Artuklu International Journal of Health Sciences

journal homepage: https://dergipark.org.tr/tr/pub/artukluder

Original Article / Araştırma Makalesi

The Efficacy of Iron and Piracetam in Breath Holding Spells and Levetiracetam in Anoxic Epileptic Seizures

Katılma Nöbetlerinde Demir ve Pirasetam ile Anoksik Epileptik Nöbetlerde Levetirasetamın Etkinliği

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ARTICLE INFO

Article History:
Received: 02.01.2023
Received in revised form: 18.02.2023
Accepted: 24.02.2023

Keywords:
Breath holding spell
Anoxic epileptic seizure
Treatment

ABSTRACT

Introduction: In this study, the patients diagnosed with breath holding spell (BHS) or anoxic epileptic seizures and initiated at least one out of iron or piracetam or levetiracetam therapies were evaluated.
Material and Methods: We retrospectively evaluated 194 BHS patients. Iron therapy was initiated in case of iron deficiency anemia or case of ferritin values under 12 ng/dl even if there was no anemia. The patients having no iron deficiency anemia, low ferritin and anoxic epileptic seizures were administered piracetam and the patients diagnosed with anoxic epileptic seizures were administered levetiracetam.
Results: One hundred and eight patients (55.7%) were male. The mean age was 21.39±12.78 months. Iron therapy was initiated in 87 patients, piracetam to 96, and levetiracetam in 11 patients. Seizure numbers were manifestly decreased in all groups by the end of the first month after treatment concerning pretreatment levels ($p<0.05$).
Conclusions: We determined that the spells were reduced or completely stopped in all groups. Levetiracetam seems to be considerably effective in patients developing anoxic epileptic seizures after BHS.

MAKALE BİLGİLERİ

Makale Geçmişi:
Geliş Tarihi: 02.01.2023
Revizyon Tarihi: 18.02.2023
Kabul Tarihi: 24.02.2023

Anahtar Kelimeler:
Katılma nöbeti
Anoksik epileptik nöbet
Tedavi

ÖZET

Giriş: Bu çalışmada, katılma nöbeti veya anoksik epileptik nöbet tanısı alan ve demir, pirasetam veya levetirasetam tedavilerinden en az biri başlanan hastalarda, ilaçların nöbetleri azaltma etkinliği değerlendirilmiştir.
Materyal and Metot: Çalışma kriterlerini karşılayan 194 hastanın dosyaları geriye dönük olarak incelenmiştir. Demir eksikliği anemisi olan veya anemi olmasa bile ferritin değeri 12 ng/dl altında olan hastalara demir tedavisi başlanmıştı. Anemi, düşük ferritin ve anoksik epileptik nöbeti olmayan hastalara pirasetam, anoksik epileptik nöbeti olanlara levetirasetam başlanmıştı.
Bulgular: Hastaların 108'i (% 55.7) erkekti. Ortalama yaş 21.39±12.78 aydı. 87 hastaya demir tedavisi, 96 hastaya pirasetam ve 11 hastaya levetirasetam başlanmıştı. Tedavi başlandıktan bir ay sonraki değerlendirmede tüm gruplarda nöbet sayısı belirgin azalmıştı ($p<0.05$).
Sonuç: Tüm gruplarda nöbet sayısının azaldığını veya tam durduğunu saptadık. Levetirasetam katılma nöbeti sonrası gelişen anoksik epileptik nöbetlerde oldukça etkili gibi görünmektedir.

1. Introduction

Breath Holding Spell (BHS) is a paroxysmal nonepileptic event occurring as a result of crying, fear, anger or frustration and revealing itself as holding breath during expiration with an open mouth as well as color changes in face or body. Its prevalence was reported as 3-5% in children. It comprises 0.1-4.6% of non-epileptic paroxysmal events (1). It is observed as cyanotic, pallid and mixed (cyanotic and pallid) forms. (2). Although its pathophysiology is not fully known, suspected mechanisms are genetic disposition (3), autonomous nervous system dysregulation (4), delayed myelination of the brain stem (5), the inadequate balance between oxidant-antioxidant systems and selenium deficiency (6). BHS diagnosis is a clinical diagnosis based on medical history and routine physical and neurologic examinations (7).

Spells generally occur between 6-12 months but start latest by the end of 2nd year of age (8). Spells are usually self-limiting and the

attacks rarely last long and hypoxia may also develop. As a result of hypoxia caused by long-lasting attacks; it may also appear as myoclonic, even generalized tonic-clonic "anoxic epileptic seizures (9,10). Spells either cease or become infrequent before school age, in 90% of the patients (2).

Generally, medical therapies are not recommended. The primary approach is to help the parents relieve their worries and fears (11). However, in patients with frequent and severe spells, it may become stressful for the parents and a pharmacological agent may be required in some of these children (12,13).

The patients diagnosed with BHS and initiated at least one out of iron or piracetam or levetiracetam therapies were evaluated in this study, regarding demographic properties, response to treatment and drug efficacies.

2. Materials and Methods

In this study, 1707 patients who applied to the Pediatric Neurology Outpatient Clinic of our hospital between January 2013 - March 2019 and were diagnosed with BHS were analysed retrospectively. The patients included in the study were those having full records and with normal results in neurologic and cardiac examinations, and electroencephalography (EEG) taken, with no systemic disease, having started at least one of the therapies out of iron or piracetam or levetiracetam, and with minimum 3 months of follow-up data after diagnosis. Those unable to meet these criteria were excluded. Demographic features, complete blood count, serum iron, total iron binding capacity, ferritin values and EEG report results were recorded from clinical follow-up files. Spell type, monthly pretreatment spell numbers and posttreatment spell numbers by the end of the first and third months and no-spell rates by the end of the first and third months were extracted from the clinical follow-up files as well as the datasheet of the parents recording the spell numbers. The study was completed with 194 patients meeting the criteria.

BHS was defined as expiratory apnea developing as a result of crying, fear, anger or frustration and cyanosis and/or pallor developing on the face or body color. BSH diagnosis and spell type was based on the anamnesis provided by the parents and by excluding the other diagnostic possibilities.

Anoxic epileptic seizure was defined as tonic, clonic or myoclonic jerks following hypoxia and syncope, developing after extended expiratory apnea (14). The diagnosis was based on anamnesis, physical examination, EEG and/or by watching video recordings of seizures. Ethical Committee Approval for the study was obtained from Gazi Yaşargil Training and Research Hospital (with date and number: 342/27.09.2019)

2.1. Therapy initiation criteria

Iron therapy was initiated in case of iron deficiency anemia or case of ferritin values under 12 ng/dl even if there was no anemia. Hemoglobin values under – 2 SD or ferritin under 12 ng/dl and transferrin saturation below 12% were regarded as iron deficiency anemia. Iron therapy was administered as daily single doses of 5 mg/kg ferric iron.

The patients having no iron deficiency anemia, low ferritin and anoxic epileptic seizures were administered piracetam at 40 mg/kg/day in two doses.

The patients diagnosed with anoxic epileptic seizures were administered levetiracetam 20 mg/kg/day in two doses (initially started with 10 mg/kg/day and increased to 20 mg/kg/day in the second week).

2.2. Statistical analysis

The data were entered in SPSS 25.0 program and calculated as the number, mean, median and percentile values. Quantitative values were checked by the Kolmogorov-Smirnov test to whether they displayed normal distribution or not. In comparing qualitative data in statistical analysis, Chi-Square Test and Fisher's Exact Test were utilized. Kruskal-Wallis analysis was used in comparing independent multilateral groups, and the Mann-Whitney U test in the bilateral comparison of subgroups along with the Bonferroni adjustment. Friedman analysis was implemented in dependent multilateral groups and Wilcoxon signed rank test in comparing bilateral groups. $p<0.05$ was considered statistically significant.

3. Results

One hundred and eight patients (55.7%) were male. The mean age was 21.39±12.78 months. No gender difference was determined between the groups, while the age was statistically significantly lower in the iron therapy group in comparison to the other groups ($p<0.05$). Iron therapy was initiated in 87 patients, piracetam to 96, and levetiracetam to 11 patients. Cyanotic seizures were determined in 150 (77.3%), pallid seizures in 30 (15.5%) and mixed seizures in 14 (7.2%) patients. Cyanotic type of seizures was statistically significantly higher ($p<0.05$). The seizure type distribution of the groups was similar. Family history was positive in 56 (28.9%) patients. Positive family history was highest in the levetiracetam group (45.5%) but there was no statistically significant difference between the groups. Demographic data, seizure types, laboratory results and initiated therapy types of the patients are displayed in Table 1.

Table 1. Demographic data of the patients, seizure type, laboratory results and initiated therapy types

		Iron (n=87)	Piracetam (n=96)	Levetiracetam (n=11)
Gender (n, %)	F	34 (39.1%)	47 (49.0%)	5 (45.5%)
	M	53 (60.9%)	49 (51.0%)	6 (54.5%)
Mean Age ± SD (Months)		18.6 ± 10.4	23.8 ±14.6	21.9 ± 7.1
Positive Family History (n, %)		21 (24.1%)	30 (31.3%)	5 (45.5%)
Type of spell (n, %)	Cyanotic	68 (78.2%)	74 (77.1%)	8 (72.7%)
	Pallid	13 (14.9%)	15 (15.6%)	2 (18.2%)
	Mixed	6 (6.9%)	7 (7.3%)	1 (9.1%)
Mean Hemoglobin ± SD (gr/dl)		9.8 ± 0.9	11.9 ± 0.7	12.4 ± 0.6
Mean Hematocrit (%)		31.13 ± 2.75	36.66 ± 2.34	38.40 ± 2.30
Mean Corpuscular Volume (fL)		68.9 ± 9.0	77.81 ± 4.39	78.3 ± 3.21
Serum Iron (µg/dl) Mean±SD		34.3 ± 19.5	69.7 ± 13.9	72.2 ± 8.3
Total Iron Binding Capacity (µg/dl) Mean±SD		377.5 ± 45.1	241.9 ± 50.9	223.2 ± 38.7
Ferritin (ng/dl) Median (Min-Max)		5.2 (1.6-28.2)	23.5 (12.1-259)	31.3 (12.6-57)

Interictal epileptic discharges were determined in only 4 patients in EEG and all were diagnosed with anoxic epileptic seizures. As for the patients diagnosed with anoxic epileptic seizures, seven had clonic, three tonic and one had myoclonic jerks. Only four of these patients had video recordings, where 3 cases were consistent with clonic and one with clonic-tonic seizures. The monthly number of seizures prior to therapy was most in the iron group but no statistically significant difference was determined with piracetam ve levetiracetam groups. Seizure numbers were manifestly decreased in iron and piracetam groups by the end of the first month after treatment concerning pretreatment levels, and also by the end of the third month concerning levels by the end of the first month ($p<0.05$). In the levetiracetam group however, the seizure numbers decreased significantly by the end of the first month concerning pretreatment levels, and although decreased proportionally by the end of the third month concerning the end of the first month, these differences were not statistically significant. When the groups were compared with each other, the number of seizures at the end of the first month was found to be statistically significantly higher in the piracetam and levetiracetam groups in comparison to the iron group. No significant difference was determined between the groups by the end of the third month. The mean and median values of seizure numbers of therapy groups, before treatment and by the end of the first and third months are displayed in Table 2. The rate of decrease in the seizures is summarized in Figure 1.

Table 2. Evaluation of the seizure numbers prior to treatment, by the end of the first month and third month, regarding administered therapy

Treatment		**Number of spells before treatment (per month)**	**Number of spells at the end of the first month after treatment (per month)******	**Number of spells at the end of the third month after treatment (per month)******	**P***
Iron	Mean±SD	17.5 ± 21.3	5.6 ± 8.1	1.8 ± 3.3	P<0,001
(n=87)	Median (Min-Max)	10 (2-120)	3 (0-37)	1 (0-23)	
Piracetam	Mean±SD	13.0 ± 16.0	3.8 ± 7.0	1.6 ± 3.0	P<0,001
(n=96)	Median (Min-Max)	7 (2-87)	1 (0-47)	0 (0-14)	
Levetiracetam	Mean±SD	14.8 ± 7.8	1.9 ± 2.2	0.2 ± 0.4	P<0,03***
(n=11)	Median (Min-Max)	13 (5-32)	1 (0-7)	0 (0-1)	
P**		p>0.05	0,025	p>0.05	

*: Friedman Variance analysis was utilized. **: Kruskal Wallis Test was utilized ***: While there was a significant decrease in the Levetiracetam group in the first month concerning pretreatment levels, no significant difference was determined between the first and third months. ****: Seizure number decreased at a higher rate in piracetam ve levetiracetam groups for the iron group on the posttreatment first month ($p<0.05$). Although it decreased in piracetam ve levetiracetam groups concerning the iron group similarly by the end of the third month, no statistically significant difference was found ($p>0.05$).

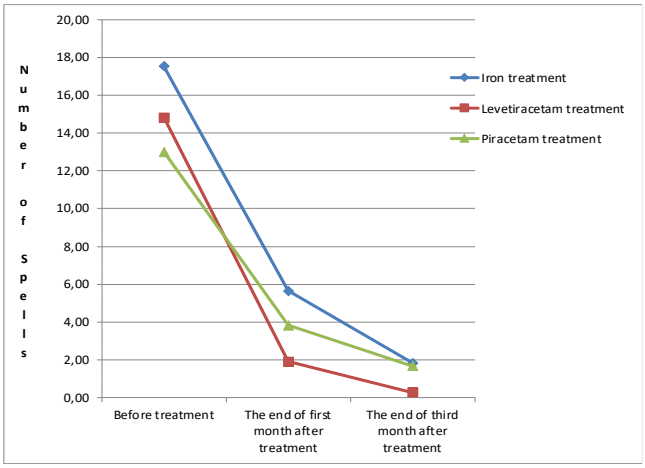

Figure 1. Pretreatment, posttreatment first month and posttreatment third month seizure numbers in relation to initiated therapies

When the groups were evaluated regarding no-seizure, all groups had statistically significant differences by the end of the first month concerning pretreatment levels.

When the groups were evaluated regarding no-seizure, by the end of the first and third months, iron and piracetam groups displayed significant differences while no significant differences were found in levetiracetam values (Table 3).

Table 3: No seizure rates by the end of first and third months in relation to administered therapies

Treatment	Patients without spells at the end of first month		Patients without spells at the end of third month		P*
	n	%	n	%	
Iron (n=87)	24	27.5	43	49.4	< 0.001
Piracetam (n=96)	41	42.7	60	62.5	< 0.001
Levetiracetam (n=11)	4	36.3	8	72.6	< 0.23**
P*	0.102		0.115		

*: Chi-square and **Fisher's Exact Test were used. There was a statistically significant difference by the end of first month with respect to pretreatment levels in Piracetam group, while there was no statistically significant difference by the end of third month with respect to first month levels in spite of a numerical increase.

4. Discussion

This is the first study evaluating patients with BHS and having initiated at least one of the therapies of either iron or piracetam or levetiracetam, and also the first study assessing the efficacy of levetiracetam in an anoxic epileptic seizure.

It is a common practice that patients with BHS, particularly those with cyanotic seizures, are referred to a cardiologist or a neurologist but in most cases, no neurologic or cardiologic disorders are determined at the end (8). In many studies, familial predisposition for BHS was reported as 20-35% (15). In our series, the rate of family history was determined to be 28.9%. EEG is not necessary if clinic and history data support BHS beyond any doubt. Nonetheless, EEG is taken in most cases, particularly in those with loss of consciousness, due to family concerns and demands to rule out the possibility of epilepsy (16). Interictal epileptic discharge was determined in EEG in only 4 patients, all having an anoxic epileptic seizure.

Generally, no medical treatment is recommended in BHS. It is sufficient to ease the fears of the parents and convince them that this situation is harmless. Nevertheless, severe BHS can be very stressful, fearful and irritating for the parents and a pharmacologic agent may be requested in some such cases (11). Several agents were tested in case of severe BHS (7). Besides administering medical therapies such as iron therapy (11), piracetam (17), levetiracetam (18), theophylline (19), fluoxetine (20), glycopyrrolate (21), atropine (22) so far, even some invasive methods such as a cardiac pacemaker (23) were also used in some children. We couldn't find any data in the literature about the rate of treated BHS patients, however, 194 (11,3%) out of 1707 patients were already initiated therapy in our series. If we disregard the patients with iron deficiency anemia or low ferritin, it turns out that only 107 (6.2%) of BHS patients initiated therapy. It is known that iron deficiency or iron deficiency anemia is related to BHS. Iron deficiency may have a disorder-causing effect on the autonomous nervous system, since iron functions as a cofactor for various enzymes and neurotransmitters in catecholamine metabolism and the central nervous system (24–26). As regards BHS, children with iron deficiency anemia are more irritable and provoked easier (11). It was shown in many studies that the treatment of iron deficiency causes the spell number of BHS patients either to decrease or to heal (4,25–27). There was iron deficiency anemia or iron deficiency in only 87 (5%) of 1707 patients. In their study on children with anemia and receiving iron therapy, Jain et al. (11), determined full response in 73% and at least a 50% decrease in spell number in 23% of 100 children suffering seizures. Gürbüz et al. (27) determined a 47.1% no spell rate after iron therapy and a more than 50% decrease in spell number in 39.1% of their patients. In our series, no seizure rate was found to be 49.4% after 3 months of iron therapy. The number of spells at the end of the first month decreased significantly concerning pretreatment levels. Our findings regarding iron therapy were found to be in concordance with the literature.

Piracetam (2-oxo-1-pyrrolidine acetamide) which is a cyclic derivative of gamma-aminobutyric acid (GABA) was reported to have an increasing effect on oxygenation of brain tissue and GABA-like inhibitor hyperpolarization, and for this very reason, it was likely to be effective in BHS (7,17). In many studies, piracetam

was reported to make partial or complete remission and to have a significant difference with a placebo (7,12,28). In our series, the number of seizures decreased at the end of the first and third months and no seizure rate was determined as 42.7% at the end of the first and 62.5% at the end of the third month. Both the average number of seizures and no seizure rates decreased statistically significantly as the period of use increased. However, a study was recently published reporting piracetam was not efficacious (29).

Levetiracetam ((S)-a-ethyl-2-oxo-1-pyrrolidine acetamide), is a new anticonvulsant agent resembling piracetam structurally (30,31). There are not too many studies in the literature on levetiracetam use in "anoxic epileptic seizures" (9) that were defined first by Stephenson in 1983. Lukkarinen et al. (18) reported a case of a ten months old girl developing bradycardia, asystole and loss of consciousness during the spell, not responding to atropine and propranolol but recovering consciousness by levetiracetam. They reported this effect could be associated with the regulation of cardiac autonomic stimulation or the effect on the calcium channel. Rathore et al. (32) reported a case of a 38-day-old girl, having anoxic epileptic seizures despite phenobarbital and having seizures decreased by levetiracetam. In another study evaluating 27 patients with anoxic epileptic seizures, it was reported that medical therapies proved inefficacious in two patients and a cardiac pacemaker was applied and valproate and carbamazepine were applied in 7 patients prophylactically and in 5 of them seizures stopped (33). And a case of a girl having generalized seizures due to BHS was cured by psychotherapy administered to the mother and child (10). In a study of 47 cases, 100% with syncope and 78.3% with anoxic epileptic seizures, all patients have installed pacemakers due to failure in medical treatment. It was reported that findings disappeared after the pacemaker in 86.4% and decreased in 13.6% of the patients (34).

In our study, 11 patients were having developed hypoxia and convulsion after expiratory apnea and were diagnosed with anoxic epileptic seizure. All patients have initiated levetiracetam. BHS as well as anoxic epileptic seizures recovered after initiating levetiracetam in 4 (36.3%) patients by the end of the first month, and in 8 (72.6%) patients by the end of the third month. In three patients with continuing seizures, seizure numbers as well as the duration and severity of seizures were observed to decrease (according to the report by the parent). These results suggest that levetiracetam should be tried before administering an invasive therapy like a cardiac pacemaker in case there is no response to initiated therapies in anoxic epileptic seizures.

When the groups were compared concerning each other, less decrease in the number of seizures at the end of the first month in the anemia group concerning the other two groups can be explained by the duration of iron deficiency therapy lasting for a minimum of 3 months and hemoglobin values reducing to age-appropriate values at the end of the first month. And yet again in the levetiracetam group, a statistically insignificant difference between first-month and third-month values in terms of a decrease in seizure numbers as well as no seizure rates may be due to peak plasma concentration of levetiracetam attaining maximum value within one hour and attaining constant plasma concentration within two days when taken two doses a day (31).

5. Conclusions

As a result, we determined that the spells were reduced or completely stopped by iron therapy in BHS patients with iron deficiency or iron deficiency anemia, and by piracetam in patients without iron deficiency. Levetiracetam seems to be considerably effective in patients developing anoxic epileptic seizures after BHS. We consider that levetiracetam should be tried as a treatment option particularly before administering invasive methods.

Limitations of the study

Having a retrospective design and having no control groups among the study groups are the limitations of this study.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Support: No financial resources were used in this study.

Ethics Committee Approval: We received ethics committee approval from Gazi Yaşargil Education and Research Hospital (with date and number: 342/27.09.2019).

Authorship Contribution:

NÖ: Data collection, planning, writing.

OA: Data collection, planning.

MÇ: Data collection, planning.

HS: Data collection, planning.

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