Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (Suppl 1) (2010) S27 – S31
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Neurosurgical treatments of intractable pain

Stylianos Nicolaidis*
Collège de France, Paris, France

Abstract

Intractable pain may require neurosurgical intervention. This review provides a critical update of neurosurgical techniques available to treat this condition. Neurosurgery can affect pain's pathways from the receptor up to the "centers" of its reception and perception, either by destroying or by stimulating them. Early in neurosurgery's development, and still today, ablative procedures are able to suppress or alleviate pain. However, in most cases, such ablations have only remained effective for a few months or, at best, a few years. This is why, from the 1960s on, a better understanding of the mechanism of pain inspired development of electrical and chemical neuromodulation procedures at every level of the nociceptive system (peripheral nerve, cord, thalamic, periventricular/aqueductal gray, and cortical centers). The encouraging outcomes that resulted are attracting increasing attention and interest among clinicians. The indications for undertaking an ablative vs a neurostimulative procedure, as well as selection of the anatomical target, depend largely on whether pain is nociceptive or neuropathic, given that most of these indications overlap to some extent. In addition, because the published outcomes are not based on universal criteria, it is difficult for the attending physician to select the type of procedure most suitable to the pain problem. This brief review surveys the various neurosurgical procedures together with their corresponding indications in the hope that the information provided will help practitioners choose (1) the type of neurosurgical therapy most appropriate to their patients' needs and (2) the neurosurgical group best equipped to implement that choice.

1. Introduction

From its very beginning, neurosurgery appeared to offer the most logical therapy for "intractable pain" because of its potential ability to directly interrupt pain's afferent nociceptive pathways. At one time or another, almost every type of pain has been treated by some form of neurosurgical procedure based on the simple notion that blocking pain's pathways, by either ablation or neuromodulation, would prevent transmission of its signals into consciousness.

Maturation of knowledge about mechanisms of reception and perception of pain has given rise to increasingly sophisticated procedural approaches, and their improving efficacy has multiplied the indications for neurosurgical analgesia.

Several surgical procedures are currently being offered for treatment of the same type of intractable pain [1-3]. Although neurosurgeons more or less agree on which procedure is most appropriate for a few types of pain, controversy remains about the procedures best suited for treatment of most types of pain. The underlying reason is that most neurosurgical teams are accustomed to using a particular repertoire of procedures that they sincerely believe to be the best available. In addition to this inherent bias, criteria for "success" have not yet been sufficiently standardized to justify confidence that an objective evaluation can be made by those who carry out one or another of the competing procedures.

In dealing with patients who suffer persisting severe pain that is not (or insufficiently) responsive to the available analgesics, practicing physicians must ask themselves several questions about the type of pain they are dealing with. The answers to these questions will help them decide whether referral to a neurosurgeon is indicated and, if so, what kind of neurosurgical approach is most appropriate for the case in question.

2. Is the pain intractable?

The essential criterion of pain justifying a neurosurgical treatment is its *intractable* character. For purposes of this

Publication of this article was supported by the Collège International de Recherche Servier (CIRS).
STATEMENT OF CONFLICT OF INTEREST: The author has nothing to disclose.
* 84 Bd du Maréchal Joffre, 92340 Bourg la Reine, France. Tel.: +331 46604760.
E-mail address: snicolaidis@laposte.net.

0026-0495/$ – see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.metabol.2010.07.018

discussion, intractable pain is pain that persists when all therapies (other than neurosurgery) have been found ineffective during a "long" period. Although the severity of the pain experienced by the patient is often obvious to the clinician, evaluation of pain's intensity requires a battery of "objective" tests that make use of visual and psychological scales [1,4]. Such tests are also necessary for a proper assessment of the patient's response to treatment over time. Needed (among other requirements) is a formal psychological evaluation by a qualified pain expert. Such an evaluation will help in identifying patients with personality disorders or those who are at especially high risk for secondary pain or poor outcome. For example, deep brain stimulation (DBS) surgery should be avoided in depressed or hypochondriacal patients [1,4]. Finally, the effect of pain on the patient's mood and quality of life needs to be assessed [3]. The acceptability of an objective criterion based on biomarkers will depend on the demonstration that one or more of them changes systematically as a function of the intensity of pain.

Another benchmark necessary to establish the intractable nature of pain is its duration—a period that may range from more than 6 months to 1 or 2 years, depending on the neurosurgical team's criteria [1,4].

Furthermore, to be eligible, the patient must be ready to accept the possibility of discontinuation of the surgical procedure, either because the trial fails to significantly alleviate the pain or because of infection associated with implanted hardware. Finally, patients who may need magnetic resonance imaging for evaluation of other health problems may have to be reclassified as being ineligible for neuromodulation procedures that use paramagnetic material.

3. Is the pain "neuropathic" or "nociceptive"?

3.1. Neuropathic pain

Neuropathic pain is caused by an insult to some part of the nervous system itself, from the tissue-bound unmyelinated fibers up to the thalamic and cortical projections of pain. Neuropathic pain may be constant, lancinating, or intermittent, and has been described as burning, shooting, or tingling. It is often associated with allodynia, where a simple touch is perceived as a very unpleasant feeling difficult to describe, sometimes resembling "electric shocks." Examples of neuropathic pain are thalamic pain, poststroke pain, phantom limb pain, pain due to multiple sclerosis, Parkinson disease, syringomyelia, brachial plexus avulsion, entrapment neuropathies, spinal cord injury, and certain kinds of low back pain.

Pharmacotherapy of this type of pain is difficult; and its effect is often unsatisfactory, particularly in the long term. Rather than classic opioids, the most efficacious drugs are antiepileptics such as gabapentin or oxcarbazepine, and tricyclic antidepressants like nortriptyline. It is the lack of efficacy of conventional analgesics in treatment of neuropathic pain that impels many medical practitioners to refer their patients to the neurosurgeon. Deep brain stimulation at the level of the ventro-postero-lateral relay nucleus (VPL) for bodily pain or of the ventro-postero-medial relay nucleus (VPM) for facial pain has been found to be helpful for many victims of otherwise intractable neuropathic pain. According to more recent data, motor cortex stimulations (MCSs) seem to be very efficacious [5], as well as peripheral nerve stimulations (PNSs) [6].

3.2. Nociceptive pain

Nociceptive pain results from tissue damage that gives rise to somatic or visceral stimuli sensed by peripheral nociceptors and transmitted by still functional afferent sensory pathways. This type of pain is generally well localized and described as aching or sharp. However, when nociceptive pain is visceral, it tends to be less well localized and can have a cramping quality. Nociceptive pain may result from trauma-caused tissue damage, infection, or chemical irritation. Some space-occupying neoplastic lesions, while leaving the nerves free from neoplastic invasion, may generate pain by exerting strain on sensory nerve receptors. Nociceptive pain is usually responsive to a number of different kinds of medication including nonsteroidal anti-inflammatory drugs, cortisol-like preparations, and various analgesics, including opioids.

Nociceptive pain is responsive to DBSs aimed at the periventricular gray (PVG) and/or periaqueductal gray (PAG) [1,4,7]. These 2 stimulations are considered to act via an opioid mechanism; they are, at least partly, reversed by naloxone (an opioid receptor antagonist). They also show cross-tolerance with opioid analgesics [3].

4. Neurosurgical approaches

Neurosurgeons distinguish 2 categories of surgery: "ablation" or "neuromodulation." Neuromodulation may be either electrical or chemical.

4.1. Ablative neurosurgery

Some of the ablative interventions are still used because of their proven efficacy and their relatively simple surgical approach. Early techniques used thermocoagulation produced via the tip of a nonpermanent electrode by applying either continuous current or radiofrequency. Alternatively, alcohol or formalin injections or cryoprobes can be used [2]. Using cryoprobes offers another advantage; both at the "site of interest" and on the pathway to the site. The procedure involves decreasing the temperature down to +5°C to suppress temporarily the function of the cooled tissue. Once the consequences of this temporary suppression of function have been observed, the surgeon can either stop the refrigeration and thus restore function, or reduce the temperature further (to between −35°C and −170°C) until

the target area has been frozen and the pathogenic tissue destroyed [2].

The principal ablative procedures include percutaneous rhizotomy; midline myelotomy; cordotomy; and, among the intracranial ablations, cingulotomy and procedures aimed at the Gasser ganglion for trigeminal neuralgia or cluster headache. The latter consists in dilacerating its capsula and/or performance of a microvascular decompression. More recently, gamma knife radiosurgery has been used because of its ability to concentrate its destructive radiations over a discrete target (such as the site of emergence of the trigeminal nerve just 2 to 3 mm away from its pontine trajectory) [2].

In addition to being irreversible, the principal disadvantage of the ablative neurosurgical procedures in general is that, after a time (which may be several months or several years), they tend to lose their analgesic effect. However, their use may be appropriate for treatment of cancer pain in certain terminal patients.

4.2. Nonablative neurosurgical interventions

Because they are reversible and also take into account the new knowledge about the physiology of pain, nonablative methods (eg, neuromodulation via implanted electrodes or chemodes) are being increasingly used for the treatment of pain—especially neuropathic pain.

4.2.1. Peripheral nerve stimulation

Peripheral nerve stimulation requires permanent implantation of subcutaneous leads and a subcutaneous generator that delivers either a continuous or pulse radiofrequency [6,8]. Recent articles have reported the use of PNS for visceral pain arising from the pelvis or mediastinum, for postherpetic neuralgia, and (via the sacral nerve) for intractable testicular pain [6]. The indications for PNS are being extended for the management of migraine or intractable headache [8,9].

4.2.2. Spinal cord stimulations

For the main locations of electrostimulation in the spinal cord, neurosugeons use 1 or 2 catheter-like mono- or multicontact electrodes [2,10]. They are inserted into the epidural space through a spinal needle or laminectomy. Carefully conducted postimplantation tests are necessary to identify the optimal electric contacts and the most suitable frequency and intensity of the electric stimulus. Because pain relief occurs only in areas where perioperative stimulation induces paresthesias, the patient is kept awake. Afterward, the electrodes are connected to an external stimulator for a trial period of 2 to 3 days to allow several sessions of test stimulations that will define their optimal parameters (frequency, voltage, pulse duration, further selection of active contacts) to be delivered by the definitive stimulator. The latter is implanted subcutaneously in the abdomen and monitored by a transcutaneous induction signal transmitted by electromagnetic coupling. The transcutaneous device also permits adjustments of the stimulation parameters. The subcutaneous unit must be replaced surgically every 3 to 5 years, depending on the life span of the battery.

Spinal cord stimulation (SCS) is increasingly recommended for a large array of indications and has few adverse effects [2,10]. The most usual indications for SCS are the pain of the “failed back” syndrome, the ischemic pain of peripheral vascular disease, angina pectoris, diabetic neuropathy, brachial plexus avulsion, cervical rhizopathy, complex regional pain syndromes I and II, postherpetic neuralgia, and phantom limb. Spinal cord stimulation is now indicated for cancer pain as well [2,10].

4.2.3. Deep brain stimulation

Deep brain stimulation is achieved with stereotactically implanted electrodes connected to a permanently implanted generator placed subcutaneously over the chest. This type of surgery is highly sophisticated; and as such, it requires a well-trained, experienced, multidisciplinary team [1]. Deep brain stimulation is generally applied in intractable pain syndromes that do not respond to less invasive options.

From the outset, it was logical for DBS to aim at the thalamic nuclei where the spinothalamic tract ends, more precisely, the VPL or VPM for bodily or facial neuropathic pain, respectively. The main indication for DBS related to nociceptive pain is its placement in the PVG and PAG [1,4,7]. The analgesic effect of these stimulations led to the discovery of a concurrent rise in endogenous opioid secretion. This phenomenon explains the cross-tolerance between PAG-PVG stimulation and opioid administration, and the suppression of the effect of PAG-PVG stimulation by naloxone pretreatment. The correct positioning of electrodes is dictated by image criteria. Moreover, stimulations along the insertion path of the electrodes and between their multiple contacts allow the surgeon to avoid undesired effects and identify responses (like paresthesia) that are associated with a favorable outcome. Treatment of mixed neuropathic and nociceptive pain requires double implantation in both PAG-PVG and VPM-VPL [1,4]. Pain due to thalamic infarction is better alleviated by DBS in the posterior limb of internal capsula, but the use of MCS seems to be a preferable approach today [4,5]. Conditions responding well to DBS include chronic low back pain and failed back syndrome, peripheral neuropathy, deafferentation pain, and pain due to brachial plexus avulsion. Thalamic pain, postherpetic pain, and pain caused by spinal cord injury are unlikely to be alleviated by DBS.

Deep brain stimulation of the ipsilateral posterior hypothalamus is particularly efficient for treatment of intractable cluster headache. Ensuring correct contacts of the electrode requires postoperative adjustments because the desired outcome often appears only after a latency of several hours. Implanting a second electrode contralateral to the initial one may help improve the analgesic outcome [1,4].

For the most part, the effectiveness of DBS lasts as long as 7 to 9 years. The main perioperative complication is local

hemorrhage (4.1%) [1] and postoperative infection or erosion of the skin [4].

Because DBS is such a demanding procedure, it is carried out by only a limited number of neurosurgical groups. Certainly, SCS and MCS (see below) are increasingly preferred today; but DBS is more promising because it can be more readily adapted to new brain locations that—inevitably—will be identified as we learn more about the mechanism of pain and pain relief.

4.2.4. Motor cortex stimulation

Twenty years ago, MCS was found (unexpectedly) by Tsubokawa et al [11] to be particularly efficient in managing patients with (mainly) intractable facial pain and central pain syndromes [5]. Motor cortex stimulation, also known as *precentral* stimulation, appears to be as efficacious as thalamic (VPM and VPL) stimulation in several other types of neuropathic pain. Motor cortex stimulation is preferred in patients with poststroke and thalamic pain. The array of indications for MCS is extending each year including trigeminal pain, chronic low back pain, and deafferentation pain [5,11].

Surgery for extradural implantation is less invasive and less complicated than DBS because it does not need stereotactic positioning. However, it requires an experienced surgeon, together with a number of delicate tests to avoid misplacements that account for most of the bad outcomes [5]. In preference to the use of a burr hole to access the motor cortex, a 5- to 7-cm craniotomy allows, under imaging guidance, a very precise determination of the epidural spot overlying the ascending primary motor gyrus. The accompanying tests include use of electrophysiologic recording methods to target with optimal precision the precise anatomical location, with epidural electrical stimulation for the initiation of controlateral member jerks and, more recently, functional magnetic resonance imaging to delineate the facial area [5]. Transcranial magnetic stimulation [12] is also used as a noninvasive tool for both research and treatment of neuropathic pain syndromes. Its perioperative use provides a good predictor of future efficacy of MCS. All of the other parameters—which involve choosing the best contacts and stimulation parameters—take several days of meticulous testing before the final connection is made to the implantable subclavicular, remotely monitored stimulator. Motor cortex stimulation also may suffer a small number of complications such as hardware problems, which, although rare, will usually require explantation of the equipment [4].

4.3. Use of chemodes in the neural space

4.3.1. Intraspinal (intrathecal) drug delivery

In most cases of intrathecal drug delivery, the infusate contains morphine or other opioids and local anesthetics [2]. There are various techniques for placement of the chronic catheter at the desired level. Connection to an outside reservoir allows a trial period of 2 to 3 days, followed by permanent implantation of the pump if the trials were efficacious. The pump is programmable for variable flow delivery; and its reservoir is percutaneously refilled every few months, lasting up to 3 years before replacement. In the past, this procedure was mainly limited to cancer pain; but more recently, it has been extended to delivery of the usual mixtures of morphine with local anesthetics and clonidine for the treatment of noncancer neuropathic pain [2,13].

The PAG delivery of microinfusions seems more efficacious than DBS. The implantation technique is similar to that of PAG for electrostimulation, where the electrode is replaced by a fine chemode and the pulse generating unit by a subcutaneous minipump connected to it [2].

It seems likely that, in the future, chemodes (or rather "stemcellodes") will be used for the mini-infusion of differentiated stem cells. They will be positioned under image control either at the level of injury in the spinal cord or stereotactically in the brain at the level of the pathologic area itself, or into the newly discovered (in the rat) paths of migration of these 'biological builder-journeymen' travelling toward the ruin to repair [14].

5. Discussion

The more-or-less invasive nature of a neurosurgical operation and its exaggerated aura, together with its great expense (at least in the United States), all combine to make the attending physician wary of neurosurgery and likely to accept it only as the very last attempt to alleviate the lengthy suffering of his or her unfortunate patient [1-4,13]. Thus, in their articles on the subject, many authors tend to come down rather heavily on precautions, exclusions, and various ethical concerns. Although it is true that all the alternative therapies have to be attempted before considering the neurosurgical option, one must ask how long should a patient's suffering be allowed to continue. The answers often specify waiting periods lasting from 6 months to several years, with the medical workup ranging from just a thorough clinical evaluation to use of the most sophisticated battery of psychological tests and computerized decisions available [1,4,13].

The reality is often more complicated; it is common for patients to have been seen and treated by a number of physicians representing various subspecialties before a neurosurgeon is consulted. Suffering from unrelenting pain over several years is likely to give rise to at least some emotional and psychological overlap, aggravating or otherwise modulating pain perception. The psychological damage that results may, by itself, constitute a contraindication to surgery [13].

The continuing parade of publications reporting new neurosurgical procedures for the management of intractable pain indicates that none is really fully satisfactory. Not only is none of them constantly efficacious, but also the indications for their use are often controversial. As mentioned previously, the difficulty in choosing one procedure rather than another is also strongly influenced by the tests and

adjectives (which generally lack objectivity) used in the published evaluations; indeed, authors often use confounding variables in their evaluation of what is "success" or "long term" or "complications." In addition, the choice will depend not only on the etiology of the pain that clamors for attention, but also on the expectation of survival, on the estimated life span of the patient, and on the adverse effects and complications encountered with each procedure.

Acknowledgments

I thank Theodore VanItallie for his valuable editorial assistance and A.L. Benabid for providing very helpful references.

References

[1] Wallace BA, Ashkan K, Benabid AL. Deep brain stimulation for the treatment of chronic, intractable pain. Neurosurg Clin N Am 2004;15:343-57.

[2] Giller Cole A. The neurosurgical treatment of pain. Arch Neurol 2003;60:1537-40.

[3] Keller T, Krames ES. "On the shoulders of giants": a history of the understandings of pain, leading to the understandings of neuromodulation. International Neuromodulation Society. Neuromodulation: technology at the neural interface; volume 12 number 2?? 200: pp 77-84 (8). Blackwell.

[4] Levy RM, Deer TR, Henderson J. Intracranial neurostimulation for pain control: a review. Pain Physician 2010;13:157-65.

[5] Machado AG, Mogilner AY, Rezai AR. Motor cortex stimulation for persistent non-cancer pain. Springer-Verlag Berlin/Heidelberg; 2009. p. 2239-49.

[6] Mazin A, Tamimi H, Davids R, Barolat G, Krutsch JF. Subcutaneous peripheral nerve stimulation treatment for chronic pelvic pain. Neuromodulation Society. Neuromodulation: technology at the neural interface, 11; 2008.

[7] Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man—acute administration in periaqueductal sites. J Neurosurg 2003;977:178-83.

[8] Reverberi C, Bonezzi C, Demartini L. Neuromodulation Society. Neuromodulation: technology at the neural interface. Peripheral subcutaneous neurostimulation in the management of neuropathic pain: five case reports, 12; 2009.

[9] Bitar RG, Teddy PG. Peripheral neuromodulation of pain. J Clin Neurosci 2009;16:1259-61.

[10] Lee A, Pititsis J. Spinal cord stimulation: indications and outcomes. Neurosurg Focus 2006;21:1-6.

[11] Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 1993;78:393-401.

[12] Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Neurophysiol Clin 2006;36: 117-24.

[13] Jamison RN, Washington TA, Fanciullo GJ, Ross EL, McHugo GJ, Baird JC. Do implantable devices improve mood? Comparisons of chronic pain patients with or without an implantable device. 2008 International Neuromodulation Society. Neuromodulation: technology at the neural interface, 11; 2008. p. 260-6.

[14] Heijnen C. Mesenchymal stem cells as an effective therapy to treat neonatal hypoxy-ischemic brain damage. EWCBR Proc, 8-15/3/2010: p 34. W. Ziegleganseberger Ed. Arcueil 92300 France.