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Review

Deep brain stimulation for pain relief: A meta-analysis

Richard G Bittar[1,2,4,5,6] MBBS PHD FRACS, Ishani Kar-Purkayastha[1] MBCHB, Sarah L Owen[2] BA ODP, Renee E Bear[3] BAPPSC(PSYCH)(HONS), Alex Green MBCHB MRCS, ShouYan Wang[2] PHD, Tipu Z Aziz[1,2] MD DMEDSC FRCS

[1]Department of Neurosurgery, Radcliffe Infirmary, Oxford, UK, [2]University Department of Physiology, University of Oxford, UK, [3]Department of Psychology, Deakin University, Melbourne, Australia, [4]Australasian Movement Disorder and Pain Surgery Clinic, Melbourne, Australia, [5]Departments of Surgery and Neurosurgery, Monash University and The Alfred Hospital, Melbourne, Australia, [6]Melbourne Neurosurgery, Victoria, Australia

Summary Deep brain stimulation (DBS) has been used to treat intractable pain for over 50 years. Variations in targets and surgical technique complicate the interpretation of many studies. To better understand its efficacy, we performed a meta-analysis of DBS for pain relief. MEDLINE (1966 to February 2003) and EMBASE (1980 to January 2003) databases were searched using key words *deep brain stimulation, sensory thalamus, periventricular gray* and *pain*. Inclusion criteria were based on patient characteristics and protocol clarity. Six studies (between 1977–1997) fitting the criteria were identified. Stimulation sites included the periventricular/periaqueductal grey matter (PVG/PAG), internal capsule (IC), and sensory thalamus (ST). The long-term pain alleviation rate was highest with DBS of the PVG/PAG (79%), or the PVG/PAG plus sensory thalamus/internal capsule (87%). Stimulation of the sensory thalamus alone was less effective (58% long-term success) ($p < 0.05$). DBS was more effective for nociceptive than deafferentation pain (63% vs 47% long-term success; $p < 0.01$). Long-term success was attained in over 80% of patients with intractable low back pain (failed back surgery) following successful trial stimulation. Trial stimulation was successful in approximately 50% of those with post-stroke pain, and 58% of patients permanently implanted achieved ongoing pain relief. Higher rates of success were seen with phantom limb pain and neuropathies. We conclude that DBS is frequently effective when used in well-selected patients. Neuroimaging and neuromodulation technology advances complicate the application of these results to modern practice. Ongoing investigations should shed further light on this complex clinical conundrum.

Keywords: deep brain stimulation, pain, failed back surgery, phantom limb pain, pain relief

INTRODUCTION

Chronic intractable pain syndromes have been treated by electrical stimulation of deep brain structures for the past half-century.[1–7] Stimulation of the periventricular grey matter (PVG) has generally been recommended for the treatment of nociceptive pain, with the sensory thalamus (ST) and internal capsule (IC) the preferred stimulation sites for neuropathic pain.

Motor cortex stimulation (MCS) has emerged more recently as a popular technique for the alleviation of central pain[8–13] however an absence of randomised controlled studies makes it difficult to legitimately compare its efficacy with that of deep brain stimulation (DBS). Specifically, differing selection criteria, thresholds for implantation following test stimulation, stimulation frequencies, and outcome measurement strategies make an accurate determination of the relative efficacy of both techniques challenging.

In order to better understand the utility of DBS in the treatment of intractable chronic pain, we present the results of a meta-analysis of previous studies examining DBS for nociceptive and neuropathic pain.

METHODS

A computerised search of MEDLINE databases from 1966 to February 2003, and EMBASE from 1980 to January 2003 was conducted for publications in any language using the key words *deep brain stimulation, sensory thalamus, periventricular grey* and *pain*. The reference lists of the retrieved articles were reviewed for additional articles.

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Correspondence to: Dr Richard G. Bittar, Australasian Movement Disorder and Pain Surgery Clinic, Suite 5, Level 4, 517 St Kilda Rd, Melbourne Victoria, Australia 3004. Tel.: +61 3 9816 9844;
E-mail: neurosurgeon@ampsclinic.com

Study selection

Inclusion criteria for the review were based on patient characteristics, clarity of protocol with regard to evaluation of outcome and follow up. The criteria are considered in detail below.

Patients

Whilst the anatomical sites for electrode implantation have varied between trials of DBS, there has been a marked consistency in patient selection criteria across the spectrum of trials.

Patients selected for chronic DBS met the following basic criteria:

1. The pain was of known organic origin.
2. All reasonable conventional methods had failed or were poorly tolerated.
3. Patients with neuroses/psychoses and severe depression were excluded. Patients with mild to moderate depression or anxiety were treated accordingly prior to commencing DBS.

There was a wide range in age, gender, aetiology, mean duration of pain and interval between onset of pain and treatment with deep brain stimulation.

Pain evaluation

Post-implantation monitoring of pain relief was usually carried out by a physician or health professional uninvolved with the team that had carried out the implantation. There was a lack of consistency between trials in the methods used to evaluate pain. Whilst

in studies of MCS percentage pain relief was a consistent primary outcome measure, no such easily quantifiable indicator was used consistently in the DBS studies. There were three studies where a visual analogue scale (VAS) was used (studies B[7], D[14] and F[15]), but in two of these studies these were combined with other criteria to create grading protocols that were unique to each study. A successful outcome in study E was described as either complete or partial relief.[16] In paper A the procedure was categorised as a success or failure based on the cumulative score from four different criteria; completeness of pain relief, duration of analgesia following stimulation, absence of adverse side effects and long term effectiveness.[6] Success in paper C was considered as a patient with no or minimal pain which was able to be controlled with additional non-narcotic analgesia.[17] Despite the variability in the protocols used to evaluate a successful outcome, the six studies have been included because the protocol used in each case was clearly described by the authors. In the absence of a universally applied primary outcome measure, such as percentage pain relief, success or failure in these six studies was taken as that defined by the investigators.

Duration of follow up

All studies have been included where the period of follow up was clearly stated and where adequate explanatory information was given in the cases of patients that were lost to follow-up. Many of the studies exhibit a wide variation of the follow up times between patients. Follow-up times for individual studies are reported in Table 1.

Study characteristics

A total of 12 studies were identified, of which only the six that have been considered in this review met the inclusion criteria detailed above (Table 1). Pre-operative psychiatric evaluation and neuroimaging was carried out in all studies. In the studies where pharmacological testing was used, the purpose was to sort pain aetiology into the two broad categories of nociceptive and deafferentation with subsequent implications for the site of electrode implantation. The surgical technique described was relatively consistent between studies.

Pre-operative screening tests

These were carried out pre-operatively in order to establish the suitability of patients for DBS and to determine the optimal electrode location. It had previously been noted that deafferentation pain was more likely to respond to stimulation of the ST and that nociceptive pain was more likely to respond to stimulation of the PAG/PVG. This was partly based on laboratory and clinical trials indicating that pain relief from PAG/PVG stimulation depended upon the release of naturally occurring opioid analogues.[18,19] Two pharmacological tests were carried out; the morphine saturation test as described by Hosobuchi et al.[20] and the pentobarbital test. No single test was used in all studies, nor was either used as the sole determinant for electrode location. The morphine saturation test was used in papers B, D and F. The pentobarbital test was used in papers C and F.

Surgical technique

This can be broken down into three main components. The first stage was identification of the target site. The second stage was the placement of a stimulating electrode, and the third was the titration of stimulation parameters. With respect to the first two stages there was some variation between the studies, particularly as neuroimaging techniques have evolved over time. Once the frame had been fixed to the patient's head, neuroimaging was performed. This was done either intra-operatively, as in the older studies (A, B, C, D, E, early patients in paper F) where contrast/air ventriculography was used; or pre-operatively, with CT or MRI. The stereotactic co-ordinates were matched with target parameters obtained from a variety of human stereotactic atlases such as the Schaltenbrand & Bailey's atlas[21] (used in papers A, C, D); Schaltenbrand & Wahren atlas[22] (used in papers B, F); Emmers & Tasker atlas[23] (used in papers B, F); Van Buren-Borke atlas[24] (used in paper E); and the Andrew & Watkins atlas[25] (used in paper B).

In patients with nociceptive pain, the electrode was usually implanted in the PAG/PVG, frequently bilaterally. In patients with deafferentation pain electrode implantation was in the contralateral ST. For those patients where there was an overlap between nociceptive and deafferentation pain both the PAG/PVG and the ST were implanted. In one study, all electrodes were implanted in the thalamus irrespective of etiology. The electrode was advanced to the target site and intra-operative stimulation performed to elicit analgesia. Proper electrode location was also indicated in PAG/PVG targeting when 5–6 mA stimulation produced a sensation of bodily warmth often accompanied by a feeling of relaxation. Correct electrode location was indicated in the sensory thalamic nuclei by the induction of paresthaesias in the region of pain (papers D & E). Titration to obtain optimal stimulation parameters was carried out post-operatively usually over one or two weeks during which the electrodes were connected to an external stimulator. Internalisation of the stimulation system was carried out after that test period only in those patients who reported a favorable outcome. In the early part of paper F and in papers A, B, C, E a radiofrequency generator was used with an external transmitter-stimulator switch. For the later part of study F the Itrel pulse generator (Medtronic Inc, Memphis, TN) was used.

RESULTS

Six studies fitting the criteria described in the methods section were identified. These were published between 1977 and 1997 (Table 1). The length of follow-up ranged from 1 month to 15

Table 1 Characteristics of the six studies selected for the meta-analysis (PVG periventricular grey, PAG periaqueductal grey, IC internal capsule, ST sensory thalamus)

Study	Year	Initial Success (n)	Long-Term Success (n)	Follow up (months)	Electrodes
A (Richardson & Akil)[5,6]	1977	7	6	>24	PVG
B (Young et al.)[7]	1985	43	35	2–60	PVG/PAG/IC/ST
C (Hosobuchi)[17]	1986	105	94	24–168	PAG/ST
D (Levy et al.)[14]	1987	83	42	24–168	PVG/IC/ST
E (Turnbull et al.)[16]	1980	14	12	1–47	ST
F (Kumar et al.)[15]	1997	53	42	6–180	PVG/PAG/IC/ST

Table 2 Rate of long-term success as a percentage of number of cases where electrodes were internalised (1) and as a percentage of the total number of cases (2) relative to the aetiology of the pain. Data has been collated from studies A, B, C, D, E, & F

Aetiology	Cases	Success on initial stimulation	Success on chronic stimulation	% success (of cases internalised) (1)	% success (of cases trialed) (2)
Thalamic pain (central lesion)	45	24	14	58.3	31.1
Phantom limb and stump pain	9	7	4	57.1	44.4
Cervical root & /or brachial plexus lesion	12	9	6	66.7	50.0
Failed back syndrome	59	54	46	85.2	78.0
Peripheral neuropathy/radiculopathy	23	16	12	75.0	52.2
Trigeminal neuropathy	4	4	4	100	100
Post-herpetic neuralgia	11	6	4	66.7	36.4
Causalgia	5	5	4	80.0	80.0
Cancer pain	23	19	15	78.9	65.2
Anaesthesia dolorosa	28	17	8	47.1	28.6
Paraplegia/paraparesis/quadriplegia	20	7	2	28.6	10.0
Post-cordotomy dysesthesia	14	11	10	90.9	71.4
Lumbosacral radiculopathy	21	20	19	95.0	90.5
Cauda equina syndrome	3	3	3	100	100
Low back & skeletal pain	103	70	56	80.0	54.4
Thoracic neuralgia	4	3	1	33.3	25.0
Miscellaneous (deafferentation)	6	4	4	100	66.7
Atypical facial pain	1	1	1	100	100
Osteoporosis	1	0	0	0	0
Spinal cord injury	10	7	5	71.4	50.0
Post-operative/traumatic pain	9	9	5	55.6	55.6
Glossodynia	1	0	0	0	0
Non-malignant pain	3	1	1	33.3	33.3
Lumbar arachnoiditis	9	8	7	87.5	77.8
Total	**424**	**305**	**232**	**76.1%**	**54.7%**

Table 3 Long term success as a percentage of total number of cases with respect to broad categories of pain (nociceptive, deafferentation) in each study

Study	Aetiology	Success (n)	Failure (n)	Success (% of Total)
A	Nociceptive	4	1	80.0
A	Deafferentation	2	1	66.7
B	Nociceptive	25	7	78.1
B	Deafferentation	10	6	62.5
C	Nociceptive	50	15	76.9
C	Deafferentation	44	32	57.9
D	Nociceptive	18	39	31.6
D	Deafferentation	24	60	28.6
E	Nociceptive	0	1	0
E	Deafferentation	13	4	76.5
F	Nociceptive	32	12	72.7
F	Deafferentation	10	14	41.7

years. A variety of stimulation sites were utilised, including the periventricular gray, periaqueductal gray, internal capsule, and sensory thalamus.

The variability in methods used to assess pain was too extensive to permit the generation of a standardised measure, therefore success or failure was taken as reported in individual studies. Table 2 shows rates of long-term success relative to the aetiology of pain with data collated from the 6 listed studies. Tables 3–5 display the long-term results according to the category of pain (deafferentation vs nociceptive; central vs peripheral). The percentages were calculated according to the following protocol:

Table 4 Overall long term rates of success and failure with respect to the two categories of pain; nociceptive and deafferentation

	Success	Failure	Total
Nociceptive	129 (63%)	75 (37%)	204
Deafferentation	103 (47%)	117 (53%)	220

Percentage 1 = No. of long term successful cases × 100/No. in whom stimulation system was internalised.
Percentage 2 = No. of long term successful cases × 100/Total no. of patients in the study.

Site of stimulation

The rate of long-term pain alleviation was highest in those patients undergoing DBS of the PVG/PAG (79%), or the PVG/PAG plus ST/IC (87%). Stimulation of the ST alone was less effective (58% long-term success) than stimulation of the PVG/PAG ± ST ($p < 0.05$). This data is summarised in Table 6. The frequency, amplitude, and pulse width of stimulation, where specified, are displayed in Table 7.

Table 5 Overall long term rates of success and failure with respect to the two sub-categories of deafferentation pain; central and peripheral

	Success	Failure	Total
Central	14 (31%)	31 (69%)	45
Peripheral	89 (51%)	86 (49%)	175

Table 6 Long-term success as a percentage of total number of cases with respect to the site of electrode implantation. Papers A, B, C, E & F included (data from paper D could not be incorporated as the site of implantation was reported in terms of number of electrodes rather than number of cases)

Site of stimulation	No. cases	No. successful	% success (2)
PAG or PVG	148	117	79.1
PAG/PVG + ST/IC	55	48	87.3
ST	100	58	58.0
ST or IC	16	6	37.5

Table 7 Stimulation parameters yielding optimum pain relief at the two target sites (stimulation parameters only specified in studies C, D and F)

Study	Site	Frequency (Hz)	Amplitude (V)	Pulse-width (ms)
F	PAG/PVG	25–50	1–5	0.1–0.5
F	ST	50–100	2–8	0.2–0.8
D	PAG/PVG	5–15	1–5	Not specified
D	ST	20–100	3–8	Not specified
C	PAG/PVG	30	3	0.2
C	ST	50–75	2–5	0.2

Aetiology

DBS was more effective for nociceptive pain than for deafferentation pain (63% vs 47% long-term success; $p < 0.01$). A long-term success rate of over 80% was attained in patients with intractable low back pain and failed back surgery syndrome who underwent successful trial stimulation and proceeded to permanent implantation. This was the largest group of patients suffering intractable nociceptive pain. Of those with neuropathic pain, success rates were lower (Tables 3 and 4). Trial stimulation was successful in approximately 50% of those with post-stroke pain, and 58% of patients permanently implanted achieved ongoing pain relief. Moderately higher rates of success were seen in patients with phantom limb pain, radiculopathies, neuropathies, and plexopathies (Table 2). Subdivision of deafferentation pain into central and peripheral categories (Table 5) demonstrated a higher success rate in those patients with peripheral lesions (51% vs 31%; $p < 0.03$).

Individual studies

In the retrospective study by Kumar et al.[15] (paper F) there was a broad representation of both deafferentation and nociceptive pain. Patients were selected for PAG/PVG implantation or for VPL/VPM implantation (or for both), depending on the etiology and response of pain to the morphine-naloxone test. Following thalamic infarcts, the posterior limb of the IC was used. The greatest success in this series was seen with 'failed back syndrome', where 65% of patients overall and 82% of patients who had had permanent electrode implantation following pain relief in the initial test phase experienced successful pain relief on long term follow-up. When pain of nociceptive origin was compared with deafferentation pain, 73% of patients with the former compared with only 38% of those with deafferentation pain experienced successful pain relief (>50%) in the long-term.

Hosobuchi[17] (paper C) studied 122 patients with both types of pain. Stimulation sites were also determined by aetiology and response to the morphine-naloxone test. Sixty eight percentage of those with pain secondary to deafferentation had immediate relief following electrode implantation and stimulation of the ST and 57% of these patients remained pain free after two years. Of those treated for nociceptive pain, successful relief was achieved in 80%.

In paper D (Levy et al.[14]), 84 of the 141 patients treated had deafferentation pain and 57 had nociceptive pain. Of those with deafferentation pain the stimulated areas included VPL/IC and PVG; 61% had initial successful pain relief and 30% had long term successful pain relief. The corresponding figures for nociceptive pain were similar (56% and 32% respectively).

DISCUSSION

Historical aspects

The genesis of stereotactic surgery for the relief of pain may be credited to Ernest Spiegel and Henry Wycis, who developed a human stereotaxic device capable of facilitating procedures on the basal ganglia.[26] This device had its first application in the creation of discrete lesions for the treatment of chronic pain.[27]

As with lesional surgery, one of the earliest applications of deep brain electrical stimulation was for the treatment of intractable pain.[1,2] Analgesia was originally noted in psychiatric patients undergoing electrical stimulation of the septal area, and the capacity to generate pain relief by stimulating this region was confirmed a few years later in patients with cancer pain.[28] Others also achieved successful analgesia by stimulating the caudate nucleus and septal area.[3,29]

Electrical stimulation of the diencephalon gradually emerged as an effective method for the alleviation of intractable neuropathic pain. Mazars et al.[4] targeted the ventroposterolateral (VPL) nucleus, whilst White and Sweet[30] reported successful pain control by stimulating the ventroposteromedial (VPM) thalamic nucleus. Overall, chronic electrical stimulation of VPL/VPM and the IC appeared reasonably efficacious in the amelioration of intractable neuropathic pain.[31,32] Analgesia was also observed when electrical currents were delivered to other thalamic regions, including the centromedian, mediodorsal, and parafascicular nuclei.[18,33,34]

Electrical stimulation of the rat PAG was undertaken by Reynolds,[35] and an analgesic effect was produced. A similar effect was found in humans following electrical stimulation of the PVG surrounding the posterior portion of the third ventricle, particularly in nociceptive pain syndromes.[5–7]

As a consequence of the aforementioned studies, stimulation of the PVG has generally been recommended for the treatment of intractable nociceptive pain, whilst the sensory thalamus or internal capsule has been advocated as the preferred targets for neuropathic pain. There is, however, an absence of Class I data to support such a rigid treatment algorithm.

Contemporary studies

The descriptive terminology used to categorise pain as nociceptive, neuropathic, deafferentation, central, thalamic is sometimes ambiguous and inconsistently used between studies. For the purposes of this study, specific etiologies were considered individually and 'central' pain was restricted to include only thalamic or suprathalamic lesions.

In the current meta-analysis, patients who had nociceptive pain generally had better outcome with reported success rates of up to 80%, compared to deafferentation pain where the highest success rate in any given study was 67%. Considering all six studies together the outcome for nociceptive pain was significantly better than for deafferentation pain ($p < 0.001$). However these numbers include deafferentation pain of both peripheral and central origin and it is specifically this second category that has proven notoriously unresponsive to deep brain stimulation. When these two sub-sets of deafferentation pain are considered separately the difference becomes quite evident. Compiling the data from the six studies on deep brain stimulation included, only 31% of patients with pain secondary to central lesions compared to 51% of patients with pain secondary to lesions in the peripheral nervous system experienced satisfactory pain relief in the long term ($p < 0.03$).

Possible mechanisms of DBS-induced analgesia

In the case of stimulation of the PAG/PVG, plausible theories regarding mechanism include analgesia produced by the release of endogenous opioids. Several groups have reported that analgesia induced by stimulation of the central grey matter is reversed by administration by naloxone.[5,18,36] The evidence in favor of endog-

enous opioid mediated analgesia is equivocal, and other mechanisms are likely to be involved.

It is now thought that ascending pathways from the PVG may also be involved in the mechanism of stimulation-induced pain relief. Increased activation of the medial dorsal nucleus of the thalamus, an area associated with the limbic system and with extensive connections with the amygdala and cingulate cortex, has been observed during stimulation of the PVG.[37] Thus, in addition to activating the descending opioid system, stimulation of the PVG may also modify the patient's emotional response to pain.

The mechanism of analgesia elicited by electrical stimulation of the ST is similarly incompletely understood. Its effect may be mediated by activation of the inhibitory corticofugal fibres[38,39] that prevent the pathological spread of painful stimuli. Gerhart et al. showed that the inhibitory effect of thalamic stimulation upon the lamina I neurons of the dorsal horn is eliminated by bilateral lesions of the dorsolateral funiculi and the ventral funiculus of the ipsilateral funiculus,[40] implicating an inhibitory thalamocortical-corticofugal pathway.

CONCLUSIONS

DBS is an effective technique when used in well-selected patients with refractory chronic neuropathic or nociceptive pain. Although the treatment effect is more marked in patients with nociceptive pain, it is nonetheless substantial in patients with deafferentation pain. Failed back surgery syndrome has a very high rate of success with DBS, and this technique may therefore be of benefit to a large number of patients with this frequent and often debilitating condition. Peripheral deafferentation pain also frequently responds well to carefully planned and executed DBS. The interpretation of studies performed several decades ago is fraught with hazards, predominantly due to differing methodologies. Major advances in neuroimaging and neuromodulation technology complicate the application of the results of these studies to modern neurosurgical practice. Ongoing investigations, preferably in the form of randomized controlled studies, should shed further light on this complex clinical conundrum.

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