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A prestimulation evaluation protocol for patients with drug resistant epilepsy

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ABSTRACT

Neurostimulation is making its way into the therapeutic armamentarium of the epileptologists, with several invasive neurostimulation modalities available today and several less invasive modalities under investigation. Clinicians will soon face a choice that should not be made randomly. We introduce the concept of a prestimulation evaluation protocol, consisting of a series of rationally chosen investigations that evaluate the presence of biomarkers for response to various neurostimulation therapies. These biomarkers should reflect the susceptibility of the individual's epileptic network to a given neurostimulation technique. This will require elucidation of the specific mechanism(s) of action of the different neurostimulation modalities. This manuscript provides a hypothetical framework that may be more applicable in the near future when pre-clinical research progresses and can be translated into human applications.

1. Introduction

Neurostimulation is making its way into the therapeutic armamentarium of epileptologists treating patients with drug-resistant epilepsy. For vagus nerve stimulation (VNS) [1], deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) [2] and the Responsive Neurostimulation System (RNS) [3], efficacy and side effects profile have been demonstrated in large multicenter RCTs (see Table 1). During the blinded phase of the randomized trials seizure frequency was reduced with 30% in VNS [1] and with approximately 40% in ANT-DBS [2] and RNS [3]. After approximately 5 years of treatment efficacy further increased in the open label extension phase for all three modalities; up to 55% for VNS [4,5], 69% for ANT-DBS [2,6] and 66% for RNS [7,8]. In patients treated with VNS for over 10 years seizure frequency reductions of up to 75% have been reported [9].

Several other neurostimulation modalities are currently under investigation in a pre-clinical or clinical setting: DBS in other brain targets (*e.g.*, hippocampus) and non-invasive neurostimulation techniques such as transcutaneous VNS (tVNS), non-invasive VNS (nVNS), trigeminal nerve stimulation (TNS), repetitive transcranial magnetic stimulation (rTMS) and transcutaneous direct current stimulation (tDCS).

Neurostimulation therapies are currently available to patients who are considered unsuitable candidates for epilepsy surgery based on the investigations performed during the presurgical evaluation protocol. For a long time, VNS was the only available neurostimulation treatment option. More recently ANT-DBS and RNS have also become available for unsuitable surgery candidates. To avoid a merely negative selection procedure and in view of an increasing number of neurostimulation options becoming available, we introduce in this manuscript the concept of a *prestimulation evaluation protocol*. We envisage a protocol consisting of a series of rationally chosen investigations that evaluate the presence of biomarkers for response to various neurostimulation therapies. A patient-tailored approach is warranted also for neurostimulation and may optimize the potential therapeutic success of neurostimulation as well as help physicians to rationally propose a specific therapy at a given moment in an epilepsy patient's life.

2. Current modus operandi

In the absence of head-to-head comparative trials with VNS, ANT-DBS and RNS, the results of the RCTs suggest that in choosing a therapy for unsuitable surgery candidates none of the neurostimulation options are superior with regards to efficacy. Differences in invasiveness and adverse events may therefor direct the choice between these options [1–3]. VNS requires a less invasive surgical procedure [10]. ANT-DBS and RNS require brain surgery and are associated with the risk of intracranial hemorrhage and/or parenchymal infection [2,3]. VNS is associated with stimulation-related side effects such as hoarseness, coughing, dyspnea or a pain sensation in the throat; side effects that typically wear off after long-term treatment [11]. ANT-DBS may cause stimulation-related neuropsychological side effects [2] and RNS an increased risk in

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Table 1
Overview of clinical efficacy of the invasive neurostimulation modalities based on the original trials and their extension follow-up studies.

		Blinded period	Open label follow-up				
		3 months	1 year	2 year	3 year	±5 year	10 year
VNS	Seizure frequency reduction	30.9%	35%	44.3%	44.7%	55.8%	75,5%
	Responder rate	38.7%	36.8%	43.2%	42.7%	63.75%	
	Seizure freedom						
	(≥6 months)					8.25%	
	(≥2 years)						15.4%
	Reference	[1]	[4]			[5]	[9]
ANT-DBS	Seizure frequency reduction	40.4%	41%	56%		69%	
	Responder rate	29.6%	43%	54%	67%	68%	
	Seizure freedom						
	(≥6 months)					16%	
	(≥2 years)					5,5%	
	Reference	[2]	[2]			[6]	
RNS	Seizure frequency reduction	37.9%	44%	53%	60%	66%	
	Responder rate	29%	44%	55%	58%	59%	
	Seizure freedom						
	(≥6 months)					23%	
	(≥1 year)					12.9%	
	Reference	[3]	[8]			[7]	

Abbreviations: VNS, vagus nerve stimulation; ANT-DBS, deep brain stimulation of the anterior thalamic nucleus; RNS, Responsive Neurostimulation System.

sudden unexpected death in epilepsy (SUDEP) [3], although the latter seems to be less important in the long-term follow-up trials [6,7].

Apart from taking into account absolute and relative contra-indications, in clinical practice the choice between the three neurostimulation options is often based on a combination of considerations and personal clinical experience of the physician or the epilepsy center where the patient is being treated. In Table 2 we have summarized some arguments in favor of or against the available treatment options. In analogy to choosing between one of many available anti-epileptic drugs, comorbidities may play a role in the choice of neurostimulation therapies. Comorbidities are prevalent in refractory epilepsy patients, with some medical and psychiatric conditions occurring up to eight times more often compared to the general population [12–14]. The positive effects of VNS on mood have clearly been demonstrated in several preclinical and clinical studies [15], while for ANT-DBS negative effects on mood have been reported in the SANTE trial [2]. The SANTE trial not only reported higher rates of self-reported depression but also of subjective memory impairment in the active treatment group. For patients with pre-existing cognitive problems other neurostimulation options may be preferred. Of notice is that in the open label follow-up ANT-DBS trial neuropsychological tests scores did not differ significantly and the long-term follow-up report of Salanova et al. even showed an improvement on multiple neuropsychological domains at the group level [6]. The presence of obstructive sleep apnea warrants caution with regards to VNS, since vagal stimulation may increase the apnea-hypopnea index (AHI). Therefor it may be recommended to perform screening for excessive daytime sleepiness (*e.g.*, the Epworth sleepiness scale or ESS) with or without polysomnography to diagnose sleep apnea before implantation, as well as to follow-up AHI after implantation [16].

Regulatory issues like reimbursement procedures may also interfere with today's treatment selection. In children and in patients with generalized epilepsy, VNS is the only approved modality. RNS is approved by the Food and Drug Administration (FDA) in the United States, with variable reimbursement, but not available in Europe, whereas ANT-DBS is only available in Europe; both RNS and ANT-DBS are indicated in patients with refractory partial epilepsy.

3. Future strategies

The currently reported efficacy outcome (30–40% response rate) of the different neurostimulation modalities are still considered to be modest. Different mechanisms of action (MOA) are hypothesized for the different neurostimulation modalities. We can therefor assume that outcome is affected by (1) a variability in underlying pathophysiology or a difference in brain networks involved in different types of epilepsy and (2) the potential of specific types of neurostimulation to affect a given underlying disturbance. Choosing a given neurostimulation modality on the basis of a particular MOA in relation to a particular type of epilepsy, may enhance outcome and decrease the number of non-responders.

Patient selection for a given treatment and the investigations to be performed should focus on *a priori* response prediction. In the past 2 decades, large patient series have been treated with VNS but retrospective correlation analyses between patient characteristics and outcome have been disappointing. Overall, VNS seems more effective in patients with younger age and shorter duration of epilepsy [17], but there are important inconsistencies with regards to etiology, localization of the ictal onset zone, etc. [17–26] and importantly none of these currently described 'predictors' for response allows to make predictions at the individual level. In depth investigations performed in patients who went through the presurgical evaluation process, have focused on the identification of an epileptogenic lesion, preferably an anatomically identifiable lesion corresponding to a neurophysiological ictal onset. It is unlikely that successful response prediction will arise from the analysis of factors that are unrelated to the MOA of the applied neurostimulation technique. In the field of neurostimulation the identification of *dynamic biomarkers* may be more appropriate. Such biomarkers should reflect one or more key features of the MOA of a given neurostimulation treatment. Accordingly the prestimulation investigations to be performed should evaluate whether the epileptic network in a particular patient is likely to be modulated by a given mode of action. Preferably this assessment should be evidence-based and standardized allowing to define a *prestimulation evaluation protocol*, in analogy to the presurgical evaluation in drug resistant epilepsy patients. A prestimulation protocol should provide strategical guidance to clinicians in objectively choosing the most optimal neurostimulation therapy at a given moment in a patient's treatment process. However, the MOA of the various neurostimulation techniques remains to be elucidated. In fact, only for VNS and more than twenty years after its initial use in patients an evidence-based hypothesis on the working mechanism and translation of the findings to patient treatment is currently under investigation [27].

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