

Review Article

Piracetam in the management of Breath holding spells

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Abstract: Breath holding spells are commonly seen in children and frightening to the parents. Various medications were tried in their management with little success. Complex pathophysiology of breath holding spells is a reason for no single drug found to be clearly efficacious. Piracetam is tried in the management, with minimal adverse effects. This article reviews the role of Piracetam in the management of severe breath holding spells.

Introduction

Breath-holding spells are paroxysmal anxiety provoking episodes in infants and children. It is seen in 4-5% of healthy children. Boys outnumber girls with a ratio of 1.3:1¹. These episodes are frightening to parents resulting in anxiety and frequent visits to health care facilities. Cyanotic and Pallid are two clinical types identified based on color change during the episode. Cyanotic attacks are usually seen in response to anger or frustration. There is a shrill cry at the beginning followed by expiratory apnoea. This may be followed by rapid onset of cyanosis of face and lips and loss of consciousness. There may be associated seizure, opisthotonus and bradycardia. Pallid spells are typically initiated by a painful experience. The child stops breathing, rapidly loses consciousness and becomes pale and hypotonic. Tonic seizures and bradycardia may be observed. Cyanotic spells are more frequently observed than pallid spells. Child can have either of the attack at one time or another in their lives². Breath-holding episodes are rarely seen below 6 months of age. Peaks occurrence of episodes occur at 2-3yrs and they become rare by 5-6yrs². Severe breath holding spells are episodes associated with loss of consciousness and convulsions or both. Seizures observed at end of episodes are due to cerebral hypoperfusion and subsequent hypoxia. Severe breath holding spell occur in 0.1%-4.6% of healthy children^{3,4}. Children experience multiple episodes per week. One third of children will have 2 to 5 episodes per day. Kelly MA et al⁵ in a series of 10 patients of severe breath holding spells observed multiple episodes a week to 30 episodes per day. Anoxic seizures upto 30 sec duration is seen in 15% of children with breath holding spells^{4,6}. Status epilepticus following breath holding spells have been reported in rare cases.

Pathophysiological mechanisms responsible for breath holding spells are not clearly understood. It has been postulated that different mechanisms are responsible for the two clinical forms. Both these types have been observed in the same family and also within the same individual. Autonomic dysfunction has been implicated as a mechanism underlying genesis of pallid spells by Di Mario et al⁷. These are due to predominantly exaggerated parasympathetic (vagal response) stimulation. Ocular compression can trigger pallid spells via the oculocardiac reflex which increases vagal tone. About 70% of children with pallid spells will develop asystole. Pathophysiology of cyanotic spells is more complex. Combination of hyperventilation induced carbon dioxide wash out, valsalva manoeuvre, expiratory apnoea and pulmonary shunting contribute to the cyanotic spells^{8,9}. Family history is positive in 15-20% of children suggesting genetic link. Family pedigree analysis of children suggested that the most likely underlying genetic inheritance pattern is an autosomal dominant trait with reduced penetrance¹⁰. Iron deficiency plays a role. Iron deficiency increases the duration of asystole. Iron's role is thought to be due to its being a cofactor in catecholamine metabolism and neurotransmitter function¹¹

Apnoeas, epileptic seizures and orthostatic syncopal attacks closely mimic breath holding spells and they should be considered in differential diagnosis. Breath-holding spells occur in response to a stimulus and can only occur when the child is in awake state. In contrast apnoeas can occur anytime while awake or asleep without a precipitating stimulus. Epileptic seizure can occur any time like apnoeas but usual sequence of tone change and posture followed by color change differentiate it from breath holding spells. EEG is helpful in differentiating epileptic seizure from breath holding spells conclusively. EEG is normal in breath holding spells¹². Abnormal rhythmic

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discharge is obtained in epileptic seizure. Orthostatic syncopal attacks are sudden spontaneous episodes precipitated by sudden change in body posture and environmental factors. There is sudden loss of body tone resulting in fall. Patient recovering on assuming horizontal posture and lack of cry preceding the spell, distinguish it from breath holding spell. Death is rarely reported as most of the children recover spontaneously. Children who had breathholding spells are predisposed to higher incidence of syncopal attacks in adolescence. About 30% of children reported concentration problems on follow up¹³.

Treatment for breath holding spell is controversial and unclear. As most spells recover without any major sequelae, avoidance of emotional conflicts and parental reassurance is advocated¹⁴. Severe breath holding spell causes serious anxiety and frequent visits to healthcare facility. In spite of benign nature of breath holding spell various forms of treatment have been tried in severe form to prevent the attacks from recurring. Atropine has been used with success in severe pallid spells with prolonged asystole¹⁵. Cardiac pace maker also been used to treat cases associated with life threatening bradycardia or asystole. Pacemakers reduced the severity of spells but breath holding spell are not abolished¹². Need for simple safe non invasive intervention was felt to abolish severe breath holding spell. Iron supplementation significantly reduced severe breath holding spell in those with concomitant anemia. Better response is seen in children with low haemoglobin¹⁶.

Piracetam is a compound similar to gamma-aminobutyric acid (GABA) and has been used to completely abolish severe spells. Cerebral anoxia is the end denominator for causing loss of consciousness and seizures. Piracetam increases brain tissue oxygen consumption and increases the inhibitory hyperpolarising process similar to GABA resulting in beneficial effects¹⁷.

Ali Abbaskhanian MD et al in their double blind prospective study on 150 children with severe breath holding spell found Piracetam to be beneficial¹⁸. In their study Piracetam at a dose of 40mg/day was given to 75 children and rest 75 received placebo. Children were observed for 3 months. 91% of children in Piracetam group showed response compared to 16% in placebo group. In children who received Piracetam, 77% showed complete response, 14% showed partial response (>50% reduction in spells) and in 9%, no response was observed. In a similar

double blind placebo controlled study by Sawires H et al¹⁹, Piracetam found to reduce median number of spells per month significantly compared to placebo group. At the start of treatment median number of spells/month in both group was 5.5 and 5 respectively. After four months of treatment, all median number of attacks/month was 1 and 5 in both groups. Piracetam was used in higher dose (50mg/day) compared to Ali Abbaskhanian et al study. There was no significant difference between types of spells and overall number of spells after treatment. Significant rate of change is observed in pallid spells after treatment.

M Metin Donma²⁰ found control in breath holding spell in 92.3% of children in Piracetam group whereas 29.7% in placebo group showed control. Elementary iron at a dose of 5mg/day was also given to 9 children who were found to be having low haemoglobin in each group. Two months of treatment was given in this study which is relatively shorter compared to other two studies. Azam et al²¹ also observed 81% reduction in frequency of breath holding spells with Piracetam and iron supplementation in child with Hb <10mg/dl. They used a higher dose of Piracetam (50-100mg/day) and their study lacked control group. Asharafi et al. found no significant advantage of Piracetam in comparison with placebo in their study²².

Piracetam is a safe drug in children and occasional side effects like anxiety, insomnia, agitation and irritability are reported more in adults²². In Ali Abbaskhanian study 2 cases of vomiting and emotional lability were reported in Piracetam group¹⁸. No significant side effect was observed in Piracetam and placebo group. Donma et al. observed no significant side effect^{19,20}.

Piracetam appears to be safe and effective drug for severe breath-holding spells. Piracetam seems to abolish severe breath-holding spells significantly. Iron supplementation in anemic children together with Piracetam shown better results. Large better quality randomised trials of Piracetam to treat severe breath-holding spells is required.

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