervention with respect to Hb ($p < 2.2 \times 10^{-16}$), MCH ($p = 5.63 \times 10^{-8}$), MCHC ($p = 0.02873$) and ferritin ($p < 2.2 \times 10^{-16}$) were significant but not with respect to MCV ($p = 0.4721$).

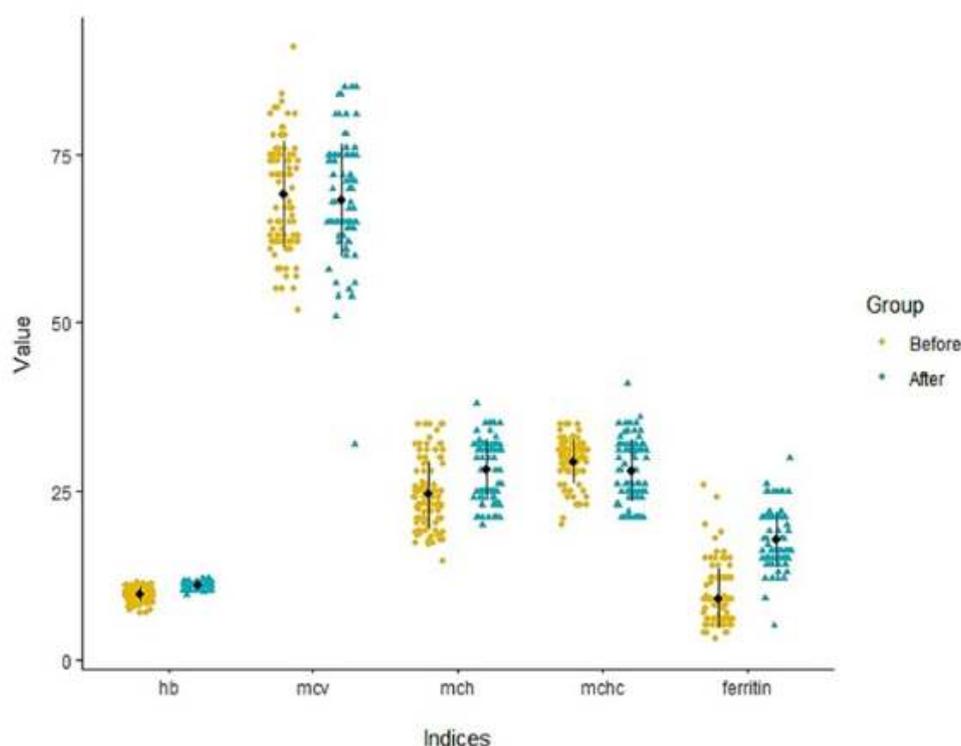


Figure 2: Distribution of RBC indices before and after intervention

Table 1 compares the recurrence of the febrile episode with the grade of anaemia after a year of follow up following the therapeutic regimen in infants. It can be observed that the children with

NIS had no recurrence of SFS. A proportional rise in the frequency of seizure episodes was observed with the increase in the severity of anaemia. However, the difference was insignificant ($p > 0.05$).

Table 1: Recurrences of simple febrile seizure in relationship to grades of anaemia

Grade of anaemia	Episodes of recurrence of febrile seizure (n=13)		P
	One Number (%)	More than one Number (%)	
Normal	0 (0)	0 (0)	0.41
Mild	03 (23.1)	01 (7.7)	
Moderate	08 (61.5)	01 (7.7)	
Severe	0 (0)	0 (0)	
Total	11 (84.6)	02 (15.4)	

Discussion

SFS is a prevalent health issue in infants and has a close association with IDA¹³⁻¹⁶. Due to an enhanced prevalence of IDA in children less than 5 years of age, the Government of India has established the NIPI. This programme caters to the iron supplementation of the pregnant, lactating women as well as children in the age range of 6 months to 19 years. It provides biweekly IFA supplementation with age appropriate deworming for the child. For children of 6 to 60 months age range, a regime of 1ml of iron and folic acid syrup containing 20mg of elemental iron and 100mcg of folic acid is given biweekly. The deworming programme is carried out for children of age 12 months and above by the Accredited Social Health Activist /Auxiliary Nurse Midwife¹⁷. Though an umpteen number of studies consider IDA as a crucial aetiological factor in the recurrence of SFS in children, there is a scarcity of studies that examine the efficacy of prophylactic IFA supplementation in the inhibition of recurrence of episodes of SFS. Hence, this study tries to fill this lacuna.

Among the 101 infants with SFS, 67.3% were male and 32.7% were female. This male preponderance is also seen in a study by Ghasemi F, *et al*¹⁵ but an analytical case study done by Fallah *et al*¹⁶ showed no statistical difference in terms of sex and concluded that both male and female children were equally affected by FS. In the current study, IDA prevalence was 93.1%. In studies by Ghasemi *et al*¹⁵, Fallah R, *et al*¹⁶ and Kwak BO, *et al*¹⁷ IDA prevalence was between 35-45%. One possible explanation for the higher percentage of IDA in our study is that India is a developing country and 58.4% of the Indian population have IDA. The prevalence of anaemia is much higher in developing countries when compared to developed countries owing to poor nutritional intake. Thus, the increased occurrence of IDA in our study indicates the nutritional status of our population and the need for treatment. Daoud AS, *et al*¹⁴ evaluated the significance of iron status as a possible risk factor. In their study the mean serum ferritin levels in the cases was 29.5 mcg/L, much lower than the 53.5 mcg/L in the controls. A study by Vaswani RK, *et al*¹⁸ had similar findings. In contrast, Bidabadi E, *et al*¹³ and Amirsalari S, *et al*¹⁹ reported no significant difference in IDA in children with or without FS.

A study conducted by Daoud AS, *et al*¹⁴ comparing children with and without FS showed that Hb, MCV and MCH were also lower in children with FS compared to children without FS, but difference was not statistically significant ($p>0.05$), which was attributed to the smaller sample size employed in the study. But in contrast

the study conducted by Ghasemi F, *et al*¹⁵, there was no significant difference among the RBC indices between the two study groups ($p>0.05$). These studies suggested evaluation of these indices after iron supplementation. However, the RBC indices studied before and after intervention in our study showed significant changes in Hb, MCH and MCHC and ferritin levels ($p<0.05$) but not in MCV ($p>0.05$).

The highlight of our study was the low attrition rate. This facilitated a comprehensive study of the NIPI organized by the Government of India. Following prophylactic iron supplementation, 63.4% of the infants showed NIS with a marked increase in Hb values and serum ferritin and 81.2% of children had no recurrence of seizure after one year of follow-up. In a study by Leung AK *et al*¹ 30-40% of children with a FS had a recurrence during early childhood. The American Academy of Paediatrics quantified that children who develop FS at an age less than one year to have a 50% chance of recurrence in the second year of life²⁰. In our study, the recurrence risk was low in comparison to the previous studies, which indicates that the correction of anaemia in children would have aided in diminishing the recurrence of SFS in children. However, there was no statistical significance ($p>0.05$). This can be attributed to the small sample size, which was a major limitation of this study. A larger, multi-centre trial would better elicit a relationship between prophylactic IFA and recurrence of SFS. Another limitation of this study was the limited period of follow up (1 year). An extensive research should be done with a larger sample size. A control group would have helped in strengthening the association of prophylactic iron supplementation to the reduction in recurrence of FS. Due to ethical issues and not assessing the compliance in our study, control group was not included in our study.

Conclusions

Reduced ferritin levels in infants with FS showed significant improvement after bi-weekly IFA supplementation. Although a reduction in the recurrence of SFS in IDA infants was noted after therapeutic dose supplementation of iron, this reduction was not statistically significant.

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