DEEP BRAIN STIMULATION IS READY FOR CLINICAL USE IN REFRACTORY EPILEPSY

P. Boon
Department of Neurology, Ghent University Hospital, Gent, Belgium

Introduction: Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to or in the neighborhood of nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Different types of neurostimulation exist mainly depending of the part of the nervous system that is being affected and the way this stimulation is being administered.
Intracerebral neurostimulation requires accessing the intracranial nervous system as stimulation electrodes are inserted into intracerebral targets for *'deep brain stimulation' (DBS).* These modalities of neurostimulation are not novel for neurological indications. Some have been extensively used e.g. for movement disorders and pain. Moreover several new indications such as obsessive-compulsive behavior and cluster headache are being investigated with promising results. The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. Moreover, the development of neurostimulation for neurological indications is stimulated by two major concerns related to standard available treatments. First, there is a general tendency to find treatments that are minimally invasive and harmful to the patient. Secondly, the refractoriness of some neurological diseases and the inability to treat them with the available means provides an impetus to search for novel treatments. A few epilepsy centers around the world have recently reinitiated trials with deep brain stimulation in different intracerebral structures such as the thalamus and the subthalamic nucleus. DBS is under investigation in experimental trials in some specialised centers with large experience in refractory epilepsy and functional neurosurgery (1).
Deep brain stimulation: The earliest reports on intracranial neurostimulation involved stimulation of cerebellar structures for the treatment of spasticity due to cerebral palsy or stroke in several hundreds of patients with implantation duration times of up to 20 years. In patients with comorbi epilepsy, cerebellar stimulation resulted into seizure freedom in 60 % and significant seizure reductions in another 20 %. Despite these promising results in epilepsy, two controlled studies in small patient groups (n=5, n=12) did not show significant effects resulting in cerebellar stimulation for epilepsy being abandoned. The selection of other targets for DBS in more recent pilot trials in humans has resulted from the progress in the identification of epileptogenic networks that play an important role in the pathophysiology of epilepsy (2). Although the cortex plays an essential role in seizure origin, increasing evidence shows that subcortical structures may be involved in the clinical expression, propagation, control and sometimes initiation of seizures. Consequently, several subcortical nuclei such as the subthalamic nucleus and the caudate nucleus have been targeted in pilot trials in humans for different types of epilepsy.

There seems to be a general consensus that the thalamocortical interactions are essential in the development of a large number of seizures and the propagation of most of them. Within the thalamus, ascending projections from the reticular formation and other brainstem cell groups impinge on pathways radiating to numerous forebrain structures including those of the neocortex, basal ganglia and limbic system. At the same time, neural inputs from diverse telencephalic regions converge on thalamic nuclei from which projections descend onto brainstem neurons. Some thalamic nuclei, referred to as specific nuclei, maintain strong and direct synaptic relations with the sensorimotor or the association cortex. Other thalamic nuclei project more diffusely to wide regions of the cortex and are called nonspecific nuclei e.g. reticular nuclei, anterior nuclei and intralaminar nuclei such as the centromedian nucleus of Luys. The thalamus has also been indicated as one of the major important structures on the central nervous pathways involved in the MOA of VNS. Large patient series have been treated with DBS in the centromedian nucleus and a multicenter pilot trial (SANTE) investigating the efficacy and safety of the anterior nucleus is currently ongoing and has recruited over a 100 patients.

Few controlled studies investigating DBS are available. Blinded crossing-over between periods during which stimulation is on and off reflects the necessary design for evaluating the true efficacy of DBS protocols. However, the most optimal design of such protocols may be difficult to develop. It has become clear, especially from the experience with VNS, but also from other studies, that increased efficacy may be observed after longer duration of stimulation, possibly on the basis of neuromodulatory changes that take time to develop. It is unknown however, how long these developments take to install exactly or whether there are individual or age-related differences and to what extent permanent protective changes can be achieved. Consequently crossover after 3 months may be too short a time to evaluate fully expressed efficacy, especially using a stimulation protocol of eg. only several hours/day.

At Ghent University Hospital, a pilot trial with DBS in the *amygdalohippocampal region* in patients with medial temporal lobe (MTL) epilepsy was performed (3). Twelve consecutive patients with refractory MTL epilepsy were included in this study. The protocol included invasive video-EEG monitoring for ictal onset localization and evaluation for subsequent stimulation of the ictal onset zone. Side effects and changes in seizure frequency were carefully monitored. 10/12 patients underwent chronic MTL DBS. 2/12 patients underwent temporal lobectomy. After mean follow-up of 31 months (range: 12-52 months) 1/10 stimulated patients was seizure free (>1 year), 1/10 patients had a >90 % reduction in seizure frequency; 5/10 patients had a seizure frequency reduction of $\geq$50%; 2/10 patients had a seizure frequency reduction of 30-49%; 1/10 patients was a non-responder. None of the patients reported side effects. In one patient MRI showed asymptomatic intracranial hemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing. Patients who underwent temporal lobectomy are seizure free (>1 year), AEDs are unchanged and no side effects have occurred. This open pilot study demonstrates the potential efficacy of long-term DBS in MTL structures that should now be further confirmed by multicenter randomized controlled trials.

References

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