A comparative study of the efficacy of using piracetam with iron therapy versus iron therapy alone in children with breath-holding spells

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Background
Breath-holding spells (BHS) are apparently frightening events occurring in otherwise healthy children. Generally, no medical treatment is recommended and parental reassurance is believed to be enough; however, in some cases BHS can be very stressful for the parents and a pharmacological agent may be desired in some of these children.
Objective
The aim of this work was to determine the efficacy of using piracetam with iron therapy versus iron therapy alone in children with BHS associated with iron-deficiency anemia.
Study design
The study design was an interventional randomized controlled one.
Patients and methods
This study was conducted at the Neuro-Pediatric Outpatient Clinic at Alexandria University Children's Hospital, Egypt. A total number of 70 children between 6 months and 5 years of age with a diagnosis of BHS and iron-deficiency anemia reporting to the clinic were randomly divided into two groups: group I included 35 children who were given only iron therapy at a dose of 6 mg/kg/day, and group II included 35 children who were given iron therapy at the same dose and piracetam at a dose of 40 mg/kg/day. Follow-up of the cases monthly for 3 months was scheduled to evaluate the frequency of the attacks and the improvement in iron deficiency by evaluating iron profile after 3 months (iron, ferritin, and total iron binding capacity).
Results
Seventy patients were enrolled in this study (42 boys and 28 girls) and completed the study. The ratio of boys to girls was 3 : 2. The patients' ages ranged between 6 months and 5 years at the time of presentation with 50% above 2 years of age. The frequency of spells varied widely, ranging from 1 to 3 per day to 3 per month, and the mean frequency was six episodes of BHS in 1 month (about 2/week) for both groups. On comparing the improvement in the frequency of attacks between the two studied groups after treatment, there was a significant difference (P=0.001) between the two groups; the median number of attacks was two attacks per month for group I and one attack per month for group II.
Conclusion
Treatment with piracetam in addition to iron therapy is better than iron therapy alone in reducing the frequency of breath-holding attacks in children with BHS associated with iron-deficiency anemia.

Keywords:
breath-holding spells, iron therapy, piracetam

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Introduction

Breath-holding spells (BHS) are a common frightening experience for the parents because children become lifeless and unresponsive for a short period of time [1]. BHS is an abrupt and involuntary episode that occurs in a healthy child [2]. They occur frequently between 6 months and 5 years of age [3,4]. Rearing up of children who have BHS is very bothersome for the parents and causes a lot of concern as to many they may seem like epileptic seizures [5]. These spells usually abate by the 5th or 6th year of life [1,2,4].

BHS are classified into three types: cyanotic, pallid, and mixed [1]. Cyanotic BHS are the most common type initiated by upsetting or scolding the child and are characterized by a brief shrill cry, a forceful expiration, and then apnea. They can lead to cyanosis, clonic jerks, and opisthotonus posturing [1,3,4].

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Among the various theories postulated for the etiology of the BHS, similar to dysfunctional autonomic nervous system [6,7], iron-deficiency anemia has also been associated with the development of BHS [8–10]. Anemia has also been documented to hamper the oxygen uptake in the lungs and decrease the amount of oxygen available for use in the central nervous system [11,12]. Several studies available in the literature have proved that treating iron-deficiency anemia has a significant effect in the reduction of the frequency of BHS [13–15].

Piracetam (2-oxo-1-pyrrolidine) is a cyclic derivative of γ-aminobutyric acid (GABA), obtained after the loss of one molecule of water followed by ring formation, and it has been used for various cognitive disorders in children [16]. In children with BHS, there appears to be a close relationship between pathogenesis of spells and diffuse cerebral anoxia. Piracetam increases oxygen consumption by the brain tissue and increases the inhibitory process in a way very similar to GABA resulting in beneficial effects [17–19].

Aim

The aim of this study was to evaluate the efficacy of piracetam with iron therapy versus iron therapy alone in the treatment of children with cyanotic BHS with iron-deficiency anemia.

Patients and methods

This interventional randomized controlled study was conducted at the Neuro-Pediatric Outpatient Clinic at Alexandria University Children's Hospital, Alexandria, Egypt. The study population comprised 70 children with the diagnosis of cyanotic BHS defined by the following clinical sequence: provocation followed by crying to a point of noiselessness and accompanying change in color (cyanotic) and ultimately a loss of consciousness with an associated alteration in body tone.

The patients were randomly divided into two groups, with every other case distributed to each group as follows: group I included 35 children with a history of BHS and laboratory-documented iron-deficiency anemia and were given only iron therapy at a dose of 6 mg/kg/day for 3 months, and group II included 35 children with a history of BHS and laboratory-documented iron-deficiency anemia and were given both iron therapy at the same dose and piracetam at a dose of 40 mg/kg/day in two divided doses for 3 months.

Inclusion criteria

(1) Age between 6 months and 6 years.
(2) Normal psychomotor development and neurological status.
(3) Iron-deficiency anemia.
(4) Frequency of spells of three spells or more/month.

Exclusion criteria

(1) A diagnosis of epilepsy, electrolyte disturbance, hypoglycemia, or impaired kidney function tests.
(2) Abnormal neurological findings during examination.
(3) Previously received or currently receiving any medications for BHS.
(4) Doubtful diagnosis.

Approval of the Ethics Committee of Alexandria University was obtained. Parents were explained about the study and written consent was obtained for examination and intervention. Demographic and laboratory data were collected and complete blood count and iron profile (serum iron, total iron binding capacity, and serum ferritin) were evaluated in all children. Cases were followed up monthly for 3 months, and documentation of the frequency of attacks and improvement in iron deficiency by evaluating complete blood count and iron profile was carried out after 3 months at follow-up.

Statistical analysis

Data were collected, revised, coded, and fed to statistical software IBM SPSS (version 20; IBM, North Castle Drive, Armonk, NY, USA). All statistical analyses were performed using two-tailed tests and an α error of 0.05. The following statistical tests were used:

(1) Descriptive statistics, which included median, mean with SD, frequencies, and percentages, to describe categorical data.
(2) Analysis of categorical data, using Pearson's χ^2-test and Monte Carlo exact test, Student's t-test, and Mann–Whitney test.

Results

Table 1 shows the distribution of both groups according to demographic data. Seventy patients were enrolled into this study. Of them, there were 42 boys and 28 girls. The ratio of boys to girls was 3 : 2. The number of boys was higher than the number of girls in both groups. The patients' ages ranged from 6 months to 5 years at the time of presentation, with

nearly half of them presenting above the age of 2 years in both groups. Age of onset of attacks ranged between 6 months and 2.5 years, with most of the cases in both groups having their age of onset of attacks before the age of 1 year.

Table 2 shows hemoglobin (Hb) levels in both groups. The mean Hb (g/dl) was 10.17±0.85 for group I and 10.70±0.55 for group II, and there was a significant improvement after 3 months of treatment with iron for both groups and an increase of an average 1 g/dl in Hb for all studied cases.

Table 3 demonstrates the iron profile in both groups before and after treatment. It was found that after the 3 months of iron therapy there was a significant improvement in the levels of serum iron, total iron binding capacity, and especially ferritin levels, which improved significantly from a median of 4.5–26 mg/ml for group I, and from a median of 5.4–36.3 mg/ml for group II, reflecting the effective treatment of iron deficiency in all cases.

Table 4 shows the improvement in the frequency of the attacks among the two groups before and after treatment. The frequency of spells varied widely before treatment. For group I the number of attacks ranged from 3 to 90 attacks per month, whereas for group II cases it ranged from 3 to 120 attacks per month with a median frequency of six episodes of BHS per month (about 2/week) for both groups. The number of spells before treatment was not significantly different between the groups (P=0.691).

After treatment with iron therapy in group I, the frequency of attacks was reduced to range from a minimum of only one attack per month to a maximum of eight attacks with a median of two attacks per month. In group II, after commencing piracetam in addition to iron therapy, the frequency of attacks was reduced to range from a minimum of only one attack per month to a maximum of four attacks with a median of one attack per month.

On comparing the improvement in the frequency of attacks between the two studied groups after treatment, it was found that there was a significantly greater decrease in the frequency of attacks in group II receiving piracetam in addition to iron compared with group I receiving iron alone (P≤0.001).

Table 1 Comparison between the two studied groups according to demographic data

Demographic data	Group I (*n*=35) [*N* (%)]	Group II (*n*=35) [*N* (%)]	Test of significance	*P*
Sex				
Male	19 (54.3)	23 (65.7)	χ^2=0.952	0.329 (NS)
Female	16 (45.7)	12 (34.3)		
Age (years)				
≤1	4 (11.4)	5 (14.3)	χ^2=0.358	0.893 (NS)
>1–2	14 (40.0)	12 (34.3)		
>2	17 (48.6)	18 (51.4)		
Age of onset of attacks (years)				
≤1	23 (65.7)	24 (68.6)	χ^2=1.156	^{MC}0.800 (NS)
>1–2	12 (34.3)	10 (28.6)		
>2	0 (0.0)	1 (2.9)		

MC, Monte Carlo.

Table 2 Comparison between the two studied groups according to HB before and after treatment

Hemoglobin	Group I (*n*=35)	Group II (*n*=35)	Test of significance	*P*
Hb (g/dl)				
Before treatment				
Min.–max.	8.50–11.50	9.90–11.60	*t*=3.106*	0.003*
Mean±SD	10.17±0.85	10.70±0.55		
Median	10.30	10.80		
After treatment				
Min.–max.	10.30–13.10	10.8–12.40	*t*=2.096*	0.041*
Mean±SD	11.69±0.76	11.38±0.47		
Median	11.50	11.3		
P_1	<0.001*	<0.001*		

Hb, hemoglobin; max., maximum; min., minimum. *P and P_1<0.05, significant.

Discussion

BHS are a well-known entity in the pediatric age group and have a prevalence of about 4–5% [2]. This condition might be mistaken for epilepsy and is quite worrisome for the parents [5]. Association of iron-deficiency anemia with BHS as an etiological factor was described as early as in 1963 by Holowach and Thurston [20] in their study. A number of theories have been postulated, which have explained the increased frequency of BHS with iron-deficiency anemia. It has been proposed that iron has a role in the metabolism of catecholamines and neurotransmitters in the central nervous system and their deficiency plays a part in the development of BHS [21]. It has also been hypothesized that clinical and hematological picture of BHS is related to the interaction of cerebral erythropoietin, nitrous oxide, and interleukin-1 [22].

As documented by Ashrafi *et al.* [4] and Tonekaboni *et al.* [2] in their studies, the current study has also found

Table 3 Comparison between the two studied groups according to iron profile

Iron profiles	Group I (*n*=35)	Group II (*n*=35)	Test of significance	*P*
Fe (mg/dl)				
Before				
Min.–max.	0.09–0.35	0.16–0.39	*Z*=0.488	0.625 (NS)
Mean±SD	0.26±0.08	0.28±0.06		
Median	0.29	0.28		
After				
Min.–max.	0.43–1.20	0.40–1.16	*Z*=0.864	0.387 (NS)
Mean±SD	0.75±0.23	0.69±0.24		
Median	0.81	0.62		
P_1	<0.001*	<0.001*		
TIBC (mg/dl)				
Before				
Min.–max.	4.18–7.0	3.52–5.87	*t*=0.154	0.878 (NS)
Mean±SD	5.04±0.76	5.02±0.52		
Median	4.70	5.03		
After				
Min.–max.	2.12–4.10	1.38–3.87	*t*=0.494	0.623 (NS)
Mean±SD	2.94±0.52	2.88±0.59		
Median	2.76	2.73		
P_1	<0.001*	<0.001*		
Serum ferritin (ng/ml)				
Before				
Min.–max.	3.0–6.50	3.50–6.80	*t*=3.447*	0.001*
Mean±SD	4.60±1.13	5.40±0.78		
Median	4.50	5.40		
After				
Min.–max.	11.20–57.50	13.0–72.0	*t*=2.271*	0.027*
Mean±SD	27.89±13.36	36.61±18.36		
Median	26.0	36.30		
P_1	<0.001*	<0.001*		

Fe, iron; max., maximum; min., minimum; TIBC, total iron binding capacity; *Z*, Mann–Whitney test. **P* and P_1<0.05, significant.

Table 4 Comparison between the frequency of attacks (/month) in both groups before and after treatment

Frequency of attacks (/month)	Group I (*n*=35)	Group II (*n*=35)	Test of significance	*P*
Before treatment				
Min.–max.	3.0–90.0	3.0–120.0	*Z*=0.397	0.691 (NS)
Mean±SD	18.0±23.48	15.4±27.24		
Median	6.0	6.0		
After treatment				
Min.–max.	1.0–8.0	1.0–4.0	*Z*=3.261*	<0.001*
Mean±SD	3.20±2.63	1.43±0.65		
Median	2.0	1.0		
P_1	<0.001*	<0.001*		

Max., maximum; min., minimum; Z, Mann–Whitney test. **P* and P_1<0.05, significant.

a greater incidence of BHS in the male population (i.e. 60 vs. 40%). Most of the children were below the age of 1 year when they experienced the first episode of BHS, which is consistent with the findings of Lermanet *et al.* (quoted in Mocan *et al.* [23]) and the study by Bridge (quoted in DiMario and Burleson [24]) as well as the study by Abbaskhanian *et al.* [25] in addition to the recent study by Hussain *et al.* [26]. In the current study, the median age of occurrence of BHS was 24 months and the decline in the frequency of spells had occurred with advancing age. These results are consistent with that reported by most of the authors, who stated that BHS usually begins between the ages of 6 and 24 months, peaking in frequency by around 2–3 years, and it usually affects boys more compared with girls in a ratio of about 1.3 : 1 [17,27,28].

The frequency of BHS ranges from multiple episodes per day to as infrequently as once per month. However, in most cases the majority of children experience multiple episodes per week. In the study by DiMario [29], 25% of the patients experienced several episodes per day during maximum frequency. In another study performed by Bhat *et al.* [30] only 18% of the patients had several episodes of BHS per day and 64% of the patients had episodes occurring on weekly basis at the time of maximum frequency. In the study by Abbaskhanian *et al.* [25], only 24% of the patients had multiple episodes of BHS per day and 68% of the patients had multiple episodes on weekly basis at the time of maximum frequency. In the current study, the frequency of attacks ranged from as little as three times per month to as frequent as four times daily, with 21.4% having episodes on daily basis, 51.5% on weekly basis, and 27.1% on monthly basis.

In the current study, after 3 months of therapy with oral iron, a rise in the level of Hb by about more than 1 g/dl was demonstrated. This differs from the results by Hussain *et al.* [26], whose study showed a rise of more than 4 g/dl, and with the results shown by Afzal *et al.* [31] in their study on treatment with iron-deficiency anemia. This difference may be attributed to the fact that they used a higher iron dose or probably used it for a longer period. In any case, this rise in Hb level helped in decreasing the frequency of BHS in our study, as also shown by Ashrafi *et al.* [4], Tonekaboni *et al.* [2], Ziaullah Nawaz *et al.* [3], and Hudaoglu *et al.* [14] in their studies.

Piracetam is a chemical compound very similar to GABA and has been previously used in some studies to completely stop severe spells [32]. Cerebral anoxia is the main cause for causing the loss of consciousness and seizures occurring in BHS. Piracetam increases oxygen consumption by the brain tissue and increases the inhibitory process in a way very similar to GABA, resulting in beneficial effects [32].

The current study aimed at comparing the use of piracetam in addition to iron therapy with the use of iron therapy on its own to decrease the frequency of BHS. In the present study it was found that in the first group the frequency of attacks was significantly reduced from a median of six attacks per month to a median of two attacks per month. Comparatively, in the second group receiving piracetam the frequency of attacks was reduced from a median of six attacks per month to only one attack per month. Comparison of the two groups revealed that giving piracetam in addition to iron is significantly more effective.

Although published data about the use of piracetam in children with BHS is scanty, in a randomized placebo-controlled trial by Donma [33], piracetam was significantly more effective compared with placebo in controlling the spells (92.3 vs. 29.7%). Garg [17] has also shown that 2 months of piracetam therapy reduced the spells significantly and concluded that the drug is safe and effective. In the study by Abbaskhanian *et al.* [25], there was a significant improvement after administration of piracetam compared with placebo. The overall control of BHS was seen in 91% of the patients with complete or partial improvement. Similar results were obtained in the double-blind, placebo-controlled trial by Sawires and Botrous [16], in which there was a significant improvement after administration of piracetam and not after placebo. In the study by Azam *et al.*[34] it was found that 44% of the children required iron supplements because of their low Hb. It seemed that piracetam and iron combination had a complimentary effect; however, the remaining 56% of the children were prescribed piracetam alone with equally good response.

Conclusion

Treatment with piracetam in addition to oral iron supplementation in children with cyanotic BHS can decrease the frequency of attacks more than using oral iron therapy alone, thus reducing the agony of the disturbed parents and suffering of their children.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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