Neurosurgery for chronic neuropathic pain

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Chronic pain has been defined as pain that lasts longer than three to six months or, as proposed by the International Association for the Study of Pain, it is pain that outlasts the period of normal healing of an acute abnormality (1). Any acute pain has the potential to become chronic, and this conversion can follow different temporal courses for different problems. Pain of primarily neural origin is termed neuropathic pain.

Common features of chronic neuropathic pain include spontaneous burning, paroxysmal jabbing or shocking pain, hyperpathia, hyperalgesia, and allodynia or touch-evoked pain. These features may occur alone or in combination. Causes of neuropathic pain include injuries to the nervous system, whether by trauma, ischemia or metabolic dysfunction. Neuropathic pain is idiosyncratic; not every patient who suffers neural injury develops this type of pain. The incidence of neuropathic pain may also vary according to the site of neural injury. It is classified as ‘peripheral type’ when it results from neural injury or dysfunction from peripheral sources or as ‘central type’, when it arises from dysfunction in the brain and spinal cord. Neuropathic pain, in contrast to somatic or nociceptive pain, usually occurs without ongoing physiological activation of nociceptors. However, neuropathic and nociceptive pain may have overlapping features, and both types may at times be complicated by psychological and psychosocial factors.

Table 1 lists the broad range of causes of peripheral and central neuropathic pain.

Only patients with chronic neuropathic pain that fails to respond to medical treatment are considered potential candidates for surgical treatment. Hence, neurosurgeons are called upon to treat these often difficult pain syndromes. The goal here is to describe neurosurgical treatments for the chronic, intractable neuropathic pain states and to provide a brief outline of current neurosurgical approaches in these settings.

Key Words: Chronic neuropathic pain; Surgery
TABLE 1
Various types of peripheral and central neuropathic pain

<table>
<thead>
<tr>
<th>Peripheral neuropathic pain</th>
<th>Central neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve injury with or without sympathetically maintained pain</td>
<td>Pain of spinal cord origin</td>
</tr>
<tr>
<td>Complex regional pain syndromes (reflex sympathetic dystrophy or causalgia)</td>
<td>Trauma</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Inflammation (eg, myelitis)</td>
</tr>
<tr>
<td>Meralgia paresthetica</td>
<td>Tumour</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>Vascular pain (eg, Wallenberg’s syndrome)</td>
</tr>
<tr>
<td>Failed back surgery syndrome or postlaminctomy syndrome</td>
<td>Iatrogenic pain (postcordotomy dysesthesia)</td>
</tr>
<tr>
<td>Trigeminal neuralgia or trigeminal neuropathic pain</td>
<td>Other (eg, syringomyelia)</td>
</tr>
<tr>
<td>Glossopharyngeal neuralgia</td>
<td>Pain of brain stem origin</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>Syringobulbia</td>
</tr>
<tr>
<td>Occipital neuralgia</td>
<td>Multiple sclerosis (symptomatic trigeminal neuralgia)</td>
</tr>
<tr>
<td>Brachial plexus neuropathy or avulsion</td>
<td>Thalamus (ventroposterior thalamus)</td>
</tr>
<tr>
<td>Incisional neuralgia</td>
<td>Stroke, tumour, abcess</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>Cortical or subcortical pain</td>
</tr>
</tbody>
</table>

Detailed review is not intended, but rather an attempt is made to establish a framework within which the practising clinician can add insights when providing care to these patients.

SURGICAL TREATMENT OF CHRONIC NEUROPATHIC PAIN

Before considering any surgical measure to treat patients with chronic neuropathic pain, appropriate medical therapeutic approaches should be thoroughly investigated and exhausted. Generally, when neurosurgical therapy is considered, neuroaugmentative or neuromodulative procedures are preferred over ablative approaches as the initial surgical modality. This is because of their reversibility and low incidence of significant side effects. These approaches are only undertaken after the primary and causative disturbances, for example compression, tumours, infections and ongoing mechanical injury, etc, have been addressed.

Pain associated with peripheral nerve abnormalities that is located primarily in the distribution of a single peripheral nerve may be treated with peripheral nerve stimulation (PNS) (2). The mechanism of action of PNS may be central or peripheral. As with other pain control operations, there must be a clear cut etiology for the pain, and a correctable pathology (eg, nerve entrapment syndrome) should be excluded. The surgery is usually done in two phases. Usually, a site proximal to the injury site is selected for electrode placement. After a skin incision and dissection to free 5 to 6 cm of nerve, the electrode is placed directly under the nerve and sutured in place. The electrode lead is then externalized through a small stab wound and connected to a temporary electrical stimulator. The effects of stimulation through the implanted electrode are evaluated over this trial phase, which can last two to three days. The settings of the temporary stimulator are considered satisfactory when the patient reports a fine tingling sensation in the nerve distribution. There are two potential outcomes of this trial. In patients where stimulation does not help the pain, the device is removed. On the other hand, patients who derive substantial pain relief, usually greater than 50% on a pain visual analogue scale, go on to permanent implantation in which the stimulating electrode is connected to a battery powered, pacemaker-like, implanted pulse generator. Results from a large series (3) indicated good to excellent pain relief in 70% to 80% of patients. These devices, like all stimulation implants, are subject to displacement, infection, breakage of leads and loss of battery power over time.

Peripheral nerve pain from multiple sources, including neuropathic pain secondary to neural injury as a consequence of degenerative disc disease, postamputation pain (eg, phantom limb pain, stump pain), reflex sympathetic dystrophy (now replaced with the term ‘complex regional pain syndrome’ [CRPS] type 1), or causalgia (CRPS type 2), may be relieved by spinal cord stimulation (SCS) (4,5) (Figure 1). A relevant animal model of chronic neuropathic pain, showing apparent relief by SCS, has been developed recently (6). Its exact mechanism of action of SCS is not fully understood but may at least partly be mediated via GABAergic and adenosine-dependent mechanisms, or modulated by influencing the transmission of A fibres and not of c fibres. Some effects of SCS may be mediated by the sympathetic nervous...
The development of percutaneous placement of electrode arrays and of improved programmable implanted electronics have been major technical advances in the application of SCS in patients with intractable neuropathic pain.

A temporary, percutaneous electrode is first placed in the patient under local anesthesia and connected to a temporary stimulation device either in a fluoroscopy suite or operating room. A permanent implant with pulse generator may be introduced to the patient if satisfactory pain results are obtained during the trial period. Both percutaneous and laminectomy designs for SCS electrodes are available. The success rates reported in the literature on SCS have varied widely, but recent long term follow-up studies based on third party evaluations indicate 52% to 66% good to excellent results (7,8). As with PNS, SCS has the inherent advantage of a low morbidity trial or test phase that is used as a predictor of the long term effect.

Although intraspinal analgesic therapy is considered to be more effective for nociceptive than for neuropathic pain, if PNS or SCS is unsuccessful or inappropriate, a trial of intraspinal analgesic therapy may be warranted. The role of intraspinal (ie, intrathecal or epidural) infusion therapy in cases of intractable neuropathic pain is not fully established, but up to 50% of patients with neuropathic pain may be improved by intrathecal or epidural analgesic substances (9,10). Despite the relative insensitivity of these pain states to systemic narcotics, significant relief has been observed in some patients by using intraspinal narcotics. Moreover, the risk of becoming dependent or addicted to these agents from long term use seldom exists. Other drugs such as clonidine and adenosine in intraspinal use are also reported to be effective in refractory cases (11-13). However, these agents and other newly introduced drugs are still considered investigational for this application.

Deep brain stimulation (DBS) (Figure 2) may be appropriate for some patients with intractable neuropathic pain, especially when other neuroaugmentation therapies fail. Theoretically, pain may be modulated by stimulation or lesioning of any of the following structures or regions of brain related to ascending or descending pain pathways: periaqueductal grey (PAG)/periventricular grey (PVG) region, thalamus, internal capsule and medial lemniscus. Although the mechanisms underlying the effects of DBS are not established, possible mechanisms may involve opiate mediation and activation of descending inhibitory pathways for PVG/PAG stimulation (14), and inhibition of spinothalamic neurons in dorsal horn or blockage of disrupted activity in various thalamic nuclei (15,16). DBS has the potential to treat chronic pain of any etiology, in any location. However, its success rate varies according to the nature of pain, the site of stimulation and the criteria used to define success. The range of success is typically from 30% to 70% (17,18). This technique is not widely available, and as with other surgically implanted pain therapies it remains expensive. Recommended brain targets for DBS electrode implantation to treat central pains related to deafferentation or neuropathic pain (eg, anesthesia dolorosa, postcordotomy dysesthesia, thalamic syndrome, brachial plexus avulsion, postherpetic neuralgia, and spinal and peripheral nerve injuries) are thalamic sensory relay nuclei, ventral posterior lateral or ventral posterior medial, and the medial lemniscus or internal capsule (19). However, implantation of electrodes on the PVG region may be more suitable for patients with nociceptive pain when other measures fail.

Electrodes are implanted stereotactically when the patient is under local anesthesia supplemented as necessary by intravenous midazolam and/or fentanyl. Electrodes are introduced according to anatomical targets, based on preoperatively obtained anterior commissure and posterior commissure...
except that mapping of the motor cortex is necessary by intraoperative somatosensory-evoked potentials. Although this technique is not widely investigated, it appears to be a new and promising possibility of pain treatment, especially in cases with chronic, refractory neuropathic pain.

Ablative procedures in the spinal cord such as cordotomy have been used in some patients with intractable nonmalignant pain but are known to be more effective in nociceptive pain than in neuropathic pain conditions. Cordotomy is seldom used to treat disorders, except malignant diseases, because of concern about the development of postcordotomy dysesthesia or fading of the level of pain relief with time.

Dorsal root entry zone (DREZ) lesions, however, can be uniquely effective in select cases of intractable neuropathic pain, including roots or plexus avulsions and postparaplegic pain, with long term success rates often greater than 50%. The segmental, end zone pain of spinal cord injury may also respond to DREZ lesions; the more diffuse, distal pain following spinal cord injury tends to be refractory. Also, it is not as successful for the treatment of postamputation stump pain (25). DREZ destroys the dorsal horn (including substantia gelatinosa), Lissauer’s tract, and the adjacent portion of the posterior and lateral funiculi, thus inhibiting incoming nociceptive inputs and modulating signals descending via the Raphe spinal, reticulospinal and cortical spinal tracts. After laminectomy and dural opening at appropriate levels have been achieved under general anesthesia, the electrode is introduced to a depth of 2 mm, and the lesion is generally made by heating the radio frequency (RF) electrode tip to 75°C and holding the temperature for 15 s. Successive lesions are spaced 2 mm apart, and spinal cord function is monitored by using somatosensory- and motor-evoked potential during the operation. In summary, pain recalcitrant to conventional therapy, in cases of neuropathic pain due to brachial plexus injury, is seen in about one-third of patients and causes significant disability. DREZ lesions mitigate this pain in approximately 60% of patients (26). In addition, although up to 50% of patients experience some neurological deficits following surgery, this occasionally results in worsening of functional impairment.

Intracranial ablative procedures, including medial thalamotomy, mesencephalic tractotomy, anterior capsulotomy, hypophysectomy and cingulotomy, have been used primarily in terminally ill patients with cancer-related pain. However, these procedures have often been associated with recurrence or worsening of pain after the procedure. Cingulotomy lesions neurons and interrupts the Papez circuit of the limbic system; its target is the anterior cingulated gyrus, caudal portion, area 24. The recommended target for thalamotomy is the medial thalamus, involving the central lateral or parafascicular nucleus (27). The results, however, do not seem to be as good as those of DBS and are usually short lived. Overall, these procedures have limited indications, are used infrequently and are not generally applicable to patients with chronic neuropathic pain. However, with improved stereotactic techniques guided by better imaging systems, refined microelectrode recordings and stimulation techniques; rela-

Figure 3 Postoperative skull x-ray showing electrodes placed on motor cortex for chronic stimulation
Surgery for chronic neuropathic pain

The main challenge facing the treatment of neuropathic pain is the incomplete understanding of its pathogenesis and consequently the limited success of its treatment. The selection of patients who are likely to respond to surgery and the choice of the surgical procedure should be carefully decided based on diligent evaluation.

Some surgical interventions have substantial potential morbidity, and this must be considered before deciding to operate. Also, no one neurosurgical procedure can relieve the pain complaints of all patients, and surgery performed because there is ‘nothing left to try’ is most likely to fail. Whichever procedure is chosen or intended, treating neurosurgeons should have the necessary neuroscience background and surgical skills to be an important member of the team caring for these multifaceted, chronically ill patients.

Neurosurgical strategies will be more diverse, and neurosurgery will likely offer better and more options for the management of chronic neuropathic pain syndromes in the future. These strategies will be driven by a better understanding of basic pathophysiological mechanisms underlying neuropathic pain. Animal models of chronic neuropathic pain are available to test novel strategies. Further, the available surgical procedures (eg, SCS, DBS and chronic cortical stimulation) are being refined and will be more widely available. Other promising modes of therapies (eg, transplantation, gene therapy) are also being intensively investigated. Advances in these surgical and pharmacological strategies will make a significant impact on the treatment of pain of neural origin.

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