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Review

Vagus nerve stimulation and the postictal state

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ABSTRACT

Vagus nerve stimulation (VNS) is an established neurostimulation therapy used to treat refractory epilepsy. The effect of acute or chronic VNS on the postictal state as a separate entity is seldom reported in clinical or experimental studies. Apart from its antiseizure effects, VNS has several other beneficial effects. These effects may be of particular benefit for patients with postictal neuropsychiatric symptoms. The hypothesized mechanisms underlying the initiation and sustainment of the postictal phase, to some extent, overlap with mechanisms involved in the seizure-suppressing effects of VNS as well as other neurological and psychotropic effects of VNS. Both the clinical symptoms and the basic research hypotheses of the postictal state show similarities with clinical effects induced by VNS and its underlying mechanisms of action.

1. Introduction

In neurostimulation therapy, electrical or magnetic pulses are used to manipulate neuronal activity. It is an emerging treatment for neurological diseases, with an increasing number of nervous system targets, indications, and administration modalities. Stimulation of the tenth cranial nerve (vagus nerve stimulation [VNS]) was developed in the 1980s [1]. Through an implanted device including an electrode, electrical pulses are administered to the afferent fibers of the left vagus nerve in the neck. Stimulation is delivered on a predetermined schedule or may be initiated individually by the patient with an external magnet. More recently, a noninvasive device, t-VNS, has been developed to transcutaneously stimulate vagal nerve branches in the ear [2]. Several studies, including two large double-blind randomized clinical trials, have confirmed the efficacy of VNS in different seizure types [1,3,4]. In contrast, much less is known about the effect of acute or chronic VNS on the postictal state.

Apart from the seizure-suppressing effects of VNS, various other VNS-related beneficial effects, in particular its effects on depression, have been observed in clinical practice and in experimental and clinical trials. Many of the beneficial VNS effects relate to the clinical symptoms frequently observed during the postictal state. Theoretically this may provide the basis for a potential role for neurostimulation in the treatment of postictal dysfunction.

The precise mechanism of action of VNS is unknown. Functional imaging studies in humans and experimental animals have shown that VNS modulates activity in bilateral projection areas of the vagus nerve such as the brainstem, thalamus, limbic structures, and different cortical regions [5–7]. One projection area of the vagus nerve that seems to play an important role in the mechanism of action of VNS is the locus coeruleus (LC) [8]. As a result of VNS-induced enhanced activity of LC neurons, increases in extracellular noradrenaline concentration have been measured in projection areas of the LC, such as the hippocampus and cortex, in VNS-treated rats [9]. The hypothesized mechanisms underlying the initiation and sustainment of the postictal phase, to some extent, overlap with mechanisms involved in the seizure-suppressing effects of VNS as well as other neurological and psychotropic effects of VNS.

2. Effect of VNS on the occurrence, duration, and severity of the postictal state

In 1990, initial efficacy results of VNS were evaluated in two pilot studies with a total of only 14 patients [EO1–EO2] [10,11]. In these studies a reduction in the duration of seizures or postictal periods was recorded and considered a favorable effect if present. In a significant number of patients, a reduction in seizure severity was reported without, however, a separate report of the effects of VNS on the postictal state. Anecdotal information suggested that patients "snap out of seizures" more quickly with VNS treatment. In two nonresponders with respect to seizure frequency, individual seizures were noted to be clearly shorter and less severe. Also, in one of these two patients, interictal alertness increased and it was easier to communicate with the patient, which may have been due to shortening of the postictal period. In one of the two randomized controlled double-blind trials that included larger numbers of patients (EO3: $n = 114$), seizure duration was a secondary outcome measure. In the EO3 trial there was no statistically significant difference in duration of seizures, although individual patients reported that VNS

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did reduce the intensity and/or severity of their seizures [2]. Neither the second randomized controlled double-blind trial (EO5: $n = 198$), nor the EO4 study of VNS in generalized epilepsy investigated the effects of VNS on the postictal state [3,12].

In only a few of the many prospective and retrospective VNS studies in various seizure types and syndromes in adults or children are the effects on the postictal state mentioned specifically. Gates et al. investigated quality of life in a large retrospective patient database and found that one-third of patients at 3 and 12 months of treatment reported a better or much better postictal recovery period as part of the quality-of-life measurement [13]. Analysis of the same patient database looking at patients being treated with VNS early in the course of epilepsy (6 years vs 22 years in the control group) revealed a significantly improved postictal state in the early treatment group versus the control group [14]. In a report by Wakai and Kotagal, one patient with generalized tonic–clonic seizures who had a 25% reduction in these seizures reported quick postictal recovery [15]. Furthermore, one retrospective study in children specifically reports a shorter and milder postictal phase in one-third of patients. In 22% of children in one study, the need for diazepam treatment to terminate seizures was considerably reduced [16]. In a retrospective multicenter study by Helmers et al., 26% of the children reported a better or much better postictal period at 3 months of treatment [17]. Remarkably, in 17% of these children, this effect was not accompanied by a reduction in seizure frequency.

Kostov et al. investigated the efficacy of VNS in patients with Lennox–Gastaut syndrome and reported that 16 of 27 patients had a milder or shorter ictal or postictal phase [18]. Three patients with an improved postictal state showed no response in seizure frequency. In 76% of patients, alertness improved. It would be interesting to investigate a potential correlation between this finding and the reported effects on the postictal phase. In this study, there was a decrease in seizure duration as a result of magnet use in 73% of the patients.

Several studies have reported effects of magnet-induced seizure termination that relate more to the potential of VNS to induce the postictal state rather than the effects of VNS on duration or severity of the postictal state. The magnet feature allows patients with auras to administer an additional stimulation train to abort an upcoming seizure. The magnet may also allow a family member or caregiver to try and interrupt an ongoing seizure.

Five centers have specifically reported on magnet-related efficacy [19–23]. The variable ways of reporting these results are a reflection of the difficulty in assessment of magnet-related efficacy. It is dependent mainly on the patient's and caregiver's reports and their ability to distinguish an aura or short-lasting seizure (without the use of the magnet) from a habitual seizure interrupted by use of the magnet. Withworth et al. reported that in a group of 50 patients, 50% were able to abort "some" of their seizures [19]. Nakken et al. reported that 47% of 47 patients experienced a "benefit" from the magnet [20]. In a series of 80 patients described by Scherrmann et al., 14% reported "mild" and 27% "strong" efficacy in terminating auras or ongoing seizures [21]. Ristanovic et al. reported '"successful" use of the magnet in 50% of the attempts performed by 10 of 13 patients [22]. Morris et al. reported the use of the magnet in 14 of 16 patients, with diminished seizure intensity in all patients and aborted seizures in 11 patients [23].

In a group of 35 patients treated at Ghent University Hospital, a prospective analysis of magnet efficacy was performed [24]. Each reported a single application of the magnet, and the reported seizures in the patient's diary were compared with logged information on magnet use that is stored by the device and can be retrieved using the programming wand and specialized software.

A positive effect of the magnet was defined as a sudden interruption of seizures at the stage of the aura or later during the habitual course, regardless whether this occurred consistently at every instance or only occasionally. In two patients, information on magnet use was considered unreliable. Three patients never used the magnet because they became seizure free early in their treatment. Nine patients were unable to use the magnet because there was no aura, seizures were too brief, or caregivers were unavailable. Sixty percent of the patients reported having used the magnet. One-third of these patients reported no benefit from the magnet. Two-thirds reported a positive effect of magnet use. Three patients were able to abort seizures themselves. Caregivers reported interruption of complex partial seizures as well as secondary convulsions. More than half of the patients who benefited from the magnet early in treatment eventually became responders.

These results suggest that the magnet is a useful tool that provides patients and caregivers with an additional means of controlling refractory seizures. The psychological impact of being able to stop a seizure should not be underestimated. More specialized and standardized investigation of acute interruption of seizures, for example, under video/EEG monitoring, might be worthwhile.

It is clear that not enough information is available from clinical practice with VNS to draw conclusions on its potential effect on the occurrence, duration, or severity of the postictal state. McHugh et al. have proposed an adjusted classification for evaluation of the clinical efficacy of VNS including specifically postictal severity as an outcome measure [25]. Despite the fact that this classification proposal does not include a separate outcome measure (e.g., class IA: improved ictal or postictal severity) it may draw clinicians' attention to this issue and remind them to interrogate patients on the effects on the postictal state.

3. VNS and postictal phenomena

The postictal state is characterized by a myriad of neuropsychiatric symptoms often compromising cognitive functions such as sedation, poor attention and concentration, poor short-term memory, decreased verbal and interactive skills, headache, psychosis, and depression. All these symptoms add to the morbidity of seizures [26]. Because of the vast experience with VNS in clinical practice (>50,000 patients treated worldwide), many clinicians have observed and reported on effects other than the seizure-suppressing neurological and psychotropic effects of VNS. Many of the observed positive side effects of VNS reported have been in the neuropsychiatric and cognitive fields: improved alertness, memory, mood, decreased headache and pain.

In the initial pilot trials with VNS, it was noted that patients were more alert. There was an increase in health-related quality of life and an enhanced well-being in patients treated with VNS [27]. It was noted that the reports on increased alertness and also mood occurred independently of the achieved seizure control. Malow et al. investigated a group of 16 patients with polysomnography and multiple sleep latency testing after 3 months of treatment with VNS [28]. They found that VNS significantly reduced daytime sleepiness and that the magnitude of the VNS-induced changes was comparable to that provided by standard treatments for sleepiness associated with narcolepsy. Three other studies investigated alertness and/or mood changes in patients after 3–6 months of treatment [29–31]. Patients showed considerable and sustained VNS-associated mood improvements independent of seizure attenuation. These observations led to the investigation of VNS in a pilot study ($n = 60$) and a double-blind randomized placebo-controlled trial ($n = 235$) for the treatment of refractory depression with promising results [32]. After 1 year of treatment, the percentage of patients free of depressive symptoms was 16% versus 5% in a control group of patients treated with medication.

Following promising animal experiments on VNS and memory, Clark et al. were able to confirm their findings in humans [33]. A subgroup of patients included in the EO5 trial showed dose-dependent enhanced verbal memory as demonstrated by increased performance in a word-recognition task when a 30-second, 0.5-mA stimulation train was administered 2 minutes following the reading of a highlighted text.