

Effects of Piracetam on Pediatric Breath-Holding Spells

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ABSTRACT

Objectives: To determine the frequency of successful response to treatment with Piracetam versus placebo in pediatric patients suffering from breath-holding spells.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan, from Jan to Dec 2022.

Methodology: This study was conducted on 100 pediatric patients suffering from breath-holding spells, who were aged between 1 and 5 years of both genders. Potential participants with a history of epilepsy, iron deficiency anemia, electrolyte imbalance, hypoglycemia, chronic kidney disease / acute kidney injury, neurodevelopmental disorders, or those who have received previous treatment for breath-holding spells, or those who were lost to follow-up were excluded. Patients were documented for the frequency of attacks per month prior to therapy and divided into two groups: in Group-A, patients received Piracetam at a dose of 20 mg/kg/dose twice daily for three months while in Group-B, patients received a placebo twice daily for three months. All patients were followed up for six months after enrollment, at which time all patients were assessed for response in terms of frequency of attack, post-therapy. Data was analyzed using SPSS 26.0.

Results: The mean age of our study sample was of 2.78±1.23 years, with a slight male majority of 56(56.0%). The number of breath-holding spells were similar in both arms, ($p=0.683$), prior to therapy initiation. However, at the last follow-up of six months, the mean number of events per month with Piracetam therapy reduced significantly compared to placebo, ($p<0.001$). The difference between development of response between the two groups was statistically significant, ($p<0.001$), where 44 (88.0%) showed a response with Piracetam versus 8(16.0%) with placebo. Complete response to treatment was seen in 34 (68.0%) with Piracetam versus only 1(2.0%) with placebo, while partial responses were seen 10(20.0%) and 7(14.0%), respectively. No response was seen in 6(12.0%) patients given Piracetam versus 42(84.0%) patients on placebo.

Conclusion: Piracetam therapy in pediatric patients with breath-holding spells is a useful treatment modality that results in a significant reduction in the number of episodes per month when compared to placebo.

Keywords: Breath-Holding Spells, Neonates, Paediatric Patients, Piracetam.

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INTRODUCTION

Breath-holding spells occur as a result of an involuntary reflex and are usually preceded by a precipitating stimulus, which results in the temporary cessation of breathing followed by loss of consciousness.¹ The disorder affects up to 4.6% of the otherwise healthy paediatric population, and the usual age of onset is around six to eighteen months of age, with the a range of incidence between one and six years.^{2,3} The disorder itself is grouped into two major types: the cyanotic sub-type is commonly precipitated by crying or anger followed by silence, cessation of breathing, cyanosis, loss of consciousness with recovery of breathing / consciousness usually occurring within a minute, and the pallid sub-type where a child undergoes a painful or frightening event

which results in a drop in heart rate, cessation of breathing, development of pallor and loss of consciousness, which may be associated with sweating, jerky movements and loss of sphincter control.⁴ It is pertinent to note here that sequelae to the disorder are rare, and complications are not typical.⁵

Breath-holding spells do not usually require treatment, as the episodes are usually rapidly self-limiting without the occurrence of long-term complications, however, they may be quite distressing to both the patient and parents and a number of treatment strategies have been advised for its management, with varying degrees of success,⁵ such as iron supplementation (with or without the presence of overt iron deficiency),⁶ Valproic acid prophylaxis,⁷ use of Theophylline to reduce the frequency of episodes,⁸ as well as newer antiepileptic drugs such as Levetiracetam.⁹ Piracetam is a nootropic drug that has

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been advocated for use in patients with breath-holding spells and belongs to the same class of drugs as Levetiracetam, the Racetams may be associated with a reduction in the number of symptomatic episodes.^{9,10}

This study was conducted to compare the efficacy of Piracetam in children with breath-holding spells versus placebo in terms of reduction in the number of episodes of breath-holding spells. Pediatric patients presenting with breath-holding spells are a common sight in the out-patient pediatric department: while assurance is the cornerstone of management, pharmacotherapy to control the frequency of episodes may be required, and Piracetam represents a potentially useful management modality in this regard. Determining whether the drug is useful in managing Pakistani children with breath-holding spells will go a long way towards reducing the morbidity and financial costs associated with management of breath-holding spells.

METHODOLOGY

This research protocol was conducted as a quasi-experimental study from January 2022 to December 2022 in the Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan on 100 pediatric patients suffering from breath-holding spells. The study commenced after obtaining informed consent from their parents or guardians. All participants were enrolled via non-probability, consecutive sampling. The WHO sample size calculator was used to calculate the sample size keeping a level of significance of (α) of 5%, a power of the test ($1-\beta$) of 95%, an anticipated population proportion 1 (P1) of 0.91 and an anticipated population proportion 2 (P2) of 0.16, which were the proportions of patients with breath-holding spells, who developed response to Piracetam and placebo at six months post-treatment initiation, respectively, from Abbaskhanian *et al.*¹¹

Inclusion Criteria: All paediatric patients between the age of 1 and 5 years, of both genders, diagnosed as suffering breath-holding spells which were defined as a clinical history of a provocative episode followed by profuse crying to the point of complete silence, accompanied by change in skin colour, with subsequent loss of consciousness and alteration in body tone, with a minimum of one episode per month.¹¹

Exclusion Criteria: Potential participants with a history of epilepsy, iron deficiency anemia, electrolyte imbalance, hypoglycemia, chronic kidney disease/acute kidney injury, neurodevelopmental disorders, or

those who received previous treatment for breath-holding spells were excluded.

All patients were documented for the frequency of attacks per month prior to therapy. Patients were divided into two groups via block randomization method: in Group-A, patients received Piracetam at a dose of 20 mg/kg/dose twice daily for three months while in Group-B, patients received a placebo (which was an inert starch tablet) twice daily for three months (Figure). The patients were blind to the treatment they received. All patients were followed up for six months after enrollment i.e., up to three months after cessation of therapy in their respective arm, at which time all patients were assessed for response. Patients were classified according to degree of response as follows: a) patient was said to have developed a complete response if there were no further episodes per month at the end of the follow-up period, b) patient was said to have developed a partial response if the frequency of attacks were reduced by half per month at the end of the follow-up period and c) patient was said to have had no response to treatment if the frequency of episodes was reduced by less than 50% of the initial frequency per month by the end of the follow-up period.¹¹

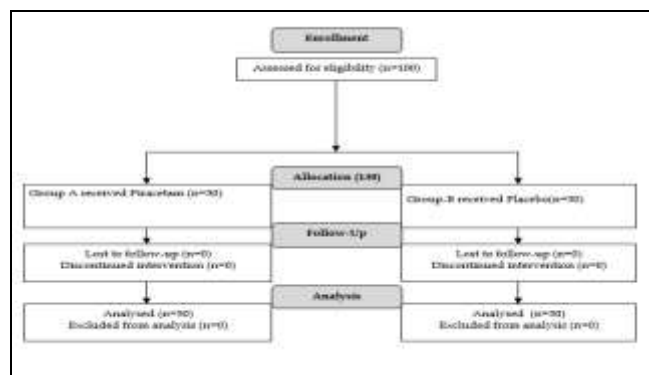


Figure: Phases of the study

Data analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). Mean and standard deviation was calculated for continuous variables specifically patient age, Median was calculated for post-treatment episodes per month, frequency of breath-holding spells at the start of therapy, frequency of breath-holding spells at the end of follow-up period. Qualitative variables like gender, consanguineous parents, family history of breath-holding spells, type of breath-holding spell, eliciting event, occurrence of side-effects and response to

treatment were recorded in terms of frequency and percentage. Quantitative variables were compared across groups using the Mann-Whitney U test while the Chi square test/Fischer exact test was used for qualitative variables and a p -value of ≤ 0.05 was considered significant.

RESULTS

We conducted this study on a total of 100 pediatric patients with a mean age of 2.78 ± 1.23 years. A total of 56.0% participants were male, while 69.0% of the had consanguineous parents. A family history of breath-holding spells was seen in 19.0% cases. Crying was the most common eliciting event: accounting for 47.0% of cases, while pain and anger accounted for 37.0% and 16.0% of all cases, respectively. A total of 69.0% patients had cyanotic breath-holding spells, while 31.0% had pallid spells. The median number of pre-treatment breath-holding spells for the entire sample was 30.00 (3.00 – 500.00) per month. Table-I shows the patient characteristics pre-treatment characteristics displayed according to treatment group.

Table-I: Pre-Treatment Patient Characteristics according to Treatment Group (n=100)

Treatment Group (n=100)			
Variable(s)	Piracetam (n=50)	Placebo (n=50)	p-value
Gender			
Male	25(50.0%)	31(62.0%)	0.227
Female	25(50.0%)	19(38.0%)	
Age (years)	2.64±1.23	2.92±1.23	0.256
Consanguineous Parents	37(74.0%)	32(64.0%)	0.280
Family History of Breath-Holding Spells	7(14.0%)	11(22.0%)	0.298
Eliciting Event			
Crying	23(46.0%)	24(48.0%)	0.773
Pain	20(40.0%)	17(34.0%)	
Anger	7(14.0%)	9(18.0%)	
Type of Breath-Holding Spells			
Cyanotic	36(72.0%)	33(66.0%)	0.517
Pallid	14(28.0%)	17(34.0%)	
Frequency of Events Pre-Treatment (Monthly)	30.00 (IQR: 91)	30.00 (IQR: 51)	0.683

Table-II shows the response to treatment of patients distributed according to treatment arm. The median post-treatment episodes per month for the complete sample was 8.00 (0 – 470), with Group-A (Piracetam therapy) showing a significant reduction in

the number of episodes versus placebo, ($p < 0.001$). Complete response to treatment was seen in 34 (68.0%)

of Group-A patients versus only 1(2.0%) in Group-B (placebo), while partial responses were seen 10 (20.0%) and 7 (14.0%) Group A and B patients, respectively. No response was seen in 6(12.0%) patients given Piracetam versus 42(84.0%) patients on placebo. The difference between development of response between the two groups was statistically significant, ($p < 0.001$). A total of 44 (88.0%) showed a response with Piracetam versus 8(16.0%) with placebo, ($p < 0.001$). No side-effects of therapy were reported in either arm.

Table-II: Groupwise Comparison of Response to Treatment(n=100)

Variable(s)	Piracetam (n=50)	Placebo (n=50)	p-value
Frequency of Events Post-Treatment (Monthly)	0.00 (IQR: 5.00)	19.50 (IQR: 42.00)	< 0.001
Degree of Response			
Complete	34 (68.0%)	1 (2.0%)	< 0.001
Partial	10 (20.0%)	7 (14.0%)	
None	6 (12.0%)	42 (84.0%)	

DISCUSSION

The results of our study show that the Piracetam therapy in pediatric patients with breath-holding spells is a useful treatment modality when compared to placebo. Breath-holding spells are frequently seen events in the pediatric practice, that can range from infrequent, short and benign events to recurrent, prolonged and distressing episodes. Our study demonstrated that these events can be managed effectively using Piracetam in comfortable dosing schedule with good responses that are durable in the short-term.

The mean age of the patients in our study sample was 2.78 ± 1.23 years. Goldman *et al.*, in their review article, reported that the majority of cases have an onset of breath-holding episodes between 6 and 18 months of age, and can present in ages up to 4 years or more.¹² Similarly, Rathore *et al.*, reported that the typical age of onset of this disorder is usually between 6 and 18 months of age, which is similar with our data.¹³

A total of 56.0% of the patients in our study were male. Abbaskhanian *et al.*, also reported on a population with slight male majority: 57.3% of their

population was male,¹¹ while Azab *et al.*, also reported on patients suffering from breath-holding spells where the population had a slight male preponderance of 58.7%, but noted that no particular gender had a predilection towards developing the disorder, ($p=0.860$).¹⁴ While the existing studies report that there is no gender predilection towards the development of breath-holding spells, further research in the form of case-control studies may be in order before appropriate conclusions can be drawn in this regard.

Approximately 69.0% of our patients were the products of marriages that were consanguineous. While consanguinity is associated with an increased risk of congenital abnormalities as well as developmental disorders,¹⁵ it is unclear whether it translates into increased risk for the development of breath-holding spells, however, studies such as Carman *et al.*, have noted that parental consanguinity is associated with an increased risk for the development of breath-holding spells, ($p<0.05$), though the sample size was too small in the study to draw a concrete conclusion and further study is required before one can adequately be made.¹⁶ It is pertinent to note here that the frequency of consanguineous marriage in our study was similar to the national average rate for such marriages in Pakistan i.e., 65.0%.¹⁷

A family history of breath-holding spells was seen in 19.0% of our cases of children reporting with breath-holding spells. Ghazavi *et al* noted that a positive family history was more frequently present in their cases suffering from breath-holding spells.⁹ Dai *et al* also reported a positive family history of breath-holding spells in 10.3% of patients suffering from the disorder.⁸ Sadek *et al* noted that 31.3% of their cases had a positive family history of the disorder, but also noted that this frequency varied greatly from population to population, and concluded that the disease may be inherited in an autosomal dominant fashion, with reduced penetration.³

A total of 47.0% cases reported crying as the primary stimulus which triggered their breath-holding event, pain as the inciting event was seen in 37.0% of cases in our study while 16.0% were triggered by anger. This was similar to Saddek *et al* who reported crying is the most common precipitant (84.4%), followed anger (15.6%).³ Additionally, Abbaskhanian *et al* also reported that crying was the most significant precipitating stimulus for triggering of a breath-holding spell in their study, accounting for 51.1%

cases, followed by pain and anger at 24.7% and 8.4% cases, respectively.¹¹

A majority of 69.0% patients had cyanotic breath-holding spells, while 31.0% had pallid spells, in the current study. Abbaskhanian *et al* reported that cyanotic spells were seen in 61.8% cases in their study, while 16.9% had the pallid type of attack, while they could not classify the remaining patients strictly into one type or the other.¹¹ Leung *et al*, in their review article, also reported that the cyanotic sub-type is usually more commonly manifested, accounting for roughly 72.0% of the cases, which was similar to our study.² Yilmaz *et al.*, reported that 82.4% of their study sample had cyanotic spells while the remaining 17.6% had pallid attacks, in keeping with our study.¹⁸

The number of breath-holding spells per months, prior to treatment varied wildly, with median number 30.00 per month for the complete sample, but with a wide range 3.00 to 500.00 attacks per month, in the present study. Hamed *et al.*, reported that most of their patients (74.4%) had at least one episode of breath-holding per day, while 19.0% had 2 or more spells.⁷ Abbaskhanian *et al.*, also reported that the frequency of attacks varied greatly across their sample with a minimum of 2 episodes per month, up to 15 attacks per day.¹¹

At six months post-treatment initiation, 88.0% patients showed any degree of response with piracetam versus only 16.0% with placebo, the difference between both groups being statistically significant, ($p<0.001$), in the current study. A complete response to treatment was seen in 68.0% with piracetam versus only 2.0% with placebo. Partial responses were seen in 20.0% with piracetam versus 14.0% with placebo, while no response was seen in 12.0% patients on piracetam versus 84.0% patients given placebo, ($p<0.001$). Ghazavi *et al.*, noted that a response with piracetam was seen in 77.1% patients in their study sample.⁹ Abbaskhanian *et al.*, also reported significant effects on the reduction of frequency of spells with piracetam compared to placebo: 91.0% patients showed response to treatment with piracetam versus 16.0% with placebo, at six months post-initiation of treatment (complete response occurred in 77.0% with piracetam, while 14.0% had a partial response, and no response was seen in 9.0% patients versus 6.0%, 10.0% and 84.0% complete, partial and no response, respectively, with placebo).¹¹ Conversely, Dai *et al* noted that only 8.8% of patients demonstrated a response to piracetam in the form of reduction of

breath-holding spells, in their study.⁸ We believe this difference arose in the manner in the way patients were selected: our study excluded patients who were iron deficient as opposed to Dai *et al*, as this appears to be significantly associated with the development of breath-holding spells,^{6,8} thus leading to a lack of response in their study.⁸ It can be postulated that iron supplementation should be provided to all patients suffering from breath-holding spells, however, this aspect requires further research.

LIMITATION OF STUDY

Our study had a comparatively shorter follow-up period of six months, three months of which were spent on therapy; it is unclear whether the benefits of piracetam are maintained in children over the long-term, especially in terms of relapse in patients who demonstrated a complete response to treatment, which may serve as the focus of future research. Our study did not focus on the occurrence of side-effects as none were reported in either intervention arm, however, further study with a much larger sample is warranted before concrete conclusions with regards to adverse effects can be drawn. Lastly, this was a single-center study conducted on the wards of military personnel and may not be generalizable to the population at large; further multi-center study on a more diverse population is warranted before conclusions can be applied to the general population.

CONCLUSION

Breath-holding spells are a common affliction that are quite distressing to both the patients and their attendants. Piracetam represents a useful drug in the repertoire of the treating clinician for the management of this disorder, which has been shown to be very efficacious in our study, and may be employed on a regular basis in such patients. Future research should review the drug in-terms of side-effects produced as well as a comparison with other drugs used for the management of the condition such as Theophylline/Levetiracetam as well as look at the efficacy of the drug in the long-term.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SAHK & QUM: Data acquisition, data analysis, critical review, approval of the final version to be published.

BA & HA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FI & SHN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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