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[Intervention Review]

Deep brain and cortical stimulation for epilepsy

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ABSTRACT

Background

Despite optimal medical treatment, including epilepsy surgery, many epilepsy patients have uncontrolled seizures. Since the 1970s interest has grown in invasive intracranial neurostimulation as a treatment for these patients. Intracranial stimulation includes both deep brain stimulation (DBS) (stimulation through depth electrodes) and cortical stimulation (subdural electrodes). This is an updated version of a previous Cochrane review published in 2014.

Objectives

To assess the efficacy, safety and tolerability of DBS and cortical stimulation for refractory epilepsy based on randomized controlled trials (RCTs).

Search methods

We searched the Cochrane Epilepsy Group Specialized Register on 29 September 2015, but it was not necessary to update this search, because records in the Specialized Register are included in CENTRAL. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 11, 5 November 2016), PubMed (5 November 2016), ClinicalTrials.gov (5 November 2016), the WHO International Clinical Trials Registry Platform ICTRP (5 November 2016) and reference lists of retrieved articles. We also contacted device manufacturers and other researchers in the field. No language restrictions were imposed.

Selection criteria

RCTs comparing deep brain or cortical stimulation versus sham stimulation, resective surgery, further treatment with antiepileptic drugs or other neurostimulation treatments (including vagus nerve stimulation).

Data collection and analysis

Four review authors independently selected trials for inclusion. Two review authors independently extracted the relevant data and assessed trial quality and overall quality of evidence. The outcomes investigated were seizure freedom, responder rate, percentage seizure frequency reduction, adverse events, neuropsychological outcome and quality of life. If additional data were needed, the study investigators were contacted. Results were analysed and reported separately for different intracranial targets for reasons of clinical heterogeneity.

Main results

Twelve RCTs were identified, eleven of these compared one to three months of intracranial neurostimulation with sham stimulation. One trial was on anterior thalamic DBS (n = 109; 109 treatment periods); two trials on centromedian thalamic DBS (n = 20; 40 treatment periods), but only one of the trials (n = 7; 14 treatment periods) reported sufficient information for inclusion in the quantitative meta-analysis; three



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trials on cerebellar stimulation (n = 22; 39 treatment periods); three trials on hippocampal DBS (n = 15; 21 treatment periods); one trial on nucleus accumbens DBS (n = 4; 8 treatment periods); and one trial on responsive ictal onset zone stimulation (n = 191; 191 treatment periods). In addition, one small RCT (n = 6) compared six months of hippocampal DBS versus sham stimulation. Evidence of selective reporting was present in four trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in five cross-over trials without any or a sufficient washout period.

Moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency (primary outcome measures) after one to three months of anterior thalamic DBS in (multi)focal epilepsy, responsive ictal onset zone stimulation in (multi)focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. However, a statistically significant reduction in seizure frequency was found for anterior thalamic DBS (mean difference (MD), -17.4% compared to sham stimulation; 95% confidence interval (CI) -31.2 to -1.0; high-quality evidence), responsive ictal onset zone stimulation (MD -24.9%; 95% CI -40.1 to -6.0; high-quality evidence) and hippocampal DBS (MD -28.1%; 95% CI -34.1 to -22.2; moderate-quality evidence). Both anterior thalamic DBS and responsive ictal onset zone stimulation do not have a clinically meaningful impact on quality life after three months of stimulation (high-quality evidence).

Electrode implantation resulted in postoperative asymptomatic intracranial haemorrhage in 1.6% to 3.7% of the patients included in the two largest trials and 2.0% to 4.5% had postoperative soft tissue infections (9.4% to 12.7% after five years); no patient reported permanent symptomatic sequelae. Anterior thalamic DBS was associated with fewer epilepsy-associated injuries (7.4 versus 25.5%; P = 0.01) but higher rates of self-reported depression (14.8 versus 1.8%; P = 0.02) and subjective memory impairment (13.8 versus 1.8%; P = 0.03); there were no significant differences in formal neuropsychological testing results between the groups. Responsive ictal-onset zone stimulation seemed to be well-tolerated with few side effects. The limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS.

With regards to centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation, no statistically significant effects could be demonstrated but evidence is of only low to very low quality.

Authors' conclusions

Except for one very small RCT, only short-term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS ((multi)focal epilepsy), responsive ictal onset zone stimulation ((multi)focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. There is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. There is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments.

PLAIN LANGUAGE SUMMARY

Electrical stimulation through implanted electrodes in contact with the brain to treat drug-resistant epilepsy

Background

Despite many antiepileptic drugs being available, about 30% of epilepsy patients are not seizure-free. Electrical stimulation through implanted electrodes in contact with the brain (i.e. intracranial electrical stimulation, referring to 'deep brain stimulation' and 'cortical brain stimulation') has been proposed as an alternative treatment for these patients. This review aimed to evaluate its efficacy, safety and tolerability.

Results

Various brain structures have been targeted with scheduled (that is seizure-independent) stimulation, including the anterior thalamic nucleus (one trial, 109 participants), the centromedian thalamic nucleus (two trials, 20 participants), the cerebellar cortex (three trials, 22 participants), the hippocampus (four trials, 21 participants) and the nucleus accumbens (one trial; 4 participants). In addition, one trial (191 participants) studied responsive stimulation (that is only upon seizure detection) of the seizure onset zone. There is evidence for a moderate (15% to 30%) seizure frequency reduction after short-term (one to three months) anterior thalamic nucleus stimulation in (multi)focal epilepsy, hippocampal stimulation in temporal lobe epilepsy and responsive seizure onset zone stimulation in (multi)focal epilepsy. However, there is no evidence for significant impact on seizure freedom, the proportion of patients with a greater than 50% seizure frequency reduction, or quality of life.

Adverse effects of anterior thalamic stimulation include self-reported depression and subjective memory impairment, and possibly anxiety and confusional state. Responsive seizure onset zone stimulation seemed to be well-tolerated with few side effects.

Evidence on anterior thalamic and responsive ictal onset zone stimulation is of moderate to high quality, whereas the evidence on hippocampal stimulation is of low to moderate quality. There is insufficient evidence to make firm conclusive statements on the efficacy



or side effects of hippocampal, centromedian thalamic, cerebellar cortical and nucleus accumbens stimulation. Intracranial implantation of the electrodes was relatively safe without permanent symptomatic sequelae in the patients included in the trials.

Conclusions

More, larger and well-designed trials on intracranial electrical stimulation treatments are needed to validate and optimize its efficacy and safety and to compare this treatment to currently available treatments (for example, antiepileptic drugs or vagus nerve stimulation).

The evidence is current to 5 November 2016.