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Effect of Fluoxetine Therapy on Breath-Holding Spells in Children: A Clinical Trial Study

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Abstract

Background: Breath-holding spells (BHS) is a sudden and reflexive phenomenon that is common in infancy and early childhood. Despite the harmless nature of BHS, being subjected to this phenomenon is very stressful for parents and sometimes requires treatment. In this study, we evaluated the efficacy of fluoxetine therapy (as an anxiolytic medication) on pediatric BHS.

Materials and Methods: The present clinical trial study was carried out on 30 patients with BHS referring to Neurology Clinic of Ghaem Hospital, Mashhad, Iran, in 2018. The subjects were randomly divided into control (n = 15), and intervention (n= 15) groups. The control group was then treated with iron and the intervention group with iron and fluoxetine for 3 months. The frequency and duration of BHS before and after treatment were compared in both groups. The results were later analyzed using SPSS version 16.0.

Results: The present study was carried out on 30 children. The mean of infants' age in the control and intervention groups was 20.26 ± 5.8 and 22.46 ± 5.2 months, respectively (P>0.05). The mean frequency and the duration of BHS decreased from 8.2 ± 4.3 to 1.6 ± 2.4 times per week (p = 0.000), and from 50.66 ± 26.26 to 5.4 ± 6 seconds (p = 0.000) in the control group; and from 7.2 ± 3 to 2.06 ± 2.7 times per week (p = 0.001), and 50.66 ± 38 to 8.8 ± 7.9 seconds (p = 0.002) in the intervention group, which was indicative of a statistically significant difference. However, the difference in the mean frequency and duration of BHS in the intervention group, which represents the effect of fluoxetine, was not statistically significant (p = 0.411 and p = 0.792, respectively).

Conclusion: The results of the present research confirm the effect of iron therapy on decreasing the mean frequency and duration of BHS, but also indicate the ineffectiveness of synergistic administration of fluoxetine and iron on decreasing mean frequency and duration of BHS.

Key Words: Breath-holding spells, Children, Fluoxetine, Iron.

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1- INTRODUCTION

Breath-holding spells (BHS) is a sudden, reflexive, and non-epileptic phenomenon that is common during infancy and early childhood (1-3). Spells usually start between 6 and 12 months of age and will approximately stop by the time the child is 4 or 5 years old, although rare cases are seen up to the age of 7 (3-7). BHS is an involuntary disorder in children and is classified based on the color change manifested by the child during the event in cyanotic, pallid, or mixed episodes. The cyanotic BHS is the most prevalent type where the crying baby holds a deep breath and doesn't breathe out, then the lips appear bruised and limbs may occasionally become stiff and sometimes develop clonic movements. These spells sometimes occur following a trauma and the crying baby may lose consciousness and turn pale and return to the original state after a few seconds. This type is called pallid. The baby rarely suffers from both cyanotic and pallid BHS after crying or trauma, which is called mixed BHS (8-11).

BHS commonly affects more than 4-5% of children over the age of 8. Previous studies have proven the role of inheritance in developing the disease and its inheritance is autosomal dominant (1, 3, 4), its etiology, however, is still unclear. The present study reported that the incidence of spells is 4.6 to 4.7% (12). These spells, which usually begin in early infancy, do not damage the baby's brain and do not cause death, but cause great fear for parents. It is often enough to reassure the parent, but in cases of repeated or severe spells, the physician will have to think about treatment. A study in Turkey investigated the effect of piracetam on 76 children with BHS and reported an improvement in 92.3% of cases (13). In some children, iron administration reduces the frequency of BHS (5, 14, 15). Some studies have also shown the efficacy of iron treating this disease (16). Results of some studies have also shown that fluoxetine is effective in treating depression and anxiety in children and adolescents (17-19). A six-week meta-analysis study of four randomized trials focusing on patient outcome (708 young people with major depression) showed that fluoxetine-treated patients were more responsive to the treatment than placebo group (30% vs. 6%); other studies have shown the efficacy of fluoxetine (20-23). BHS occur in 5% of children less than 5 years of age, most of which are of cyanotic and pallid types and affect children and families. In most cases, these spells are benign and stop until the age of 4 to 5 years, as parents experience high levels of anxiety and stress due to these spells and they are sometimes forced to submit to their child's desires, which in turn leads to behavioral disorders in later life stages. It is thus recommended to carry out therapeutic intervention using iron, piracetam and even anticonvulsants such as levetiracetam, theophylline, glycopyrrolate, atropine, and scopolamine (4). However, there have been no studies so far on the effect of fluoxetine in treating BHS in Iran. The aim of the present study was to investigate the effect of fluoxetine as an anxiolytic drug in treating BHS in children.

2- MATERIALS AND METHODS

2-1. Study design

This double-blind clinical trial study was conducted on 30 children with BHS referred to the Pediatric Neurology Clinic of Ghaem Hospital who met the inclusion criteria from March 2018 to March 2019. Since the present study was the first to use fluoxetine for the treatment of all types of pediatric BHS, it was thus conducted as a pilot study and the sample size was calculated 15 patients in each group according to prevalence rate (1, 3, 12). Patients were randomly divided into intervention and control groups.

Electrocardiogram (ECG or EKG) test was taken from all children and those with abnormal ECG were excluded. The intervention group (n = 15) received fluoxetine and iron drops, and the control group (n = 15) received iron drop only for 3 months. Fluoxetine is an antidepressant. It can work effectively in cases of depression, anxiety, fear, etc. that disrupt the chemical imbalance in the brain. The fluoxetine syrup (4 mg / ml) used in this study contains 4 mg of active ingredient per ml and was prepared from Abidi Pharmaceutical Co. The drug was administrated at doses of 5-10 mg/day and packaged in 60ml glass syrup bottle. The drug dose was extracted from the results of similar studies. 125 mg iron drop (25 mg/ml elemental iron) was administrated at a dose of 1 ml daily (after breakfast).

The mean frequency of BHS, including cyanotic, pallid or mixed types occurred during the last 3 months, was recorded before the study. The medication was prescribed by the pediatric neurologist and then the frequency and duration of spells (per week) were recorded 3 months later. Patients were followed up via telephone and, if desired, by the pediatric neurology clinic. The medication was discontinued in case of any side effect, such as loss of appetite or sleep disorders (in case of disruption with weight gain or quality of life). After three months, the frequency of spells per week was calculated in two groups and results analyzed by SPSS software version 16.0.

2-2. Inclusion criteria

Inclusion criteria included: infants aged less than 2.5 years of age, BHS with frequency of at least once every 2 weeks or more, normal EKG, and parental consent for participation.

2-3. Exclusion criteria

Exclusion criteria included: Possible suspicion of epilepsy (based on clinical and familial evidence and brain EEG if necessary), abnormal EEG, systemic disorders, family history of epilepsy in first degree relatives, abnormal ECG and cardiac examination, and fluoxetine use due to another problem or disorder.

2-4. Ethical Considerations

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1397.379), and registered in Iranian Registry of Clinical Trials (IRCT) (IRCT20161230031668N3). Parents completed the consent form and the subjects had the right to voluntarily participate and withdraw from the study at any time.

2-5. Data analysis

The collected data were analyzed by SPSS software version 16.0. Then, mean and standard deviation (Mean ± SD) indices were used to describe quantitative data and tables and graphs for qualitative data. Chi-square and t-tests were used for data analysis. P-value<0.05 was considered as the significance level.

3- RESULTS

The mean ± SD of infants' age in the control and intervention groups was not significantly different (20.26 ± 5.8 and 22.46 ± 5.2 months, respectively) (p = 0.286). In the present study, the baseline data comprised 66.6% (n=10) of boys in control and 80% (n=12) of boys in intervention groups (p = 0.682). Both control and intervention groups had 100% normal Apgar score and development (p = 1.000). The frequency of infants with previous hospitalization in the control and intervention groups was 7 (46.7%), and 8 (53.3%) individuals, respectively (p = 0.669). The reason for previous hospitalization included icterus, infection, others (rejection of seizure) and there was no significant difference between the two groups in this regard (p = 0.669) (**Table.1**).

Table-1: Baseline Characteristics in the intervention and control groups.

Variables	Sub-group	Control group, (Iron)	Intervention group (Iron+ Fluoxetine)	P-value
Age, month		20.26 ± 5.8	22.46 + 5.2	0.286
Gender	Boy	10 (66.7)	12 (80)	0.682
	Girl	5 (33.3)	3 (20)	
Parental Family Ratio	Yes	4 (6.26)	5 (33.3)	0.690
	No	11 (73.4)	10 (66.6)	
Age gap with previous child, year		3.1	1.4	0.103
Pregnancy problems	Yes	2 (13.3)	2 (13.3)	1.000
	No	13 (86.6)	13 (86.6)	
Type of delivery, number (%)	Normal	10 (66.6)	12 (80)	0.409
	Cesarean section	5 (53.3)	3 (20)	
Apgar score, number (%)	Normal	15 (100)	15 (100)	1.000
	Abnormal	0	0	
Previous hospitalization history, number (%)	Yes	7 (46.6)	8 (53.3)	0.715
	No	8 (53.3)	8 (53.3)	
Reason for previous hospitalization, number (%)	Icter	2 (13.3)	3 (20)	0.669
	Infection	2 (13.3)	2 (13.3)	
	Others (seizure rejection)	3 (20)	3 (20)	
	No	8 (53.3)	7 (46.6)	
History of trauma, number (%)	Yes	1 (6.6)	0	1.000
	No	14 (93.3)	15 (100)	
Family history of seizures,	Yes	0	0	1.000
	No	15 (100)	15 (100)	
Improvement, number (%)	Normal	15 (100)	15 (100)	1.000
	Abnormal	0	0	

The age of onset of the first spell in the control and intervention groups was 13.4 ± 6 and 10.4 ± 3.6 months, respectively, which was not statistically significant between the two groups (p = 0.105). The frequency of infants with cyanotic, pallid, mixed spells was 13 (86.6%), 1 (6.6%), and 1 (6.6%) in the control group and 15 (100%) infants with cyanotic spell in the intervention group (p = 0.483). Crying was the trigger of spells in 11 (73.3%) and 9 (60%) infants in the control and intervention groups, respectively. Trauma was not reported as the trigger of spells in both groups, and concurrent crying and trauma triggered spells in 4 (26.7%), and 6 (40%) cases in the control and intervention groups, respectively (p = 0.439) (**Table.2**).

Table-2: Comparison of the onset of the first spell, the type of attack and the onset of the attack in the intervention and control groups.

Variables	Sub-group	Control group (Iron)	Intervention group (Iron+ Fluoxetine)	P-value (t-test)
The age of onset of the first spell, month		13.4 ± 6.0	10.4 ± 3.6	0.105
Type of spell	Cyanotic	13. (86.6)	15 (100)	0.483
	Pallid	1 (6.6)	0	
	Mixed	1 (6.6)	0	
The trigger for the attack	Crying	11 (73.3)	9 (60)	0.439
	Trauma	0	0	
	Mixed	4 (26.7)	6 (40)	

Results showed that there was a significant statistical relationship between the mean number of attacks (per week) before and after treatment in the control and intervention groups ($p<0.05$). There was a significant statistical relationship between the mean duration of attacks (second) before and after treatment in the control and intervention groups ($p<0.05$) (**Table.3**).

Table-3: Assessment of the number of attacks and duration of attacks in the control and intervention groups, before and after treatment.

Groups	Sub-group	Before treatment Mean ±SD	After treatment Mean ±SD	P-value (t-test)
Number of attacks (per week)	Control group	8.2 ±4.3	1.66 ± 2.4	0.001
	Intervention group	7.2 ± 5.3	2.06 ± 2.7	0.001
Duration of attacks (second)	Control group	50.66 ±26.0	5.5 ± 6.0	0.001
	Intervention group	50.66 ± 38.0	8.8 ± 7.9	0.002

As shown in **Table.4**, the difference in the mean frequency of spells in the control and intervention groups was -6.5 ± 4.2 and -5.2 ± 5 weeks, respectively, which was not statistically significant ($p = 0.411$). The difference in the mean duration of spells in the control and intervention groups was -45.2 ± 25 and -41.8 ± 41.6 seconds, respectively, which was not statistically significant ($p = 0.792$).

Table-4: Comparison of the number of spells and the duration of spells between the control and intervention groups.

Variables	Control group (Iron)	Intervention group (Iron+ Fluoxetine)	P-value
Difference in the number of spells (week)	-6.5 ± 4.2	-5.2± 5.0	0.411
Difference in the duration of spells (second)	-45.2 ± 25.0	-41.8 ± 41.6	0.792

4- DISCUSSION

BHS is a well-known problem among children, with an average prevalence of 5% to 27% among child population. Overall, BHS is more common in boys than in girls, with a ratio of 1.3: 5% reported in most studies (5). In the present study, the age of the children in the intervention group was 22.46 months. In a study on 83 patients, Bridge et al. showed that the first symptoms of the disease were seen among children younger than 18 months of age in 80% of cases (12). In terms of family history, previous articles reported that 27% of parents and 21% of patients' brothers and sisters had a history of BHS and after family studies, the possible inheritance of the dominant autosome with variable infiltration has been discussed (24). The present study, however, reported no cases of the family history of seizures and BHS in patients, which is probably due to the lack of awareness of the history of these attacks in our patients' parents. According to most previous studies, cyanotic BHS was the most common type of BHS (5, 25, 26), which is consistent with the present study. Donma et al. (1998) investigated the therapeutic effect of piracetam in treating 76 patients with BHS. The patients were randomly divided into two groups: control (placebo), and intervention (piracetam 40 mg / kg) in two periods. The results showed that BHS symptoms were

controlled in 92.3% of patients of the intervention group and 29.7% of the control group (26). Walsh et al. (2012) investigated the effect of fluoxetine in reducing PBH symptoms in 6 patients aged 12-60 months. The results showed that fluoxetine reduced the incidence of syncope in 5 out of 6 patients; no side effects were reported for fluoxetine (23). Although the results of the current study confirm the effect of iron therapy in decreasing the frequency and duration of BHS, they also indicate the synergistic effect of fluoxetine + iron in decreasing the frequency and duration of spells.

However, we prescribed iron and fluoxetine concurrently in this study, and fluoxetine alone may have different effects. Carano et al. (2013) showed that combination therapy, including concurrent administration of oral glycopyrrolate (0.5 mg three times daily), and anhydrous theophylline every 12 hours (80 mg twice daily) can be effective in suppressing and refluxing BHS-related anoxic seizures (27). The present study showed no significant difference between the two groups in terms of the frequency of spells (per week) before treatment. However, the frequency of spells (per week) was significantly reduced in both groups after treatment. Polskaya et al. (2013) investigated the efficacy of pantogam syrup 10% (Hopantenic acid) in treating BHS. The results of clinical and neuropsychological studies showed clinical improvement was significantly higher in the intervention group (73.3%) than the control group (16.7%) after treatment. The anxiety levels were significantly decreased in the intervention group after treating neuropathic pain. A comparative analysis of electroencephalographic indices showed a significant decrease in the strength of slow rhythms and symptoms of the functional brain failure in the patients of the intervention group ($p < 0.05$). These results provide evidence indicating high effectiveness of pantogam syrup in treating children with BHS (28). Hamed et al. (2018) evaluated the clinical, laboratory, and therapeutic characteristics of children with cyanotic BHS and concluded that not only Iron-deficiency anaemia (IDA) but also non-anaemic iron deficiency (NAID) are associated with the risk of cyanotic BHS. Iron therapy decreases the frequency of BH by increasing ferritin and iron levels (29). In our study, 11 individuals in the control and 13 in the intervention group had a history of iron administration, which was not statistically significant. Furthermore, five infants in the control group and six infants in the intervention group received adequate iron doses, and there was no significant difference between the two groups. Al-Shebani (2018) investigated the effect of phenobarbital in treating severe BHS.

Results showed that the frequency of spells decreased significantly in infants of all age groups in the intervention group after one-month follow-up. After six-month follow-up, the frequency and severity of spells did not change in the phenobarbital-treated group. No phenobarbital-related side effect was also observed (30). In the present study, we investigated factors such as pregnancy problems, type of delivery, and previous history of hospitalization of children, gender and age, type of BHS, triggers, and family history of the child, but there was no difference between the intervention and control groups in this regard. Garg et al. (2015) stated that cyanotic BHS is usually benign and is treated spontaneously by the age of 4 to 5. Treatment with iron and other drugs in selected cases has been used frequently and severely. The above study described a 10-year-old boy who was recently affected by cyanotic BH. Oral iron+ piracetam therapy was ineffective. However, oral theophylline therapy significantly improved symptoms and they concluded

that theophylline plays an important role in controlling the disease by stimulating the nerves of the central nervous system (31). The results of the present research showed that the iron therapy had a significant effect in reducing the frequency and duration of BHS. Nonetheless, addition of fluoxetine to iron does not significantly reduce the frequency and duration of spells. However, we prescribed iron and fluoxetine, and fluoxetine alone may have different effects.

4-1. Study Limitations

The low sample size is one of the limitations of the present study. Another limitation of this study is the lack of parental consent for continued treatment of their infants for 3 months. In this study, we administered iron and fluoxetine concurrently and did not investigate the effect of fluoxetine alone, which may be one of the limitations of the present study.

5- CONCLUSION

The results of the present study confirm the effect of iron therapy in decreasing the frequency and duration of BHS, and indicate the ineffectiveness of synergistic administration of fluoxetine and iron in reducing these spells at the same time. In this study, however, we prescribed iron and fluoxetine concurrently, and fluoxetine alone may have different effects. Therefore, adding one of the iron products and assuring parents at the same time can be effective in reducing BHS.

6- CONFLICT OF INTEREST: None.

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