Seizure xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Brain stimulation as a neuromodulatory epilepsy therapy

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ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form 27 October 2016
Accepted 27 October 2016
Available online xxx

Keywords:
Epilepsy
Neuromodulation
Brain stimulation
Vagus nerve stimulation
Deep brain stimulation
Closed-loop stimulation

ABSTRACT

Brain stimulation is increasingly used in epilepsy patients with insufficient therapeutic response to pharmacological treatment. Whereas vagus nerve stimulation with implanted devices has been used in large and heterogeneous patient groups, new devices also enable targeted brain stimulation at the site of seizure generation (responsive neurostimulation) or at network hubs (thalamic stimulation). Both responsive neurostimulation systems targeting the epileptic focus and the latest vagus nerve stimulators are intended to stimulate during the ictal phase to disrupt clinical seizure manifestation of reduce seizure severity. Furthermore, transcutaneous stimulation approaches are now available, although their efficacy remains uncertain. This review explains the concepts underlying brain stimulation, provides an overview of efficacy and tolerability data and discusses the rational use of the growing spectrum of neuromodulatory strategies available.

1. Introduction

Neuromodulation using stimulation devices has been increasingly studied and introduced into clinical therapy over recent years [44,46]. In the face of mounting dissatisfaction with the additional benefit of newly developed antiepileptic drugs [30], neuromodulation offers conceptually different treatment approaches which avoid several problems associated with medical polytherapy [15,45].

Unlike systemic pharmacological treatments affecting all brain areas expressing the individual drug ligands, neuromodulation can be applied to a defined target region and its associated network circuitry. This enables clinicians specifically to design stimulation approaches for different focus regions and help to reduce unwanted effects. However, this approach may be of limited efficacy if epileptogenic regions are extended or if there is rapid spread of epileptic activity. Beyond the stimulation sites, the effects of electrical stimulation critically rely on the stimulus parameters chosen from a wide und multidimensional parameter space. At present, the mechanisms contributing to the antiepileptic efficacy of neuromodulatory approaches are not completely understood. High frequency stimulation may cause local inactivation of target brain tissue by preferential activation of GABA-ergic inhibitory neurons and alter extracellular potassium concentrations. It may furthermore desynchronize neural activities and lower the recruitability of neurons to epileptic rhythms. Low frequency stimulation may reduce excitability by induction of long-term depression, and DC stimulation may diminish action potential generation by hyperpolarization of neuronal membrane potentials (e.g. [20,29,49]). Activation of brainstem nuclei with widely divergent projections may have extended net inhibitory effects.

Presently, the limited efficacy of the neurostimulation approaches available means that they can only be considered as palliative treatments, used to reduce patients' seizure burden and improve quality of life. This review explores the efficacy and tolerability of currently available and certified neuromodulation techniques using peripheral nerve stimulation and direct brain stimulation (Table 1) and discusses possible criteria for the selection of individual approaches.

1.1. Peripheral nerve stimulation

The stimulation of cranial nerves was first shown to exert anti-seizure effects in acute and chronic animal models a long time ago [40,14]. Since its FDA approval in 1997, vagus nerve stimulation (VNS) with an implant has been used in over 100,000 patients [9]. Over the last few years, a transcutaneous vagus nerve stimulator [3], and a new paradigm for implantable VNS aimed to automate ictal stimulation have been introduced. Furthermore,

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http://dx.doi.org/10.1016/j.seizure.2016.10.026
1059-1311/

Table 1
Approved invasive neuromodulatory approaches for epilepsy.

	Vagus nerve stimulation	Thalamic stimulation	Responsive focus stimulation
Approval	1997 (FDA)/(EU) (since 2015: also heart-rate triggered)	2011 (EU)	2013 (FDA)
Stimulation site	Left vagus nerve (neck)	Anterior nuclei of the thalamus (bilaterally)	Epileptic focus (cortex)
Stimulator placement	Subcutaneous, left pectoral/subclavicular	Subcutaneous, abdominal	Within the skull
Stimulation mode	Open-loop/closed-loop based on detection of tachycardia	Open-loop	Closed-loop based on detection of ictal EEG patterns
Stimulus parameters	Intensity: 0,25–3 mA Frequency: 20–30 Hz Pulse width: 250–500 μs Duty cycle: 30 s on/5 min off (standard); 7 s on/30 s off ("rapid cycling")	Intensity: 5 V Frequency: 145 Hz Pulse width: 95 μs Duty cycle: 1 min on/5 min off	Intensity: ~1 mA Frequency: 200 Hz Pulse width: 160 μs Duty cycle: ~5,9 min/day; closed loop)
Side effects of implantation	1.6% infections (E05) 1% vocal cord paralysis	12,7% infections 4.5% incranial bleeding 18.2% paresthesia at implantation site 10.9% local pain	7.8% infections 4.7% intracranial bleeding 9.9% transient pain at implantation site
Side effects of stimulation	Hoarseness (intensity-dependent up to 66%), cough (up to 45%)	14.8% depression 13.0% memory impairment	–
Efficacy in blinded studies (stimulation − control/sham)	Seizure frequency Δ − 12.7%/−18.4% responder Δ 7%/18%	Seizure frequency Δ − 25.9% responder rate Δ 3%	Seizure frequency Δ − 20.6% responder rate Δ 2%

Basis characteristics of invasive stimulation approaches. Adverse events and efficacy is stated based on data from randomized controlled trial phases; this may underestimate long-term efficacy and overestimate experience-dependent complication rates of the implantation procedure. Stimulus parameters can usually be chosen over wider areas and are given as most frequently applied. Δ: difference between stimulation group and active control (VNS) resp. sham stimulation (thalamic stimulation, responsive focus stimulation).

transcutaneous trigeminal nerve stimulation has undergone initial clinical trials and may offer a novel, non-invasive alternative using a similar mode of action as VNS treatment.

1.2. Vagus nerve stimulation

Stimulation of the vagus nerve activates brain stem nuclei including the N. tractus solitarii; secondary activation of the N. coeruleus and its noradrenergic projections are critical for its antiepileptic efficacy [26]. The efficacy of VNS correlates positively with noradrenaline-release in potentially epileptogenic regions [32]. Prospective, randomized clinical trials comparing effective and assumedly ineffective stimulation modes have proven the efficacy of VNS in focal epilepsy ([48,21] Fig. 1); there are, however issues of blinding in all studies of peripheral nerve stimulation as patients are aware of the stimulation. Nevertheless, these earlier results were confirmed in a prospective trial by Amar et al. [1], and a 2015 Cochrane Review [38] found an odd's ratio of 1.73 [1.13–2.64] in favor of a positive treatment response with 20–30 Hz VNS vs. active controls based on five prospective studies.

In regulatory trials, VNS implantation was associated with an up to 11% risk of infection (E05) and an about 1% risk of vocal cord paralysis. A recent retrospective study reported infections in 2.6%, postoperative hematoma in 1.9%, vocal cord paralysis in 1.4%, pain in 1.4%, cable break in 0.2%, and other local surgical complications in 0.6% of cases. Over time, lead fracture occurred in 3.0%, lead

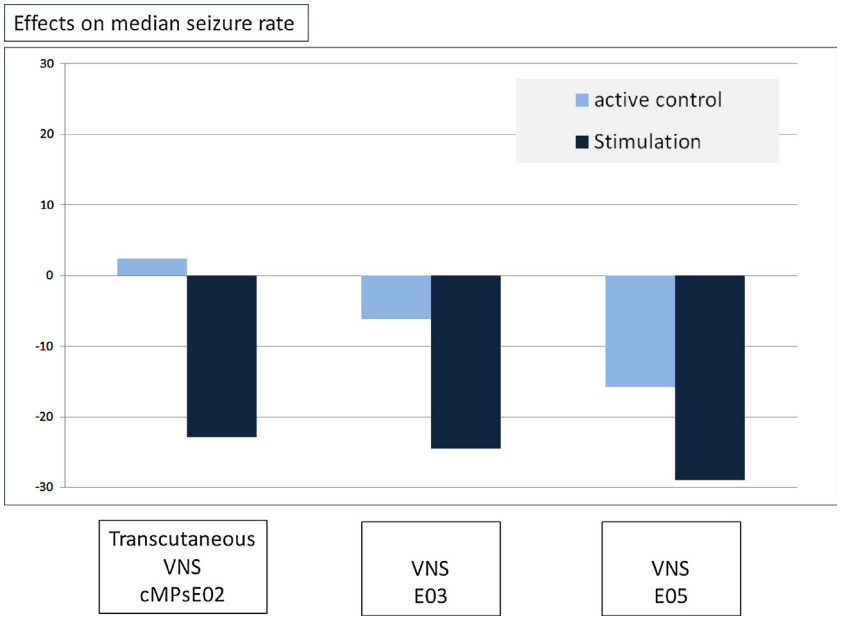

Fig. 1. Efficacy of transcutaneous and standard vagus nerve stimulation treatment on median seizure frequency in controlled prospective trials. Note that in all peripheral nerve stimulation trials no complete blinding is possible as electrical stimulation is perceived by patients, depending on stimulus intensity, and thus "active controls" with low intensity stimulation are used instead of sham stimulation as applied in studies with intracranial stimulation trials.

Please cite this article in press as: A. Schulze-Bonhage, Brain stimulation as a neuromodulatory epilepsy therapy, Seizure: Eur J Epilepsy (2016), http://dx.doi.org/10.1016/j.seizure.2016.10.026