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ORIGINAL ARTICLE

Effect of FeSO4 therapy on children presenting with migraine at a Tertiary Care Hospital, Karachi, Pakistan.

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ABSTRACT… Objective: To determine the effect of $FeSO_4$ therapy on children presenting with migraine at a tertiary care hospital. **Study Design:** Quasi-experimental study. **Setting:** Pediatrics Department of National Institute of Child Health, Karachi, Pakistan. **Period:** January 2025 to September 2025. **Methods:** A total of 170 children, aged 5–15 years and diagnosed with migraine were included. Iron deficiency anemia (IDA) was labeled using age and gender specific hematologic and biochemical thresholds. Children having IDA received oral $FeSO_4$ 3–6 mg/kg/day for 3 months, while non-IDA children were given standard care. Data were analyzed using IBM-SPSS v26 applying appropriate statistical tests taking $p<0.05$ as statistically significant. **Results:** Among 170 children, 93 (54.7%) were males, and the median age was 10.0 years (IQR 8.0–13.0). IDA was diagnosed in 46 (27.1%) children. After three months of $FeSO_4$ therapy, median hemoglobin increased from 10.4 (9.9–10.9) to 12.2 g/dL (11.8–12.6), ferritin from 15.3 (12.4–17.8) to 30.8 ng/mL (27.6–33.2), and serum iron from 48.4 (43.0–52.9) to 87.1 µg/dL (80.2–94.6), while TIBC declined from 396.0 (380.7–410.9) to 328.3 µg/dL (312.4–340.8) (all $p<0.001$). Migraine frequency reduced from 9.0 (7.4–11.5) to 4.0 (3.0–6.5) episodes/month, duration from 6.2 (5.0–7.5) to 3.1 (2.0–4.4) hours, VAS score from 7.2 (6.0–8.5) to 4.3 (3.0–5.5), and school absenteeism from 4.1 (3.0–5.3) to 1.6 (1.0–2.5) (all $p<0.001$). **Conclusion:** Among children with migraine, correction of IDA with oral $FeSO_4$ resulted in significant improvement in hematologic parameters and meaningful reductions in attack frequency, duration, and intensity.

Key words: Children, Ferrous Sulfate, Hemoglobin, Iron Deficiency Anemia, Migraine.

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INTRODUCTION

Migraine is one of the most prevalent primary neurological disorder in paediatric population.[1] About 2 to 5% of pre-school children, 10% of school going children and 20 to 30% of female adolescents have episodic migraine.[2,3] Around 20% of children with migraine experience their first episodes before the age of 5 years and most of them have family history of migraine.[4] Child's quality of life is adversely affected by repetitive nature of migraine, which also affects their ability to learn, socialize, and maintain healthy family relationships.[5,6]

Iron deficiency is the most common micronutrient deficiency that affects at least one third of global population.[7,8] Globally, anemia affects around 273 million children below 5 years of age, with iron deficiency affecting about 50% of these children.[9,10] Poor dietary iron intake, particularly excessive consumption of cow's milk is a most prevalent cause of iron deficiency anemia (IDA) in children. Other factors that contribute to IDA include increased iron requirement during growth phase, insufficient iron absorption and blood loss.[11] Iron plays a crucial part in the synthesis of serotonin, dopamine and norepinephrine.[12] A study conducted among adults in turkey, analyzed relationship between IDA and migraine showed that 36.2% IDA patients had migraine.[13]

After doing a thorough literature search, no published study is on view in Pakistan about the role of $FeSO_4$ in Pakistani paediatric migraine population. So, it is important investigate the effects of $FeSO_4$ supplementation in children with migraine at a tertiary care hospital. Although current pharmacological prophylaxis and lifestyle measures form the cornerstone of migraine management in children, these are not universally effective and often associated with side-effects, cost, and

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limited accessibility. Nutritional interventions such as correction of iron deficiency, if effective, could represent a low-cost, accessible adjunctive therapy, particularly in resource-limited settings.

METHODS

This quasi-experimental study was conducted at the Pediatrics Department of National Institute of Child Health, Karachi, Pakistan, during January 2025 to September 2025 following approval from the Institutional Ethical Review Board (IERB-49/2024, dated: 17th January, 2025). Inclusion criteria were children aged 5 to 15 years who fulfilled the diagnostic criteria for migraine. Migraine was defined as either migraine without aura as recurrent headaches lasting 4–72 hours, unilateral in location, pulsating, of moderate to severe intensity, aggravated by routine activity, and associated with nausea, photophobia, or phonophobia. Migraine with aura was labeled as recurrent attacks accompanied by fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are followed by headache. Children with known systemic diseases (renal, hepatic, or cardiac disorders), those who had received iron supplementation within the previous 6 months, or those diagnosed with hemolytic anemia were excluded. Non-probability consecutive sampling was adopted. Written informed consent was obtained from parents or legal guardians of all enrolled children.

A sample size of 170 was calculated using the OpenEpi version 3.01 calculator based on a previous study which reported that 31.6% of children with migraine to have IDA[14], at a 95% confidence level and 7% margin of error. The diagnosis of migraine was confirmed by a consultant pediatric neurologist. Demographic characteristics including age, gender, and residence, along with clinical information like headache onset, duration, frequency, severity, aggravating or relieving factors, and family history were documented. Venous blood samples were obtained from all children for relevant laboratory assessment.

Children with both migraine and IDA were given oral $FeSO_4$, while non-IDA children with migraine served as an internal comparison group. IDA was diagnosed using age- and sex-specific thresholds as hemoglobin <11.5 g/dL for children aged 5–11 years, <12 g/dL for those aged 12–14 years, and <12 g/dL in girls or <13 g/dL in boys aged 15–19 years; mean corpuscular volume <77 fL (5–12 years) or <78 fL (12–18 years); serum ferritin <20 ng/mL; serum iron <60 µg/dL; and total iron-binding capacity >350 µg/dL. $FeSO_4$ was administered exclusively to children with IDA at a dose of 3–6 mg/kg/day of elemental iron, divided into two daily doses, for a period of 3 months. Parents were counseled regarding adherence, timing (preferably on an empty stomach), and dietary precautions (avoidance of tea or milk with the medication). Compliance was assessed by pill count and follow-up interviews during monthly visits. All children, irrespective of their iron status, received standard non-pharmacological and symptomatic management for migraine including counseling on lifestyle modification (adequate hydration, regular sleep, stress reduction, avoidance of trigger foods, and screen-time limitation) and reassurance for both child and parents. For acute attacks, age-appropriate analgesics such as paracetamol (10–15 mg/kg/dose every 6 hours as needed) or ibuprofen (7–10 mg/kg/dose every 8 hours as needed) were prescribed under supervision. No child received prophylactic agents such as topiramate, flunarizine, or propranolol during the study period. In cases where children presented with severe or frequent episodes requiring hospital admission, intravenous fluids, antiemetics (metoclopramide or ondansetron), and rest in a quiet, dark room were provided in accordance with standard pediatric neurology practice.

After completion of the 3 month treatment period, repeat laboratory investigations (hemoglobin, RBC indices, serum ferritin, serum iron, and TIBC) were performed in the same laboratory using identical techniques for consistency. Children were reassessed after for headache parameters like monthly attack frequency, mean duration, and intensity using visual analog scale (VAS) and a structured headache diary (maintained by parents/caregivers). Children without IDA continued on routine migraine management without receiving $FeSO_4$ but were followed up at identical intervals to compare variations in migraine symptoms.

All collected data were coded and analyzed using IBM-SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as per normality distribution (checked by Shapiro–Wilk test). Categorical variables were expressed as frequencies and percentages. Comparisons were made both within the IDA group (pre- versus post-$FeSO_4$ therapy) and between the IDA and non-IDA migraine groups to evaluate treatment-related improvements. As the quantitative data were non-normally distributed, the Wilcoxon signed-rank test for non-parametric paired data, and Mann-Whiteny U test were used for the comparison of independent numeric variables. Chi-square test or fisher's exact test was used for the comaprison of categorical comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

In a total of 170 children, 93 (54.7%) were males, and 77 (45.3%) females, with a male-to-female ratio of 1.2:1. The median age was 10.0 years (IQR 8.0–13.0). Urban residence was reported among 119 (70.0%) participants. Based on the ICHD-3 criteria, 137 (80.6%) children had migraine without aura, whereas 33 (19.4%) had migraine with aura. A family history of migraine was present in 53 (31.2%) participants. The median duration of migraine symptoms was 9.5 months (IQR 6.3–12.8). IDA was identified in 46 (27.1%) children. Figure-1 is showing study flow diagram. Table-I is showing comparison of baseline characteristics among children with and without IDA.

Following three months of $FeSO_4$ therapy, hematological indices improved significantly. Significant increase were observed in terms of median hemoglobin (p<0.001), MCV (p<0.001), serum ferritin (p<0.001), and serum iron (p<0.001) levels, whereas median TIBC declined significantly post-treatment (p<0.001), and the details are given in Table-III.

Post-treatment, among children with IDA, the median monthly attack frequency declined from 9.0 episodes (IQR 7.4–11.5) at baseline to 4.0 episodes (IQR 3.0–6.5) after treatment (p<0.001). The median duration of each attack reduced significantly (p<0.001) from 6.2 hours (IQR 5.0–7.5) to 3.1 hours (IQR 2.0–4.4), and the median pain intensity score on VAS decreased significantly (p<0.001) from 7.2 (IQR 6.0–8.5) to 4.3 (IQR 3.0–5.5). School absenteeism decreased substantially (p<0.001) with the median number of days missed per month decreasing from 4.1 (IQR 3.0–5.3) to 1.6 (IQR 1.0–2.5). Table-III is showing details about the comparison of migraine related outcomess before and after 3 month FeSO4 therapy among IDA children.

After 3 months, the median monthly attack frequency was 4.0 episodes (IQR 3.0–6.5) in the IDA group compared with 7.2 episodes (IQR 6.0–9.7) in the non-IDA group (p<0.001). The median duration of migraine attacks was shorter in children with IDA who received treatment, at 3.1 hours (IQR 2.0–4.4), compared with 5.1 hours (IQR 4.0–6.2) in those without IDA (p<0.001). The median VAS pain intensity score was lower among children with IDA, 4.2 (IQR 3.8–5.5), compared with 6.3 (IQR 5.1–7.7) in the non-IDA group (p<0.001). School absenteeism also differed significantly, with treated IDA children missing a median of 1.7 days per month (IQR 1.1–2.6), whereas non-IDA children missed 3.2 days per month (IQR 2.6–4.1) (p < 0.001). Comparative analysis between children with IDA after receiving ferrous sulfate therapy and those without IDA are given in Table-IV.

FIGURE-1

Study flow diagram

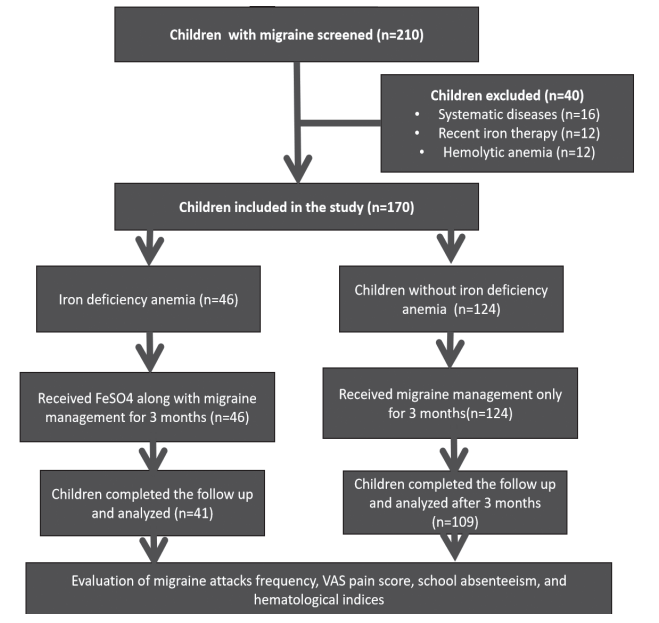

TABLE-I

Comparison of baseline demographic and clinical characteristics of children with migraine (N=170)

Characteristics		Total (%)	IDA (n=46)	Non-IDA (n=124)	P-Value
Gender	Male	93 (54.7%)	24 (52.2%)	69 (55.6%)	0.686
	Female	77 (45.3%)	22 (47.8%)	55 (44.4%)	
Age (years)		10.0 (8.0-13.0)	10.0 (8.0-13.0)	10.0 (8.5-13.2)	0.925
Residence	Urban	119 (70.0%)	31 (67.4%)	88 (71.0%)	0.651
	Rural	51 (30.00%)	15 (32.6%)	36 (29.0%)	
Migraine type	Without aura	137 (80.6%)	35 (76.1%)	102 (82.3%)	0.366
	With aura	33 (19.4%)	11 (23.9%)	22 (17.7%)	
Family history of migraine		53 (31.2%)	13 (28.3%)	40 (32.3%)	0.617
Duration of symptoms (months)		9.5 (6.3-12.8)	9.8 (6.0-12.2)	8.9 (7.0-12.8)	0.517

TABLE-II

Hematological profile before and after 3 month $FeSO_4$ therapy among IDA children (N=46)

Characteristics	Pre-treatment (n=46)	Post-treatment (n=41)	P-Value
Hemoglobin (g/dl)	10.4 (9.9-10.9)	12.2 (11.8-12.6)	<0.001
Mean corpuscular volume (fL)	72.0 (70.0-74.5)	78.0 (76.4-80.2)	<0.001
Serum ferritin (ng/mL)	15.3 (12.4-17.8)	30.8 (27.6-33.2)	<0.001
Serum iron (ug/dl)	48.4-43.0-52.9)	87.1 (80.2-94.6)	<0.001
Total iron binding capacity (ug/dl)	396.0 (380.7-410.9)	328.3 (312.4-340.8)	<0.001

TABLE-III

Comparison of migraine related outcomes before and after 3 month FeSO4 therapy among IDA children (N=46)

Characteristics	Baseline (n=46)	Post-treatment (n=41)	P-Value
Attack frequency (episodes / month)	9.0 (7.4-11.5)	4.0 (3.0-6.5)	<0.001
Duration of attack (hours)	6.2 (5.0-7.5)	3.1 (2.0-4.4)	<0.001
Pain intensity (VAS 0 to 10)	7.2 (6.0-8.5)	4.3 (3.0-5.5)	<0.001
School absenteeism (days/month)	4.1 (3.0-5.3)	1.6 (1.0-2.5)	<0.001

TABLE-IV

Comparison of migraine related outcomes between IDA and non-IDA children after 3 months (N=170)

Characteristics	IDA (n=41)	Non-IDA (n=109)	P-Value
Attack frequency (episodes / month)	4.0 (3.0-6.5)	7.2 (6.0-9.7)	<0.001
Duration of attack (hours)	3.1 (2.0-4.4)	5.1 (4.0-6.2)	<0.001
Pain intensity (VAS 0 to 10)	4.2 (3.8-5.5)	6.3 (5.1-7.7)	<0.001
School absenteeism (days/month)	1.7 (1.1-2.6)	3.2 (2.6-4.1)	<0.001

DISCUSSION

The present study demonstrated that IDA was identified in 27.1% of children presenting with migraine, and $FeSO_4$ supplementation over a period of three months resulted in significant hematological and clinical improvement. These findings postulate that correction of iron deficiency may play a beneficial role in reducing migraine burden, possibly by improving cerebral oxygenation and neurotransmitter balance. Fallah and colleagues from Iran[14], evaluating children between 5–15 years, found the prevalence of IDA among migraine patients as 31.6%, and observed that children with IDA had higher monthly attack frequency and intensity scores before start of the treatment. The frequency of IDA in this study is somewhat lower to 53.1% documented by another local study conducted among young female migraine patients.[15]

These differences highlight the possibility of gender-specific influence since reproductive-age women are more likely to have IDA due to menstrual blood loss. Another study from Turkey also reported a significant association between IDA and migraine, with a prevalence of 21.7% compared with 12.9% in controls.[16] Lee et al.[17], analyzing Taiwan's National Health Insurance Database found that participants with IDA had a 1.68 times higher risk of developing migraine when compared to non-anemic individuals. The link between IDA and migraine risk suggest that anemia correction is not only restorative but potentially preventive in predisposed patients. The association between low ferritin levels and increased headache burden was also highlighted by Sari and Basci from Turkey[18], who documented an inverse relation between serum ferritin and VAS pain scores in migraine patients, particularly those with menstrual migraine. This study also showed that improvement in ferritin levels reflected in reduction in VAS pain scores from 7.2 to 4.3 after $FeSO_4$ therapy. These findings indicate that serum ferritin may be serving as a useful indicator for the assessment of disease burden and treatment response among children with migraine and IDA.[19]

The magnitude of clinical improvement observed after $FeSO_4$ therapy in this study. Fallah et al.[14], observed a decline in monthly frequency from 22.9 to 10.1 and severity score from 8.1 to 5.1 following a combination therapy of topiramate and ferrous sulfate. The reduction in school absenteeism in this research further signifies meaningful improvement in functional outcomes. A systematic review summarized that iron supplementation consistently reduced headache frequency and intensity in patients with IDA, particularly women, and emphasized the role of nutritional correction as a non-pharmacologic component of migraine management.[20-22] Integrating IDA assessment into the routine workup in this population can allow timely identification and correction of a reversible aggravating factors.[23,24]

This study had certain limitations. The quasi-experimental design without randomization may introduce selection bias, and follow-up duration was limited to three months, which may not reflect long-term sustainability of symptom control. The use of a single-center sample may limit generalizability.

CONCLUSION

Among children with migraine, correction of IDA with oral $FeSO_4$ resulted in significant improvement in hematologic parameters and meaningful reductions in attack frequency, duration, and intensity. Early recognition and management of iron deficiency in pediatric migraine may offer a safe, cost-effective strategy to improve outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Zahira Khalid:** Acquisition, data analysis.
2	**Shazia Soomro:** Study design.
3	**Shazia Kulsoom:** Critical revisions.
4	**Shazia Bhutto:** Interpretation of data.