Epilepsy Research 141 (2018) 95–101

Contents lists available at ScienceDirect

Epilepsy Research

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

Review article

Neocortical electrical stimulation for epilepsy: Closed-loop versus open-loop

Albena Vassileva[a,b,c,1], Dorien van Blooijs[a,*,1], Frans Leijten[a], Geertjan Huiskamp[a]

[a] Department of Neurology and Neurosurgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands
[b] Institute for Neuroscience and Medicine (INM-3, INM-7), Research Center Jülich, Wilhelm-Johnen-Straße, 52428 Jülich, Germany[2]
[c] Institute for Systems Neuroscience, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

ARTICLE INFO

Keywords:
Brain stimulation
Cortical electrical stimulation
Epilepsy
Open-loop
Closed-loop

ABSTRACT

The aim of this review is to evaluate whether open-loop or closed-loop neocortical electrical stimulation should be the preferred approach to manage seizures in intractable epilepsy.

Twenty cases of open-loop neocortical stimulation with an implanted device have been reported, in 5 case studies. Closed-loop stimulation with an implanted device has been investigated in a larger number of patients in the RNS System clinical trials. With 230 patients enrolled at the start of the Long-term Treatment Trial, 115 remained at the last reported follow-up. Open-loop stimulation reduced seizure frequency in patients on average with over 90% compared to baseline. Closed-loop stimulation reduces seizure frequency with 60%–65%.

Even though open-loop neocortical electrical stimulation has only been reported in 20 patients, and closed-loop in much a larger sample, evidence suggests that both approaches are effective in reducing seizures. It remains an open question which should be clinically preferred. Therefore, a head-to-head adaptive clinical study comparing both approaches is proposed.

1. Introduction

Intractable epilepsy is a condition in which seizures cannot be controlled by antiepileptic drugs (AEDs). Perhaps the most effective treatments for those patients are resective surgery and laser ablation (Curry et al., 2012; Gonzalez-Martinez et al., 2014) of the epileptogenic tissue. However, for some patients, surgery might fail to control seizures, due to mislocalisation of the epileptogenic focus (Salanova et al., 2005), insufficient resection, as well as other factors (Harroud et al., 2012). When surgery is ineffective or not recommended, electrical stimulation has been used as an alternative treatment for medically intractable epilepsy. The most prevalent method is vagus nerve stimulation (VNS). Another is deep brain stimulation (DBS), and targets that have been chosen include the hippocampus, anterior thalamic nuclei, centromedian nucleus, caudate nucleus and the cerebellum. Non-invasive transcranial magnetic stimulation (TMS) generates intracranial electrical currents that may similarly influence cortex excitability (Lundstrom et al., 2017) and could decrease seizure frequency (Sun et al., 2012). Since TMS is not a wearable device, it is outside this review.

An alternative method to manage seizures is by cortical electrical stimulation (CES) directly to the seizure focus. It has been shown that electric pulses can suppress epileptiform activity (Kinoshita et al., 2004, 2005; Kossoff et al., 2004; Lesser et al., 1999; Schrader et al., 2006; Yamamoto et al., 2002, 2006) or reduce seizure rate after short-term continuous CES (Valentin et al., 2017; Valentín et al., 2016). CES can be performed either in an open-loop, or in a closed-loop approach. The open-loop method uses pre-scheduled stimulation, irrespective of ongoing electrophysiological activity in the brain. It is also referred to as “chronic” stimulation, when it is continuous. VNS and DBS are usually delivered in an open-loop manner. Their targets are not neocortical and are therefore beyond the scope of this review. Neocortical open-loop stimulation for epilepsy is a novel approach, which has not yet been extensively clinically tested.

Closed-loop CES means that stimulation starts in response to signals of an impending seizure. It is hence also termed ‘responsive stimulation’ and aims at preventing or early termination of the clinical symptoms of seizures. To achieve this, electrical brain activity is continuously monitored with subdural implanted electrodes (electrocorticography (ECoG)). Upon detection of abnormal patterns, CES is delivered to terminate seizure onset. Closed-loop neocortical stimulation has been studied in more patients compared to open-loop.

1.1. Available devices

The RNS System (by Neuropace) is currently the only fully implantable responsive neurostimulator. The procedure involves a

* Corresponding author at: Department of Neurology and Neurosurgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail address: d.vanblooijs@umcutrecht.nl (D. van Blooijs).
[1] These authors contributed equally.
[2] Present address.

https://doi.org/10.1016/j.eplepsyres.2018.02.010
Received 1 February 2017; Received in revised form 15 November 2017; Accepted 16 February 2018
Available online 19 February 2018

craniotomy and the implantation of the neurostimulator within the curvature of the skull. The whole device is then covered by the scalp. Two electrode leads are connected to the stimulator to monitor and deliver treatment to up to two seizure onset zones.

In all case studies, Medtronic neurostimulators were used for chronic open-loop stimulation. Unlike the RNS, this stimulator is implanted in the chest, rather than within the curvature of the skull. Although typically used for DBS, ECoG leads can also be attached.

1.2. Scope and significance of the review

This review compares open-loop and closed-loop CES, delivered to the neocortical seizure focus. So far, there has been no scientific or medical consensus on which approach is superior to the other, or which method should be preferred in any individual case. Therefore, this review seeks to establish whether open-loop or closed-loop CES should be the clinically preferred method for reducing the frequency and severity of epileptic seizures. The following specific review questions are addressed:

- Which method, open-loop or closed-loop CES, results in a bigger reduction of seizure frequency and severity in the long-term (more than 1 year after the start of the treatment)?
- Which method results in dramatic seizure frequency/severity reduction faster (i.e. how long after onset of treatment)?
- Which method carries less risk of adverse effects for the patient?
- Which method is more practical from the technical perspective (eg. battery life)?

2. Methods

2.1. Inclusion criteria

Inclusion criteria for article selection were:

1. CES to a neocortical seizure focus was performed with an implanted device with the goal of reducing seizure frequency/severity.
2. Either open-loop or closed-loop CES was delivered.
3. Large sample clinical studies when available, otherwise − case studies.
4. Human studies only.
5. Data published in original articles, research letters and supplementary material.
6. Year of publication: 1990–2017.
7. Language of publication: English.

2.2. Search strategy

The article search was performed in PubMed. Keywords were: cerebral; cortex; electrical; stimulation. Articles were chosen based on the inclusion criteria. Additional articles were chosen from the reference lists of already included publications.

2.3. Data collection and analysis

The data for this review were collected from the results sections of the chosen articles and/or supplementary materials. The data of interest included number of participants, study design, type of seizure, seizure focus location, stimulation parameters, type of treatment (open/closed-loop), duration of treatment, seizure frequency before treatment, percent seizure frequency reduction shortly after onset of treatment (immediately up to 1 year), percent seizure frequency reduction in the long-term (1 year and above after onset of treatment), percent of patients with adverse side effects/adverse events, and, if available, improvements in quality of life, including improvements in cognitive and non-cognitive (eg. motor) functioning.

The percentages of seizure reduction between methods were compared. Meta-analyses were not performed due to the different study designs of the chosen articles.

3. Results

3.1. Selected articles

The search in PubMed resulted in 940 articles. After reading titles, abstracts, and total articles, only eight articles were selected for review (for details, see Supplementary materials – Table S1). For the closed-loop paradigm, three publications were chosen, which present the results from the Pivotal RNS System clinical trial and the Long-term Treatment Trial (LTT): (Heck et al., 2014; Morrell, 2011) – Pivotal trial; (Bergey et al., 2015) – LTT trial).

For open-loop stimulation five articles, presenting case reports, were selected: (Elisevich et al., 2006) – 1 patient; (Velasco et al., 2009) – 2 patients; (Child et al., 2014) – 2 patients; (Valentin et al., 2015) – 2 patients, (Lundstrom et al., 2016) – 13 patients. To our knowledge, those are the only publications to date which report data from open-loop neocortical electrical stimulation for epilepsy.

3.2. Closed-loop stimulation

3.2.1. Study design

The RNS System Pivotal trial started with a 3-month baseline period, in which seizure frequency was evaluated. Patients had to have at least three disabling seizures per month (while on AEDs) to be eligible for implantation. Surgery was performed at the end of the baseline period. It was followed by a 4-week post-op stabilization period with ECoG monitoring and no stimulation. At the end of the monitoring phase, the patients were randomized into a treatment group and sham group. A 4-week stimulation optimization period followed, in which stimulation parameters were adjusted. The blinded evaluation phase started at 8 weeks' post-implant and continued for 3 months. During this period, only the patients in the treatment group received stimulation. The neurostimulators in the sham group were not programmed to deliver treatment, but patients had undergone sham programming. AEDs were kept constant in the blinded phase. At month 5 after implantation (end of blinded period), all patients transitioned into the open label phase. All patients received stimulation from this moment onwards. AEDs could be adjusted in this period. The end of the open label period continued until 2 years after implantation.

The LTT trial scope was from year 2 (end of open label period of Pivotal trial) onwards. The same patients from the Pivotal trial transitioned into the LTT. Some had dropped out.

Changes in seizure frequency during both the Pivotal and LTT trials were compared against the pre-implant baseline period.

3.2.2. Patient demographics

A total of 256 patients were implanted with the RNS System. 65 patients were implanted in an initial Feasibility study, which is not discussed here. 191 patients were implanted in the Pivotal trial. 187 of them completed the blinded phase, 182 reached one year post-implant and 175 reached two years post-implant. Participants in the LTT included patients who had completed the Pivotal trial, as well as patients who had participated in a previous Feasibility study, with a total of 230 patients. The number of patients that reached year 6 of the LTT was 115. The mean follow-up period was 5.4 implant years.

Around 50% of patients in both trials had seizure foci on neocortex (specific locations not reported), 7%had combined neocortical and mesial temporal lobe epilepsy (MTLE). The rest had mesial temporal lobe epilepsy (MTLE). Seizure types included simple partial motor seizures, complex partial seizures and secondarily generalized tonic-clonic seizures.

Around one third of patients had prior epilepsy surgery, one third