

What's New with Acute Pain Services and its Clinical Implications

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Approximately 23 million people undergo surgery annually in the United States. Acute Pain Services (APSs) have their origins in inadequate postoperative pain management causing prolonged recovery and potential complications. In one survey of 500 U.S. households, 57% who had surgery related their concerns and anxiety about pain after surgery as their primary fear experienced before surgery. In adults, a detailed survey from 2000, conducted structured interviews of 200 patients up to 72 hours after elective surgical procedures, and showed that moderate to severe pain was common, especially on movement. An extensive review of postoperative pain and pain relief after major surgery indicated that about 1 in 5 patients experiences only fair to poor pain relief as well as moderate or severe pain at rest or with movement. Acute pain after surgical procedures is one of the few opportunities in the clinical practice of pain medicine in which the cause of the pain syndrome is known before its occurrence and that pain is reliably expected to occur. Despite its common occurrence, its predictability, and its known cause, the management of postoperative pain remains inadequate in many cases.

Anesthesiology-based APSs have been developed for the purpose of providing acute pain management modalities to surgical patients who might benefit from them, anesthesiology-based APSs have been developed. First described by Ready in 1988, an APS can provide a comprehensive, inter-disciplinary support team to safely and effectively manage complex post-operative pain. Found originally mainly in academic centers, APSs are now found in the private hospital setting as well and overall are now found in 43% of all hospitals in the United States with an additional 13 % having plans to establish such a service.

Therapeutic pain relief cannot be achieved solely through the use of opioid analgesics in all postoperative patients. Many pain treatment modalities have become available that have been shown to provide superior analgesia when compared with intramuscular as-needed opioid administration. PCA provides excellent analgesia to patients in a variety of settings. More recently, aggressive use of regional anesthetic techniques has become popular again, and the use of opioid and non-opioid analgesics and neural blockade techniques may provide improved analgesic efficacy and reduced opioid-related side effects. The combination of various analgesic techniques, known as balanced or multimodal analgesia, appears to improve postoperative pain relief, reduce postoperative opioid requirements and opioid-related side effects, and enhance postoperative rehabilitation.

Uncontrolled postoperative pain can result in several negative physiologic effects that include disturbances of normal respiratory, cardiac, gastrointestinal, coagulation, renal, and sympathetic and central nervous system function. Surgical trauma and pain cause an endocrine response that increases the secretion of cortisol, catecholamines, and other stress hormones. Surgery also leads to suppression of immune function which appears directly related to the invasiveness of the surgery. Such responses set up pronounced reflex changes which result in vicious circles that result in progressively increasing pathophysiology. If the situation continues, it could result in significant dysfunction in a substantial number of organ systems which may progress to organ damage and even failure. Thus it is possible for acute pain to result in significant morbidity and even mortality. Many of these negative physiological effects can be reduced with improvements in postoperative pain management and postoperative rehabilitation efforts. A problem that needs to be addressed is whether the effort extended to prevent postoperative pain and ablate the stress response to acute injury results in improved outcome. The use of effective postoperative analgesia as a component of a multidisciplinary accelerated postoperative rehabilitation effort may provide the greatest effect in improving postoperative outcome and reducing hospital stay.

From the time of the noxious stimulus to the perception of pain, a series of complex electrochemical events occurs. Nociception includes transduction or receptor activation and is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, and topical local anesthetics. Transmission, the process by which the information is relayed to the central nervous system, is the propagation of action potentials from peripheral nociceptive endings to second-order neurons in the dorsal horn and ascending to reach supraspinal targets via the spinothalamic tract and can be blocked by local anesthetics and opioids. Modulation and central facilitation, the processes by which the information is modified, primarily in the dorsal horn of the spinal cord involves the activation of N-methyl-D-aspartate (NMDA) receptors associated with increased sensitivity and firing frequency of dorsal horn neurons and can be inhibited by NMDA antagonists such as Ketamine. Modulation, mediated by descending enkephalinergic, adrenergic, and cholinergic nerve fibers, which either inhibit release of nociceptive transmitters from primary afferents or blunt responses of second-order cells that can be enhanced by neuraxial administration of opioids, clonidine and local anesthetics. Ultimately perception, in which the final pain message relayed to the brain produces an unpleasant sensory and emotional experience, is blunted or suppressed by anxiolytics, opioids, beta-adrenergic antagonists, and regional blockade.

The nociceptive afferent pathway from the peripheral tissues to the central nervous system involves numerous neurophysiologic processes and neurochemical substances that serve to augment and intensify the stimulus-response (hyperalgesia). The painful phenomenon of hyperalgesia results from nociceptive stimuli that produce tissue damage causing an increased sensitivity to subsequent stimuli because of the enhanced responsiveness of the involved receptors. Hyperalgesia at the original site of tissue damage is classified as primary resulting from enhanced sensitivity of the nociceptors. Hyperalgesia is classified as secondary when the contiguous surrounding areas are affected and may result from either sensitization of peripheral nociceptive with branches

in the immediate vicinity of the tissue damage or sensitization of central nociceptive neurons caused by sustained afferent input. Tissue damage, inflammation, or nerve injury may result in persistent pain as a result increased excitability of primary afferent nociceptors (peripheral sensitization) and from increased excitability of spinal neurons after noxious stimulation (central sensitization). Secondary to the stepwise intensification and amplification associated with subsequent steps in the nociceptive pathway, anesthetic and analgesic techniques directed at the more peripheral processes of transduction and transmission should be more efficient in limiting the physiological response to pain and may have the benefit of preventing some of the secondary hyperalgesic effects associated with activation of spinal cord dorsal horn neurons and supraspinal centers.

In the last few years, efforts in several aspects of acute pain management allow acute pain services to offer significant advances in therapeutic regimens to hopefully provide greater patient satisfaction and improved patient outcomes. These include: modification of currently available opioids and their mechanisms of delivery; development of nonopioid and adjuvant analgesics whose efficacy is determined by examining opioid-sparing effects; refining continuous regional anesthesia techniques that enable patients to be discharged home with continuous perineural analgesia for postoperative pain control with a comprehensive protocol for patient follow-up; redirect focus from timing (preemptive analgesia) of the analgesic technique to the duration and efficacy of each particular analgesic treatment with regard to the effects of intensive and prolonged multimodal analgesic interventions that attempt to reduce central sensitization that arises from noxious inputs across the entire postoperative period (not just incision). Multimodal analgesic techniques and strategies combine a variety of analgesic interventions, which effectively block nociceptive pathways, and may be combined to achieve enhanced, balanced pain control. Local anesthetics (regional blocks), opioid analgesics, and non-opioid analgesics (NSAIDs, alpha 2 agonists, NMDA antagonists) may be used to block afferent nociceptive stimuli both at the periphery and at the central nervous system. This can be effectively managed through a perioperative protocol organized and run through a multidisciplinary APS team that will hopefully achieve better compliance with postoperative rehabilitation, fewer side effects and improved patient satisfaction and outcomes.

Preemptive analgesia was based on the idea that analgesics given before the onset of surgery could have effects that outlast the pharmacokinetic presence of the intervention. In 1983, the concept of preemptive analgesia was investigated by Woolf, who showed evidence for a central component of postinjury pain hypersensitivity in experimental studies. Various antinociceptive techniques applied before injury appeared more effective in reducing the postinjury central sensitization phenomena when compared with administration after injury. These promising experimental findings were taken into clinical testing. Although early reviews of clinical findings were mostly negative, there was still a widespread belief of the efficacy of preemptive analgesia among clinicians. S. Moiniche et al performed a large systematic review of preemptive analgesia for postoperative pain relief and the role of timing of analgesia. There were a total of 80 trials meeting the strict inclusion and exclusion criteria were identified with a total of

3,761 patients studied. They focused on one aspect of the issue as to whether the timing of the analgesic therapy (preoperative versus intra/postoperative) has an impact on postoperative pain relief and did not consider preemptive versus no treatment. They concluded that preemptive analgesia for postoperative pain relief provides no more analgesia than the same intervention than the same intervention given after surgery. The timing of preemptive treatment did not influence the quality of postoperative pain control.

In their conclusions, Moiniche et al determined that their results did not preclude a possible beneficial effect of an aggressive, perioperative, analgesic intervention on short- and long-term pain after surgery. It was suggested that future studies redirect their focus from timing of perioperative analgesia (preemptive analgesia) to protective analgesia, aimed at the prevention of pain hypersensitivity. It was their opinion that these studies should investigate the effects of intensive and prolonged, multimodal analgesic (“protective”) interventions versus less aggressive, conventional perioperative analgesia on immediate and late postoperative pain. A recent article in the November, 2004 issue of *Anesthesiology* by Scott S. Reuben M.D. builds on the conclusion and recommendations of S. Moiniche et al by reviewing the development of Complex Regional Pain Syndrome (CRPS) after surgery by outlining the surgical procedures that are believed to increase risk for development of CRPS and describes pharmacologic and regional analgesic techniques for preventing the development of CRPS after surgery. It has been hypothesized that one of the pathophysiologic mechanisms of CRPS is an ongoing barrage of nociceptor input from the periphery to the central nervous system leading to a state of central hyperexcitability. Current analgesic techniques are aimed at reducing central sensitization that arises from noxious inputs across the entire postoperative period (preventive analgesia) and not just those brought about by the incision (preemptive analgesia). There is evidence that “preventive analgesic” techniques demonstrate analgesic benefit and are likely to prevent the development of central hyperexcitability. It is currently recommended that combined analgesic regimens (multimodal analgesia) operate through different sites be used, as it is difficult to achieve optimal pain relief permitting improved function with a single drug or technique.

Tissue trauma during surgery modifies the central processing pathway for pain perception. These changes decrease stimulus threshold and amplify postoperative pain. The induction and maintenance of such central sensitization may be dependent on the activation of N-methyl-D-aspartic acid (NMDA) receptors. Ketamine, dextromethorphan, and methadone have NMDA antagonist properties and may reduce hyperalgesia and allodynia in postoperative pain. Ketamine is an IV anesthetic with analgesic properties in subanesthetic doses. The preoperative administration of ketamine should prevent central sensitization and may improve postoperative pain relief (preemptive analgesia). However, despite the overwhelming success in animal experiments, clinical reports confirming the preemptive effects of ketamine were not forthcoming. However, previous studies concentrated on major surgery, where intense noxious stimuli continue throughout the procedure and may even extend into the postoperative period. It is therefore surprising that a relatively small bolus of ketamine, given before the incision, cannot block the continuous noxious afferent stimuli

adequately. In this regard, a larger dose of ketamine provides preemptive analgesia in patients undergoing abdominal surgery, but emergence hallucinations and nightmares have limited the usefulness of large-doses. Minimally invasive surgery produces less tissue trauma. The interaction between drug dosage and stimulus intensity must not be overlooked. An insufficient dose of ketamine or an intense noxious stimulus may initiate NMDA-receptor activation and subsequent hyperalgesia. Insufficient afferent block may account for many studies that have found a lack of evidence for preemptive analgesia. A recent systematic review of ketamine as an adjuvant analgesic to opioids concluded that small dose ketamine is a safe and useful adjuvant to standard practice opioid-analgesia. Ketamine should be considered as an additive in the surgical population with large opioid requirements, such as major abdominal surgery, best used as continuous infusion (0.12-0.6mg/kg/hr) in these patients. Interestingly, adding ketamine to PCA morphine has not been found to be useful. In minor surgical procedures, a single dose of ketamine ranging from 0.15-1.0 mg/kg in addition to opioids may be useful.

Promising new developments of alternative delivery systems for analgesics that improve patient satisfaction and outcomes are now becoming available to Acute Pain Services. A PCA transdermal system using iontophoresis to deliver fentanyl provided postsurgical pain control equivalent to that of a standard intravenous morphine regimen delivered by a PCA pump. Existing PCA therapies infuse opioid analgesics through an IV line at a preset rate by electronic pumps or by disposable, fixed-volume devices when a patient activates a dosing button. Problems that compromise patient safety, such as programming errors, uncontrolled delivery of syringe contents, and patient tampering, have been reported. To overcome these problems, a fentanyl hydrochloride patient-controlled transdermal system (PCTS) has been developed as an alternative method that delivers small doses of fentanyl by iontophoresis with electro-transport delivery platform technology. The system uses a low-intensity direct current to move fentanyl from a hydrogel reservoir in the skin. The self-adhesive unit, about the size of a credit card, is worn on the patient's upper arm or chest, does not have the IV tubing, cables, and large pump of the IV PCA, and may facilitate patient mobility. Also available now is a sustained-release epidural morphine, DepoDur™ that has the advantage of obviating the need for an indwelling epidural catheter. The extended duration of action of DepoDur™ is due to proprietary DepoFoam™ technology that is FDA-approved liposome-based drug-delivery technology. DepoFoam™ consists of naturally occurring lipid particles suspended in saline solution. The particles, 10-30 microns in diameter, contain discrete water-filled chambers that contain the delivered drug and as the lipid is metabolized, the drug is released. According to a recent randomized, multicenter study of hip arthroplasty patients, DepoDur™ resulted in a significant reduction in postoperative narcotic use versus placebo as well as significantly delaying the time to first analgesic request.

Alpha2-adrenergic agonists inhibit transmission of nociceptive stimuli in the dorsal horn of the spinal cord. Their effect mimics that of noradrenalin released by inhibitory descending pathways. Noradrenaline inhibits the evoked activity of wide dynamic range neurons and causes analgesia in laboratory animals. Moreover, alpha2-agonists increase the analgesic effect of opiates and interact with cholinergic neurons to do so. They augment local anesthetic blockade as well as prolong duration. Clonidine has been used

by epidural, spinal, perineural, intraarticular, and parenteral routes to obtain postoperative analgesia. The use of clonidine via the epidural route as the sole agent to achieve analgesia cause significant, unwanted side effects such as sedation, hypotension, and bradycardia. The combination of epidural clonidine with either opioids and/or local anesthetics is more commonly used for postoperative analgesia in dose ranges between 10 and 15 mcg/kg/hr. Other medications now being utilized in an adjunctive role to improve postoperative analgesic management include lidocaine, phenergan, dextromethorphan, gabapentin, and magnesium sulfate. Many investigational trials are currently underway assessing the efficacy of these medications and to determine if they can become an effective part of an APS multimodal regimen that ultimately improves patient outcomes.

Werner et al completed a large systematic review in 2004 to determine if an APS improves postoperative outcome. The thrust of this review of the evidence on APSs is that they probably improve pain, may reduce common unwanted effects, but may result in more cases of rare but serious harm. Also, they concluded APSs probably costs more. Pain relief after surgical procedures continues to be a major medical challenge. Alleviation of pain has been given a high priority by the medical profession and the health authorities. The APS represents an instrument to improve pain relief and outcome. In the context of improved pain relief and outcome, there needs to be well defined quality criteria for the provided service. Pain relief per se did not significantly improve postoperative outcome, with the exception of patient satisfaction and pulmonary complications. Thus, postoperative morbidity and hospital stay are dependent on multiple factors, including preoperative information, quality of analgesia, and existing programs for postoperative care and rehabilitation. Therefore for an APS to improve postoperative morbidity and hospital stay, multimodal rehabilitation programs (fast-track surgery, clinical pathways) must be established in which postoperative pain relief is integrated into a rehabilitation program with early mobilization and oral nutrition, with well defined discharge criteria. Future strategies should focus on the integration of the APS and multimodal rehabilitation techniques on outcome in specific procedures. Current data suggest that a major improvement in outcome must be achieved to assure the survival of APSs in the present economic constraints in health care and the requirement for cost-effective therapeutic interventions.

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