Original Article

The Comparison of Levetiracetam and Piracetam Effectiveness on Breath-Holding Spells in Children: A Randomized Controlled Clinical Trial

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Abstract

Background: We aimed to compare the effectiveness of Levetiracetam and Piracetam on the severity and frequency of spells in children with severe breath-holding spells (BHS), i.e. bening, paroxysmal, and nonepileptic events that are common in early childhood. **Materials and Methods:** This study is a randomized controlled clinical trial in 71 children from 6 months to 6 years of age with BHS. They were randomly assigned to the two study groups (Levetiracetam and Piracetam group). The frequency and severity of BHS and the response to treatment were recorded on monthly visits during our 3 months follow-up. **Results:** There was a significant decline in the average number of frequency of spells before and after 3 months of treatment in each group in this study. Levetiracetam had significant effects on the average incidence of the loss of consciousness and seizure-like movements in our study, while Piracetam had no significant effect on the loss of consciousness. Our result showed better response in the Levetiracetam group (88.9% partial or complete response after treatment) compared with the Piracetam group (77.1% partial or complete response after treatment); however, it was not significant. It seems that Levetiracetam had better effect than Piracetam in some aspects in the treatment of BHS. **Conclusions:** Both Piracetam and Levetiracetam are safe and had significant effects on the frequency of BHS in our study, however, levetiracetam showed superior effects on the severity of BHS.

Keywords: *Breath holding, child, frequency, levetiracetam, piracetam, treatment*

Introduction

Breath-holding spells (BHS) are sudden, reflexive, and nonepileptic phenomenon that is common in infancy and early childhood. Involved patients usually go to pediatric neurology and cardiology clinics for heart disease or seizures.[1-3] Attacks usually begin in the first 6–12 months of life and improve almost at the age of 4–5 years, although some will continue up to the age of 7 years.[2-4] The hereditary nature of the disease and its autosomal dominant inheritance is proven.[1,4] Although its etiology is still unclear, autonomic system dysfunction and increased vagal tone leading to cardiac arrest and cerebral anoxia may be considered as the underlying factor.[2,3,5] Diagnosis is usually made by observing the spells. Spells always occur at waking time and usually less than a minute after mild trauma or stress, etc., It often consisted of a period of crying, followed by a state of exhaustion. Based on the facial change, it manifests in three forms: cyanotic, pallid, and mixed.[3] The most common form is cyanotic, in which the crying child holds his breath in an exhaled state and does not inhale until the lips become bruised, and rarely, their limbs may become rigid and sometimes shows clonic movements.[2] The pallid type of spells is less common than cyanotic type. Parasympathetic hypersensitivity may cause cardiac bradycardia, decreased cardiac output, decreased blood pressure, and consequently, pale appearance.[2,6] Sometimes, these spells are triggered by trauma. In this type, the child becomes loose and pale as he/she cries and then returns to its normal state after a few seconds. Rarely, the child becomes both cyanotic and pale while he/she is crying, which is called the mixed type.[2,3] As previous study showed, the incidence of BHS in every affected child is 4.6–4.7 per month. These attacks, which usually begin in early infancy, do not damage the child's brain but cause great fear and anxiety for

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parents. Often, it is enough to reassure the parents, but in the case of repeated or severe attacks, a treatment might be needed.[1,4,7] It was thought that the disorder would gradually resolve with the maturation of the autonomic nervous system, but recent studies have yielded different results on the prognosis of these children. For example, studies demonstrated that the risk of fainting and sinus arrhythmia in these children would be higher in the future, and QT will be significantly prolonged in these patients. During severe BHS, the muscles may become stiff and sometimes shows clonic movements, which may be confused with seizures or even, they might be a cause of seizures.[2] Treatment and prevention of recurrence of these attacks are necessary because sometimes they fright the families, especially when cyanosis is present. In some children, iron supplementation has been found to reduce the attacks. In some studies, the use of Piracetam had resolved the spells.[8,9] Previous studies have shown that anticonvulsants can be used in these patients. One of the commonly used anticonvulsant drugs is Levetiracetam, which, due to its safety, is widely used in the treatment of partial, myoclonic, and tonic-clonic epilepsies.[10] Levetiracetam could also regulate the cardiac autonomic signaling system. Although the precise mechanism of Levetiracetam has not yet been elucidated,[7] it is suggested that this drug works by preventing the release of repetitive action potentials in neurons, without affecting the normal neuronal action potentials. Furthermore, it is thought that Levetiracetam would stimulate synaptic vesicle A2 protein and therefore, inhibit neurotransmitter release.[11] It should be noted that the safety of using Levetiracetam and its counterpart, Piracetam, in the pediatric population has been approved.[10,12] The efficacy of Piracetam has been investigated in the treatment of BHS,[13] but there is limited evidence regarding the efficacy of Levetiracetam in children with BHS.[8,12,14] Although studies have noted side effects for Levetiracetam (e.g., restlessness and irritability), due to possibly life-threatening conditions following severe BHS, use of Levetiracetam in severe BHS may improve families' quality of lives.[10] To the extent of our knowledge, no study has compared the efficacy of anticonvulsants in children with BHS. Furthermore, sometimes approved treatments do not have adequate effects on controlling BHS in children. Therefore, in this study, we compare the effectiveness of Levetiracetam and Piracetam on the severity and frequency of spells in children with severe BHS.

Materials and Methods

This study is a randomized controlled clinical trial on children from 6 months to 6 years of age with BHS. 71 patients with severe BHS (at least three times a month or with seizure-like movements or loss of consciousness[2]) with normal growth and development were recruited. Children with abnormal cardiovascular, cerebral and neurological examinations, any electrolyte disorders, hypoglycemia and iron deficiency, and history of any seizures or neurological problems or epilepsy were excluded from the study. All of the children who entered the study had received iron supplementation, but spells were not stopped. Furthermore, observing any drug reaction or neurological disorders or the inability of the patients to follow-up, contributes to their exclusion. In this study, started in winter 2018, 71 patients were selected consecutively from the patients referred to the neurological clinic of Imam Hossein Hospital, in Isfahan, if they met the inclusion criteria. After complete explanations of the study for parents, written informed consent was obtained. Full demographic information including age, sex, weight, family history, development status was collected. A well-designed checklist was used to collect data about their electroencephalogram (EEG) status, the current number of spells per month, and the severity of spells (loss of consciousness and seizure-like movements). Then, full history, physical examination, and specific laboratory tests (CBC, Electrolytes, Ca, FBS, ferritin) were done to make sure of the absence of any other abnormalities or disorders. Then, they were randomly assigned to the two study groups (Levetiracetam and Piracetam) using binary blocks. Levetiracetam group was treated with Levetiracetam syrup at a dose of 40 mg/kg daily, and the Piracetam group was treated with Piracetam syrup at a dose of 100 mg/kg daily for 3 months. After starting treatment, patients were visited monthly for 3 months. The frequency and severity of BHS were recorded on monthly visits. Eventually, the response to treatment was classified as follows:[12] "Complete Response" as Complete caseation of spells (>75% decline in the number of spells); "Partial response" as 50%–75% decline in the number of spells; "Poor response" as 25%–50% decrease in the number of spells and "No response" as <25% decline in the number of spells.

Patients' data were divided into quantitative and qualitative variables. Statistical indices appropriate to the nature of the variable were used to describe the variables, including mean, standard deviation, frequency, and percentages. Kolmogorov–Smirnov test was used to evaluate the normality of the data, and Levene tests were used to assess the homogeneity of variances. We used the parametric tests when assuming the normality of the data distribution and homogeneity of variances. We used the independent *t*-test and repeated measures analysis of variance test to determine and compare the effectiveness of the drugs regarding the number of attacks and their severity in two groups during the consecutive months of study. Non-parametric Mann–Whitney U was used while data is not normally distributed. Chi-square and independent t-tests were used to compare the variables in the two groups. For variables with more than two groups, the ANOVA test was used. Data were analyzed

by SPSS software version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.)

Results

The characteristics of the patients are shown in Table 1. The incidence of BHS in boys compared to girls was 1.56:1. The median age for overall studied patients was approximately 2.7-year-old (range: 6 months to 6 years old). In this study, in 87.3% of the cases, the spells developed under the age of 2 years. There was a positive familial history of BHS and seizures in 69.01% and 59.15% of the children, respectively. All of the participants had normal EEG and electrocardiogram. In our study, 35.2% of the patients had 12 attacks or more per month at the time of peak frequency before treatment. There were no significant differences between the age of patients, family history of seizures, the severity of spells, and the overall number of attacks before treatment in the Piracetam and Levetiracetam group in our study, however, significant differences between gender and family history of BHS in our groups were reported [Tables 1 and 2]. There was a significant decline in the average frequency of spells before and after 3 months of treatment in each group in our study [Table 2]. However, there were no significant differences in the average number of frequency of spells after 3 months of treatment between Piracetam and Levetiracetam group, which means both medications had the same effect on the frequency of spells. Piracetam had significant effects on the average incidence of seizure-like movements, but not the loss of consciousness. Levetiracetam had significant effects on the average incidence of loss of consciousness and seizure-like movements in our study [Table 3]. Figure 1 shows the details of the response to treatment in both groups. 77.1% of children in the Piracetam group and 88.9% of children in the Levetiracetam group had a partial or complete response to 3-months of medication [Figure 1]. It should be noted that patients with family history of seizure (but not BHS) significantly have a poorer response (no response to poor response) to treatment (P = 0.01, odds ratio = 9.94). Reported side effects of piracetam were some levels of irritability and mild diarrhea in two patients in our study, however, the side effects were mild and did not lead to exclusion from the study.

Discussion

BHS is a kind of syncope observed in early childhood. It was first described almost 500 years ago.[15] It has been reported to occur in approximately 0.1%–4.6% of children.[12] In the majority of patients, the prognosis is good and the patient's attacks disappear by school-age;[16] however, death, though rare, has been reported.[15] The mainstay of management is education and reassurance,[15] however, most pediatricians and child neurologists probably would agree to find out an effective drug for prevention of these spells,[3] because parents whose children have severe and frequent BHS would prefer drug treatment. Furthermore, it is impossible for the child to avoid provoking factors. In a survey, only 21% of mothers of children with BHS indicated that knowing about the benign nature of BHS was helpful.[17] There is a variety of treatments, from Chinese herbal medicine to cardiac pacing which has been tried in these children. Antiepileptic and atropine with variable results have been also advised.[2] Furthermore, Iron therapy has been reported effective in these children with or without iron deficiency anemia.[15] Multiple studies have reported the use of Piracetam in children with BHS,[9,12,16] however fewer studies had been conducted about Levetiracetam in

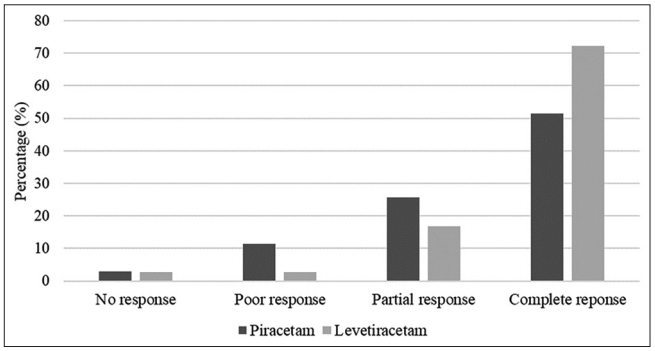

Figure 1: Response to three months treatment in Piracetam and Levetiracetam groups in children with breath-holding spells (ANOVA *P* = 0.167)

Table 1: Patients characteristics in Piracetam and Levetiracetam Group

Variables	Piracetam (n=35)	Levetiracetam (n=36)	Total (n=71)	$P^{\dagger}$
Gender				
Boy	17	26	43	0.041*
Girl	18	10	28	
Age (year)	2.63±2.32	2.75±1.99	-	0.806
Weight (kg)	12.24±5.52	13.23±5.33	-	0.445
Positive family history of BHS	28	21	49	0.048*
Positive family history of seizures	21	21	42	0.886
Associated symptoms				
Loss of consciousness	20	21	41	0.919
Seizure-like movements	20	18	38	0.546

*P<0.05 is considered significant, †Chi-square and t-test were used. BHS: Breath-holding spell

children with BHS.[6] The age of onset of BHS in most of the studies has been in the first 12 months of life. The occurrence of BHS is rare in the first 6 months of life and questionable in the neonatal period.[3,18] There is only one case report in a 3-day old neonate with an early presentation of BHS.[19] In this study, in 87.3% of the cases, the spells developed under the age of 24 months, which is consistent with a similar study that the spells developed in 78% of cases between 6 and 24-month-old children.[12] In this study, we found that the median age of occurrence of BHS was 2.69 ± 2.14 years old. These results are consistent with 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.[2] We found a higher incidence of BHS in boys compared to girls (1.56:1) which were approximately similar to studies conducted by DiMario and Donma.[3,20] A 20%–30% rate of positive familial history in children with BHS indicates that genetic maybe the causality factor for the occurrence of these spells.[3] In our study, there was a positive familial history of BHS and positive familial history of seizures in 69.01% and 59.15% of the children, respectively. The frequency of BHS varies from multiple episodes per day to even no episode for a month or more. The majority of children; however, experience multiple episodes per week. In the study performed by Bhat *et al*., 64% of the patients had multiple episodes occurring every week at the time of peak frequency.[18] In our study, 35.2% of the patients had 12 attacks or more per month at the time of peak frequency before treatment and it declines to 8.5% of cases after 3 months of treatment. The overall control of BHS (complete or partial response: more than 50% decrease in the number of spells after treatment) in both groups was observed in 83% of the patients. In a randomized double-blind controlled trial study, complete and partial response was observed in 91% of the patients in the group taking Piracetam as compared with 16% in the group taking placebo. Abbaskhanian *et al*. found significant improvement after the administration of Piracetam, but not after the placebo.[12] Garg have also reported that 2 months of Piracetam therapy reduced the spells significantly.[21] In the study of Azam *et al*., the efficacy of Piracetam was identical (90%) with a relatively higher dose (50–100 mg/kg/day).[16] Although Piracetam was safe and effective in treating BHS, especially when administered at a single dose,[15] however, in a study conducted by Ashrafi *et al*., Piracetam in comparison with the placebo did not show a particular advantage.[22] In addition to Piracetam, Glycopyrrolate, theophylline, fluoxetine, and Levetiracetam have also been used to treat BHS in individual cases but not clinical trials.[15] Levetiracetam is a new anticonvulsive agent that is structurally similar to the prototypical drug, Piracetam, that has been successfully used to treat BHS.[6] There is some evidence in current studies that suggest that Levetiracetam may have therapeutic potential outside the central nervous system and it may modify the autonomic signaling to the heart. However, the exact mechanism by which Levetiracetam exerts its effects remains unknown.[23] Our result showed that better response of Levetiracetam group (88.9% partial or complete response after treatment) compared with Piracetam group (77.1% partial or complete response after treatment), however, it was not significant. We aimed to compare the effectiveness of Piracetam as an acceptable treatment for BHS and Levetiracetam as a new treatment that has been more applicable recently, especially in the treatment of seizures in children as a safe drug. According to our results, it seems that Levetiracetam had a better effect than Piracetam in some aspects like decrease in the loss of consciousness in the treatment of BHS. The main limitation of this study was that, although our center was a referral center and we ultimately recruited 71 patients in our study. Further studies with a large sample size and more follow-up duration, would be needed to assess the effect more reliably.

The main strength of this study is that to the best of our knowledge this was the first study to compare the effectiveness of anticonvulsants in the treatment of severe BHS.

Table 2: The frequency (attacks/month) of spells before and after treatment in Piracetam and Levetiracetam Group

Variables	Groups	Before treatment	After treatment	*P*
Frequency	Piracetam	17.74±15.41	6.08±7.57	<0.001*
	Levetiracetam	12.59±21.18	2.95±9.98	0.001*
P		0.246	0.141	

**P*<0.05 is considered significant. Independent sample *t*-test was used

Conclusions

Both Piracetam and Levetiracetam are safe and had significant effects on the frequency of BHS in our study, however, levetiracetam showed superior effects on the severity of BHS. Long-term benefits and serious side effects of Levetiracetam in the prevention of severe BHS should be considered in future studies.

Table 3: Severity of spells before and after treatment in Piracetam and Levetiracetam Groups

Severity of spells	Piracetam		*P* (paired test)	Levetiracetam		*P* (paired test)
	Before treatment	After treatment		Before treatment	After treatment	
Loss of consciousness	1.60±0.49	1.42±0.50	0.263	1.94±0.23	1.41±0.50	<0.001*
Seizure-like movements	1.65±0.48	1.42±0.50	0.030*	1.94±0.23	1.50±0.50	<0.001*

**P*<0.05 is considered significant

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Conflicts of interest

There are no conflicts of interest.

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