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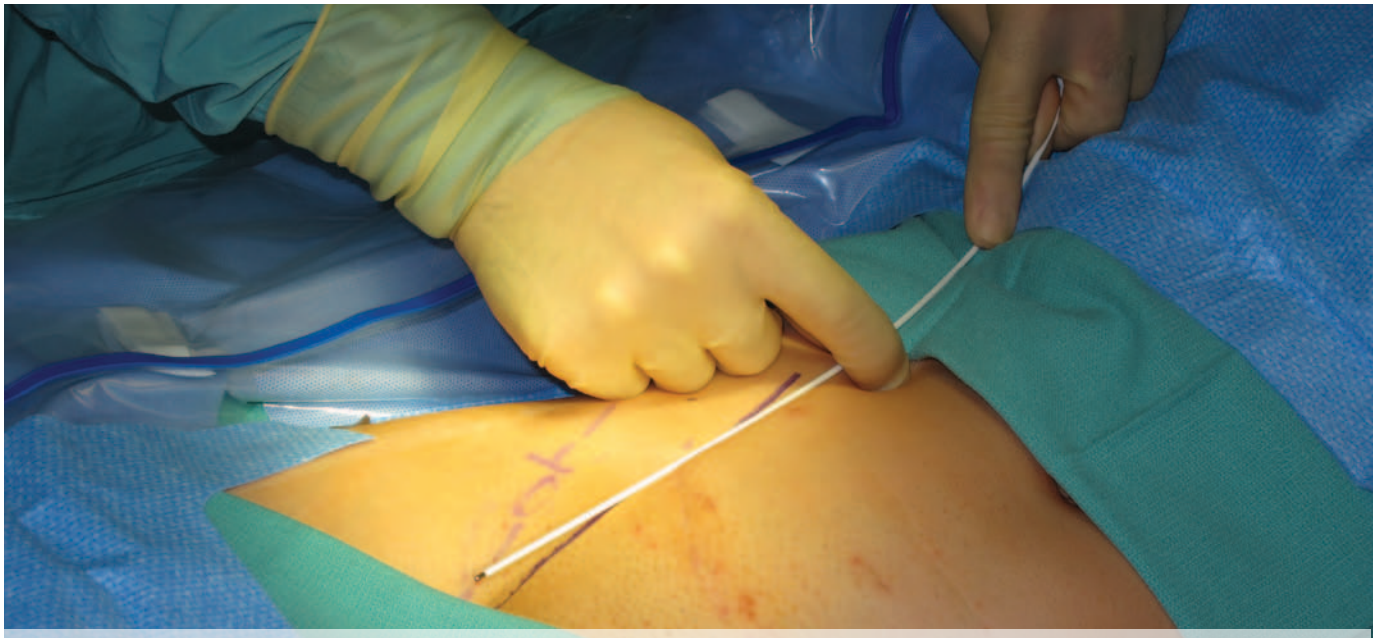

Implant Technologies for Severe Pain: Why, When, and the Outcomes

Implantable devices are ususally reserved for situations of severe pain and when less invasive techniques are limited by side effects or have proven ineffective.

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For more than 40 years, clinicians have been using and developing implantable technologies for the control of severe pain. For the purpose of this article, the technologies are categorized into three groups:

- Spinal cord stimulators deliver electric current to the dorsal columns of the spinal cord in an effort to block or alter the neural pain signals.
- Peripheral nerve stimulation is a technique that was not widely used because of concerns for potential trauma to the peripheral nerves. However, in recent years, there is renewed interest in stimulation within peripheral nerve fields, with electrodes kept at a safe distance from the major peripheral nerves.
- Spinal pump technology allows for the continuous infusion of medication directly into the cerebrospinal fluid. This has enabled clinicians to deliver more potent doses of analgesics with lower systemic side effects.

In most circumstances, these implantable technologies are reserved for situations of severe pain and when less invasive techniques are limited by side effects or have proven ineffective.

This article provides the reader with a current and comprehensive review of these three implantable technologies, focusing on their indications and efficacy.

Spinal Cord Stimulators

Spinal cord stimulation (SCS) has been used for the treatment of refractory pain, especially for failed back syndrome and for complex regional pain syndrome (CRPS). It has undergone significant advancements in technology and placement techniques.[1]

The SCS device consists of a radiofrequency-controlled neurostimulator or generator—about the size of a stopwatch, which is surgically implanted in the abdomen or

Table 1. Placement of SCS Leads

Location of Pain	Placement of Leads
Upper extremity	Mid-cervical cord
Abdominal and visceral	Mid-thoracic cord
Low back and lower extremity	Lower thoracic cord

SCS, spinal cord stimulation

buttocks. It delivers mild electrical signals to the epidural space near the spinal cord through one or more thin wires called leads.

SCS is based on generating an electrical field over the spinal cord that blocks or diminishes the perception of neuropathic pain, not nociceptive pain.[1] The neurostimulator produces mild electrical impulses (a tingling sensation) that reaches the brain before the pain signal arrives.[2]

The *mechanisms* by which electrical stimulation of the dorsal columns and afferent fibers attenuate or modulate a patient's sensation of pain are not completely understood. However, their efficacy in practice has been established with decades of literature describing SCS techniques.[3]

SCS *consists* of placing lead(s) in the epidural space along the posterior aspect of the dorsal columns. Leads can be placed essentially at any point along the spinal cord. The placement of SCS leads depends on the location of the patient's pain (see Table 1).

Individual electrode arrays may be placed over each hemicord for the independent manipulation of left and right sides separately.[3]

To achieve optimal pain relief effects, stimulation paresthesias should cover the area of pain. The electric field is propagated by an implanted, programmable generator containing a battery pack, an antenna, and a computer module for external programming.[1]

Currently there are two different SCS systems routinely used. One involves percutaneously placed electrode leads. The other involves laminectomies for placement of the electrodes.[4]

The first system uses percutaneous insertion of electrodes into the epidural space and either transcutaneous connection to an external generator (allowing a trial period of stimulation) or subcutaneous connection to the implanted receiver or an implanted pulse generator (IPG).[4] When trial stimulation is used, if the test stimulation alleviates the pain, then the electric pulse generator is internalized in a second procedure.

The second system involves the implantation of paddle-type leads into the epidural space after laminectomy. As with percutaneously placed electrodes, the electrode leads may be connected to an external generator (allowing a trial period of stimulation), or they may be connected subcutaneously to an IPG—identical to the programmable generator used for the percutaneous electrodes.[4]

With either system, the patient has the option to set the intensity, frequency, and the pulse width with the transmitter. The battery-powered unit can be transcutaneously programmed and customized to meet the needs of the patient by allowing the alteration of stimulation parameters, including electrode selection via a computerized telemetry system.

The patient can adjust the strength and location of stimulation using a handheld programmer. Furthermore, the patient can adjust the levels of stimulation at various times of the day or for various activities.

Indications/Uses for SCS

A recent consensus document published by the British Pain Society recommended the following as good indications (patients likely to respond) to SCS implantation:[5]

- Neuropathic pain in the leg or arm following lumbar or cervical spine surgery (FBSS)
- CRPS
- Neuropathic pain secondary to peripheral nerve damage
- Pain associated with peripheral vascular disease
- Refractory angina
- Brachial plexopathy[5]

There has also been effective use of SCS for radiculopathies, peripheral neuropathy, peripheral vascular disease, chronic unstable angina, tumors, brachial plexus injuries, spinal cord injury, phantom limb pain, ischemic limb pain, multiple sclerosis, and arachnoiditis.[3,4] The FDA's approved indications for SCS are outlined in Table 2.

SCS implantation is most effective in managing patients with neuropathic pain. In those with mixed nociceptive and neuropathic pain, such as FBSS, those patients with predominant radicular pain should be considered candidates. Typically, patients with a past or current history of substance abuse are excluded.[6]

Table 2. SCS: FDA-approved Indications

- FBSS or postlaminectomy pain: persistent or recurrent pain, mainly of the lower back and legs that remains after unsuccessful spine surgery
- Radiculopathy: nerve root damage, which can produce neurogenic pain; may be associated with FBSS or a herniated disc
- Plexopathy: a form of neuropathy
- Arachnoiditis: chronic inflammation and scarring of the meninges at the exit site of the nerve roots from the spinal cord that can occur after spine surgery
- Epidural fibrosis: recurrent leg pain, which is a result of back surgery
- Painful peripheral neuropathy
- Multiple sclerosis
- CRPS: burning pain, hyperesthesia, swelling, hyperhidrosis, and trophic changes in the skin and bone of the affected area[7]

CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; SCS, spinal cord stimulation

Table 3. SCS: Contraindications and Cautions[7]

SCS Contraindications	SCS Cautions
• Pregnancy • Previous dorsal root entry zone lesions • Critical central spinal stenosis • Substance abuse • Serious neurologic deficit with surgically correctable pathology • Anatomic spine instability at risk for progression • Need for future magnetic resonance imaging (MRI) • Coagulopathy, immunosuppression, or other surgical risk • Ongoing requirement for therapeutic diathermy • Severe cognitive impairment and inability to operate the device • Unacceptable living situation or social environment	• Do not drive or operate dangerous or heavy equipment during stimulation. • Use caution when exposed to ultrasonic equipment, radiation therapy, aircraft communication systems, and other sources of strong electromagnetic interference, as there is a potential for interaction. • Avoid exposure to MRI, diathermy and electrocautery. Electrical energy can be induced though the implant, causing damage to the device, electrodes, and surrounding tissue, resulting in severe injury or even death. • Patients must not scuba dive deeper than 10 meters or sustain pressures in a hyperbaric chamber above 2 atmospheric absolute.

SCS, spinal cord stimulation

SCS implantation is a relatively safe procedure. However, less invasive alternatives should be attempted first before a patient is recommended for SCS. A formal psychologic evaluation is typically recommended before implantation.[3] We have found these evaluations to be very helpful for ensuring that the patient understands the procedure and the long-term implications of having an implanted device. It is also important to assess how the patient will respond to treatment failure: Will they be overwhelmed by feelings of hopelessness? Furthermore, if significant psychopathology is present, this should be treated prior to proceeding with implantation.

Contraindications and Cautions for SCS

Kries and Fishman provide a useful summary of contraindications and cautions when selecting a patient for SCS implantation (see Table 3).[7]

Safety for SCS

Cameron et al reported that complications due to SCS may be technical or biological. The most frequently reported technical complications are electrode dislocation and breakage, as well as pulse generator or battery failures. The most frequently reported biological complications are infection, cerebrospinal fluid (CSF) leakage, and pain located at the incision, electrode, or receiver site.[4]

Peng et al reported that the most common complication was lead problem (such as migration/breakage) requiring revision (23%). Other less common complications included equipment failure (10%), stimulator removal (11%), mostly because of infection, equipment failure or lack of analgesic effect and superficial infection (4.5%).[6]

Table 4. Contraindications for IT Pumps and IT Opioids[15]

IT Pumps	IT Opioids
• Major psychiatric disorders (active psychosis, severe depression, hypochondria, or somatization disorder) • Poor compliance and/or insufficient understanding of the therapy • Lack of appropriate social support • Drug and alcohol abuse or drug-seeking behavior	• Allergy to opioids • Infection at injection site • Concomitant anticoagulation therapy • Obstruction of CSF flow • Clotting disorders

CSF, cerebral spinal fluid; IT, intrathecal

Effectiveness of SCS

Two systematic reviews on SCS implantation suggest positive analgesic effects in patients with CRPS, angina, and FBSS.[8,9] Krames reports that for appropriate indications, SCS provides approximately 60% to 80% long-term pain relief in 60% to 80% of patients.[1]

According to Stuart et al, electrical stimulation of the spinal cord has some limitations. Lead migration, progressive loss of efficacy over time, and postural variability in stimulation intensity (related to the mobility of the spinal cord within the spinal canal during patient movement) are all examples of potential problems with these systems.[3] In addition, SCS provides incomplete or inconsistent coverage of many areas, which are often problem areas for patients who have chronic pain, including the low back, buttocks, feet, groin, pelvis, and neck. Furthermore, some pathways such as those supplying the S2–S5 dermatomes, are located somatotopically deep within the spinal cord, and tend to be out of reach from SCS. Pain syndromes located in these areas are often more responsive to other forms of neurostimulation.[3]

Peripheral Nerve Stimulators

Since 1965, peripheral nerve stimulation (PNS) has been used for the treatment of chronic peripheral neuropathic pain.[10] PNS is one form of neuromodulation by the application of electric current to peripheral nerves causing the sensation of paresthesias within the painful areas, subsequently reducing the subjective experience of pain.[11] The use of neurostimulation technology for peripheral nerve stimulation has not yet achieved FDA approval.

According to Barolat, the mechanism by which PNS produces analgesia is still unclear. One theory is that the use of high-frequency low-intensity electrical current stimulates the myelinated A (beta) fibers and causes analgesia by activating the "gate control" mechanism. The implantation of PNS proximal to the site of injury may produce analgesia in patients with traumatic nerve injuries by this mechanism.[9]

PNS proximal to the injury site has been used for more than 30 years to treat a variety of intractable painful peripheral mononeuropathy conditions, and we are currently seeing technological advancement with improved electrode designs and refined percutaneous lead implant techniques.[10]

Localized neuropathic pain is particularly suitable for a treatment that delivers targeted relief to the precise distribution of the pain. The primary advantage of PNS is the ability to focus stimulation (paresthesias) into the distribution of a specific peripheral nerve or a particular region without unwanted stimulation of unaffected areas. Over the years, PNS has been refined and able to better treat peripheral neuropathic pain that until recently was either untreatable or poorly treated with traditional SCS techniques.[12] Newer techniques involve targeting the field or zone of pain with subcutaneous electrodes, rather than electrodes implanted in close proximity to major peripheral nerves.[9]

Indications/Uses for PNS

Some of the current applications of PNS include conditions affecting the trigeminal, occipital, upper extremity, and lower extremity nerve distributions.

Treated conditions include postherpetic neuralgia involving the supraorbital and infraorbital nerves, as well as occipital nerve dysfunction following trauma or surgery, atypical migraines presenting with occipital pain, cluster headache, and cervicogenic occipital pain (see Figures 1 and 2). PNS also may be used to target larger nerves through an open approach. For example, tibial and peroneal nerve stimulation may provide relief for foot pain.[12]

PNS is indicated for pain in a discreet region that is readily accessible. It should be noted that in some settings, placement of a spinal stimulator may

be less invasive than surgically exposing a peripheral nerve.[12]

According to Weiner, peripheral nerve trauma and chronic entrapment syndromes, such as failed carpal tunnel or ulnar neuropathy conditions with or without a sympathetic component (CRPS), respond by pain transmission blockade using electrodes implanted proximal to the injury site. Most upper and lower extremity pain conditions, such as chronic radiculopathy, CRPS, and even phantom limb and stump neuroma pain, are treated with spinal cord stimulation techniques. Identification of a mononeuropathy component not covered by spinal dorsal column stimulation may be successfully treated with the addition of a peripherally placed electrode modulated concurrently with the spinal cord stimulation implant.[10]

Selection Criteria

The contraindications and cautions for PNS are largely the same as for spinal cord stimulation, though without the concerns for spinal stenosis or instability.

There is some debate regarding appropriate criteria for PNS. At our institution we recommend:

- Pain in a discreet region that is readily accessible for subcutaneous electrode positioning and tunneling to an appropriate IPG site
- Failure of more conservative treatment therapies
- Lack of surgically correctable pathology
- No significant drug dependence issues or other major, untreated psychopathology
- Adequate patient motivation and understanding
- Clear understanding that PNS neuromodulation is designed to help control chronic pain but not cure the underlying disease process
- Successful trial stimulation

Safety for PNS

Percutaneous wire electrode migration can occur in up to 20% of implants.[10] If the electrode is near a major nerve, and if it is not properly anchored, paddle electrode placement can cause a compression neuropathy due to a 90-degree turn of the paddle into the nerve.[10] Even percutaneous leads may "poke" an adjacent nerve, or they could potentially trigger scarring that might affect the nerve. This risk is avoided with the use of subcutaneous, field stimulation rather than direct nerve stimulation. According to Weiner, one of the main limiting factors in prescribing and using PNS as a treatment modality has been the requirement for extensive surgical dissection and electrode placement in the region of an (at times) already injured peripheral nerve. Newer percutaneous electrode placement techniques will allow for more frequent use of PNS in a variety of chronic pain conditions.[10]

Effectiveness of PNS

The peripheral field stimulation technique is substantially less invasive than spinal cord stimulation, and therefore may become the preferred technique in appropriate cases.

Weiner reports that the long-term success rate (greater than 50% pain relief) for PNS depends on the indication and, probably, the surgical technique. PNS for posttraumatic causalgia/CRPS II has been effective in 60% of advanced intractable cases presenting with symptoms, including allodynia, vasomotor disorder, trophic changes, motor weakness, and temperature changes. Subcutaneous stimulation for occipital headache syndromes, with up to a 9-year follow-up, has shown a 70% to 75% success rate, with several distinct subgroups of patients responding to this type of neurostimulation. These include cases of chronic daily transformed migraine headaches that require constant neurostimulation and a group that can successfully abort the onset of a migraine headache by activating their devices during the prodrome of an attack.[10]

Waisbrod et al state that PNS can result in long-term pain relief in the majority of carefully selected patients and has a relatively low complication rate. It should therefore be considered as a reasonable treatment option for patients suffering from otherwise intractable and isolated painful neuropathies.[12]

Intrathecal Pumps

The intrathecal (IT) pump system is a programmable system consisting of a pump implanted into an abdominal, subcutaneous pocket with an attached, tunneled catheter inserted into the IT space of the spine. There is an external, physician-controlled programmer that programs the infusion rate and records medication concentration, volume, and dosage. In the office, the pump is refilled regularly (every 1 to 3 months) via its subcutaneous port. The pump is removed and replaced when the battery fails or is depleted.[13] Current pump batteries last for seven years.

Since the discovery of opioid receptors in the spinal cord, IT opioid delivery has gained attention as another treatment option for chronic pain.[14] According to Deer et al, the IT pump delivers low doses of opioids or other analgesics directly into the IT space. Intraspinally administered opioid analgesic doses are a fraction of those required for systemic administration. They affect primarily the presynaptic and postsynaptic receptors in the substantia gelatinosa of the posterior horn of the spinal cord—therefore, producing potent analgesia without interfering with sensations

of touch, motor function, or sympathetic reflexes. The IT pump system improves pain relief, reduces suffering, and enhances quality of life in the small proportion of patients who do not respond well to oral analgesics, including oral morphine.[15]

The advantage of the IT opioid delivery system over systemic administration includes continuous medication delivery directly into the region of spinal opioid receptors, lower drug doses, and a reduced risk of side effects.[1,16]

The IT pump system is usually considered when spinal-acting analgesics or antispasmodics administered via the oral or transdermal routes fail to control patients' pain or are associated with unacceptable side effects. This type of centrally acting drug administration bypasses the blood-brain barrier, resulting in much higher CSF concentrations while using reduced amounts of medication to achieve equipotent doses. When compared to the epidural route, the IT approach is associated with higher rates of pain relief and lower rates of treatment failures and technical complications.[17]

The IT pumps were approved by the FDA a few decades ago and are considered to be a safe alternative to other routes of medication. Although the procedure is relatively safe, there are still minor complications, such as needle injury, wound infection, drug side effects, or catheter malfunction.[14]

Indications/Uses for Intrathecal Pumps

IT pump delivery systems are indicated for chronic, moderate to severe pain in patients who have failed conservative options. Typically, most of these patients have failed oral opioids because of side effects or lack of efficacy. Pumps are used to treat both cancer and non-cancer pain. More recently, the use of these devices has

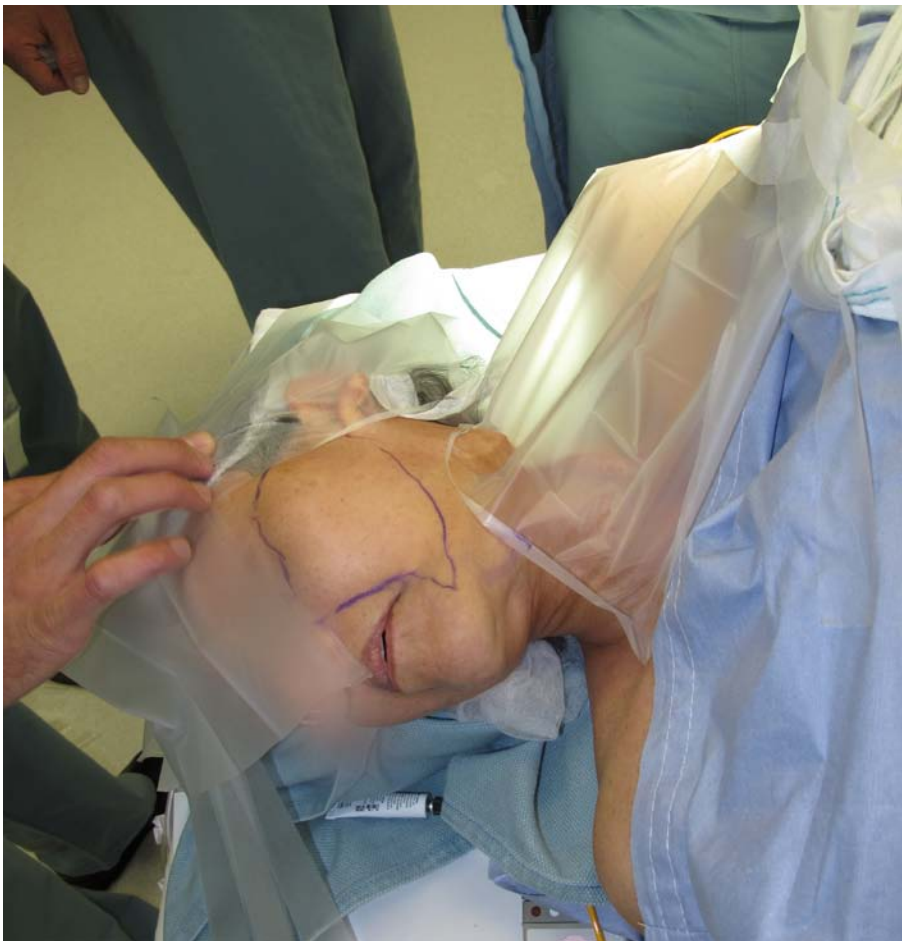

Figure 1. Peripheral nerve stimulation of the face for atypical facial pain. Mapping the patient's atypical facia pain.l

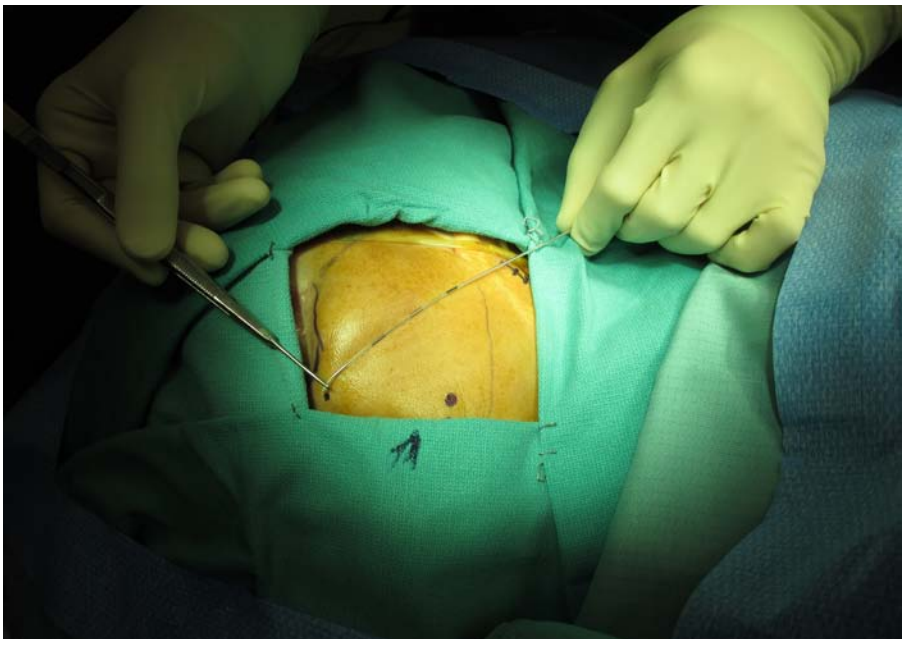

Figure 2. Peripheral nerve stimulation of the face for atypical facial pain. Preparing to insert the electrode lead.

increased since the development of new medication options.[14]

Prior to placing a pump, a SCS should always be considered in a patient with neuropathic pain. When appropriate, an SCS should be considered as an alternative to IT drug delivery system for visceral pain syndromes. PNS can be considered as an adjuvant to SCS when the latter therapy gives only a partial (but incomplete) coverage pattern. Many clinicians consider SCS and PNS to be preferable to IT pumps since they do not involve the risks of drug under- or overdosing and because they do not involve regular refills. IT drug delivery should be considered in the algorithm when SCS with or without PNS fails or is not appropriate.[14]

Chronic, constant pain responds best to long-acting analgesics or long-term infusion of analgesics delivered around-the-clock in anticipation of pain rather than in response to pain symptoms. Around-the-clock dosing refers to a regular, fixed dosing schedule—it does not mean that the patient is waking up in severe pain. Patients who require around-the-clock dosing of opioids may be a candidate for the IT pump system.

Certain types of cancer, including pelvic, pancreatic, and metastatic cancer in the bone are most responsive to intrathecal opioid delivery. Therefore, patients with these conditions are particularly good candidates for implantation.[15]

Therapeutic options with intrathecal delivery are also expanding beyond the use of opioids only. Deer demonstrated that the combination of intrathecal bupivacaine and opioids increased efficacy beyond that of opioids alone.[18] Staats demonstrated the efficacy of intrathecal ziconotide, a relatively new agent derived from sea snail toxin.[19] Ziconotide is indicated for the use of severe, chronic pain.

Contraindications for Intrathecal Pumps

Several contraindications exist regarding the use of IT pumps and regarding the specific use of IT opioids (see Table 4). Evaluation of the patient by an experienced psychologist is an important part of the preimplantation assessment.

Safety for Intrathecal Pumps

In general, the benefits of IT drug delivery (ie, lower doses and reduced side effects, cost effectiveness, and possible increase in patient survival) outweigh the risks (ie, possible postoperative infection, wound infection, meningitis, and postdural puncture headache) in patients whose pain is not controlled by systemic opioids, or in patients who cannot tolerate opioids due to systemic side effects.[15]

Deer et al reported that catheter disruption, battery failure, or human error may lead unexpectedly to drug withdrawal accompanied by unpleasant side-effects that may vary, depending on the medication involved. Furthermore, there are potential catheter-related risks, such as catheter material and design problems, mechanical issues (dislodgements, tears, microfractures, displacement), and complications of the catheter placement (macrotrauma to the spinal cord and/or granuloma formation at the tip of the catheter).[20]

Effectiveness of Intrathecal Pumps

According to Deer et al, the response to IT opioid delivery often depends on the type of pain (visceral/somatic nociceptive, neuropathic, and mixed neuropathic/nociceptive pain) the patient experiences.[15]

Visceral nociceptive pain is characterized by a constant, aching pain that is often associated with nausea and arises from soft tissue cancers (eg, pancreatic cancer). Visceral pain patients respond quite well to IT delivery of opioids.

Patients with somatic nociceptive pain report a dull, constant, achy pain that is well localized. These patients are classically the best candidates for IT opioid delivery because this type of pain is responsive to morphine.

Neuropathic pain is burning, electric-like, shooting pain. Patients with neuropathic-type pain were previously thought to be poor candidates for IT delivery. However, a recent study by Winkelmüller shows that IT opiate therapy can reduce neuropathic pain by an average of 62%, measured on a visual analog scale (VAS), even after several years. In addition, the experimental use of IT clonidine, ziconotide, and local anesthetics (eg, bupivacaine) shows promise for the relief of neuropathic pain.[15,18,19]

Both cancer and nonmalignant pain can involve a mix of nociceptive and neuropathic pain. Patients with mixed pain are the hardest to treat and require a drug "cocktail"—usually a combination of an opioid with a local anesthetic or clonidine.[15] Krames reports that intrathecal therapies with opioids, such as morphine, fentanyl, sufentanil, meperidine, or non-opioids (eg, clonidine, bupivacaine), provide analgesia in patients with nociceptive or neuropathic pain syndromes.[1]

A special use of the IT pump technology is the use of baclofen. IT baclofen provides profound relief of muscle spasticity due to multiple sclerosis, spinal cord injuries, brain injuries, or cerebral palsy.[1] This antispasmodic effect can improve motor function and mobility as well as decrease spasm-related pain.

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