

NEUROPATHIC PAIN



Multidisciplinary Panel on
Neuropathic Pain

神經痛跨學科研究小組

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Forward any comments on this
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Challenges in Neuropathic Pain is a newsletter brought to you by the Multidisciplinary Panel on Neuropathic Pain. The feature articles in this issue include a review on the use of implantable devices for pain control and a case presentation on postchemotherapy neuropathic pain. Regular features, including a literature review, useful Web sites and a calendar of upcoming conferences, will keep Hong Kong clinicians informed of the latest news on neuropathic pain.

Implantable Device Therapy for Relief of Chronic Pain

When patients have failed to achieve adequate pain relief with less invasive and less expensive analgesic modalities, it is reasonable to consider implantable methods of pain control, such as spinal-cord stimulation (SCS) or an implanted drug-delivery system.¹ The choice of device depends on a number of factors, including the type and distribution of pain. Analgesics given intrathecally can target both neuropathic and nociceptive pain, while SCS is only effective in neuropathic pain.¹

Spinal-Cord Stimulation

SCS was developed over 35 years ago in accordance with the 'gate control' theory of analgesia.^{1,2} Despite considerable subsequent improvements in the sophistication of neurostimulatory devices, the basic technique still involves insertion of electrodes into the epidural space. The electrodes deliver a low-voltage electric current that modulates spinal transmission of pain, so that the patient perceives mild paraesthesia rather than pain. The mode of action of SCS is not completely understood, but probably has little to do with the gate control hypothesis that inspired its development.¹

Regardless of the mechanism, SCS can provide long-term relief for neuropathic pain (eg, failed back-surgery syndrome, radiculopathies, arachnoiditis and complex regional pain syndrome), and it is also effective in treating pain associated with vascular insufficiency (eg, intractable angina), although the mechanism in this case may not be analgesic in nature.² SCS is not effective for nociceptive pain.^{1,3}

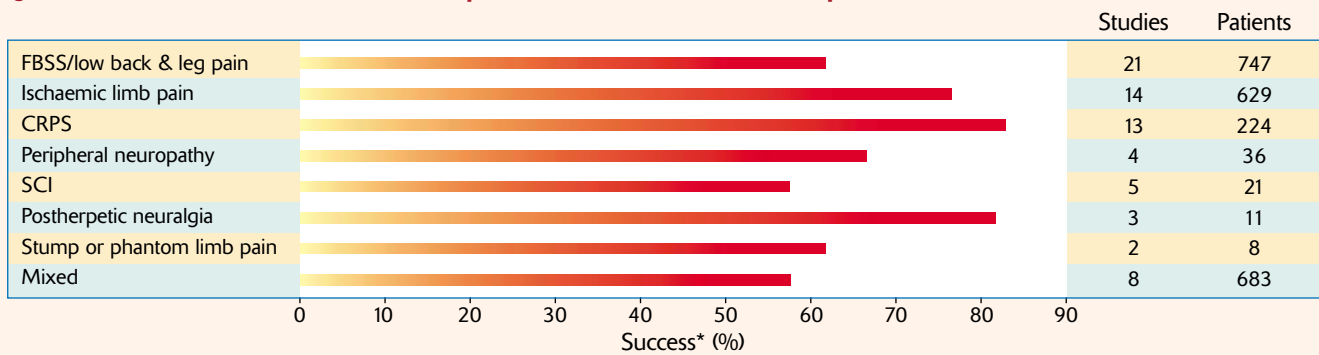
System components

Neurostimulation systems may have internal leads and an external pulse generator, or both the leads and generator can be surgically implanted.^{1,4} The latter is more expensive, but offers patients greater convenience and comfort. Clinicians can select from single, double or multiple electrode arrays to treat unilateral, bilateral or multiple sites of pain, and the availability of four and eight contact electrodes enables finely tuned positioning of the stimulation. Also, computer control of the current delivered (pulse rate, current level and bandwidth) can optimize pain control and comfort.^{1,4}

Placement of electrodes

The electrodes are inserted into the epidural space either percutaneously using fluoroscopic guidance or by direct placement into the target area through a laminotomy incision. Percutaneous insertion is performed under light sedation with local anaesthetic so that the patient can assist in

Figure 1. Overview of the success rates of spinal-cord stimulation in various painful conditions



* Success was defined as either >50% pain relief or significant reduction in visual analogue scale score.
 FBSS = failed back-surgery syndrome; CRPS = complex regional pain syndrome; SCI = spinal cord injury.

Adapted from reference 2.

locating the optimal position. An initial trial stimulation is routinely used to assess the patient's potential response to a permanent system.¹⁴

Efficacy and cost-effectiveness

Used in appropriately selected patients, SCS provides long-term pain relief in around 60% to 80% of patients.¹² It can also improve a patient's functionality and quality of life, and reduce the use of other pain treatments.¹³ Importantly, although the procedure is expensive, studies have shown it to be cost-effective compared with standard treatment. In those patients for whom SCS is effective, the therapy can pay for itself within 2.1 years.³

Complications

Until recently, lead migration or breakage has been the main complication (up to 14% of cases), but rates have declined with the use of newer multichannel leads.^{3,4} Infection (usually subcutaneous) has been reported at a rate of 2.5% to 7%.

Implanted Intrathecal Drug Delivery

Intrathecal (IT) administration of opioids and non-opioid medications for the control of intractable pain is now a widely accepted practice. In the United States alone, there are over 13,000 patients being managed with this technique.³ Table 1 summarizes the advantages and disadvantages of IT drug delivery for treating pain.

Table 1. Advantages and disadvantages of intrathecal (IT) drug delivery

Advantages	Disadvantages
<ul style="list-style-type: none"> • Uses significantly lower drug doses • More consistent analgesia with a lower incidence of some side effects (eg, opioid) • Theoretical advantages in treating patients who are chemically dependent (no euphoria and drug delivery cannot be manipulated by the patient) 	<ul style="list-style-type: none"> • Surgical risks with any implanted device • Risk of spinal injury from the catheter or infused drug • Risk of side effects specific to IT administration of a drug

Adapted from reference 3.

Pharmacological agents

The existence of μ -opioid receptors in the spinal cord provided the initial impetus for IT administration of analgesics.¹ However, there are a multitude of pain transmission targets in the spinal

cord, including receptors for *N*-methyl-D-aspartate (NMDA), glutamate, γ -aminobutyric acid (GABA), substance P, catecholamines and prostaglandins, and nitric oxide and calcium channels. Various non-opioid medications can also be given intrathecally, either alone or in combination.^{12,4}

Implanted intrathecal delivery systems

Both the infusion pump and the intraspinal catheter are fully implanted; the implantation technique is similar to that for an injection port. The pump is refilled percutaneously every 1 to 2 months, depending on the drug concentration and dosage. The mode of drug delivery varies between devices, from patient-activated intermittent administration (with a lockout interval) to electronically controlled continuous infusions with optional bolus dose delivery.¹⁴

Because there is often a very strong placebo response in patients suffering intractable pain, IT administration needs an extended trial before permanent placement of a delivery system. Indicators of effectiveness include a significant reduction in pain intensity (eg, 50%), improvement in function and a reduction in other analgesic use.¹

Efficacy of intrathecal drug delivery

A recent systematic review found there was moderate evidence supporting the long-term effectiveness of IT systems in both neuropathic and nociceptive pain. Also, at least two studies have reported the procedure is cost-effective compared with conventional therapies for long-term pain management.³

Summary: Patient selection criteria for implantable therapies

- More conservative therapies have failed
- Evident pathology consistent with the pain complaint
- Further surgical intervention is not indicated
- Drug habituation is not a problem
- A suitable psychological profile
- No contraindications to implantation
- A successful trial of therapy

Adapted from reference 1.

References

1. Krames E. *Best Pract Res Clin Anaesthesiol* 2002;16:619-649.
2. Cameron T. *J Neurosurg* 2004;100(3 Suppl):254-267.
3. Manchikanti L, Staats PS, Singh V, et al. *Pain Physician* 2003;6:41-46.
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CASE PRESENTATION

In each issue, a case study is presented on a relevant neuropathic pain syndrome. Reviewing case studies will help to improve your diagnostic approach to neuropathic pain and increase your understanding of how to select treatment strategies based on presenting symptoms. In this issue, a case of postchemotherapy neuropathic pain is discussed.

Postchemotherapy Neuropathic Pain

Presenting Symptoms

A male patient aged 51 years with diffuse large B-cell lymphoma presented with burning pain and numbness in both feet, and with more severe pain in his right ankle. The pain had started to disturb his sleep and was not relieved by a paracetamol-codeine combination drug prescribed by his GP.

Medical History

The patient had been diagnosed with lymphoma after presenting with gastrointestinal bleeding and a mediastinal mass. Histology was confirmed by gastroscopy and biopsy. Following radiotherapy to reduce the tumour size, the patient underwent gastrectomy and was subsequently treated with eight cycles of a combined regimen of cyclophosphamide/vincristine/doxorubicin.

Clinical Examination

On examination, the toes and soles of the patient's feet had decreased sensation to touch. There was a loss of sensation to vibration and the ankle reflexes were impaired. The patient also reported allodynia.

Interpretation

The patient's clinical picture was consistent with pain associated with vincristine-induced peripheral neuropathy that can affect the hands

and/or feet. Vinca alkaloids (vincristine), platinum compounds (cisplatin) and taxanes (paclitaxel) can cause dose-related peripheral neuropathies of varying severity. Initially, the symptoms are sensory but may progress to include motor signs. The polyneuropathy can manifest as paraesthesia or dysaesthesia in the feet and later, as the neuropathy progresses, spread to the lower legs. Sensory loss is usually observed over both feet and deep tendon reflexes are lost. Treatment generally involves decreasing or stopping the neurotoxic agent (when possible) and providing appropriate analgesia. Recovery is variable after the agent has been discontinued.

Some other possible causes of neuropathic pain in patients with cancer include tumour compression or infiltration of peripheral nerves, nerve damage as a result of cancer surgery and, rarely, a sensory neuropathy associated with a paraneoplastic neurological syndrome.

Management

Like other neuropathic pain syndromes, vincristine-related polyneuropathy responds poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. Treatment usually involves tricyclic antidepressants, anticonvulsants or both.

In this case, the patient's neuropathic pain was eased with dothiepin 25 mg at night, and gabapentin titrated to a dose of 300 mg tds. His management also included general education about protecting his feet from temperature, pressure and trauma.

PAIN WEB SITES

As highlighted in the case presentation in this issue, cancer treatments (or the cancer itself) can cause pain in cancer patients. The Web site at www.cancer-pain.org provides information on cancer pain for patients, caregivers and healthcare professionals, including explanations of the causes of pain and treatments available (pharmacological and nonpharmacological) to alleviate pain.

The American Pain Society (www.ampainsoc.org) has a comprehensive Web site, with information on pain management and the society's activities. Highlights include details of '2001-2010 Decade of Pain Control and Research' and summaries from current issues of *The Journal of Pain*.

LITERATURE REVIEW

Dworkin RH, Backonja M, Rowbotham MC, et al. *Advances in neuropathic pain; diagnosis, mechanisms, and treatment recommendations.* Arch Neurol 2003;60:1524-1534.

In recent years, there have been significant advances in the understanding and treatment of neuropathic pain. This paper reported the findings of a comprehensive review of randomized, controlled trials undertaken by members of the faculty of the fourth annual *International Conference on the Mechanisms and Treatment of Neuropathic Pain*. This expert panel identified five first-line drugs or drug classes that provided statistically significant and clinically meaningful treatment benefits in patients with neuropathic pain. The recommended first-line drugs were gabapentin, a 5% lignocaine patch, opioid analgesics, tramadol and tricyclic antidepressants. These agents have consistently demonstrated efficacy in a number of randomized trials in a range of neuropathic pain indications. Gabapentin, for example, has been studied in postherpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barré syndrome, and acute and chronic pain associated with spinal cord injury.

The safety profiles of the drugs were also considered in the recommendations. To decrease adverse effects and increase patient adherence to treatment, initial dose titration was advised for the four oral first-line medications. In addition, suggestions were made regarding the selection of an appropriate first-line therapy in accordance with clinical circumstances. The panel also advised that if patients failed to respond to one of the first-line agents, another one should be tried because of the different mechanisms involved. In some situations, a combination of these medications might be beneficial in patients who only partially responded to one of the agents.

Q & A

Forward your question on diagnosis, treatment or management of neuropathic pain to the *Multidisciplinary Panel on Neuropathic Pain* at mpnp@medimedia.com.hk or fax to +852 2559 6910.

What is complex regional pain syndrome?

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy or causalgia, is an uncommon and poorly understood neuropathy that normally affects the limbs. Symptoms include burning or aching pain in the affected limb, hyperalgesia, allodynia, autonomic dysfunction (such as changes in sweating, skin temperature and colour, and oedema), trophic changes (such as muscle wasting and thickened nails) and motor dysfunction. The International Association for the Study of Pain (IASP) definitions of CRPS are:

- Type I: occurs after an initiating noxious event or period of immobilization. Pain symptoms, such as allodynia or hyperalgesia, continue after the event, with the painful symptoms disproportionate to the inciting event.
- Type II: associated with known nerve injury.

CRPS may or may not be associated with sympathetic-maintained pain (SMP). Fracture, particularly Colles' fracture, is one of the more common triggers for CRPS, while no precipitating cause can be ascertained in up to one quarter of cases.



The hands of a patient with CRPS, showing characteristic swelling and redness in the affected right hand

Diagnosis of CRPS is based on a review of the patient's medical history and a physical examination, and tests such as bone scintigraphy or X-ray, thermography, nerve function assessment and sudomotor evaluation.

In treating CRPS, an overall rehabilitation programme is essential. Physiotherapy and occupational therapy are very important and should be commenced immediately. If possible, consider surgical restoration. Drug treatment includes anti-inflammatory agents, such as NSAIDs, and anticonvulsant drugs (eg, gabapentin) or tricyclic antidepressants (eg, amitriptyline) for neuropathic pain symptoms. Opioids should be reserved for rescue medication, while sympathetic blocks can be considered for SMP. For cases that do not respond to these treatment strategies, consider interventional techniques such as spinal-cord stimulation, epidural clonidine or intrathecal baclofen.

CONFERENCE CALENDAR

Annual Scientific Meeting in Anaesthesiology

12-14 November 2004, Hong Kong

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Sino-British Joint Conference on Neurology

15-17 November 2004, Beijing, China

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Web site: www.chinamed.com.cn/sbjcn

11th Asian & Oceanic Congress of Neurology

26-28 November 2004, Singapore

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