Implantable technology for pain management

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Abstract
Chronic pain has now been recognized as a disease entity in its own right. Significant numbers of patients suffer from intractable chronic pain. Neuromodulation has been defined by the International Neuromodulation Society as ‘the therapeutic alteration of activity in the central or peripheral nervous system either electrically or pharmacologically’. It can be achieved either by electrical stimulation of peripheral nerves, spinal cord or brain, or by delivering pharmacological agents directly into the intrathecal, epidural or intracerebroventricular sites. Neuromodulation is expensive, invasive and not without complications. Patients requiring neuromodulation should undergo multidisciplinary assessment for suitability. Clinical effectiveness is possible with appropriate patient selection and attention to technical details.

Keywords
Intrathecal drug delivery; neuromodulation; neuropathic; nociceptive; opioids; spinal cord stimulation

Spinal cord stimulation (SCS)
SCS involves the use of pulsed electrical energy to stimulate the dorsal columns of the spinal cord. Intact dorsal columns are therefore a prerequisite for SCS. Electrical leads are implanted in the epidural space to transmit this pulsed energy to the spinal cord to modulate pain transmission. Although the gate theory was initially proposed as the mechanism of action, the exact neurophysiological changes that occur are not well understood. At the dorsal horn SCS suppresses the hyperexcitability of wide dynamic neurons by reducing excitatory amino acids glutamate and aspartate. Supraspinal effects enhance descending inhibition by neurons by reducing excitatory amino acids glutamate and g-aminobutyric acid (GABA) and noradrenaline. Analgesia in ischaemic pain is thought to occur through restoration of oxygen supply by altering sympathetic tone.

Indications for SCS are listed in Table 1.

Patient selection
Patients should fulfil the following inclusion criteria: a diagnosis amenable to SCS therapy; pain of more than 6 months’ duration; failure of conservative management. Those with specific contraindications are excluded:
- local or systemic infection (absolute)
- coagulopathy or anticoagulation (relative)
- immunosuppression (relative)
- psychiatric illness (relative)
- demand pacemaker or implanted defibrillator (relative).

Procedure
A percutaneous electrode is introduced into the epidural space. An external trial stimulator is used to assign positive (anode) and negative (cathode) contact points to complete the circuit. Stimulation is achieved by varying the frequency (Hz), amplitude (voltage) and pulse width (milliseconds) of the impulse. The aim is to place the electrodes at a spinal level corresponding with the painful dermatomes such that elicited paraesthesia covers the painful area.

The trial period is variable and can last up to 4 weeks. Successful trial criteria vary and may include pain relief of at least 50%, paraesthesia coverage of at least 80% but should include improvement in function.

Learning objectives
After reading this article you should be able to:
- understand the principles of neuromodulation
- describe the basics of patient selection, trial and implantation of spinal cord stimulator and intrathecal drug delivery

Equipment
An electrode lead is inserted into the epidural space percutaneously under fluoroscopic guidance, while plate or paddle electrodes are surgically implanted via laminectomy or partial laminectomy. These electrodes are connected to extension cables that in turn connect to an implantable pulse generator (IPG). The IPG contains the battery and electronics to produce pulsed electrical stimulation. An external transcutaneous telemetry device activates and programmes the IPG. Adjustments can be made to the frequency, amplitude and pulse width. IPGs with a rechargeable battery are available for high usage with a life span of 10–25 years. Non-rechargeable IPGs are cheaper but have a battery life of only 2–5 years. A remote-control handheld device allows patients to control their own IPG.

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Indications for spinal cord stimulation (SCS)  

Conditions likely to respond (good indications)
- Neuropathic limb pain (e.g. following spinal surgery)
- Complex regional pain syndrome (CRPS)
- Persistent neuropathic pain due to peripheral nerve damage
- Pain associated with peripheral vascular disease
- Refractory angina pectoris
- Ischaemic limb pain

Conditions that may respond (intermediate indications)
- Amputation pain (stump pain responds better than phantom pain)
- Axial pain following spinal surgery
- Intercostal neuralgia (following thoracotomy or post-herpetic neuralgia)
- Pain after incomplete spinal cord damage

Conditions that rarely respond (poor indications)
- Central neuropathic pain (central post-stroke pain)
- Spinal cord injury with complete loss of posterior column function
- Perineal or anorectal pain

Conditions that are unresponsive to SCS
- Nerve root avulsion
- Complete transaction of spinal cord
- Nociceptive pain

Complications
- Lead migration requiring revision (5–14%).
- Lead fracture requiring revision (0–23%).
- Dural puncture (with Tuohy needle or electrode).
- Infection (rare).
- Neurological injury due to direct trauma, haematoma or abscess (rare).

Special precautions

The presence of a cardiac pacemaker is a relative contraindication for SCS. It is recommended that a bipolar sensing pacemaker should be used, as this is less sensitive to interference than unipolar pacemakers.

Unipolar shortwave diathermy, microwave diathermy and therapeutic ultrasound diathermy are contraindicated in patients with SCS because of the risk of heat-induced neurological damage at electrode contact points. However, it is safe to use bipolar shortwave diathermy.

Exposing a patient with SCS to magnetic resonance imaging (MRI) can potentially cause injury to the patient or damage to the IPG. MRI can induce electrical currents in either the IPG or leads that may cause heating resulting in tissue damage. MRI may reset the parameters requiring IPG reprogramming or it may cause permanent damage necessitating replacement. Some MRI conditionally safe neurostimulation systems are now available.

Outcome studies

Several randomized controlled trials of SCS have been undertaken for failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), refractory angina pectoris and critical limb ischaemia. All the studies conclude that this technique should be reserved for patients who have failed conservative management. Clinical results are positive with appropriate patient selection and attention to technical details.

Peripheral, deep brain and cortical stimulation

See Neurosurgical techniques in the management of chronic pain on pages 540–542 of this issue.

Intrathecal drug delivery (ITDD)

Neuromodulation can also be achieved by implantable drug delivery systems. In ITDD, a pump filled with the desired drug(s) is implanted subcutaneously. This is connected to an intrathecal catheter that allows direct administration of drug(s) into the cerebrospinal fluid. The pump is powered by a computer-programmed rotor or a hydraulic-driven continuous flow pump. Drugs administered via ITDD systems avoid first pass metabolism and the blood–brain barrier.

Opioids (morphine, hydromorphone) are the main drugs for intrathecal use. They exert analgesia by hyperpolarizing pain transmitting neurons. They act on opioid receptors at supraspinal centres too (e.g. periaqueductal grey and rostral ventromedial medulla). Co-administration of other drug admixtures can act synergistically and will consequently reduce opiate side-effects. Local anaesthetics (bupivacaine, levo-bupivacaine), clonidine, ketamine or alternatives such as ziconotide, and baclofen have all been used in this manner.

Indications for ITDD

There are three main indications for ITDD: chronic non-malignant pain; cancer pain; and spasticity.

Contraindications
- Coagulopathy.
- Sepsis (local or systemic).
- Obstructed cerebrospinal fluid flow.

Equipment

A percutaneous intrathecal catheter system can be used for the initial trial of ITDD or in patients with limited life expectancy (less than 3 months).

Alternatively the intrathecal catheter can be completely implanted subcutaneously and connected to subcutaneous injection port, or connected to an implanted pump that incorporates a pump reservoir, battery and electronics (Figure 2). These fully implanted ITDD systems are more expensive but are suitable for long-term use.

Trial and implantation of ITDD

Patients considered for ITDD should undergo a multidisciplinary assessment to confirm their suitability. A trial of ITDD is
considered best practice before implantation for long-term use.7 Strict aseptic precautions should be followed to prevent potentially serious CNS infection. A pain management consultant or a neurosurgeon usually implants the ITDD system.

**Complications of ITDD**

Complications of ITDD can be related to the device, catheter or the infused drug. Catheter complications are more prevalent beyond 3 months post-implantation (21.6%) and include catheter obstruction, dislodgment and migration.6 Catheter tip granuloma caused by localized inflammatory reaction to some opioids (commonly morphine) is a potential serious late complication thought to be related to opioid concentration.6

Common pharmacological side-effects of intrathecal opiates include nausea and vomiting (25%), urinary retention (19%), pruritus (17%), sedation (17%), and respiratory depression (less than 3%). Long-term use of intrathecal opioids can influence hormonal function, which can lead to altered libido,

### Vertebral levels for electrode placement

<table>
<thead>
<tr>
<th>Indication</th>
<th>Vertebral level</th>
</tr>
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<tbody>
<tr>
<td>Neck/upper limb pain</td>
<td>C2 – T1</td>
</tr>
<tr>
<td>Refractory angina pectoris</td>
<td>C7 – T2</td>
</tr>
<tr>
<td>Back/lower limb pain</td>
<td>T9 – L1</td>
</tr>
<tr>
<td>Ischaemic lower limb pain</td>
<td>T11 – L1</td>
</tr>
</tbody>
</table>

**Table 2**
hypogonadism, amenorrhoea, oedema and sweating. Ziconotide can cause serious but rare side effects like rhabdomyolysis, psychosis and suicide.

**Outcome studies**

*Cancer pain* — a randomized multicentre study by Smith et al. compared ITDD with comprehensive medical management in refractory cancer pain. The ITDD group had significant better results in regards to fatigue, drowsiness and quality of life. A Cochrane review published in 2005 concluded that neuraxial opioid therapy is effective for cancer pain refractory to conventional management.

*Spasticity* — the use of intrathecal baclofen for treating spasticity due to cerebral palsy, multiple sclerosis and spinal cord injury is well established.

*Chronic non-cancer pain* — evidence for effectiveness of ITDD for non-malignant pain is not strong but there are a few studies supporting its efficacy.

Other non-malignant conditions successfully treated with ITDD are peripheral neuropathy, chronic abdominal pain, post-herpetic neuralgia, post-mastectomy and post-thoracotomy syndrome.

**In summary**

Neuromodulation is a valuable tool for patients suffering from intractable chronic pain that has not responded to conventional measures. Initial outlay costs are high but it can be cost-effective in the long term. Multidisciplinary assessment and appropriate patient selection are important for good outcome.

**REFERENCES**