ORIGINAL ARTICLE

Evaluation of the Effectiveness of Risperidone in Treating Breath-Holding Spells in Children

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Abstract

Objectives

Breath holding spells (BHS) are a type of syncope in children that is commonly seen in the first years of life. Although these attacks do not cause serious damage to the child's brain, in severe or repeated cases, they expose the brain to hypoxia and cause a lot of stress in parents. In these cases, the clinician should consider therapy. The purpose of this study is to investigate the effectiveness of Risperidone in the treatment of BHS in children visiting the neurology clinic of the Children's Medical Center Hospital.

Materials & Methods

In this randomized clinical trial, the statistical population included patients with the history of Breath Holding spells grades 2 to 3 (after ruling out of seizure disorders) over one year old, visiting the neurology clinic of Tehran Children's Medical Center in 2019. The subjects were randomly selected from patients visiting the clinic using a table of random numbers from the admit ion list. After providing the necessary explanations and obtaining informed consent from their parents, they were treated with low-dose Risperidone (maximum 1 mg) for three months. The patients were observed for three months in terms of frequency and severity of spells monthly.

Results

In this study, the median (25th and 75th percentile) age of subjects was 2.3 (2.0-2.6) years. Both the number and severity of seizures in the subjects had a statistically significant decrease in the period after treatment with Risperidone ($P<0.001$). The studied boys and

girls experienced statistically significant decrease in terms of both the frequency of spells (P-value of 0.002 and 0.039) and intensity of seizures (P=0.016) and P=0.008), respectively after treatment with Risperidone. Also, in the studied children under 2 years old and over 2 years old, both the frequency (P=0.021 and P=0.004) and intensity of spells (P=0.008) 0.016 for subjects under and over 2 years, respectively) had a statistically significant decrease after treatment with risperidone compared to pretreatment.

Conclusion

According to the results of this study, it seems that both the frequency and the intensity of spells in children (regardless of gender and age group), experienced a statistically significant decrease after treatment with Risperidone. We suggest conducting a more comprehensive study considering a larger sample size in order to estimate this issue more correctly.

Key words: Breath holding spells, grade of BHS, Risperidone, gender, children

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Introduction

Breath-holding spells (BHS) are sudden, reflexive, non-epileptic phenomena common in infancy and early childhood. Patients usually visit neurology and pediatric cardiology clinics on suspicion of suffering from heart disease or seizures (1-3), so breath-holding attacks are one of the most common imitators. Outbreaks appear to be exacerbated during the first 6 to 12 months of life and usually improve between four and five years. However, rare cases have been reported up to the age of seven years (1, 3-4). More than 4-5% of children over the age of eight years have breath-holding attacks. Hereditary predisposition to the disease has been justified, and its inheritance is autosomal dominant (1, 3-4). Although its etiology is still unknown, dysfunction of the autonomic system and increased vagus nerve tone, leading to cardiac arrest and cerebral anoxia, has been suggested as a significant cause. Previously, it was believed that this disorder would slowly improve as the autonomic nervous system matured. (1, 5-6). Diagnosis is usually made by observing spells. Seizures always occur when patients are awake and last almost always for less than a minute, following a mild trauma or psychological distress and the child being deterred from doing something by parents or caregivers. It often involves a period of crying followed by a silent state of exhalation, characterized by discoloration of the skin, either paleness or cyanosis, leading to a decrease in the level of consciousness and tone, and resolves spontaneously without any action (4). Although these attacks often last 10 to 60 seconds and are benign, they may be followed by severe

syncope attacks, tonic posture, and anoxic seizures (7). It is divided into two types based on the skin color change during the attack: cyanotic and pale. However, many children develop a combination of these two during seizures (1, 4). Notably, the pale type of attack is rare. Parasympathetic hypersensitivity may cause cardiac bradycardia, decreased cardiac output, hypotension, and consequently pale appearance. The treatment of breath-holding attacks focuses on supporting and reassuring parents. In the past, these attacks were thought to disappear with aging and maturation of the individual's autonomic system (1, 3-4). Differentiating this type of spell from seizure disorders is based on the history of witnessing the event at the child's bedside or seeing a video made by the parents. Typically, an EEG is not required for diagnosis unless it is impossible to clinically dismiss the possibility of a seizure disorder (8).

Management of BHS has been an area of many clinical works for years, and little has been acquired so far. Among the measures studied to reduce the frequency of breath-holding attacks are psychological interventions and assessment for iron deficiency and its correction (9-11). Nevertheless, these cases are only a subgroup of patients with BHS and a group of patients with neither iron deficiency nor a psychological risk factor in their family. Other therapies used for this disease include atropine at a dose of 0.01 mg/kg two to three times a day in pallor type, piracetam with a chemical structure similar to GABA at a dose of 50-100 mg/kg, fluoxetine, theophylline, as well as anticonvulsants such as levetiracetam and phenytoin have also been used. Therefore, it is necessary to study more comprehensive therapeutic measures for this disease that is worrisome for parents and affects the quality of life of both parents and children (10, 11).

Risperidone, an atypical antipsychotic agent, has long been utilized in clinical practice to treat psychological conditions such as bipolar mania, delirium, disruptive behavior disorders, schizophrenia, and Tourette syndrome. It has been associated with some adverse reactions, including activating/sedating effects, angioedema, dyslipidemia, extrapyramidal symptoms (EPS), hematologic abnormalities, hyperglycemia, hyperprolactinemia, neuroleptic malignant syndrome, orthostatic hypotension, QT prolongation, temperature deregulation, and weight gain, some of which are more common, including endocrine and metabolic reactions, constipation, increased appetite, nausea, upper abdominal upset, vomiting, urinary incontinence, akathisia, anxiety, dizziness, drooling, drowsiness, EPS, fatigue, headache, insomnia, parkinsonism, tremor, cough, nasopharyngitis, rhinorrhea, and fever; none of which are hardly an indication to stop the therapy(12).

According to a review we conducted in various databases, no trials on the effect of risperidone to stop BHS have been recorded in the data banks. Risperidone is one of the selected therapies for treating psychological disorders in children, and in some cases, its therapeutic effect on severe BHS, even those with asystole, has been reported (11). Therefore, the present clinical trial aimed to investigate the therapeutic effects of this drug on pediatric BHS.

Materials & Methods

In this randomized clinical trial, all patients with a diagnosis of BHS (after ruling out actual seizures) over one year of age who attended the neurology

clinic of Tehran Children's Medical Center Hospital in 2021 with a history of breath holding with Grade 2 or 3 were included in the study (Grade 1: He cries and his voice goes away. Grade 2: He cries, his voice goes away, and he is cyanotic. Grade 3: He cries, his voice goes away, he is cyanotic, and he also has a low level of consciousness, which mimics seizures). Based on previous studies and following the study's objectives, 30 cases were assigned. Sampling was randomized using a table of random numbers from the admission list.

Inclusion criteria:

1- Normal EKG (to rule out heart disease, including prolonged QT)
2- Ruling true seizures out
3- Normal EEG (looking for epileptic waves)
4- No history of taking anticonvulsant drugs or other drugs such as piracetam, levetiracetam, phenytoin, etc. (in this study, those using iron supplements were not excluded)
5- No respiratory involvement

Exclusion criteria:

1- Existence of seizures
2- Use of anticonvulsant drugs or other drugs such as piracetam, levetiracetam, phenytoin, etc.
3- Lung diseases
4- No informed consent
5- Have any drug-related side effects

Procedure

After providing the necessary explanations and obtaining informed consent, the subjects were treated with low-dose risperidone (maximum 1 mg daily) for three months. The subjects and their guardians were fully informed about the possible side effects of the medication. In addition, the contact number of the researcher was provided to them to contact in the case of any event. Patients were monitored for the frequency and severity of spells for three months, and the mean frequency and severity of attacks were assessed monthly. Response to therapy was evaluated in two ways: 1. Reducing the frequency of spells (more than 50% decrease) 2. Effect on the clinical grade of spells. Whenever the frequency of seizures decreased by more than 50% or the grade of the spells improved by 1 degree, it was considered a positive response. Notably, the evaluation method was as before and after treatment, i.e., each patient was compared with him/herself before and after taking the medication. Patients' data, including demographic characteristics and the number and severity of spells, were collected by parents monthly using a checklist.

Statistical Analysis

Data were analyzed using SPSS statistical software version 26. The normality of the data was evaluated using the K-S test. Frequency (percentage) was used to describe qualitative data, mean (standard deviation) was used for quantitative data, and median (25th and 75th percentiles) was used if the distribution of data was not expected. Paired t-test was used to analyze quantitative data with normal distribution in time sequence, and the Wilcoxon test was used for the data without normal distribution. A sign test was also used to analyze ranking data in time sequence. The statistical significance level (P-value) was considered 5% (0.05).

Results

This study selected 30 patients aged 14 months to four years, with a median age of 2.3.

As can be seen in Table 1, most subjects were

males, with 18 cases (0.60%).

The effect of risperidone on the frequency and severity of BHS in the subjects is shown in Table 2. As can be seen in this table, both the frequency and severity of BHS in the subjects had a statistically significant decrease after treatment with risperidone compared to before treatment (P <0.001).

The effect of risperidone on the frequency and severity of spells according to sex is shown in Table 3.

As can be seen in this table, in males, both the frequency (P = 0.002) and severity of BHS (P = 0.016) had statistically significant decreases after treatment with risperidone, so did in females with p-values of 0.039 and 0.008, respectively.

Finally, the effect of risperidone on the frequency and severity of BHS concerning age groups is depicted in Table 4.

As can be seen in Table 4, regardless of the age group of subjects, both the frequency (p-values of 0.021 and 0.004 for subjects under and over 2 years, respectively) and severity of spell frequency (p-values of 0.008 and 0.016 for subjects under and over two years, respectively) had a statistically significant decrease after treatment with risperidone compared to pre-treatment.

Table 1. Demographic characteristics of the subjects.

variable	Groups	Frequency(percentage)
sex	male	18(60%)
	female	12(40%)
Age(months)	minimum	14 mo
	maximum	48 mo
Age(years)	Mean(percentile25-75)	2.3(2.0-2.6)

Table 2. The effect of Rispiridone treatment on the frequency and severity of spells in the subjects.

variable		*Pre treatment values	*post treatment values	P-value
Number of spells		2 (1.0 -2.0)	1(0.75 -2.0)	0.001
BHS-Grade	Grade 1	0	14(46.7%)	0.001
	Grade 2	26(86.7 %*)	9(30%)	
	Grade 3	4(13.3%)	0 (0.0 %)	

* P-value by Wilcoxon Signed Ranks Test.

** P-value by Sign Test.

Table 3. The effect of Risperidone treatment on the number and severity of seizures by sex in the subjects.

sex	variable	Groups	*Pre treatment values	*post treatment values	P-value
male	Number of spells	-	2 (0.0 -2.1)	1(0.0 -2)	0.002
	Grade of spells	1	0	6(33.3%)	0.016
		2	16(88.9%)	6(33.3%)	
		3	2 (11.1%)	0 (0.0 %)	
Female	Number of spells	-	2 (0 -2.1)	1 (0.1 -1)	0.039
	Grade of spells	1	0	8 (66.7%)	0.008
		2	10 (83.3%)	3 (25%)	
		3	2 (16.7%)	0 (0%)	

* P-value by Wilcoxon Signed Ranks Test.

** P-value by Sign Test.

Table 4. The effect of Raspiridone treatment on the number and severity of seizures by age groups in the subjects.

Age	variable	Groups	Pre treatment values	post treatment values	P-value
age<2 years	Number of spells	-	1 (0.0 -1.2)	1(0.0 -1.1)	0.021
	Grade of spells	1	0	8(53.3%)	0.008
		2	12(80%)	4(26.7%)	
		3	3 (20%)	0 (0.0 %)	
Age>2 years	Number of spells	-	2 (0 -1.3)	1 (0 -1.2)	0.004
	Grade of spells	1	0	6 (40%)	0.008
		2	14 (93.3%)	5 (33.3%)	
		3	1 (6.7%)	0 (0%)	

* P-value by Wilcoxon Signed Ranks Test.

** P-value by Sign Test

Discussion

This study aimed to evaluate the efficacy of risperidone in treating BHS in children visiting the neurology clinic of the Children's Medical Center Hospital.

The study results show that the subjects' frequency and severity of BHS had a statistically significant decrease after treatment with risperidone (P<0.001). The same applies to the subjects regardless of their sex and the age group they belong. Seemingly, the effect is more significant in those with severe spells, with response to risperidone reported in all subjects, though the number of subjects was limited.

To the best of our knowledge, there is no trial assessing the efficacy of risperidone to stop BHS, so this study intend to compare its effectiveness with other therapies in clinical use so far.

Another medication that has historically been used with different therapeutic effects is piracetam. Abbaskhanian et al., in a clinical trial, examined the efficacy of paracetamol on 150 children with

severe breath holding spells and their age and sex-matched counterparts receiving a placebo and found that the frequency of spells in the group receiving piracetam was significantly lower than controls. (13) In a placebo-controlled clinical trial conducted by Ashrafzadeh et al., the number of BHS two months before and after treatment were compared. The results showed that in 19 subjects (90.5%) receiving piracetam, a good response was observed, as opposed to the placebo cohort, with eight subjects (40%) experiencing spells (P = 0.002). They concluded that piracetam is an effective agent for treating BHS without any major side effects (14). On the other hand, Ashrafi et al. conducted a clinical trial on 32 subjects over six months to assess the efficacy of piracetam on BHS and they did not find any significant difference between those receiving piracetam and placebo(P = 0/17) (15).

Some clinicians have suggested fluoxetine, a serotonin-specific reuptake inhibitor antidepressant, as a therapy for BHS. Walsh conducted a prospective study on six patients with pallid PBH who received fluoxetine, of whom five patients became symptom free without experiencing any side effects (16). In another case-control study by Farzadfard et al., the control group was treated with iron and the intervention group with iron and fluoxetine for three months. The study's results confirmed the effect of iron therapy in reducing the mean frequency and duration of BHS, but the co-administration of fluoxetine and iron did not add any further benefit concerning decreasing the mean frequency and duration of BHS (17).

Hamed et al. studied 180 children with cyanotic spells in three groups: Iron deficiency anemia, iron deficiency without anemia, and without iron deficiency. They found that iron deficiency with or without anemia was associated with a high risk of BHS, and iron therapy reduces the frequency of these attacks (10). In a clinical trial by Khashabi et al., the results of oral administration of iron at a dose of 6 mg/kg for three months in 28 infants with BHS with a mean age of 19.5 months were evaluated. The results showed that at the end of three months of iron therapy in 75% of the subjects, BHS completely disappeared, followed by 14% of participants reporting more than 50% decrease in frequency of spells and 11% of cases with less than 50% recovery (20). In a systematic review and meta-analysis by Hecht et al., the findings indicated a significant reduction in BHS after iron therapy (18). In addition to these studies, several studies show a positive and significant effect of iron administration for treating BHS in children, including the study of Daoud et al. (In 1997, on 33 children with an average age of 15 months) (19), a study by Abosdera et al. (In 2016, on 40 children aged 4 to 48 months) (20), a study by Bhat et al. (in 2006, on 35 children under 36 months of age) (21), a study by Dai and Demiryürek et al. (in 2019, on 146 children aged 12 to 48 months) (22), Ghareib et al.'s study (in 2017, on 35 children aged 6 to 72 months) (23), Gurbuz et al.'s study (in 2018, on 312 children 1 to 48 months) (24), Handan et al.'s study (in 2005, on 22 children 3 to 48 months old) (25), Hussain et al.'s study (in 2016, on 45 children 6 to 72 months) (26), Jain et al.'s study (in 2017, on 100 children aged 6 to 36 months) (27), Mocan et al.'s study (in 1999, on 63 children 6 to 30 months old) (28), a study by Tonekaboni et al. (2006, on 35 children aged 3 to 60 months) (32), and a study by Ziaullah et al. study (in 2005, on 50 children aged 6 to 60 months) (29).

In Conclusion

In this study, both the frequency and the severity of BHS in the subjects had a statistically significant decrease after treatment with risperidone. This effect was seen in all subjects regardless of their sex and age. This effect was dramatically increased in those with severe types of BHS. With these results, seemingly, risperidone can be an option for treating higher-grade BHS. Indicatively, risperidone can at least be a promising agent to stop severe cases of BHS. This research suggests that clinical trials, including patients with severe BHS, are conducted to examine the efficacy of risperidone to stop these spells so that this study can generalize these findings and propose a new therapy for BHS.

The current study suggests that the efficacy of risperidone on BHS is examined in a clinical trial, including two cohorts: One treated with just iron and the second with iron and risperidone, and larger sample size so that the results of the study could be applied to the general population.

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Author's Contribution

Zamani. GH suggested the idea and was involved in drafting the first and the last manuscript and supervised the whole process. Abdi. Alireza drafted the proposal and final manuscript and collected and analysed the data.Heydari. Morteza supervised the process. Ashrafi.MR was involved in drafting the final manuscript. Tavasoli. AR contributed to collecting data and reviewed the final draft.

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Conflict of interest

None

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