Hot Developments in Neurosurgery for Pain

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We are currently halfway through the Decade of Pain Control and Research, declared by the 106th United States Congress as part of an effort to improve pain management and facilitate research on pain. Neurosurgeons have long contributed to both pain research and patient care, and we continue to do so today, although too few of us have taken up this important facet of neurosurgery. The joint Section on Pain of the Congress of Neurological Surgeons/American Association of Neurological Surgeons is quite active, but its members are a small fraction of the neurosurgeons in our country. I have been asked to discuss several areas of the neurosurgical pain relief endeavor that I think are likely to have significant clinical usefulness in the future. Now, my crystal ball is no more translucent than anyone else's, therefore, the three areas that I have chosen to talk about may fade away rather than blossom; alas, another Loeser folly!

SPINAL CORD STIMULATION FOR ANGINA

Spinal cord stimulation for relief of pain has been clinically available for longer than 30 years throughout the world. In the United States, we have seen it used primarily to treat failed back surgery syndrome, complex regional pain syndrome, and peripheral neuropathies. In Europe, on the other hand, it is now used predominantly to treat angina and vascular disease. Perhaps this discrepancy is caused by the excessive number of patients who have had low back surgery in this country, but I think that it is also a demonstration that healthcare is a social convention and is rarely driven by science. Whereas there is considerable debate regarding the usefulness of spinal cord stimulation for the treatment of peripheral vascular disease, there is clear-cut evidence to support the use of spinal cord stimulation for intractable angina that has not responded to medication. Although there are dozens of papers regarding this topic from Europe, there are none from the United States at the time of this writing.[7,10] I have selected seven of the better papers that support the allegation that spinal cord stimulation is a better treatment for angina than coronary artery surgery.

In 1998, Hautvast et al.[9] published a randomized, controlled efficacy study with 26 patients studied at 6 weeks after spinal cord stimulation or best medical management. He found that the spinal cord stimulation group manifested significant increases in exercise duration, time to angina, and quality of life, and decreases in nitroglycerin consumption, ischemic episodes, and chest pain. Mannheimer et al.[11] compared spinal cord stimulation to coronary artery bypass graft (CABG) surgery in a group of 104 patients randomly assigned to each group. This study demonstrated significantly lower mortality in the spinal cord stimulation group; however, there were equivalent increases in exercise capacity, and decreases in ST-segment depression and symptom relief. Ten Vaarwerk et al.[17] studied 517 patients with a mean follow-up of 23 months. They found no differences in death rate or cardiac events in patients treated with spinal cord stimulators versus CABG procedures.

Murray et al.[13] retrospectively compared patients with angina who had undergone CABG procedures with those who had a spinal cord stimulator implanted. In a group of 19 patients, he found that admissions per year for cardiac problems and duration of stay per admission were dramatically less in the spinal cord stimulation patients. Ekre et al.[5] showed that spinal cord stimulation and CABG equally improved quality of life at 6 and 60 months after surgery in the same group of 104 patients described by Mannheimer et al.[11] Andrell et al.[2] analyzed the same 104 patients and reported that spinal cord stimulation was significantly less expensive, led to fewer hospitalizations, had no serious complications, and did not influence the cause of death or the death rate when compared with CABG. Finally, Di Pede et al.[4] reported on another prospective study of 104 patients followed for longer than 1 year. Of these patients, 73% had greater than a 50% reduction in angina attacks, and there was a significant reduction in hospital admissions and duration of stay. No serious complications were described in this group.

To summarize these and other papers, including some fascinating animal data on cardiac function, spinal cord stimulation may provide relief of angina by any or all of the following mechanisms:

- Reduction of transmission of nociceptive impulses in the spinothalamic tract
- Improved myocardial blood flow as demonstrated on positron emission tomographic (PET) scan
- Decreased sympathetic tone via norepinephrine kinetics

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- Decreased myocardial oxygen consumption
- Increased myocardial microcirculatory blood flow

Spinal cord stimulation is a useful and efficient treatment for patients with medically or surgically intractable angina. Almost 80% of patients will report good relief of pain. It does not increase the cardiac mortality rate; there is no protective value of experiencing angina. This was also observed 75 years ago, when sympathectomies were performed for angina. Spinal cord stimulation is just as effective as CABG for medically intractable angina.

Spinal cord stimulation for angina is not approved by the United States Food and Drug Administration (FDA), and, as far as I can tell, it is not likely to be approved in the near future. Very few cases have been reported in the United States. Will cardiologists and cardiac surgeons ever refer patients for spinal cord stimulation if it is approved? The major manufacturer of spinal cord stimulators in the world, Medtronic, does not see much market potential and their clinical research project on this topic is "on the back burner." Nonetheless, I foresee widespread use of this technology in the near future.

MOTOR CORTEX STIMULATION FOR RELIEF OF NEUROPATHIC PAIN

Similar to spinal cord stimulation for the treatment of angina, motor cortex stimulation has been developed abroad and is not yet FDA approved or clinically available in the United States outside of research studies. The treatment strategy for the most difficult of chronic pain states to treat, central denervation pain, was first described by Tsubokawa et al.[18] longer than 15 years ago. Large series of patients have been reported on from Japan and from Europe in the intervening years. Meyerson et al.[12] reported on a retrospective series of 10 patients, 5 of whom had trigeminal neuropathic pain and reported 60 to 90% pain relief. One of two patients with pain after peripheral nerve injury reported pain relief, and none of three patients with central pain after cerebrovascular accidents reported pain relief. Nguyen et al.[14] concurred with the results of Meyerson et al.[12] in a series of 20 patients: trigeminal neuropathic pain patients were the most likely to exhibit a favorable response. Nuti et al.[15] reported a retrospective study of 31 patients with refractory neuropathic pain followed for 4 years. Good or excellent relief was found in 52% of cases, and poor or negligible results in 38%. Rasche et al.[16] reported a series of 10 facial neuropathic pain and 7 stroke-induced pain patients, with a mean follow-up of 3.5 years and some patients followed for 10 years: 8 of 17 patients experienced greater than a 50% reduction in their pain. This group noted that the response to treatment after 1 week was strongly predictive of the long-term results. Fregni et al.[6] reported on a sham-controlled trial of motor cortex stimulation for central pain after spinal cord injury and was impressed by the favorable responses from patients.

Motor cortex stimulation has been used successfully in the treatment of chronic pain after cerebrovascular accident, traumatic brain injury, brachial plexus avulsion, spinal cord injury, postherpetic neuralgia, anesthesia dolorosa, and neuropathic pains of the face.[3] It seems to be most likely to succeed with the pains of facial neuropathies. The reported success rates vary widely in the reported series. Whether this is caused by patient selection, technical aspects of the stimulator implant, or differing outcomes criteria is not clear. The major studies are from abroad, and the FDA is not about to approve this treatment without domestic clinical trials. Although, at one time, Medtronic had such a multicenter trial in progress, it seems also to have placed this treatment strategy "on the back burner," because the company does not see sufficient marketing potential to justify the expenditure to obtain FDA approval.

INTRATHECAL DRUGS FOR RELIEF OF PAIN

Clinically useful and FDA-approved delivery systems for the chronic administration of intrathecal drugs have been available in the United States since 1990. The first drug approved was baclofen; morphine was approved in 1995. A long list of medications has been administered to patients by this route; evidence-based outcomes are indeed nonexistent. Nonetheless, some promising observations have been made, and this is clearly a potential growth area for neurosurgical pain management.[8] The medications that have been reported on to date are listed in *Table 1.1*. Results vary widely among the case series reports and conclusions regarding the best drugs and favorable combinations are based on personal experience and not on good outcomes data. Some observations do allow for generalizations. This technology allows one to circumvent the blood-brain barrier, thus permitting the delivery of drugs that are normally denied entry into the central nervous system. A catheter can also be placed intraparenchymally for delivery of drugs to a specific nucleus in the brain. The current delivery technology, using a pump that is driven by a motor, consumes a significant amount of electricity, thereby making battery life a significant problem. Alternative methods of releasing a drug, for example, by osmotic pumps, elution systems, or injection of cells to produce the drug, may lead to much more efficient drug delivery at less expense. Intrathecal injection can include not only drugs, but larger, complex proteins, whole cells, genes, antisense genes, ribonucleic acid, and other compounds that may have use in altering nervous system function. Furthermore, drug delivery systems (DDS) offer unusual opportunities to deliver drugs and avoid problems such as poor solubility, rapid breakdown in vivo, unfavorable pharmacokinetics, poor bioavailability, and lack of selectivity for target tissues. DDS uses nanoparticles and microparticles with diameters of 200 nm or less to alter drug properties and enhance delivery to the target sites.[1]

Further development will depend on FDA approval of new substances for intrathecal administration. Off-label use of intrathecal drugs is widespread, and the sole manufacturer

TABLE 1.1. Intrathecal medications reported[a]

Drug type	Preclinical	Clinical
Opioids		
Morphine	Yes	Yes
Hydromorphone	Yes	Yes
Fentanyl	No	Yes
Sufentanil	No	Yes
Methadone	No	Yes
Meperidine	No	Yes
Local anesthetics		
Bupivacaine	Yes	Yes
Ropivacaine	No	Yes
Tetracaine	No	Yes
Adrenergic agonists		
Clonidine	Yes	Yes
Tizanidine	Yes	No
N-methyl-D -aspartate antagonists		
Ketamine	Yes	Yes
Other agents		
Adenosine	No	Yes
Aspirin	No	Yes
Baclofen	Yes	Yes
Droperidol	No	Yes
Gabapentin	Yes	No
Ketorolac	No	Yes
Midazolam	Yes	Yes
Octreotide	No	Yes
Ziconotide	Yes	Yes

[a]Adapted from Hassenbusch SJ, Portenoy RK, Cousins M, Buchser E, Deer TR, Du Pen SL, Eisenach J, Follett KA, Hildebrand KR, Krames ES, Levy RM, Palmer PP, Rathmell JP, Rauck RL, Staats PS, Stearns L, Willis KD: Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery—Report of an expert panel. **J Pain Symptom Manage** 27:540–563, 2004 (8).

of pumps in the United States, Medtronic, has little incentive to fund clinical trials. Costs are high, and additional market share is not likely. How delivery of drugs directly to the nervous system will evolve in the next decade is unclear, but I predict that it will become a commonplace method for treating a diverse group of central nervous system diseases.

CONCLUSIONS

Predicting the future is always dangerous, and committing one's predictions to the printed word is even more hazardous, for someone may recall what one has said or written, with some ridicule. Nonetheless, these three areas of neurosurgical endeavor seem to me to be particularly promising for those interested in the relief of pain and suffering. The technologies may be applicable to other aspects of neurosurgical care as well. Our specialty is dynamic, and benefits for our patients can be expected.

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