Cardiology in the Young

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The efficacy of the use of atropine in children with reflex anoxic syncope during pallid breath-holding spells: can cardiac pacemaker implantation be avoided?

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Abstract

Objectives: Reflex anoxic syncope is the result of an overreaction of the vagal system, resulting in hypotension and bradycardia or brief cardiac arrest. Because of the benign character and the absence of complications in short or long term, treatment is only necessary in case of frequent or severe clinical presentation. Treatment options are anticholinergic drugs or cardiac pacemaker placement. We investigated atropine treatment and aimed to examine if pacemaker placement can be avoided. *Methods:* We retrospectively reviewed patients treated with atropine for severe reflex anoxic syncope in our centre from January 2017 until May 2023, and compared our results to those in the literature. *Results:* The study population consisted of 10 children, 70% female, with an age ranging from 5 months to 3 years (mean 14.5 months) when atropine treatment was started (dose 17–50 microg/kg/day). All patient's parents reported adequate symptom management during atropine treatment, with complete resolution in 10%. Minor side effects were reported in 60% (dry mucosa in 40%, obstipation in 20%, and nausea or blurry vision in 10%). *Discussion:* We consider atropine a safe and effective treatment to manage reflex anoxic syncope with similar success rate to pacemaker implantation. However, pacemaker implantation entails substantial risk for complications (up to 25%) such as infection or technical problems and morbidity such as scar formation. This might be considered redundant for a benign and temporary condition, certainly given the possibility of other efficient treatment options. Consequently, we recommend atropine treatment over implantation of a cardiac pacemaker in children with severe reflex anoxic syncope.

Total loss of consciousness or syncope occurs in 1–5% of all infants. A clinically important phenomenon is the "breath holding spell", although the definition and terminology are confusing. Historically, the differentiation was made between the two entities described as "cyanotic" and "pallid" breath-holding spells. The similarity lies in the frightening, painful, or other minor noxious stimulus that triggers the spells, as well as the probability of loss of consciousness. However, the pathophysiology as well as the clinical course are very different.[1–3] Severe breath-holding spell, defined as frequent and clinically severe episodes (defined by prolonged syncope or seizures), occurs in 0.1–4.6% of infants.[1,2,4] In patients with severe breath-holding spell, 20% present with reflex anoxic syncope. These children are typically slightly older at onset, with the first episode mostly occurring between the age of 6 to 24 months.[2,4]

Pallid breath-holding spells are a manifestation of an over-action or rather overreaction of the vagal system due to the oculo-cardiac reflex with afferent pathway by the trigeminus nerve and efferent pathway through the parasympathetic vagal nerve. This leads to hypotension and bradycardia or brief cardiac arrest. The role of autonomous dysregulation is supported by the observation of significantly more sinus arrhythmia in children with pallid breath-holding spell and the excessive response to ocular compression in former studies.[5,6] During a spell, the infant can experience loss of consciousness and exhibit pallor, both of which are self-limiting. Because of the decrease in cardiac output, cerebral hypoxia occurs and loss of consciousness follows. Breath-holding is a minor component in pallid breath-holding spell. Cardio-inhibitory syncope, reflex anoxic syncope, or reflex asystolic syncope are therefore more accurate terms to describe this entity.[1–3,7] If the cerebral hypoxaemia lasts longer than 45 seconds, convulsions may occur. Those are defined as anoxic epileptic seizures.[3] In reflex anoxic syncope, the golden standard for diagnosis is history and clinical presentation. Description of these spells can be difficult for parents or bystanders.[1,2] An electrocardiogram or more extensive cardiac monitoring is performed to document significant bradycardia, sinus pauses, or asystole (>5 seconds) during the pallid breath-holding spells. The simultaneous occurrence of the clinical presentation and cardio-inhibition on cardiac monitoring confirms the diagnosis. As long QT syndrome should be excluded as a cause for syncope, a baseline electrocardiogram should always be performed. Echocardiography can be useful to exclude underlying CHDs or pulmonary hypertension in

patients in whom the clinical presentation is doubtful. Patients with reflex anoxic syncope have no higher incidence of abnormalities on echocardiographic screening.[7,8]

Because of the impressive clinical presentation with loss of consciousness and bradycardia, many parents and physicians fear severe complications or even a fatal outcome in pallid breath-holding spells. However, when other cardiac or neurological causes are excluded, the anxiety is unnecessary.[3,9] A reflex anoxic syncope in itself is not dangerous, but the actions of bystanders can be. Literature reveals only one infant with a fatal outcome related to breath-holding spells, after aspiration of gastric residue, following basic life support by the child's caretaker.[3] Additionally, long-term prognosis of reflex anoxic syncope is favourable as well. Some of the children exhibit a lower threshold for vasovagal syncope at later age, but no other complications have been described.[2,3,5,8] One study described a slight predisposition for attention deficit disorders, with no significant difference in school results.[10] Even in children with frequent anoxic epileptic seizures, studies show a normal psychomotor development with normal cranial MRI studies.

Because of the benign character of pallid breath-holding spells with no complications in short or long term, treatment is seldom required. As a result, the fundamental part of management is reassurance and education of the parents and caretakers. However, treatment can be recommended in case of frequent spells and/or severe clinical presentation, impacting the quality of life or daily activities of the child and its parents.[1–3,6,7,11]

Given the suspicion of an over-activation of the autonomic nervous system in these spells, treatment with a non-selective muscarinic acetyl cholinergic antagonist is believed to be beneficial. Atropine is a short-acting anticholinergic agent and is easily titrated in dose. Adverse effects tend to be less severe compared to longer-acting agents such as glycopyrrolate. Previous studies showed a 93–100% reduction in spells with atropine treatment.[1] Other medicinal options are iron supplements, fluoxetine, theophylline, piracetam, and levetiracetam.[2–7,12–16] More recent publications describe implantation of a cardiac pacemaker as a successful treatment in severe cases by intercepting the bradycardia that follows the exaggerated vagal response. As a result, treatment with atropine has fallen into disuse because of the lack of recent supporting data.

Recommendation for pacemaker implantation in children with pallid breath-holding spells strongly varies among different centres and guidelines. In some recommendations, it is advised as a primary treatment option when severe bradycardia is observed during breath-holding spells.[2–7,17–19] This was supported by the 2021 PACES expert consensus statement that reported a class IIa recommendation for a pacemaker implantation in children with severe recurrent breath-holding spells with documentation of cardio-inhibitory response on electrocardiogram monitoring and complicated with prolonged syncope, prolonged post-anoxic convulsions, and other bradycardia-induced symptoms. Previously, the 2015HRS Expert Consensus Statement already gave a class IIb recommendation for implantation in paediatric patients with recurrent syncope with documented symptomatic asystole refractory to medical therapy.[20–25] However, cardiac pacemaker implantation itself is not without risk. The decision to implant a cardiac pacemaker should therefore not be taken lightly, certainly not if equally successful treatment options are available. To facilitate this decision-making, we compared the results of children with reflex anoxic syncope receiving atropine in our hospital to treatment results in literature. In this study, we will solely focus on the treatment of reflex anoxic syncope with atropine.

Materials and methods

Approval for this study was granted by the Ethics Committee of University Hospital of Ghent (Date 14/07/2021 /No BC-09927). Electronic informed consent was obtained from the parents.

The data for this study were recruited from all children with pallid breath-holding spells treated with atropine from January 2017 until May 2022 in UZ Gent and from new patients who presented themselves during the study period, where atropine sulphate was administered or would be started. Patients were included after reflex anoxic syncope was diagnosed, based on the presence of typical clinical symptoms resulting in loss of consciousness after a painful or emotional trigger, combined with significant bradycardia (heart rate < 60 bpm) or sinus pause on Holter monitoring during symptoms. The assessment of whether clinical symptoms were fitting for a pallid breath-holding spell resulting in a reflex anoxic syncope was made by an experienced paediatric electrophysiologist based on thorough history taking and, if possible, combined with videographic footage.

Children with complex congenital cardiopathies or prolonged QTc were excluded. After obtaining informed consent from the parents, parameters were obtained from the electronic patient file. A questionnaire was sent to patients and their families (after agreement to participate in the study) to fill in missing data and to further assess the clinical symptoms before and after treatment in detail, focusing on how they were experienced by patients and their environment.

All the data obtained were collected in REDcap, by manual entry of the investigators. A statistical database was generated manually. An extensive descriptive analysis of the results was formed. Statistical analysis was performed by SPSS.

Results

We included 10 patients with reflex anoxic syncope who were treated orally with atropine sulphate. No patients were prospectively included. Because of the limited patient population and subsequently limited power, we focused on descriptive statistical analysis.

Before atropine treatment

Seven out of the ten patients were female (70%). The mean age at which the symptoms first presented was 6 months. The mean age at which they first visited a paediatric cardiologist was 12 months and the mean age at which treatment with atropine was started was 14,5 months. Five out of the ten patients (50%) had a positive family history of breath-holding spells. Nine of the 10 patients (90%) had a normal structural echocardiography. One patient had a patent ductus arteriosus which closed spontaneously during follow up, which was considered not significant in relation to the reflex anoxic syncope. Five patients (50%) received treatment for reflex anoxic syncope before atropine was initiated, among which were iron supplements (20%), glycopyrronium (10%), piracetam (10%), and Belladonna (10%), although insufficient in controlling the symptoms.

The symptoms reported by the parents and other caregivers were pallor in 80%, loss of consciousness in 100%, convulsions in 60%, and all were triggered by emotion or pain. Fifty per cent of the parents additionally reported cyanosis. The frequency of the episodes varied between 2 times a year to 3 times per day, with a mean of 27 episodes per month. The duration of the episodes varied from 30 s to 5 minutes with a mean of 1,5 minutes. Holter monitoring was performed in all patients. In seven patients (70%), significant sinus pauses were documented during Holter monitoring. The duration of documented sinus pauses varied between 5 s

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Table 1. Episode characteristics before atropine treatment

	Frequency episodes before treatment	Duration symptoms before treatment (minutes)	Cyanosis	Pallor	Loss of consciousness	Convulsions	Triggered by emotion or pain	Duration of sinuspauses on Holter monitoring (seconds)
1	≥1 time /day	1,5	Yes	No	Yes	Yes	Yes	1
2	≥1 time /day	0,1	Yes	Yes	Yes	Yes	Yes	25
3	2–6 times /week	1,0	Yes	Yes	Yes	No	Yes	7
4	1–4 times /month	3,0	No	Yes	Yes	Yes	Yes	20
5	2–6 times /week	1,0	No	Yes	Yes	No	Yes	16
6	<1 time /month	1,0	No	Yes	Yes	No	Yes	1
7	≥1 time /day	0,5	No	Yes	Yes	Yes	Yes	5
8	≥1 time /day	0,1	No	Yes	Yes	No	Yes	11
9	2–6 times /week	2,0	Yes	No	Yes	Yes	Yes	0
10	2–6 times /week	1,2	Yes	Yes	Yes	Yes	Yes	28

and 28 s, with a mean of 16 s. In the three patients (30%) without significant sinus pauses, sudden episodes of significant bradycardia (heart rate < 60 bpm) were documented, correlating with the clinical presentation. Reasons to start atropine treatment were the frequency of the episodes in 30% of the patients, the severity of clinical presentation with impact on the patient, or the environment in 40% and the combination of both in 30%. Descriptives of the episodes in our patients are presented in Table 1.

Atropine treatment

Efficacy

In the studied population, the atropine treatment was started at an age of 5–35 months, with a mean age of 14,5 months. The weight at start of the treatment varied between 4.5 kg and 13.9 kg with a mean of 9.5 kg. Atropine sulphate treatment was started at a dose of approximately 5–15 micrograms per kilogram per day 3 to 4 times daily, resulting in a mean total dose of 32 micrograms per kg per day. If symptoms were well managed, the dose was reduced in some patients while monitoring that adequate symptom management was still achieved.

Patient follow up in the clinic occurred one month after start of treatment in most patients (7/10); in three other infants, follow up took place after 3–8 months because of the absence of complaints. During atropine treatment, the frequency of episodes varied from absent to 12 times per month with a mean of 4 times per month. In one patient, no episodes re-occurred since the start of atropine. In the other patients, the frequency of the episodes decreased by 56–99% (with a mean of 75%). The duration of the episodes after treatment varied from absent to 1.5 minutes with a mean of 15 s. In one patient, who still experienced reflex anoxic syncope, the duration of the episodes remained unchanged. In the other patients with remaining episodes, duration decreased by 33–99% (with a mean of 87%). All parents reported first effect after only a couple of doses when optimal dosage was achieved. Comparison of the frequency and duration of the episodes before and during atropine treatment is presented in Figures 1 and 2. Cyanosis remained present in four patients (40%), pallor in six patients (60%), loss of consciousness in seven patients (70%), convulsions in two (20%), and triggered by emotion or pain in seven patients (70%). Episode characteristics during atropine treatment are presented in Table 2.

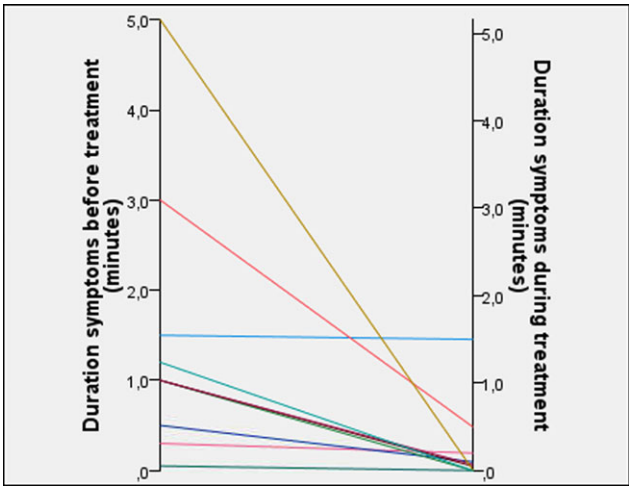

Figure 1. Difference in episode duration before and during treatment.

The dose of atropine was increased in four patients (40%) because of weight gain during follow up. In two patients (20%), dosage was titrated down according to symptoms. In four patients (40%), the dose remained unchanged during the treatment.

Safety

We questioned patient's parents on the occurrence of side effects. Dry mucosa was reported in four patients (40%), obstipation in two patients (20%), and blurred vision in one patient (10%). Nausea and/or vomiting were reported in one patient (10%). No parents reported rash as a side effect. All parents reported these side effects as not severe, with no significant impact. One parent (10%) reported alteration in behaviour with increased agitation, resulting in treatment cessation. Afterwards, no significant change in behaviour occurred, raising doubt about the correlation with the atropine treatment. All side effects except the behavioural changes, occurred in patients treated with a dose > 40 micrograms per kilogram per day.

Treatment cessation and symptom relief

Our patients reported all symptoms to end at an age varying from 4,5 months to 6 years with a mean age of 3 years and 5 months. Atropine treatment was stopped at an age varying from 10 months

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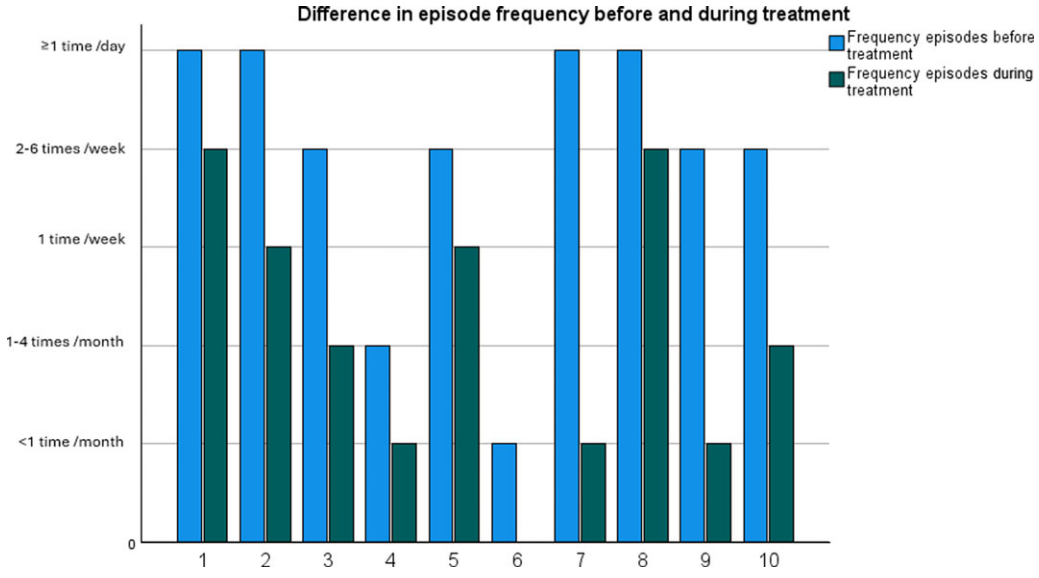

Figure 2. Difference in episode frequency before and during treatment.

to 5 years, with a mean of 2 years and 4 months, including the patient who stopped because of behavioural changes. The patient who stopped the treatment because of behavioural changes was treated orally with glycopyrrolate and subsequently valproic acid, with a decrease in episode frequency but without complete symptom relief. One patient had recurrence of episodes 9 months after atropine treatment was stopped. Because of the suspicion of an underlying syndromic condition (Coffin-Siris syndrome) and the probability of continuing symptomatic sinus pauses, a pacemaker was implanted, complicated by bilateral pleural effusions. After pacemaker placement, one episode of reflex anoxic syncope re-occurred.

Discussion

Treatment of reflex anoxic syncope as a result of pallid breath-holding spells should be considered when there is an important impact on the child's well-being. In particular, anxiety of the child's caretakers can lead to major discomfort and even lead to dangerous situations.

In our analysis, ten patients were included in which loss of consciousness was triggered by emotion or pain with documented asystole or significant bradycardia on Holter monitoring. According to some parents, their child appeared rather cyanotic than pale during some of the spells, but in all these patients a significant bradycardia or sinus pause was documented during the spells. In a typical cyanotic breath-holding spell, violently crying is followed by the performance of a Valsalva manoeuvre and an expiratory apnoea, leading to intrapulmonary shunting and ventilation-perfusion mismatch. The subsequent arterial hypoxaemia leads to central cyanosis and the reduced cerebral perfusion can cause a brief loss of consciousness, but does not cause significant bradycardia or sinus pauses. Therefore, the presence of significant arrhythmias on Holter monitoring helps to differentiate pallid breath-holding spells resulting in reflex anoxic syncope from cyanotic breath-holding spells.

Which treatment is preferred in patients with reflex anoxic syncope, has changed over time and differs between centres. Regarding pacemaker placement, studies report success rates ranging from 50 to 86%, with no change in symptoms in up to 20% of patients.[9,26] The remaining symptoms after pacemaker implantation are hypothesised to be a result of bradycardia-independent hypotension secondary to vasodilatation. The implantation of a pacemaker entails risk for a variety of complications such as infection, poor tolerance, technical malfunctioning, poor pulse capture and/or reduced sensing, lead fracture and battery depletion resulting in system revision, scar formation, and issues around magnetic fields.[7] These complications are not infrequent.[26] A complication rate of 37.5 % is described by Sartori et al, of which 26% are technical difficulties and 11,5% are medical complications (of which 50% is poor tolerance).[18] Similar numbers are reported in other studies, with a reported need for revision in 20–25% of the patients. In contrast, Kolterer et al. as well as Peach et al. reported no pacing-associated adverse events during follow up.[9,18,20,26]

Treatment with an orally administered anticholinergic agent could be considered a logical choice, given it is widely accepted that a hyperstimulation of the vagal nerve lies at the base of the pathophysiology of pallid breath-holding spells and an anticholinergic agent would counter this mechanism. In our opinion, atropine sulphate is the preferred drug choice because of the shorter acting time and minor reversible side effects.

One patient reported altered behaviour resulting in treatment cessation, with no significant behaviour changes afterwards.

In all children receiving atropine (100%), a clear decrease in the frequency and/or duration of the spells was observed by the parents, with adequate management of symptoms. One patient (10%) even experienced total resolution of the spells. Since the decision to treat is based on negative impact of the spells on the patient's well-being and their family's functioning, a significant decrease in the symptoms can be considered the main goal. In six of the patients in this study (60%), minor side effects were reported under atropine, without the need to stop the treatment except in one child. As they rapidly disappear after dose reduction or treatment cessation without long-term effects, the impact is far less than that of the complications reported after pacemaker placement which are often permanent.

A complication rate of up to 25%, resulting from an invasive treatment for a condition that is benign and temporary in absence of underlying pathology, is to be avoided if possible when an

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Table 2. Episode characteristics during atropine treatment

	Frequency episodes during treatment	Duration symptoms during treatment (minutes)	Cyanosis	Pallor	Loss of consciousness	Convulsions	Triggered by emotion or pain
1	2–6 times /week	1,5	Yes	No	Yes	Yes	Yes
2	1 time /week	0,01	Yes	Yes	No	No	Yes
3	1–4 times /month	0,07	No	Yes	No	No	No
4	<1 time /month	0,5	No	Yes	Yes	No	Yes
5	1 time /week	0,05	No	No	Yes	No	Yes
6	None	0	No	No	No	No	No
7	<1 time /month	0,1	No	Yes	Yes	Yes	Yes
8	2–6 times /week	0,2	No	Yes	Yes	No	Yes
9	<1 time /month	0,01	Yes	No	Yes	No	No
10	1–4 times /month	0,01	Yes	Yes	Yes	No	Yes

equivalently effective but far less harmful alternative is available. We, therefore, advise against pacemaker placement for healthy children with severe reflex anoxic syncope and prefer a pharmacological option, with a preference for atropine treatment.

Study limitations

Firstly, as parent questionnaires were used, recall bias might be present, possibly leading to an over or underestimation of the efficacy of the treatment and its side effects. Secondly, our patient group is limited, comparable to the number of patients in previous studies concerning pharmacological options. No prospective patients were included in this study, possibly as a result of the COVID epidemic. Therefore, additional research with larger patient groups and prospective strategies is necessary to provide more insight into the optimal treatment of children with RAS due to pallid breath-holding spells. Thirdly, as pallid breath-holding spells are self-limiting over time, the natural course might contribute to the clinical improvement in patients during and after treatment. A comparative study with control patients would be more indicative of the actual efficacy of atropine treatment. Lastly, the studied patients did not undergo a repeat Holter registration during or after treatment, so only subjective clinical parameters are available. Holter registration is considered helpful for the diagnosis of reflex anoxic syncope but is not needed to determine the efficacy of the treatment.

Conclusion

Given the benign nature of the spells and the good long-term prognosis, coupled with the success and complication rates as described, we do not recommend implantation of a cardiac pacemaker in children with severe reflex anoxic syncope as a result of pallid breath-holding spells. A temporary oral treatment with atropine sulphate should be preferred to effectively reduce symptoms in children with severe reflex anoxic syncope.

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Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant European guidelines on human experimentation (MDR) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee (Ethics Committee of University Hospital of Ghent).

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