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EFFECTIVENESS OF ORAL IRON VS. THEOPHYLLINE AND IRON COMBINATION THERAPY IN CHILDREN WITH BREATH-HOLDING SPELLS

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ABSTRACT

Background: Breath-holding spells are no epileptic paroxysmal events in young children, and can be a source of parental anxiety. These episodes are associated with iron-deficiency, and the benefits of theophylline remain uncertain.
Objectives: To compare the efficacy of iron alone and iron plus theophylline on the frequency and severity of breath holding spells and to determine demographic and clinical factors that were associated with the efficacy of the treatment.
Methodology: A non-randomized controlled trial was conducted in Khyber Teaching Hospital Peshawar with 110 children aged 6 months to 5 years who presented with breath holding spells to the Department of Pediatrics. After 12 weeks, participants were then divided into two groups – one taking oral iron and the other taking oral iron and theophylline. These included assessment of the frequency and severity of the spells, laboratory indices, caregiver satisfaction and treatment response. Complete remission, partial remission, and no response were defined by a change in spell frequency. Descriptive statistics, Mann–Whitney U, chi square, Fisher's exact and Wilcoxon signed-rank tests were used to analyze data, and $p<0.05$ was considered significant.
Results: No significant difference was found between groups when evaluating the amount of reduction in spell frequency from baseline to 12 weeks ($p<0.001$). Complete remission was achieved in 58.2% of those treated with iron alone and 83.6% of those treated with both iron and combination therapy ($p=0.006$). There were also fewer spells in the combination group at month 2 ($p=0.002$) and 3 ($p=0.02$) and a larger mean percentage reduction at 12 weeks (94.1% versus 78.3% $p=0.002$). Only a significant association of treatment allocation with complete remission was seen.
Conclusion: Oral iron was effective in reducing breath-holding spells, and the combination of theophylline and oral iron resulted in a higher remission rate and improved symptom control. Effectiveness and safety needs to be confirmed in larger randomized trials.

KEYWORDS: Breath-holding spells; oral iron therapy; theophylline; iron deficiency; children; complete remission; treatment effectiveness.

1. INTRODUCTION

Breath-holding spells (BHS) were involuntary, paroxysmal and no epileptic events occurring in healthy young children after anger, frustration, fear, pain or minor injury. Population-based studies suggested that BHS only occurred in a small fraction of children, and most cases occurred during the first two years of life and spontaneously resolved by school age [1,2]. Although the disease is of a generally benign and self-limited course, individual episodes may include crying, forced expiration, apnea, changes in skin color, loss of consciousness, altered muscle tone and occasionally brief convulsive movements. Parents frequently experienced excessive fears and frequent health care visits due to sudden and dramatic presentations that were perceived as suffocation, epilepsy, cardiac arrest, and imminent death [2].

BHS were traditionally divided into cyanotic, pallid and mixed. The more common form was cyanotic spells, which tended to be induced by anger or frustration. The episodes generally evolved into violent crying, expiratory apnea, cyanosis and brief loss of consciousness. Pallid spells, on the other hand, more frequently occurred due to sudden pain or fear, and were associated with brief periods of consciousness loss, pallor, and bradycardia, with little or no crying [2,3]. The diagnosis was mostly clinical, but in some atypical, prolonged, or spontaneous seizures, the EEG was important for the differentiation from epileptic seizures, reflex syncope, metabolic disorders, and cardiac arrhythmias.

Past neurological and cardio logical investigations highlighted the need to take a thorough history, perform a physical examination, obtain blood counts and iron indices and take an electrocardiogram if indicated [7]. This was especially crucial because breath-holding-like episodes may coexist with long-QT syndrome, but not be part of it [8].
Pathophysiology of BHS was thought to be complex and multifactorial. Abnormal autonomic regulation, such as changes in heart-rate variability, exaggerated vagal responsiveness, and imbalance in sympathetic and parasympathetic action had been shown [3–5]. Additionally, neurophysiological findings indicated that pathways in the brain stem responsible for respiration and cardiovascular control matured or myelinated delayed [6]. Such anomalies may impair the ability of a child to ensure proper cerebral beat-to-beat blood flow and oxygenation in response to emotional and/or physical stress. The episode was thus more likely to be interpreted as a reflex response to holding the breath, instead of a conscious attempt to hold the breath. This distinction was relevant when counselling families since it would reduce the likelihood of their punishing the patient and enable the caregiver to respond appropriately during attacks.
Iron deficiency was the most frequently mentioned modifiable risk factor for BHS. Hemoglobin synthesis, oxygen transport in tissues, myelination, and activity of enzymes in neurotransmitter metabolism were the major areas of focus for Iron. RBCs with lower levels of hemoglobin or ferritin, or low serum iron level, therefore may render the neurons more sensitive, might be less able to transport oxygen, and may worsen autonomic instability. The oral use of iron has been reported repeatedly in controlled and observational studies to reduce the number and intensity of breath-holding spells [9-13]. The positive therapeutic response to iron as compared to placebo was shown by Daoud et al. [9] and Mocan et al. reported significant improvement in children with IDA [10]. The effects of iron-deficiency correction on the autonomic nervous system function further confirmed that this effect was physiological and not just behavioral [11].

The benefit of iron treatment was not restricted to the children who fulfilled the diagnostic criteria of anemia. Studies of both prospective and retrospective design showed that some nonacademic and apparently iron-replete children achieved complete remission or a significant decrease in the number of attacks when supplemented [12-15]. Jain et al. noted an improvement in most of the children treated, even those who didn't have biochemical signs of iron deficiency [12]. This is similar to the results obtained by Hamed et al., Gürbüz et al., and Arslan et al. who reported similar results, but with varying response rates depending on baseline frequency of spells, iron status, adherence to treatment, and study design [13–15]. These results provided justification for oral iron as a good basis for therapy. In some children, however, the failure to achieve a complete response, however, suggested that further therapeutic interventions should be investigated.
Theophylline was a central respiratory stimulant and adenosine-receptor antagonist that was a methyl xanthine. Thus, it might modulate respiratory drive and autonomic control. There was limited evidence for its use in BHS, but one comparative study found that theophylline was more effective at reducing simple breath-hold attacks than were iron or paracetamol [16]. It had also been employed in the treatment of severe pallid spells and thus had a biological plausibility in the treatment in selected children [17]. However, it had not been sufficiently determined if there was an increase in remission with the use of theophylline in addition to regular iron treatment, or if iron treatment was safe, and more satisfying for the caregiver.
Hence, the present study aimed at comparing the efficacy of oral iron only treatment with combined oral theophylline and iron treatment in children between 6 months to 5 years of age. It also looked at demographic and clinical factors related to treatment response. The results were measured after 12 weeks of treatment for complete remission, partial remission, spell frequency, spell severity, biochemical iron status and caregiver satisfaction. The findings of this study compared the two treatment groups and helped to address an important local evidence gap, giving information that could be used to improve the management of children with persistent or frequent breath-holding spells.

2. METHODOLOGY

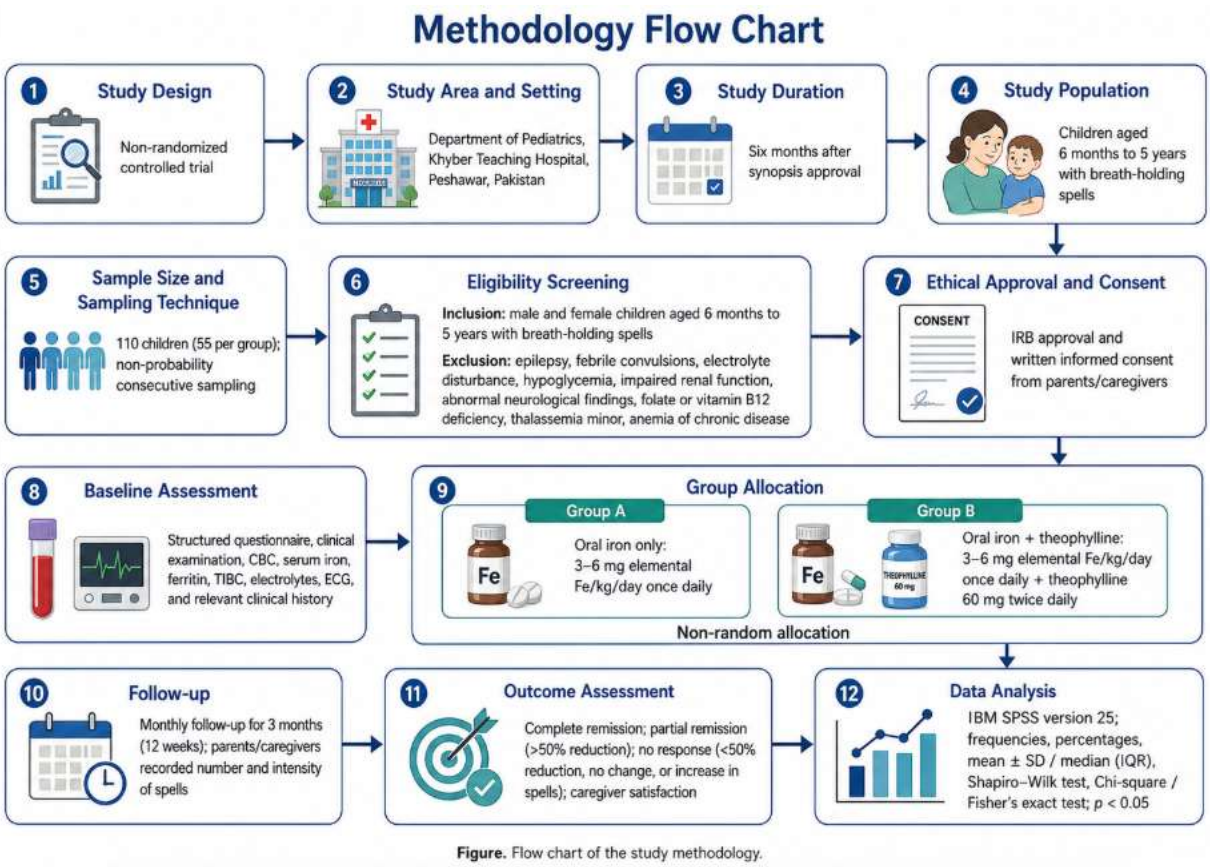

Figure 1. Flow Chart of the Study Methodology for Comparing Oral Iron Therapy with Iron–Theophylline Combination Therapy in Children with Breath-Holding Spells

2.1 Study Design

A non-randomized controlled trial was undertaken to determine whether oral iron alone is effective in reducing the number and degree of breath-holding spells as compared to oral iron and theophylline in children.

2.2 Study Area

The study was carried out in Peshawar, Khyber Pakhtunkhwa, Pakistan. Children who had breath holding spells were recruited from the pediatric health care services of Khyber teaching hospital Peshawar.

2.3 Study Setting

The study was carried out in Khyber Teaching Hospital, Peshawar in Department of Pediatrics. Children who presented to the department during the study period were screened and enrolled to the study based on the predetermined selection criteria.

2.4 Study Duration

The study took place six months after the research synopsis was approved. Children were treated for 12 weeks, with assessments taking place every month for three months.

2.5 Study Population

A study population of male and female children, ages 6 months to 5 years, with breath-holding spells was used. A breath holding spell was defined as a brief (<1 minute) and unexpected episode of cessation or decrease in breathing that did not occur during an actual seizure. The spells were classified as cyanotic, pallid or mixed according to clinical history and change of colour of the skin during the spell.

2.6 Sample Size

A sample size was determined for comparison of the effectiveness of treatments between two groups at 95% confidence level, 80% statistical power level. The numbers were calculated based on previous reported treatment-response rates of 58.8% for iron therapy and 82.9% for theophylline therapy. A total of 110 children were calculated and 55 children in each treatment group.

2.7 Sampling Technique

A non-probability consecutive sampling technique was used. Children who were seen with breath-holding spells during the study period were assessed to determine eligibility for the study and were enrolled in the study consecutively until the needed number of children were reached.

2.8 Inclusion Criteria
Children of either sex were included in the study if they met the operational criteria for breath-holding spells, and if aged between 6 months and 5 years. All cyanotic and pallid breath-holding spells were included.

2.9 Exclusion Criteria
Children were excluded if they had epilepsy, febrile convulsions, electrolyte disturbances, hypoglycemia, impaired renal function tests, abnormal neurological examination findings, folic acid deficiency, vitamin B12 deficiency, thalassemia minor or anemia due to chronic disease. Additionally children who had long QT intervals or other clinical conditions that could account for the episodes were excluded from the treatment assessment.

2.10 Participant Recruitment and Allocation
Children who met the criteria for enrollment were enrolled following the written informed consent of parents/legal guardians. The two groups of participants were not randomly allocated to the two treatment conditions. Group A was the children that were given only oral iron while Group B was children that were given oral iron and oral theophylline.

2.11 Treatment Intervention
Children assigned to the Group A group got elemental iron 3- 6mg per kg per day orally once a day. Group B children were given the same elemental iron dosage along with oral theophylline 60 mg twice a day. All patients in both groups were treated for 12 weeks. Treatment response was assessed during monthly visits at the end of the three-month intervention period.

2.12 Data-Collection Procedure
A structured questionnaire and clinical assessment form were used to gather the data. Parents/caregivers were contacted for information about the child's age, sex, weight, socioeconomic status, consanguinity, family history of breath-holding spells, duration of condition, age at first episode, type of breath-holding spell, duration and frequency of episodes, precipitating factors, previous treatment, and nutritional practices. Consumption of high amount of cow's milk and low amount of meat, especially at the second year of life, were included in dietary information. Breath-holding attacks were counted at baseline, in number per week and per month. The parents/carers were asked to document all breath holding episodes the child has had throughout the treatment period with an indication of the number of episodes and the intensity of each one. The interviews were done by trained medical officers, who also performed a clinical examination and recorded the results.

2.13 Clinical and Laboratory Assessment
A detailed clinical examination was performed at baseline in all participants. Samples of blood were drawn for complete blood count, serum electrolytes, serum iron, total iron binding capacity, and serum ferritin. Iron-deficiency status was determined based on the serum iron and ferritin levels at presentation.

Anemia was categorized using the World Health Organization (WHO) hemoglobin cut-off values by age. Mild anemia was defined as having a hemoglobin level of 10.0-10.9g/dL, moderate anemia as having a hemoglobin level of 7.0-9.9g/dL and severe anemia as having a hemoglobin level less than 7.0g/dL in children 6-59 months of age. All the children had electrocardiography to rule out prolonged QT interval. Laboratory tests were repeated at the end of treatment after 12 weeks.

2.14 Outcome Assessment
After 12 weeks the treatment results were evaluated as complete remission, partial remission, or failure to respond. There was no breath-holding spell noted during the follow-up period defined as complete remission, which was deemed an effective treatment outcome. Partial remission was defined as more than 50% decrease in the frequency of breath holding spells from baseline. A reduction of less than 50%, no change or an increase in spell frequency was considered a 'no response'. The average number of episodes in the three-month follow-up period also was determined. The effectiveness of treatment was evaluated by determining the difference in the number and severity of spells prior to and after treatment in each group.

2.15 Parent or Caregiver Satisfaction
A 10-point rating scale was used to gauge parent/caregiver satisfaction with treatment. A score of 1–2 appeared to have no effect or poor response, a score of 3–4 indicated some effect but not satisfactory, a score of 5–6 indicated moderate effect, a score of 7–8 indicated good/satisfactory response and a score of 9–10 indicated a very good/highly satisfactory response.

2.16 Ethical Considerations
Ethical approval was ensured from the Institutional Review Board before the beginning of the study and permission was taken from College of Physicians and Surgeons Pakistan. Informed written consent was provided by the parent/guardian of all children involved. The purpose, procedures, possible benefits and potential risk of the study were explained to the parents. All data was anonymized and participants were asked to give their informed consent.

2.17 Statistical Analysis
Data were collected and analyzed via IBM SPSS version 25. Categorical variables such as sex, consanguinity, family history of breath-holding spells, type of spell, severity of anemia, nutritional factors, treatment group, treatment response and efficacy were shown as frequencies and percentages. The Shapiro–Wilk test was used to determine

normality of the continuous variables such as age, body weight, duration of breath-holding spells, serum iron level, serum ferritin, and number of spells per week. Means and standard deviations were used for normally distributed data and medians (interquartile ranges) were used for non-normally distributed data. The effectiveness of treatment was assessed by chi square test or Fisher's exact test (when applicable) in these two groups. The same statistical tests were used to test the association between treatment outcomes and demographic/clinical factors after stratification. All p-values were taken to be statistically significant if < 0.05.

3. RESULTS

Demographic and clinical details of the 110 children who had been included in the analysis are given in Table 1. The mean age was 23.8 ± 9.4 months in the iron-only group and 21.5 ± 9.0 months in the iron-plus-theophylline group. The difference was not statistically significant ($p = 0.176$) so that the children in both groups were similar in age at enrolment. The proportion of male and female children in the group receiving iron-only treatment was 61.8% and 70.9%, respectively, in the group receiving combination treatments, with no significant difference in gender between the two groups ($p = 0.420$). Breath-holding spells were reported in 16.4% of children who were given iron, and 18.2% of children who were given iron and theophylline. The same p-value (1.000) meant that there was no significant difference between the groups. The most common clinical type was cyanotic breath-holding spells in both treatment groups (87.3% of the total in each arm). The prevalence of moderate or severe anemia was 58.2% for both groups, with 90.9% of the children in the iron-only group and 92.7% in the iron combination group having iron deficiency. There were no significant differences in severity of anemia or in iron status between the groups of treatment. There was no statistical difference between the mean baseline hemoglobin levels in the iron-only group (9.5 ± 1.4 g/dL) and the iron-plus-theophylline group (9.8 ± 1.0 g/dL) ($p = 0.278$). Likewise, there were no significant differences in median ferritin levels or baseline spell frequency. The baseline spell frequency distribution of mild, moderate and high was also similar ($P = 0.600$). In general, Table 1 shows that the two treatment groups were fairly matched prior to treatment; therefore, differences between groups are likely to be attributed to the treatments applied.

Characteristic	**Iron only (n = 55)**	**Iron + theophylline (n = 55)**	**p-value**
Age, months, mean ± SD	23.8 ± 9.4	21.5 ± 9.0	0.176
Male, n (%)	34 (61.8)	39 (70.9)	0.420
Family history of BHS, n (%)	9 (16.4)	10 (18.2)	1.000
Cyanotic BHS, n (%)	48 (87.3)	48 (87.3)	1.000
Moderate/severe anemia, n (%)	32 (58.2)	32 (58.2)	1.000
Iron deficiency, n (%)	50 (90.9)	51 (92.7)	1.000
Baseline hemoglobin, g/dL, mean ± SD	9.5 ± 1.4	9.8 ± 1.0	0.278
Baseline ferritin, ng/mL, median (IQR)	9.4 (5.8–13.1)	7.7 (5.0–11.1)	0.128
Baseline spells/month, median (IQR)	13 (9.5–17)	11 (9–15)	0.296
Baseline spell-frequency severity, n (%)			**0.600**
Mild	9 (16.4)	10 (18.2)	
Moderate	30 (54.5)	34 (61.8)	
High	16 (29.1)	11 (20.0)	

Table 1. Baseline demographic and clinical characteristics of the study participants

The rate of breath-holding spells is summarized in Table 2 for the two treatments over the 12-week follow-up. The median number of spells/month was 11 in the iron-only group and 13 in the iron-plus-theophylline group at baseline. There was no significant difference between the two groups ($p = 0.296$), and both groups had similar numbers of breath-holding spells prior to therapy. In the first month of treatment, the frequencies were five and four from eight spells per month, respectively in the iron-only and combination-treatment group. The group combination did not reach statistical significance for a smaller number of spells ($p = 0.093$). By the second month, the median number of spells had decreased to three in the iron-only group and two in the iron-plus-theophylline group. This difference was statically significant ($p = 0.002$), demonstrating that the combination therapy had a greater improvement over the course of treatment. Median number of spells was zero in both groups after the 3rd month. The wider range (0–5) in the interquartile range for the iron-only group, however, suggested that there were a number of children with attacks even after treatment, while the narrow interquartile range (0–0) for the combination group indicated that most children were without attacks even after treatment. This between group difference was statistically significant ($p = 0.002$). The mean percentage reduction in breath-holding spells after 12 weeks was 78.3 ± 34.2% in the iron-only group and 94.1 ± 16.3% in the iron-plus-theophylline group. This marked difference in change in the combination group ($p = 0.002$) shows that iron alone was more effective at controlling breath-holding spells when combined with theophylline. Both groups improved significantly from baseline but the amount of improvement was larger in children who were given the combination therapy.

Assessment	Iron only (n = 55)	Iron + theophylline (n = 55)	p-value
Baseline spells/month, median (IQR)	13 (9.5–17)	11 (9–15)	0.296
Month 1 spells/month, median (IQR)	8 (5.5–10)	6 (5–9)	0.093
Month 2 spells/month, median (IQR)	3 (2–6.5)	2 (1–3)	**0.002**
Month 3 spells/month, median (IQR)	0 (0–5)	0 (0–0)	**0.002**
Reduction at 12 weeks, %, mean ± SD	78.3 ± 34.2	94.1 ± 16.3	**0.002**

Table 2. Comparison of breath-holding spell frequency during the 12-week treatment period

The mean monthly number of breath-holding spells per month changed from baseline to end of 12 weeks treatment in both groups (figure 2). There was a slight difference between the two groups at baseline, with a mean number of 13.56 and 12.58 spells per month for the iron-only and iron-plus-theophylline groups, respectively. Both groups had similar baseline values, suggesting a similar baseline frequency of breath-holding spells. In both groups, the mean spell frequency decreased over the 3-month period following treatment. In the first month, the average number of spells per month dropped to 8.36 in the iron-only group and 7.20 in the combination treatment group. Both treatments were able to generate an early reduction, but the difference between the two was relatively small at this point. Iron-theophylline showed a more significant decrease in the second month. The mean number of spells of sickness/month was reduced to 2.60 episodes/month in the combination group and 4.44 episodes/month in the iron-only group. The mean episodes of seizures per month were also lower at the end of the third month in children who had received iron plus theophylline (0.76) compared to those who had received iron alone (2.69). Greater reduction in breath-holding spells was seen in the combination group, which suggests that the combination of theophylline and oral iron was related to a faster and larger decrease in breath-holding spells. The separation of the two lines in the second and third months showed that combination therapy was more effective at maintaining control of the episodes. In general, Figure 1 confirms that both treatments had a favorable effect on spell frequency as time went on, and that iron-plus-theophylline treatment was more effective.

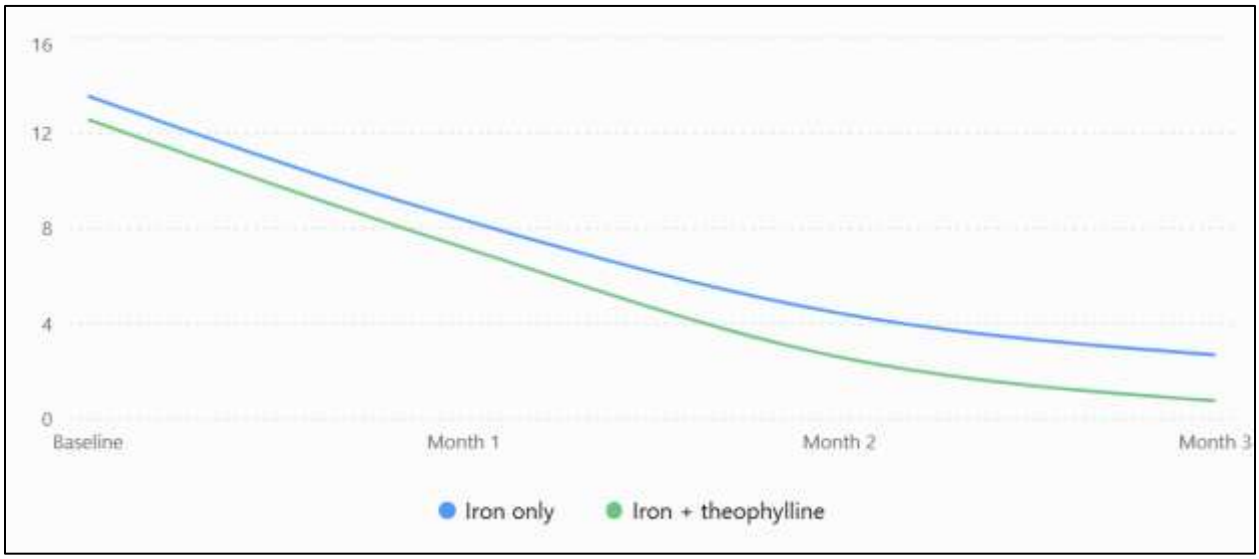

Figure 2. Mean monthly frequency of breath-holding spells according to treatment group

Treatment outcome and residual severity of breath-holding spells after 12 weeks of treatment are shown in table 3. Thirty-two children (58.2%) of the iron-only group and 46 children (83.6%) of the iron-plus-theophylline group achieved complete remission. The chance of partial remission was 27.3% in the children who were given iron alone and 12.7% in the children who were given the combination treatment. The iron-only group recorded no response in 14.5% of the cases while the combination group recorded no response in 3.6% of cases. There was a significant difference in overall distribution of complete remission (CR), partial remission (PR), and no response (NR) between the two groups of treatment ($p = 0.011$). The results of these studies suggest that children who were given iron and theophylline had a better chance of having a complete remission and lower chance of being unresponsive, compared to children who were treated with oral iron alone. Table shows also the severity of residual spells at the end of treatment. Twenty-nine percent of children in the iron-only group and 16.4% of children in the combination group reported no spells. The percentage of children who had mild residual spells was 32.7% in the iron group versus 14.5% in the iron + theophylline group. In 7.3% of the groups, moderate residual spells were seen and in 1.8% of the groups, high frequency spells; and in one child in the iron only group, high frequency spells persisted. The difference between

the severity of the spells was significant (p = 0.013). Thus, the combination therapy not only improved the chance for complete remission, but also made the spells less severe in children who didn't achieve complete remission.

Outcome	Iron only (n = 55)	Iron + theophylline (n = 55)	p-value
Treatment response, n (%)			**0.011**
Complete remission	32 (58.2)	46 (83.6)	
Partial remission	15 (27.3)	7 (12.7)	
No response	8 (14.5)	2 (3.6)	
Spell-frequency severity at 12 weeks, n (%)			**0.013**
No spells	32 (58.2)	46 (83.6)	
Mild residual spells	18 (32.7)	8 (14.5)	
Moderate residual spells	4 (7.3)	1 (1.8)	
High residual spells	1 (1.8)	0 (0.0)	

Table 3. Treatment outcomes and spell severity after 12 weeks

The percentages of children who achieved complete remission, partial remission or no response after 12 weeks of treatment are compared in figure 3. Complete remission was the most frequent result in both groups, but more children who got both iron and theophylline had complete remission. The combination-treatment group had a higher rate of complete remission (83.6%) than the group of children who received iron alone (58.2%). The iron-only group had a higher percentage with partial remission (27.3%) versus the iron-plus-theophylline group (12.7%). This difference implies that more children taking iron alone were helped but not cured of their breath-holding spells. By contrast, many of the children with the combination group improved and went on to complete remission. Also, fewer children in the combination-treatment group were not responding. Only 3.6% of children who were taking iron and theophylline did not respond, while 14.5% of those who were taking iron did not respond. Thus, children on the combination therapy were less likely to have an inadequate treatment response. The overall trend in Figure 2 is towards better outcomes in the iron plus theophylline group. The higher complete-remission rates and lower partial-remission and no-response rates suggests combination therapy was more effective than iron monotherapy in controlling breath-holding spells after 12 weeks.

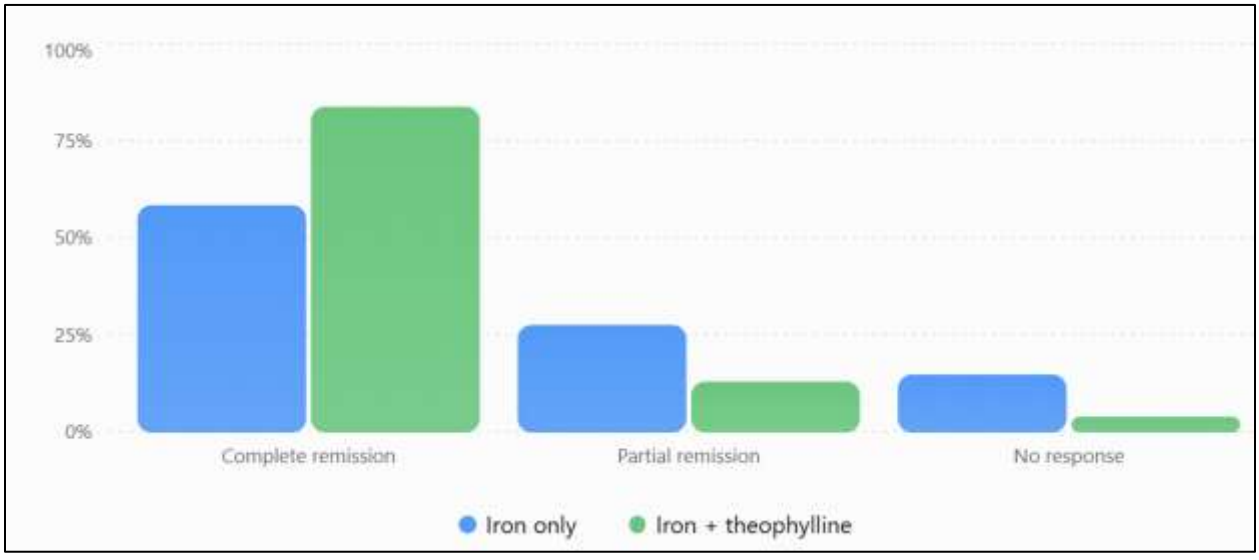

Figure 3. Treatment outcomes after 12 weeks

The demographic and clinical factors in relation to complete remission are examined in table 4. The only significant association with the outcome was with treatment group. Complete remission was seen in 58.2% children who were treated with iron alone and 83.6% children who were treated with iron and theophylline. This difference was statistically significant (p = 0.006), and indicated that the type of treatment was important in determining remission. There was no significant relationship between age and treatment outcome. Complete remission occurred in 72.3% of children aged 6–24 months and 68.9% of those aged 25–60 months (p = 0.831). Likewise, there was no significant difference in the remission rate between males and females children (p = 0.826).

Complete remission was not significantly affected by a family history of breath holding spells. There was no difference in the remission rates between children with a positive family history (73.7%) and those without a confirmed family

history (70.3%) (p = 1.000). There was also no significant association between type of spell and outcome. The rates of CR for children with cyanotic spells and pallid/mixed spells were 71.9% and 64.3% respectively (p = 0.544). There were no significant relationship between the severity of anemia and the status of iron-deficiency and complete remission. The remission rate for children with no/mild anemia was 71.7% and for those with moderate/suffering anemia, it was 70.3%. Likewise, 70.3% of the iron deficient and 77.8% of the non-iron deficient children went into complete remission. Such differences were not significant. The severity of the spell at the beginning of the experiment also did not correlate with whether the spell was successful or not. There were no differences between the children who had mild, moderate, and high frequency of spells at baseline (68.4% vs 73.4% vs 66.7% of children achieving complete remission, respectively, p = 0.803). There was no significant association between remission and nutritional factors such as high cow's milk consumption and low meat intake.

Factor	Category	Complete remission, n/N (%)	p-value
Treatment group	Iron only	32/55 (58.2)	**0.006**
	Iron + theophylline	46/55 (83.6)	
Age group	6–24 months	47/65 (72.3)	0.831
	25–60 months	31/45 (68.9)	
Gender	Male	51/73 (69.9)	0.826
	Female	27/37 (73.0)	
Family history of BHS	Yes	14/19 (73.7)	1.000
	No/not sure	64/91 (70.3)	
Type of spell	Cyanotic	69/96 (71.9)	0.544
	Pallid/mixed	9/14 (64.3)	
Anaemia severity	None/mild	33/46 (71.7)	1.000
	Moderate/severe	45/64 (70.3)	
Iron-deficiency status	Deficient	71/101 (70.3)	1.000
	Not deficient	7/9 (77.8)	
Baseline spell severity	Mild	13/19 (68.4)	0.803
	Moderate	47/64 (73.4)	
	High	18/27 (66.7)	
High cow's milk intake	Yes	36/51 (70.6)	1.000
	No	42/59 (71.2)	
Low meat intake	Yes	43/60 (71.7)	1.000
	No	35/50 (70.0)	

Table 4. Demographic and clinical factors associated with complete remission

4. DISCUSSION

Both oral iron (monotherapy) and oral iron + theophylline treatment in the present analysis was found to decrease the number and intensity of breath holding spells over a 12 week treatment period. The combination therapy, however, yielded a better therapeutic effect. 83.6% of children taking iron and theophylline achieved complete remission, compared to 58.2% taking iron alone. The relative risk for complete remission was 1.44 and the absolute difference between the groups was 25.5 percentage points. The results suggest that theophylline added to the treatment of iron deficiency might be a clinically relevant benefit in children who have frequent or persistent breath-holding spells. The benefits seen with oral iron alone was similar to what was previously reported. However, Daoud et al. have found that iron therapy did lead to a significant decrease in the number of breath-holding spells compared to placebo, especially in children with iron deficiency [16]. Similarly, children with breath-holding spells who had iron-deficiency anemia showed significant clinical improvement after iron supplements [17]. Oral iron treatment has also been reported to induce complete remission or a decrease of over 50% in spell frequency in most children as reported by Jain et al. [18]. Importantly, some children, who did not have any confirmed hemoglobin deficiency, showed improvement as well, indicating efficacy of iron therapy beyond just correcting hemoglobin concentration [18]. This may be related to the biological activity of iron. Iron is involved in the synthesis of hemoglobin, transportation of oxygen, myelination, and metabolism of neurotransmitters. Iron deficiency can be associated with irritability, reduced cerebral oxygenation and autonomic instability during emotional or painful stimuli. A systematic review and meta-analysis has confirmed the benefits of iron supplementation in reducing both frequency and severity of breath holding spells, and thus this would be a primary therapeutic option [19]. Iron treatment also affects autonomic nervous system function, with improvements in some cases, which could be partly due to improvements in autonomic regulation [20]. The decrease seen in the combination-treatment group was in line with the results of Dai et al., who found that the combination treatment (theophylline and iron) showed more improvement in breath holding attacks than the iron treatment alone

[21]. The discrepancy between the two groups increased during the second and third months of follow-up in the present study. There is a trend in this pattern, and the benefits of theophylline may become more apparent over time. Theophylline is a central respiratory stimulant, adenosine-receptor antagonist and may enhance respiratory drive and autonomic control. Low dose theophylline has also been shown to improve clinical symptoms in children with severe pallid breath-holding spells but should be used with careful monitoring due to its narrow therapeutic index and side effects [22]. The study population were frequently iron deficient and the most prevalent clinical type was cyanotic spells. These results corroborated the existing literature that shows an association between iron deficiency and autonomic dysfunction and breath-holding spells [20, 23]. However, there were no significant relationships between complete remission and age, gender, family history, severity of anemia, iron deficiency status, baseline spell frequency, high cow's milk consumption, or low meat consumption. Only treatment allocation was found to be significantly associated with outcome. In some instances, there were no significant associations for the other variables because of the small sample sizes in each of the subgroups. Results need to be viewed with the limitations of the non-randomized, single center design, the relatively short follow-up period, and reliance on the caregiver-reported spell frequency. The absence of blinding might also have affected reporting of the outcomes. More randomized controlled trials with standardized theophylline dosing, safety surveillance, serum level measurement and duration of follow-up are needed. Overall the oral iron was effective; but when theophylline was added, there was an increase in remission rate, reduction in the number of residual spells, and reduction in attack frequency.

5. CONCLUSION

The present study demonstrated that the oral iron supplementation and the combination of oral iron and theophylline were effective in decreasing the frequency and severity of breath-holding spells in children between the age of 6 months and 5 years. However, there was greater therapeutic response when the two were used together than when iron alone was used. Children who had received the combined treatment had a significantly larger reduction in the number of spells per month, a significantly lower number of residual spells at the end of follow-up (12 months) and a significantly higher complete remission rate. Eighteen point six percent of children who were treated with iron and theophylline achieved complete remission, while 58.2% of children treated with iron alone achieved complete remission. The number needed to treat suggested that around four children need iron only therapy and combination therapy to obtain a complete remission in one additional child. These observations of a progressive decrease in the number of breath-holding spells in both groups confirmed the importance of oral iron as a treatment component. The combination group did, however, show a more rapid and sustained decrease in the second and third months indicating that there was a therapeutic advantage of theophylline. The only significant association with complete remission was treatment allocation. Other factors such as age, gender, family history, nature of the breath-holding spell, severity of anemia, iron-deficiency status, baseline spell frequency and dietary factors did not show significant association with treatment outcome. The results indicate that oral iron should continue to be considered as a obligatory treatment for children with breath-holding spells, especially those with ID or anemia. For children with frequent, severe or persistent spells, requiring more symptom control, the addition of theophylline may be considered. However, caution is used in using theophylline due to its narrow therapeutic index and side effects. Future randomized, double-blind, multicenter trials with longer study periods, weight-based dosing, theophylline level monitoring and systematic safety evaluation are suggested to establish comparative effectiveness and long-term safety of combination therapy.

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