EDITORIAL VIEWS

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Refractory Head and Neck Pain

A Difficult Problem and a New Alternative Therapy

After nearly two decades caring for patients in the African jungle, Albert Schweitzer wrote, "We all must die. But that I can save him from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself."[1] This quote, selected for the introduction to John Bonica's textbook, *The Management of Pain,*[2] underscores the obligation and privilege of physicians caring for patients with pain. Patients also are extremely concerned about the possibility of suffering from pain. For example, one of the greatest fears of patients with terminal cancer is that of experiencing severe intractable pain.

Despite concerns of patients and pioneering physicians, such as Bonica and Schweitzer, widespread recognition that pain is a serious problem has occurred only recently. Recognition that pain associated with cancer often was poorly treated led to the development of World Health Organization (WHO) guidelines[3] and the introduction of Cancer Pain Initiatives into several state legislatures in the United States. However, the WHO cancer pain relief guidelines were introduced in 1986, and the first Cancer Pain Initiative was passed in Wisconsin a few years later.[4] Guidelines for acute and chronic pain therapy were only recently developed and widely dispersed.[5] These consensus documents correctly suggest that most patients with pain will obtain adequate pain relief with oral analgesics. However, a small subset of patients will require more aggressive and invasive treatment, such as neurolysis, implantable intrathecal or epidural catheters for infusion of analgesic medications, or neuroaugmentative procedures.

Considerable effort has been focused on treating this subset of patients with pain that is refractory to oral analgesics. As a result, options for aggressive therapy have expanded greatly in the past decade. On the whole, we can be proud of the contributions made by members of our specialty to improving pain therapy in the general population. However, despite dramatic improvements in overall efficacy, certain classes of pain remain relatively refractory to current techniques of analgesic therapy.

In this issue of ANESTHESIOLOGY, Appelgren *et al.* describe a group of patients with malignant or nonmalignant chronic head and neck pain that was refractory to conventional analgesic therapies.[6] In these patients, pain control was inadequate despite aggressive treatment including: surgery, radiation therapy, or chemotherapy directed at neoplasms and pain relief; systemic analgesic therapy with nonsteroidal antiinflammatory drugs, anticonvulsants, antidepressants, phenothiazines, benzodiazepines, and oral and parenteral opioids; cranial nerve neurolysis with techniques such as diathermic coagulation of the gasserian ganglion or through injection of glycerol; peripheral neurolysis with techniques such as epidural phenol injections; local anesthetic-induced neural blockade with techniques such as continuous epidural analgesia or stellate ganglion blockade; insertion of a dorsal column stimulator at a cervical level; transcutaneous nerve stimulation; acupuncture; and therapy with hormones or steroids. Patients either had inadequate pain relief with these regimens or suffered intolerable side effects from the systemic opioid therapy. Thus, the patients included in this article represent a subset of patients with pain refractory to conventional therapies.

Numerous invasive techniques have been employed in an attempt to treat similar patients with refractory head and neck pain. However, previous therapies—such as intracisternal[7] or intraventricular[8] injections of morphine, neurolysis of the gasserian ganglion or other cranial nerves, rhizotomy, cordotomy, or thalamotomy—often provided inadequate pain relief or produced unacceptable side effects. For example, in one study, control of pain was attempted with injection of phenol into the cisterna magna.[9] Eighteen percent of patients had long-lasting, disabling neurologic deficits, and 71% had less severe complications. Furthermore, this approach provided relatively inadequate pain relief in the majority of patients. More extensive neoplastic disease causing severe pain has been treated by per-

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forming a posterior craniotomy and sectioning the roots of cranial nerves VII, IX, and X and the sensory roots of the upper cervical nerves. However, many patients cannot tolerate a major operation, and sectioning of the glossopharyngeal and vagus nerves produces paralysis of pharyngeal and laryngeal muscles.

In contrast to the poor results observed with the above therapies, the technique described by Appelgren *et al.* provided relatively effective analgesic therapy in select patients. The authors presented 13 patients with complex, refractory pain who received continuous intracisternal or high cervical subarachnoid infusions of bupivacaine as a method to control pain in the head, face, mouth, neck, and upper extremities. For most patients, infusions of bupivacaine provided satisfactory pain relief, decreased systemic opioid consumption, improved nocturnal sleep patterns, and improved overall function. Associated side effects generally were dose-related and similar to those described with lower sites of infusion (*e.g.*, orthostatic hypotension, paresis). Novel side effects included one patient experiencing severe tiredness, faintness, and malaise and one experiencing somnolence and sleep. These novel side effects were transiently associated with relatively high infusion rates or large bolus doses and resolved after decreasing the infusion rate or withholding the bolus dose. No patient experienced gross impairment of phrenic nerve activity. The magnitude of analgesia described in this study surpasses that achieved in previous reports for this group of patients.

This manuscript presents several other interesting observations. Clinically, the authors employed this technique in patients with complicated problems and demonstrated efficacy when multiple other analgesic techniques had failed. In patients with diffuse upper neck and head pain, the source of pain often involves multiple nerves. Cranial nerves and peripheral somatic nerves often coexist to provide nociceptive afferent information. In addition to severe sharp somatic pain, burning discomfort may result from nociceptive pathways within the sympathetic chain. The multiplicity of potential nociceptive pathways can make individual nerve block therapy relatively ineffective. Similarly, local invasion of tumor can make peripheral neural blockade impractical.

The approach described by Appelgren *et al.* can be performed at a site relatively distant from the site of pain—access to the intrathecal space is from a posterior approach at a thoracic vertebral level. The techniques described in this series of patients are similar to those employed by the authors to treat pain from lower dermatomal levels.[10–12] However, placement of the catheter tip at higher cervical vertebral levels extends the applicability to effectively treat pains originating from dermatomes innervated by cervical and cranial nerves. For head and neck pain, the best location for the catheter seemed to be at the level of the C1 or C2 vertebral body. For patients with shoulder and arm pain, better analgesia was obtained with the catheter tip in the mid-cervical (C4–C5) location. Administration of bupivacaine through these catheters produced bilateral analgesia for pain that appears to be conducted *via* cranial, somatic, or sympathetic nociceptive pathways. The ability of this technique to inhibit multiple nociceptive pathways is likely responsible for the improved analgesic efficacy observed in a group of patients for whom previous techniques had been relatively ineffective.

The ability of bupivacaine, or any local anesthetic, to produce analgesia when administered in low doses to the central nervous system raises obvious questions concerning the mechanism of analgesia. Local anesthetics classically are thought to provide anesthesia and analgesia by blocking neuronal sodium channels and inhibiting neural conduction. However, the doses of bupivacaine injected would not be expected to produce complete axonal blockade as seen in peripheral conduction block. Despite the absence of complete neural blockade, analgesia could result from an effect on the sodium channels if subblocking concentrations (less than that required to produce complete conduction blockade) of local anesthetics effectively degrade coding of information contained in neuronal discharge patterns without blocking conduction of single neuronal impulses.[13] In other words, subtle effects on the pattern of neural transmission may alter perception of pain even in the absence of complete conduction blockade. Another explanation may be that the analgesic effect results from an action of local anesthetics on membrane channels other than the sodium channel or on other enzymatic activities.[14] For example, recent evidence suggests that spinally administered local anesthetics are likely to inhibit or interfere with nociceptive synaptic transmission mediated by tachykinins or excitatory amino acids.[15,16] Although the actual mechanism of analgesia remains unknown, the low doses of bupivacaine used in this study (range 1–5 mg/h) suggest the possibility of a central neuronal analgesic effect, and future research is warranted to explore this possibility.

The authors have provided a provocative and interesting alternative technique for pain relief in a difficult group of patients. The clinical utility of this technique cannot be established by reviewing the limited experience reported in this preliminary report and can be judged only after greater experience is obtained. The most appropriate venue for collecting this information would seem to be in the context of controlled clinical studies. Until then, the potential for serious complications from this technique cannot be overemphasized.[17] Placement of a catheter juxtaposed to neural tissue at the high cervical or cisternal level can theoretically cause significant and irreversible nerve damage. Any bleeding into the spinal cord at this level would be devastating. Although the risk of meningitis, encephalitis, or other serious infection associated with long-term percutaneous catheterization appears to be acceptably low,[6,10–12] the total experience with these techniques is relatively limited.

Other potential risks that may be associated with chronic intracisternal administration of bupivacaine largely remain speculative. Despite extensive experience with chronic epidural and intrathecal infusions, very little is known concerning the effects of these agents when administered near intracranial neural structures, and many questions remain to be answered. What are the potential toxicities associated with acute boluses or long-term infusions of bupivacaine at this level? What is the therapeutic window between analgesia and serious respiratory depression or unconsciousness? How much bupivacaine is required to exceed the seizure threshold? Can other idiosyncratic reactions occur in patients when local anesthetics are administered into the cisterna magna? Finally, an unrelated but as yet unanswered question relating to risk: Would the addition of opioid to the local anesthetic reduce or increase the risk of associated morbidity?

Acute and chronic toxicity studies performed in appropriate animal models may help to answer some of the above questions. Although clinical trials in terminally ill patients with refractory pain probably should not be delayed, knowledge gained from toxicity studies in animals may provide insights for reducing associated patient morbidity. The risk-benefit analysis in patients with chronic benign pain is less clear. It may be prudent to avoid this technique in patients with benign pain until more information is available. In addition to the safety issues, laboratory research may help to identify the mechanism(s) by which local infusion of bupivacaine produces analgesia.

We applaud Applegren *et al.* for their courage and foresight in developing a new technique, one that clearly expands our options for alleviating the suffering seen in this subset of patients. For patients with refractory pain due to terminal illness, the approach described by Appelgren *et al.* may dramatically reduce pain and improve the quality of the remaining days of life. Although we embrace these new techniques, we strongly caution practitioners who consider the use of this technique based on the current paper. Despite the relative safety demonstrated by the authors, the potential for catastrophic complications is real, and the relative risks remain ill defined.

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New Technology A

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