NEUROMODULATION & INTERVENTIONAL SECTION

A Systematic Literature Review of Brain Neurostimulation Therapies for the Treatment of Pain

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Abstract

Objective. To conduct a systematic literature review of brain neurostimulation for pain. **Design.** Grade the evidence for deep brain neurostimulation (DBS). **Methods.** An international, interdisciplinary work group conducted a literature search for brain stimulation. Abstracts were reviewed to select studies for grading. Randomized controlled trials (RCTs) meeting inclusion/exclusion criteria were graded by two independent reviewers. General inclusion criteria were prospective trials (RCTs and observational) that were not part of a larger or previously reported group. Excluded studies were retrospective or existed only as abstracts. Studies were graded using the modified Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment, the Cochrane Collaborations Risk of Bias assessment, and the United States Preventative Services Task Force level-of-evidence criteria. **Results.** Two high-quality RCTs and three observational trials supported DBS, resulting in Level II (moderate) evidence. **Conclusion.** Moderate evidence supports DBS to treat chronic pain. Additional Level I RCTs are needed to further the strength of the evidence in this important area of medicine, but the current evidence suggests that DBS should be considered as an option in treating complex pain cases.

Key words: Deep Brain Stimulation; Chronic Pain; Systematic Review; Pain Management

Figure 1. PRISMA diagram illustrating the literature used in the creation of the systematic review of DBS studies.

Introduction

This invited systematic literature review synthesizes the current evidence for deep brain stimulation (DBS) in treating chronic intractable pain. Consensus statements and best practices for neurostimulation to treat chronic intractable pain are available [1–7]. However, DBS has been more extensively studied as a treatment for Parkinson’s disease than for pain. In this comprehensive systematic literature review, functional neurosurgeons and neuromodulation experts grade and discuss the evidence for DBS in treating pain.

Methods

Task Force Development

Participants in the international, interdisciplinary brain work group were nominated by the Executive Committee of the West Virginia Society of Interventional Pain Physicians and the American Society for Pain & Neuroscience based on experience with the neuromodulation techniques under study, participation in research and publications, practice specialty, diversity, and practice setting.

Literature Search

The reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A systematic literature search was conducted by the lead author (SF) of the

Cochrane and PubMed databases from January 1980 to November 2017 using the following key words: “DBS for pain,” “cortical stimulation for pain,” “cranial stimulation for pain,” and “motor cortex stimulation for pain,” which yielded 282 results. Data sources, including cited articles and relevant systematic reviews, were searched manually for possible additional studies, and duplicates were excluded. When evaluated by the group and narrowed to include clinical trials and case series (with more than four patients), the search yielded 30 results (Figure 1).

Study Eligibility and Inclusion Criteria

We limited the inclusion criteria to randomized controlled trials (RCTs) or prospective observational trials that enrolled patients with chronic and intractable pain, including multiple pain patterns, of more than one year’s duration. We used the definition of intractable or refractory pain proposed by Deer et al.: “Pain is defined as refractory when 1) multiple evidence based biomedical therapies used in clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects, and when 2) psychiatric disorders and psychosocial factors that could influence pain outcomes have been assessed and appropriately addressed” [8].

The inclusion criteria were 1) must be prospective, 2) must include a minimum of four patients, and 3) must

Table 1. Characteristics of DBS studies

Study	Study Details	Study Design	Length of Follow-up	Outcome Measures	Site of Implant	Diagnoses
Lempka et al. 2017 [9]	Randomized, double-blinded, sham-controlled w/ crossover, open-label	Prospective, randomized (N = 10)	24 mo (3 mo crossover/6 mo blinded, 18 mo open-label)	PDI, BDI, MADRS, VAS, MPQ, EQ-5D	VS/ALIC	Poststroke pain syndrome
Fontaine et al. 2010 [10]	Randomized, double-blinded, sham-controlled, open-label phase	Prospective, randomized (N = 11)	1 mo randomized, 10 mo open-label	Attacks/wk, pain intensity, sumatriptan use, HAD-A, HAD-D, SF-12	Posterior hypothalamus	Chronic cluster headaches
Rasche et al. 2006 [11]	Case series	Prospective, randomized (N = 32)	42 mo (12–96 mo)	VAS, SF-36, MMPI, BDI	18 VPL/PVG, 8 PVG, 5 VPM/PVG, 1 VPL	13 FBSS, 6 CRPS II, 6 dysesthesia dolorosa, 4 phantom limb pain, 12 spinal cord injury, 11 poststroke, 2 postherpetic neuralgia, 2 nociceptive pain
Pereira et al. 2013 [12]	Case series	Prospective, observational (N = 12)	12 mo	SF-36, VAS, BPI, UWNPS	VPL thalamus	5 phantom limb, 7 deafferentation/brachial plexus injury
Kumar et al. 1990 [13]	Prospective, non-randomized, not placebo-controlled	Prospective, observational (N = 48)	Mean 42 mo	63% benefit	DBS-PVG-VPL	FBSS, cancer, thalamic pain, cauda equina, phantom limb pain

ALIC = anterior limb of the internal capsule; BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; CRPS = complex regional pain syndrome; EQ-5D = EuroQol 5 dimension; FBSS = failed back surgery syndrome; HAD-A = Hospital Anxiety and Depression–Anxiety; HAD-D = Hospital Anxiety and Depression–Depression; MADRS = Montgomery Åsberg Depression Rating Scale; MMPI = Minnesota Multiphasic Personality Inventory; MPQ = McGill Pain Questionnaire; PDI = Pain Disability Index; PVG = periventricular gray (matter); SF-12 = Short Form 12 (health survey); SF-36 = Short Form 36 (health survey); UWNPS = University of Washington Neuropathic Pain Score; VAS = visual analog scale; VPL = ventral posterior lateral (nucleus); VPM = ventral posterior medial (nucleus); VS = ventral striatum.

have a minimum of six weeks follow-up. Five studies met these inclusion criteria (Figure 1, Table 1). Two were case series, and one was an observational trial. Due to the small number of studies and subjects, quantitative analysis (meta-analysis) was not planned or performed.

Evidence Grading

The strength of the evidence for each full-text article was evaluated using the Cochrane, QAREL, and mIPM RCT criteria (Supplementary Appendix A includes the criteria used to grade evidence). The risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool [14]. This tool assesses the risk of bias attributed to the method of randomization, allocation concealment, blinding of patients and all research personnel, baseline imbalance, and inclusion of all study subjects in primary and secondary data analyses consistent with intent-to-treat principles (Supplementary Appendix A). For nonrandomized observational trials, we used the validated Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) tool to assess the quality and estimate the risk of bias (Supplementary Appendix A). This tool was developed by the American Society of Interventional Pain Physicians (ASIPP) as a

way to reliably evaluate the quality of nonrandomized trials in the interventional pain literature [15,16]. The same group also developed a similar tool to assess RCTs, the Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment tool (IPM-QRB) [17]. We used this as an additional quality assessment tool, in addition to the Cochrane Risk of Bias tool, to evaluate RCTs. We used the United States Preventive Service Task Force hierarchy of studies to assign a final evidence level [18]. Supplementary Appendix A describes the nomenclature used throughout this review to assign levels and describe evidence. Supplementary Appendix B summarizes DBS study scoring.

Consensus Process

The entire group participated in article selection and compilation of the evidentiary table, although no author was allowed to review and score a study for which he/she was a co-investigator. Each reviewer compiled information and submitted the findings to the entire group for review. Consensus was reached through voting, discussing, and eventual approval (see Supplementary Appendix B for composite scoring results). To finalize recommendations and gauge the strength of recommendations, where

differences in opinion arose, the guidelines were modified such that all members were in accord. When a unanimous decision could not be reached, the question was asked of the entire group. When full inclusion and exclusion criteria could be met and a consensus of greater than 50% from the task force was also obtained, the guidelines would be proposed as long as there was no objection from a task member. The described method was approved by all task force members.

Results

Table 1 describes the five selected studies. Each member of the committee was informed of the Cochrane criteria and allowed to vote on each paper for grading until a consensus was obtained. Although there is a risk of bias for the studies chosen for inclusion, it was felt that the consensus process and individual grading would limit this risk.

DBS targeting the periventricular gray (PVG) matter and the lateral somatosensory thalamus (ventral posterior lateral [VPL] or ventral posterior medial [VPM] nucleus) has proven to be efficacious in treating various forms of refractory chronic pain, most markedly for failed back surgery syndrome (FBSS), brachial plexus avulsion (BPA), and chronic pain of peripheral origin [11–13]. Overall, FBSS patients experienced the most pain relief with DBS, more specifically when the PVG and VPL were targeted, with a 71% mean success rate in two studies of DBS for various chronic pain types [11,13]. Using PVG/VPL DBS for phantom limb pain has had mixed results, with one study reporting highly significant improvements ($P < 0.001$) [12] and another reporting greater than 50% relief in only one of four amputee pain patients [11]. Although only based on one finding, the use of VPL DBS for BPA has been shown to provide significant pain relief ($P < 0.001$) [12]. Use of the posterior hypothalamus as a target has proven efficacious in reducing the frequency of headaches in chronic cluster headache (CCH) patients [10], with a majority of patients experiencing more than a 50% reduction in headache frequency, but it has not been explored as a treatment option for other forms of chronic pain within the studies examined. DBS targeting the ventral striatum/anterior limb of the internal capsule (VS/ALIC) has proven effective for treating poststroke pain in the short term, with DBS-on patients experiencing significantly more relief than DBS-off patients, yet declines in efficacy occurred over the long term, with only a third of patients reporting 50% relief after an 18-month open phase [9]. It is important to note that Kumar et al. reported a similar decrease in efficacy with an increased follow-up time, reporting tolerance in 21% of PVG-DBS patients and 10% of the sensory thalamus (S-Th) DBS patients after a mean follow-up of 42 and 36 months, respectively [13]. A better understanding of development of tolerance is needed to ensure that DBS is a viable treatment option for refractory chronic pain in the long term.

DBS Study Quality Analysis

1. USPSTF: DBS has Level 1 evidence based upon two RCTs.
2. mIPM-QRB RCTs and observational trials: DBS has Level II evidence based upon scoring from two RCTs and three observational trials.
3. Cochrane criteria: The Cochrane criteria support the findings of mIMP-QRB with regard to moderate risk of bias.

Discussion

In 1990, Kumar et al. [13] reported on 48 patients with 54 leads implanted to treat refractory chronic pain in a prospective observational trial. Follow-up time periods ranged between six months and 10 years, with a mean of 50 months per implant. Leads were either implanted in the PVG ($N = 41$) or the S-Th ($N = 13$). Although 93% of PVG patients proceeded with permanent implantation, only 54% of S-Th patients went on to have permanent implantation after a one- to two-week trial period; thus 39 patients had long-term follow-up, as nine patients failed the stimulation trial. Patients were evaluated preoperatively and six months postoperatively using the McGill Pain Questionnaire (MPQ) and a visual analog scale (VAS). Patients were determined to be successfully treated with DBS if their pain was reduced by 50% or more with occasional analgesics and adjuvant therapies. In the intention-to-treat analysis, 30 of 48 (63%) patients achieved pain relief after a 40-month follow-up; of the 38 patients who had PVG implants, the greatest success was obtained in the FBSS patients, with a 94% internalization rate and a 73% long-term success rate. There were 13 complications, including three equipment malfunctions and two seizures. Eight of the 38 PVG-implanted patients developed tolerance after a mean follow-up of 42 months, whereas one of 10 S-Th patients developed tolerance at 36 months. If the nine patients who did not internalize the implants after the one- to two-week trial period are excluded, the overall success rate was 77% (divided as 77% for PVG electrodes and 75% for S-Th electrodes).

In 2006, Rasche et al. [11] conducted a study examining the effects of DBS on 56 patients with various forms of refractory chronic pain. Leads were placed in the PVG and either the VPL or VPM. Patients were evaluated both preoperatively and postoperatively (with a mean follow-up of 3.5 years), using the VAS, Beck Depression Inventory (BDI), Minnesota Multiphasic Personality Inventory (MMPI), and SF-36 as metrics for pain relief. Results were particularly promising for FBSS patients, with 69.2% (nine of 13) patients having 50–100% pain relief. Patients with neuropathic pain of peripheral origin also exhibited significant pain relief, with 66.7% (four of six) of patients exhibiting 50–100% pain relief. In patients with trigeminal neuropathic pain and/or dysesthesia dolorosa, DBS was moderately successful in providing pain relief, with 50% (three of six) of patients

having 50–100% pain relief. Disappointingly, those treated for phantom limb pain, spinal cord injury, and poststroke injury had a mean of only 14.1% patients exhibiting 50–100% pain relief. No complications were noted.

In 2010, Fontaine et al. [10] conducted a study evaluating the effects of DBS targeting the posterior hypothalamus in 11 patients with refractory CCH. The double-blind crossover trial consisted of two one-month periods separated by a one-week washout period. The 11 CCH patients were randomly assigned to one of two groups: active stimulation followed by a sham stimulation period (on–off) or the opposite (off–on). All patients then participated in a 10-month open stimulation phase. Patients were evaluated based on VAS scores, Hospital Anxiety and Depression (HAD) scores, 12-Item Short-Form Health Survey (SF-12) scores, attacks per week, and sumatriptan injections per week. At the end of the randomized phase, the frequency of attacks did not significantly differ between the on and off periods. At the end of the 10-month open phase, the mean weekly attack frequency decreased by 48.4%. Six of 11 (54.5%) patients were deemed responders (experienced more than a 50% decrease in attack frequency). Three serious adverse events (AEs) were reported, including a subcutaneous infection, micturition syncope, and preoperative loss of consciousness closely following test stimulation.

In 2013, Pereira et al. [12] reported on 12 chronic neuropathic pain patients treated with VPL-DBS in a prospective case series. Of the 12 patients, five were amputees and seven had BPA. One patient was excluded after a failed preoperative trial, leaving 11 patients to proceed to implantation. Patients were evaluated one month preoperatively and at one, three, six, and 12 months postoperatively, and then annually, using the VAS (recorded twice daily in a pain diary for 14 days postoperatively, as well as during scheduled visits), University of Washington Neuropathic Pain Score (UWNPS), Brief Pain Inventory (BPI), and SF-36. In the amputation group, the mean VAS scores improved by $90.0\% \pm 10.0\%$ ($P=0.001$), the UWNPS improved by $80.4\% \pm 12.7\%$ ($P<0.001$), and the BPI improved by $79.9\% \pm 14.7\%$ ($P<0.001$). In the BPA group, the mean VAS score improved by $52.7\% \pm 30.2\%$ ($P<0.001$), and the BPI improved by $38.4\% \pm 41.7\%$ ($P=0.018$) after 12 months. There were no significant complications or stimulation side effects.

In a 2017 study, Lempka et al. [9] reported on nine poststroke pain patients who underwent a double-blinded, crossover, randomized, placebo-controlled study of DBS targeting the VS/ALIC. Although there were 10 patients originally, one dropped out before randomization. Nine patients were randomly assigned to either the first group, with active stimulation for the first three months and sham stimulation for the next three months, or the second group, where sham stimulation preceded

active stimulation. All patients then underwent an 18-month open stimulation phase. Patients were evaluated at one, two, and three months after randomization, one, two, and three months after crossover, and then at nine, 12, 18, and 24 months, using the PDI, BDI, Montgomery-Åsberg Depression Rating Scale (MADRS), VAS, MPQ, and EuroQol five dimension scale (EQ-5D). There were significant results for MADRS (44% improvement with DBS-on vs 19% DBS-off, $P=0.020$) and the BDI (45% improvement with DBS-on vs 27% DBS-off, $P=0.004$). At the end of the 18-month open phase, about one-third of the participants maintained a 50% improvement on the MADRS (three of nine), BDI (four of nine), and McGill Affective Pain Rating Index (three of nine). There were 14 serious AEs, three of which were related to DBS: one seizure that was resolved with medication and two infections.

Conclusions

The use of DBS for the treatment of chronic pain is moderately supported in the literature, with a recommendation of additional prospective long-term studies. The currently available data in admittedly small numbers of subjects from randomized studies suggest efficacy for poststroke pain syndrome and chronic cluster headache. Larger-scale trials are needed in this burgeoning area of research and clinical treatment.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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