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ORIGINAL ARTICLE

Double-blind, placebo-controlled trial on the effect of piracetam on breath-holding spells

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Abstract Breath-holding spells (BHS) are apparently frightening events occurring in otherwise healthy children. The aim of this study was to evaluate the efficacy of piracetam in the treatment of breath-holding spells. Forty patients with BHS (who were classified into two groups) were involved in a double-blinded placebo-controlled prospective study. Piracetam was given to group A while group B received placebo. Patients were followed monthly for a total period of 4 months. The numbers of attacks/month before and monthly after treatment were documented, and the overall number of attacks/month after treatment was calculated in both groups. The median number of attacks/month before treatment in the two groups was 5.5 and 5, respectively, while after the first month of treatment, it was 2 and 5, respectively. The median overall number of attacks/month after treatment in both groups was 1 and 5, respectively. There was a significant decline of number of attacks after piracetam treatment compared to placebo (p value$<$ 0.001). There were no reported side effects of the piracetam throughout the study period. In conclusion, piracetam is a safe and effective drug for the treatment of breath-holding spells in children.

Keywords Piracetam · Breath-holding spells · Pallid spells · Cyanotic spells

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Introduction

Breath-holding spells (BHS) are apparently frightening events occurring in otherwise healthy children. The spells, a type of syncope, are common in infants and young children. Most spells start at 6–28 months of age, but may occur as early as the first month of life and usually disappear by 5 or 6 years of age [9].

Generally, no medical treatment is recommended, and parental reassurance is believed to be enough. However, severe BHS can be very stressful for the parents, and a pharmacological agent may be desired in some of these children [3].

There is strong evidence that autonomic nervous system dysfunction in the form of high resting heart rate and diastolic blood pressure is associated with BHS [2, 6].

Children with breath-holding spells are often prescribed sedative or anti-convulsant drugs either because a mistaken diagnosis of epilepsy is made or because of the belief that these drugs will prevent or reduce the frequency of the spells. However, there is absolutely no evidence to support this view [10].

Pallid breath-holding spells may respond to atropine when the ocular compression test shows significant asystole during ECG monitoring. Other treatment options include pacemaker implantation [12].

Evidence now suggests that iron deficiency anemia occurs in greater frequency in patients with breath-holding spells than in healthy control subjects, and correction may eliminate the breath-holding spells [14].

Piracetam (2-oxo-l-pyrrolidine) is a cyclic derivative of gamma-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 of children. In adults, this has been used for post-anoxic action myoclonus. In children with breath-holding spells, there appears to be a close relationship between pathogenesis of spells and diffuse cerebral anoxia [9, 11, 13].

The aim of this study was to evaluate the efficacy of piracetam in the treatment of breath-holding spells

Methods

Forty patients with BHS of both sexes aged between 6 months and 5 years were involved in a double-blinded placebo-controlled prospective study. Patients were recruited from the outpatient clinic, Beni-Suef University Hospital, between January 2011 and November 2011.

Patients with BHS were classified into two groups (20 patients for each group which were selected in an alternate manner). Piracetam (Stimulan® syrup, 1 g/5 ml, Amoun Pharmaceutical Company) was given to group A in a dose 50 mg/kg/day in two divided doses for 4 months while group B received placebo syrup with the same dosage, frequency, and duration. Both the patients and the researchers were kept in the dark about the method of selection and about which group was receiving which treatment (double-blinded).

Data were collected from the patients in the form of: age, sex, and full description of the attacks (character, frequency, duration, previous consultation, and previous or current treatment). Breath-holding spells were diagnosed on clinical ground based on classic history and free meticulous clinical examination. EEG was done to exclude patients with epileptic focus. Serum electrolytes (Na, K, Ca, and Mg), random blood sugar, and kidney function tests were done to exclude any abnormalities in those patients.

Patients with the following diagnoses were excluded from the study (n=18): epilepsy, electrolyte disturbance, hypoglycemia, iron deficiency anemia, impaired kidney function tests, those with abnormal neurological findings during examination, those who received or were receiving any medications for BHS, or those with doubtful diagnosis.

Patients were followed monthly for a total period of 4 months. In each visit, compliance of the patients was assured. A report of the frequency of breath-holding spells and any reported side effects were documented.

Calculated data

The overall number of attacks/month after treatment was calculated as follows: sum of attacks after treatment in the 4 months/4. The rate of change after the first month was calculated as follows: (number of attacks/month before treatment−number of attacks in the first month after treatment)/number of attacks/month before treatment× 100. The whole rate of change was calculated as follows: (number of attacks/month before treatment−overall number of attacks/month after treatment)/number of attacks/month before treatment×100. The study protocol was approved by the local ethics committee, and informed written consent was obtained from the parents of the patients.

Statistical methods

Quantitative (numerical) and calculated data (overall number of attacks/month after treatment, rate of change after the first month, and whole rate of change) were presented as median and ranges (minimum and maximum). Qualitative (categorical) data were presented as frequencies. Spearman's correlation coefficient was used to determine significant correlations between quantitative data. Wilcoxon Signed Rank Test was used to compare between numbers of attacks before and after treatment in each of the studied groups while Mann–Whitney test was used to compare response of treatments between piracetam and the placebo groups. Also, Mann–Whitney test was used to compare response of treatments and type of BHS (cyanotic or pallid). The significance level was set at $p<0.05$. Statistical analysis was performed with Statistical Package for Scientific Studies (SPSS) 16.0 for Windows.

Results

The characteristics of the patients are shown in Table 1. The median age for overall studied patients was 32.5 months (range, 9, 52).

The number of attacks/month, the overall number of attacks/month after treatment, rate of change after the first month, and the whole rate of change for the two groups are

Table 1 Characteristics of patients with breath-holding spells included in the study

	Group A (piracetam) (n=20)	Group B (placebo) (n=20)
Age (months), median (range)	34.5 (9, 52)	31 (11, 52)
Sex		
Male	14	13
Female	6	7
Type of spells		
Cyanotic	11	11
Pallid	9	9

Table 2 Number of breath-holding spells; median (minimum, maximum)

	Group A (piracetam)	Group B (placebo)	*p* value
No. of attacks/month before treatment	5.5 (1, 12)	5 (2, 12)	0.723
No. of attacks/month after 1 month	2 (0, 5)	5 (2, 10)	<0.001
No. of attacks/month after 2 months	0 (0, 3)	5 (2, 10)	<0.001
No. of attacks/month after 3 months	1 (0, 2)	4 (1, 9)	<0.001
No. of attacks/month after 4 months	1 (0, 2)	5 (2, 11)	<0.001
Calculated data:			
Overall number of attacks/month after treatment	1 (0, 3)	5 (2, 9)	<0.001
Rate of change after the 1st month (%)	72.08	4.55	<0.001
Whole rate of change (%)	83.85	12.5	<0.001

shown in Table 2 and Fig. 1. It was found that the number of attacks has been reduced in the first month after piracetam in 14 out of 20 patients in group A, and this decline was maintained or further decline happened during the rest of study. Five out of six patients, who did not respond initially in group A, responded to piracetam in the second and third months after treatment. On the other hand, the number of attacks has been reduced in the first month after placebo in 4 out of 20 patients in group B, and even this response was not consistent during the rest of the study.

It was found that there was a significant negative correlation between age of the patients and the number of attacks/month before treatment in the two groups (p value=0.003 and 0.004, respectively) (Figs. 2 and 3).

Group A (piracetam)

There was significant decline in overall number of attacks after treatment with piracetam (p value<0.001). Such decline was significant after the first and second months (p value <0.001), but it is not significant after the third and fourth months (p value=0.145 and 0.317, respectively).

There was no significant difference between types of BHS (cyanotic and pallid) and the overall number of attacks after treatment (p value=0.161), but the rate of change after the first month and the whole rate of change are significantly higher in pallid spells (p value=0.001 and <0.001, respectively). There were no reported side effects of piracetam throughout the study period.

Group B (placebo)

There was no significant decline in the number of attacks after placebo in the first, second, third, or fourth months (p value=0.136, 0.522, 0.902, and 0.805, respectively). The overall number of attacks after placebo was significantly reduced (p value=0.018).

There was no significant difference between types of BHS (cyanotic and pallid) and the rate of change after the first month and the whole rate of change (p value=0.765

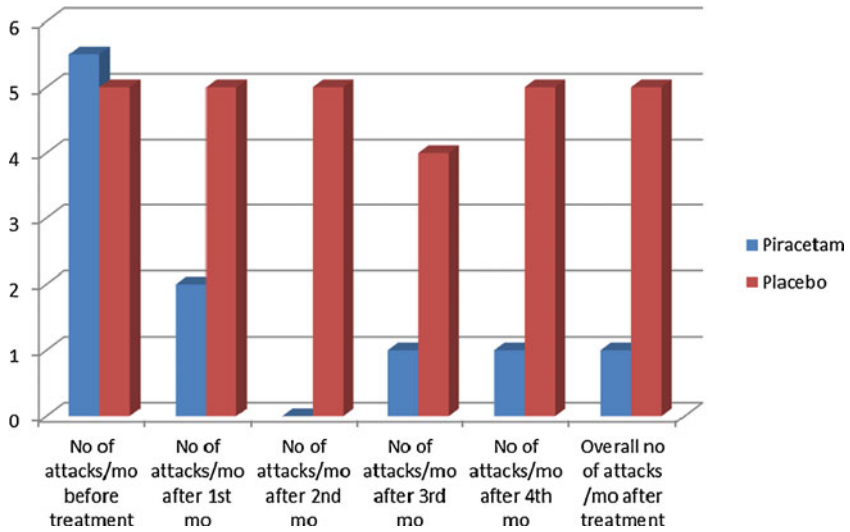

Fig. 1 Number of attacks/month throughout the study period in the two groups (median values)

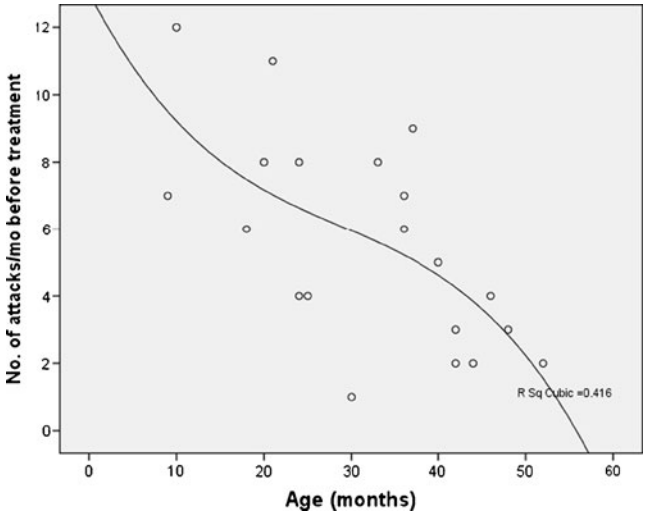

Fig. 2 Correlation between age of the patients (months) and number of attacks/month before treatment in group A (piracetam group)

and 0.145, respectively). There were no reported side effects of the placebo throughout the study period.

Discussion

Breath-holding spells consist of a stereotypical sequence of pulmonary and cardiovascular responses to strong, usually adverse, emotions. Vagally mediated cardiac inhibition generally occurs in the pallid type of breath-holding spells, whereas reflex-induced forceful and prolonged expiration causes the cyanotic type. Cerebral anoxia, whether produced by asystole or prolonged apnea, apparently causes the loss of consciousness [4].

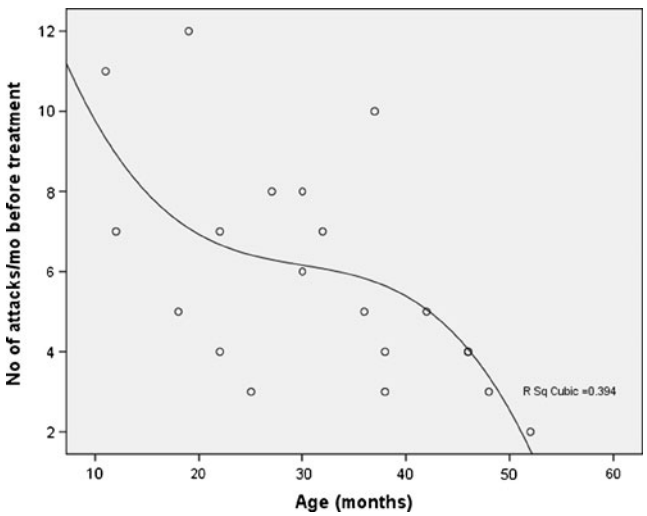

Fig. 3 Correlation between age of the patients (months) and number of attacks/month before treatment in group B (placebo group)

In our study, we found that the median age of occurrence of BHS was 32.5 months and the decline in frequency of spells had occurred with advancing age. Also, we found a higher incidence of BHS in males compared to females (ratio, 2:1). These results are consistent with most of the authors who stated that BHS usually begin between the ages of 6 and 24 months, peaking in frequency by around 2 to 3 years, and it usually affects boys more than girls in a ratio of about 1.3:1 [1, 5, 9].

In this study, the ratio of cyanotic spells to pallid spells was 1.2:1 which is slightly different than other studies who found that the cyanotic type of BHS prevails over the pallid type in a ratio of about 2.5–3:1 [5, 8].

Although the vast majority of children do not require any medication, several treatments have been given to severe cases. In this study, piracetam was used in a placebo-controlled study.

We found significant improvement after administration of piracetam and not after placebo. The significant decline in the number of attacks/month after administration of piracetam was marked in the first and second months, and it was less pronounced in the third and fourth months when compared with the first and second months. Our results are in agreement with many authors who found that piracetam is an effective drug in the treatment and prophylaxis of BHS [3, 7].

Piracetam is associated with increased brain tissue oxygen consumption and its ability to increase the inhibitory hyperpolarizing processes in a manner similar to that of GABA. For these reasons, piracetam could be effective in controlling the breath-holding attacks [11].

Cerebral anoxia is found in both types of BHS, and this explains that there was no difference in response to piracetam between both types as regards the number of attacks/month after treatment, but the higher incidence of the pallid type in this study may explain why we found a significantly higher rate of change after the first month and the whole rate of change in the pallid type compared with the cyanotic type.

We did not detect side effects of neither piracetam nor placebo treatments. Donma found that incidence of side effects of piracetam was not different from that of placebo [7]. Winnicka et al. reported that piracetam generally has minimal or no side effects. It is interesting to note, however, that piracetam is occasionally reported to have side effects of anxiety, insomnia, agitation, and irritability more in adults [13].

In conclusion, piracetam is a safe and effective drug for the treatment of breath-holding spells in children and should be considered in the management of severe and more frequent spells.

Conflict of interest The authors declare that they have no conflict of interest.

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