Original Article

Role of Oral Iron Supplementation in Reducing Breath-Holding Attacks in Children under Five Years

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ABSTRACT

Objective: To evaluate the effect of oral iron supplementation in the reduction of severity and frequency of breath-holding spells in children under five years.

Methodology: This observational follow up study included 50 patients aged 6 to 60 months with breath-holding attacks (BHAs) and concomitant iron deficiency anemia. It was conducted in the outpatient department of pediatrics in collaboration with the department of pathology at Independent Medical College, FSD, from December 2012 to March 2013 after taking ethical approval. Demographic, clinical and laboratory features were recorded and analyzed. The type, frequency, and severity of breath-holding attacks were recorded on the basis of history. All patients prescribed oral elemental iron at 6mg/kg/day in two divided dosages for 12 weeks were followed every 4 weeks. On completion of 12-weeks of iron therapy, patients were assessed for reduction or remission in frequency and severity of breath-holding attacks.

Results: The majority of children with BHAs (74%) presented during the first 18 months of life. Age of onset of BHAs was predominant in the 06 to 11 months age group (50%). Male children had a higher percentage of BHAs (74%) than females. The frequency of BHAs per week was up to 10 episodes in most children (76%). The cyanotic subtype of BHA was seen in 96% of cases with 66% being severe BHAs. Moderately severe iron deficiency anemia was a predominant finding (70%). The majority of children (95.65%) reported no adverse events with iron supplementation. 91.30% of children showed a complete response with no attacks while 8.69% showed a good response. There was a complete resolution of severe BHAs with only 8.69% remaining in the not-severe BHAs category.

Conclusion: Frequency and severity of breath-holding attacks in iron deficient children are effectively reduced after treatment with oral iron supplements

KEYWORDS: Breath-holding spell, Children, Iron deficiency anemia, Iron therapy.

INTRODUCTION

Breath-holding attacks (BHAs) are episodes of paroxysmal attacks of involuntary holding of breathing spells followed by loss of consciousness, opisthotonos posture and seizures, that recover spontaneously.[1] Usually, these spells are triggered by fear, anger, minor trauma, painful and emotionally disturbing events.[2] BHA is a benign, nonepileptic paroxysmal disorder of infancy and early childhood affecting 0.1- 4.6% of healthy children.[1,3] Its diagnosis is based on the stereotyped sequence of clinical events that begin in response to provoking factors such as frustration and anger followed by the short period of crying vigorously, end-expiration apnea, cyanosis or pallor and opisthotonic rigidity.[4] Severe attacks might progress to flaccidity or convulsive movements and loss of consciousness.[2] Cyanotic and Pallid are the two common clinical forms of BHA. However, some researcher also described the mixed form that was rarely found in children.[2,4] Breathing holding spells are manifested because of acute cerebral hypoxia. It is found in children age ranging from 6 months to 6 years

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and 76% of these occurs from 6 to 18 months of the age.[2,5] Treatment options available for BHAs include parental counseling about its benign nature and spontaneous resolution with age and medications along with behavioral management.[5] It has been suggested that dysfunctional autonomic nervous system, inheritance, asystole due to enhanced vagal tone and iron-deficiency anemia (IDA) are contributing factors for the development of breath-holding spells.[1,2]It is estimated that almost 50% of children under five years of age in developing countries were iron deficient.[6] Strong evidences are available showing iron deficiency anemia attributed to approximately 23% of cases of BHAs. Iron has a crucial role in catecholamine metabolism and functions as a cofactor for various enzymes and neurotransmitters of central nervous system (CNS). Hence iron deficiency results in dysregulation of cerebral neurotransmission causing breath-holding attacks regardless of its type.[2] Furthermore, the lower hemoglobin adversely effects on uptake of oxygen from the lung and results in anemic hypoxia affecting central nervous system leading to cerebral anoxia.[7]Children with iron deficiency become more irritable and easily provoked to BHAS.[8] Despite being benign and self-resolving it remains frightening and stressful for the parents of the affected children causing depression in them. Several researchers have observed a reduction in the severity of an episodic attack of breath-holding with oral iron therapy. There is a paucity of data from Pakistan concerning this issue that affect the quality of life of these patients as well as their family.[9] We designed this study to evaluate the effect of oral iron supplementation in the reduction of severity and frequency of breath-holding spells in children under five years as this age group is more prevalent for BHAs associated with iron deficiency anemia.

METHODOLOGY

This observational follow up study was conducted by the department of pediatrics in collaboration with the department of pathology at the outpatient department of Independent University Hospital which is a teaching hospital attached with Independent Medical College, Faisalabad. The study period was 4 months, from December 2012 to March 2013. Fifty children between the age group of 06 months to 60 months i.e 05 years with breath-holding attacks of both types (cyanotic or pallid) and concomitant iron deficiency were included in the study. Diagnosis of a breath-holding attack and its subtype (cyanotic or pallid) was made on clinical grounds by taking history of BHAs from the parents BHAs was defined by the following clinical sequence: provocation followed by crying to a point of noiselessness and accompanying change of color (cyanotic), alteration in body tone (pallid) and ultimately loss of consciousness. Those BHAs resulting in loss of consciousness or convulsions or both were categorized as severe breath-holding attacks. The Electroencephalogram (EEG) and Electrocardiogram (ECG) were performed to rule out the differential diagnosis of BHA (Epilepsy and Prolonged QT interval) were conducted in each case. Diagnosis and severity categorization of iron deficiency anemia as Mild (Hb 8-12gm/dl, MCV 60-75fl) Moderate (Hb 5-8gm/dl, MCV 50-59fl) and severe (Hb <5gm/dl, MCV <50fl) were made using laboratory measurements of hemoglobin levels (Hb, gm/dl), mean corpuscular volume (MCV,fl) and peripheral blood smear (PBS, microcytic hypochromic). Other laboratory tests for confirmation of iron deficiency included serum iron, serum ferritin, and total iron-binding capacity. Children with epilepsy or family history of epilepsy, neurologic deficits, febrile convulsions, congenital or acquired cardiopulmonary disease, children already on iron therapy, severe iron deficiency anemia requiring blood transfusion, severe malnutrition, and children with other causes of microcytic hypochromic anemia were excluded from the study. Approval of the research protocol was obtained from the independent medical college and university hospital ethical committee (Eth/177/144).Written informed consent was obtained from at least one parent or caregiver in each case enrolled in the study. A structured proforma was used to record observations of the study. Age and sex of the child and age of onset, frequency (number of episodes per week), severity and subtype of breath-holding attack, and severity of the iron deficiency, were recorded in each case on enrolment in the study before starting oral iron supplementation. Iron (Ferrous Sulphate) in a dose of 06mg/kg/day in two divided dosages was supplemented for 12 weeks. Follow-up visits were advised at 04 weeks, 08 weeks, and 12 weeks of iron supplementation. Each child was evaluated on follow-up for any change in frequency and severity of BHAs. The frequency of attacks was based on the number of episodes during that period that had been reported by the mother or any other family member taking care of the child. Children were also evaluate for iron deficiency anemia and for adverse effects of oral iron therapy on the basis of laboratory parameters such as complete blood picture and peripheral blood smear showing picture of iron deficiency anemia. Reduction in the frequency and severity of BHAs were taken as the primary outcome

variables. According to the data obtained on the reduction of frequency and severity of BHAs, patients were categorized into 04 groups: 01- Complete response (no attack) 02- Good response (>50% reduction in attacks) 03- Poor response (10-50% reduction in attacks) and 04- No response.

Statistical analysis: Data were analyzed by using SPSS -19 software. Student t-test was used for quantitative data and chi-square test was used for qualitative data. A *p-value* ≤0.05 was considered statistically significant.

RESULTS

A total of 50 children between the age group of 6 months to 60 months i.e. 05 years with breath-holding (Table 1). Attacks (BHAs) and concomitant iron deficiency anemia (IDA) were included in the study. Their demographic and clinical characteristics are tabulated in table 01. Majority of children with BHAs (74%) presented during the first 18 months of life. Age of onset of BHAs was predominant in the 06 to 11 months age group (50%). Comparatively male children had a higher percentage of BHAs than females (74% versus 26%). The frequency of BHAs per week was up to 10 episodes in most children. A cyanotic subtype of BHA was seen in 96% of cases with 66% being severe BHAs Laboratory Parameters of Iron Deficiency Anemia before and 12 weeks after oral iron supplementation are presented in table 02. As all children included in this study were confirmed iron deficient, microcytic hypochromic blood picture on peripheral blood smear was seen in all cases. Moderately severe iron deficiency anemia was a predominant finding (70%). After 12 weeks of iron supplementation, while 34.7% had mild anemia.

Table 1: Demographic & Clinical Characteristics (n=50)

Characteristics	Frequency (%)
Age of Presentation (Months)	
06-11	12(24)
12-17	25(50)
18-23	08(16)
24-29	02(4)
30-35	02(4)
Age at Onset of BHAs (Months)	
0-05	02(4)
06-11	25(50)
12-17	12(24)
18-23	08(16)
24- 29	02(4)
30-35	01(2)
36-60	00(0)
Sex	
Male	37(74)
Female	13(26)
Frequency (Number of Episodes per Week)	
<05	23(46)
06–10	20(40)
11–15	06(12)
>15	01(2)
Severity of BHA	**Severity of BHA**
Severe	33(66)
Not Severe	17(34)
Subtype of BHA	**Subtype of BHA**
Cyanotic	48(96)
Pallid	02(4)

Table 2: Laboratory Parameters of Iron Deficiency Anemia before and after Oral Iron Supplementation

Parameter	Before Iron Supplementation	After Iron Supplementation
	(n (%), n = 50)	(n (%), n = 46) at 12 weeks
Severity of Anemia		
Mild	09(18)	16(34.7)
Moderate	35(70)	02(4.3)
Severe	06(12)	00(0)
Peripheral Blood Smear		
Microcytic Hypochromic	50(100)	18(39.1)
Normocytic Normochromic	00(0)	28(60.8)

p-value ≤0.05 was considered statistically significant

During follow-up visits, 4 children were dropped from the study as they stopped reporting for follow-up visits. So 46 children (n-46) complied with the study protocol by the end of 12 weeks of oral iron supplementation. The majority of children (95.65) reported no adverse events with iron supplementation. Only 2 children (4.34%) reported loose stools needing iron dosage changes. Table 3 shows the response to 12-

Table 3: Response (Reduction in frequency and severity of BHAs) to Oral Iron Therapy completion at 12 weeks

Variable	n(%) n=46	Response	p-value
Number of BHAs			
No Attacks	42(91.30)	Complete	0.00*
1-9	04(8.69)	Good	0.02*
≥10	00(0)	Poor or No Response	0.00*
Severity of BHA			
Severe	00(0)	Complete	0.000*
Not Severe	Good	0.022	
Adverse effects of Iron			
Presented with adverse effects	02(4.34)		0.002*
Without adverse effects	44(95.65)		

p-value ≤0.05 was considered statistically significant

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week oral iron supplementation therapy in terms of reduction in frequency and severity of BHAs. 91.30% of children showed a complete response with no attacks by the end of 12-week iron therapy while 8.69% showed a good response. There was a complete resolution of severe BHAs (Severity) with only 8.69% remaining in the not-severe BHAs category (Table 3).

DISCUSSION

This study was conducted to highlight the importance of oral iron therapy on reducing the frequency and severity of BHAs in the iron deficient children with cyanotic and pallid breathing holding spell. AS there is high prevalence of iron deficiency anemia and associated BHAs in our population, we aimed to observe the outcome of oral iron supplements in patients of breath hold spell among the children of under five-year age.[10] Current results shows that 74% of the children presented with BHAs during the first 18 months of life. Of total subjects, 50 % of the children being affected with BHA were in age groups from 06 to 11 months. Our these results are in accordance with Lal et al study conducted at larkana Pakistan showing majority of the cases were presented from 9-12 months which are almost of same age groups to our results.[5] Least age presentation with BHA age in our study was 36-60 moths i.e 3 to 5 years and this clicnical presentaion in terms of age is in accordance to the previous study doumenting that 90% of children the spells got remission by school age and the persistence is extremely rare beyond 4 years.[3,11] In present study BHAs attacks were most frequently found in male children as compared to females (74% versus 26%). Congruent findings were reported by previous studies conducted at Pakistan and Iran showing the male predominance in term of BHAs.[7,11,12] Present results reveals, frequency of BHAs per week was up to 10 episodes in most children. A cyanotic subtype of BHA was seen in 96% of cases with 66% being severe BHAs. These results are in line with the previous study carried out by Lal et al, reporting majority of the subject presented with cyanotic spells.[5]Current results are also in agreement with the study conducted by Khan et al that reported 79.1% of participant were presented with cyanotic spell, reflecting predominance of cyanotic BHAs.[12] Current results shows70%,18% and 12% of the participants presented with moderate, mild and severe anemias respectively. After oral iron supplementation for 12-week in terms of reduction in frequency and severity of BHAs, we found 91.30% of children showing a complete response with no attacks while 8.69% showed a good response. These results are supported by the Jain et al showing that improving anemia with iron is helpful for managing BHA.[13] Congruent results are reported by Kahn et al reporting statistically significant fall in the frequency and severity of BHAs with 12 weeks of iron treatment.[12] A study by Bidabadi et al reporting that 76.19% of the study participants showed complete control of BHA, after iron therapy.[14] These findings are in accordance with the results of our study. Some previous studies have suggested that It is self-resolving condition and remission usually occur before school going age , but the attitude problems in the parents and the child may trigger spells and with proper psychotherapy consultation with the parents, these spells may be prevented to a large extent.[15]

Limitations: Small sample size and absence of control were the limitation of the study. Results were not generalized to whole population. Current results might still be widely applicable as they are similar to results reported by previous international studies and will help in establishing patient-specific treatment.

CONCLUSION

Frequency and severity of breath-holding attacks in iron deficient children are effectively reduced after treatment with oral iron supplements.

Recommendations: To validate these results, future researches on wider scale for more duration follow-up, optimal dose and length of treatment should be considered to evaluate long-term benefits and serious side effects of iron supplements in the prevention of severe BHAs

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***Authors' contribution*:**

Dr. Sadida Amir	Study design, acquisition of data and manuscript write up. Reviewed and approved the manuscript.
Dr. Shakil Ahmad	Study design, Data collection, Critically revised all the content, reviewed and approved the manuscript.
Dr. Muhammad Usman	Study design Perform lab test, and provide lab reports for data analysis, compiling and analysis of data, interpretation of results, revise manuscript and approved it.
Dr. Imran Sarwar	Data collection, data analysis write up and Revising manuscript critically for study design important intellectual content and approved the manuscript
Dr. Nisar Khan Sajid	Data analysis and interpretation of results, manuscript writing and approved the manuscript.
Dr. Tanveer Ahmad	Study design, help in data analysis , critically revise and approved the manuscript All authors are responsible for research work , data integrity of the data and the accuracy of the data analysis

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