Preemptive analgesia applied to postoperative pain management

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Acute postoperative pain can cause detrimental effects on multiple organ systems. To treat pain effectively, a thorough knowledge of the anatomy and physiology of pain and its transmission is necessary. Painful stimuli, like that produced by a surgical incision, can lead to a hyperexcitable state in the spinal cord. This hyperexcitable state can exacerbate postoperative pain. Once the hyperexcitable state has been established, a larger dose of analgesic drug is needed than if hyperexcitability had been prevented. When an analgesic is administered before the bombardment of painful stimuli that occurs with surgical incision, postoperative pain can be greatly diminished. Epidural, intravenous, and intramuscular opioids have been shown to reduce the severity of postoperative pain to a greater extent when administered before surgical stimuli rather than following it.

Key words: Central sensitization, peripheral sensitization, preemptive analgesia, primary hyperalgesia, secondary hyperalgesia.

OBJECTIVES
At the completion of this course, the reader should be able to:

1. Describe benefits to effective pain relief in addition to patient comfort.
2. Demonstrate an understanding of pain receptors and their normal functioning.
3. Describe the components of and descriptive terms associated with sensory hypersensitivity.
4. Describe the physiologic effects of pain.

5. Describe the benefits and application of preemptive analgesia.

Introduction
For many years physicians, nurses, and even patients have considered pain a normal occurrence after surgery. This attitude has sometimes resulted in delayed and inadequate treatment of pain. Postoperative pain has routinely been treated on a pro re nata (prn) basis, sometimes resulting in unnecessary patient suffering. Patient comfort should be the top priority of effective pain relief; but relieving postoperative pain also has physiologic benefits, such as a reduction in pulmonary and vascular complications.

Pain occurs due to a number of factors. Each must be considered when discussing its acute, postoperative treatment. Pain and its perception are quite variable and subjective; therefore, its treatment can be complicated. The sensation of pain can be described as excruciating, incapacitating, irritating, unpleasant, and intense. A more complete understanding of the pain mechanism mandates improvements in postoperative pain management.

When an analgesic is administered before a noxious stimulus such as a surgical incision, pain can be decreased or even prevented altogether. Administering an analgesic before a painful stimulus may simply supply pain relief before the pain, or it may reduce the formation of pain at both spinal and cerebral levels. The term “preemptive analgesia” has been coined to describe the latter phenomenon. The concept of preemptive...
analgesia dates back to at least 1913 when Crile used a combination of regional and general anesthesia to block pain transmission before a surgical incision. Crile sought to determine the causes of shock and exhaustion that often occurred during the postoperative period. He observed a decrease in heart rate, the incidence of postoperative fever, and postoperative morbidity when regional anesthesia was instituted before surgery and general anesthesia.

Since Crile’s time, many studies have demonstrated the benefits of using analgesics preemptively in an effort to block the transmission of painful stimuli from the peripheral nervous system to the central nervous system (CNS). Opioids, local anesthetics, N-methyl-D-aspartate receptor antagonists (such as ketamine), and nonsteroidal anti-inflammatory drugs have each been shown to produce preemptive analgesic effects.

**Pain receptors**

Pain is a type of somatic sensation and has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain receptors, called nociceptors, are found in the skin, periosteum, arterial walls, joint surfaces, and on the falx and tentorium of the dura mater. Nociceptors detect the quality and intensity of a noxious stimulus. Three types of stimuli activate nociceptors:

1. Mechanical stimuli produced by touch, pressure, and vibration,
2. Thermal stimuli produced by temperature changes, and
3. Chemical stimuli produced by changes in the cellular environment.

Nociceptors are termed unimodal if they respond to a single type of stimulation (mechanical, thermal, or chemical) or polymodal if they respond to more than one type of stimulus. A number of chemical substances can sensitize nociceptors resulting in inflammation and increased sensitivity; among them are prostaglandins and substance P.

Some types of sensory receptors are adaptable. Constant, unchanging stimulation results in a reduction of the information sent to the CNS. When a cutaneous touch receptor adapts, an awareness that something is touching the skin is lost until it moves or the amount of pressure being applied changes. In contrast with other types of sensory receptors, nociceptors do not adapt. This lack of adaptation can result in a state of hyperexcitability termed “hyperalgesia.” Hyperalgesia is present when the sensitivity of nociceptors increases because of excessive stimulation.

**Pain transmission**

Two general classes of pain fibers transmit impulses through the spinal cord and on to the brain. “Fast” pain is perceived within a few milliseconds and often is described as sharp or acute pain. Fast pain usually is generated by mechanical or thermal stimuli and is carried by relatively small-diameter type A delta nerve fibers at great speed. “Slow” pain is perceived within a few seconds or minutes after a noxious stimulus and often is described as aching, throbbing, or chronic pain. Slow pain is carried by even smaller type C nerve fibers at slower speeds. Slow pain is usually generated by chemical stimuli and usually involves tissue destruction.

Two divisions of the spinothalamic tract exist that are responsible for carrying pain signals to the brain: (1) the neospinothalamic tract and (2) the paleospinothalamic tract. The neospinothalamic tract contains type A delta nerve fibers and is responsible for fast pain transmission. Type A delta nerve fibers secrete the excitatory neurotransmitter glutamate, which is active for only a few milliseconds. The paleospinothalamic tract contains type C nerve fibers, which are responsible for slow, chronic pain transmission. These fibers synapse in the dorsal horn of the spinal cord in an area called the substantia gelatinosa. Substance P is a neurotransmitter in type C slow pain fibers. This slow pain tract ascends to terminate primarily within the brain stem, although a few fibers go on to the thalamus. This type of pain is poorly localized, unlike the highly localized fast pain.

**Accentuation of pain**

Pain associated with surgery can have detrimental effects on the human body. Postoperative pain is a result of direct stimulation and manipulation of tissue and the resulting mediators of inflammation that are produced. Numerous studies have been conducted into the various mechanisms of pain production and enhancement. Pain is accentuated through peripheral and central means and through the development of a state of sensory hypersensitivity.

- Sensory hypersensitivity. Woolf categorized pain as physiologic or clinical. Physiologic pain is considered protective and has a stimulus–response relationship; the greater the stimulus, the greater the pain to a certain threshold. Myelinated A delta and unmyelinated C fibers carry the impulses that convey the sensation of physiologic pain, and their nociceptors require intense and noxious stimuli to initiate a painful response. The stimuli responsible for producing physiologic pain are very different from the stimuli that produce innocuous sensations.

Clinical pain is divided into inflammatory pain and neuropathic pain. Neuropathic pain is the result of some type of lesion in the peripheral nervous system or the CNS. The most important difference that Woolf
points out between physiologic and inflammatory pain is that inflammatory pain is associated with sensory hypersensitivity. Sensory hypersensitivity involves 2 essential parts: hyperalgesia and allodynia.\textsuperscript{6,8-11} Hyperalgesia is characterized by a lower pain threshold or an increased response to noxious stimuli.\textsuperscript{6,8,11} Allodynia is characterized by pain being produced by a stimulus that would not normally produce it.

- **Hyperalgesia.** Hyperalgesia was studied as early as 1937 when Lewis and Pochin\textsuperscript{17} described a state of increased sensitivity that occurred in the undamaged skin that surrounded an area of tissue damage. They proposed that although hyperalgesia occurred in the injured area (primary hyperalgesia), it also could occur in the undamaged tissue surrounding the injured area (secondary hyperalgesia). They believed that this secondary hyperalgesia was a result of continuous input from stimulation near the injured area and was not produced in the CNS. Years later, Hardy et al\textsuperscript{18} conducted a similar study but came up with different results. They concluded that there was a central mechanism that produced this secondary hyperalgesia.\textsuperscript{18,19} More recent studies have confirmed that there are 2 distinct mechanisms that produce the change in sensitivity found in the hyperalgesic state: a peripheral and a central hypersensitivity.\textsuperscript{6,8-13}

- **Peripheral sensitization.** Peripheral sensitization is the first mechanism involved in the production of hyperalgesia when the body initiates the inflammatory process.\textsuperscript{6,8-13} Once tissue injury has occurred, the area within the injury exhibits primary hyperalgesia, while the uninjured tissue surrounding the injury exhibits secondary hyperalgesia.\textsuperscript{17} The area of primary hyperalgesia becomes very sensitive to thermal and mechanical stimuli, while the uninjured area becomes sensitive exclusively to mechanical stimuli.\textsuperscript{12} An increase in sensitivity of nociceptors enables a low-intensity stimulus to cause pain (allodynia).\textsuperscript{5,8} Thermal receptors produce a greater change in response to stimuli than do mechanical receptors.\textsuperscript{13}

- **Central sensitization.** An injury in the peripheral nervous system can change the way the CNS responds to stimuli. This concept is known as central sensitization.\textsuperscript{6,8,11,19} Lamotte et al\textsuperscript{12} described central sensitization as a change in neuron excitability produced by injury that sensitizes neurons in the dorsal horn of the spinal cord. They found that afferent input could change the way that spinal sensory neurons responded and that this change could last for a long time. The change persisted even after local anesthetic was injected into the injured tissue. The hypersensitivity produced by central sensitization is abnormal. Pain is produced by low-intensity stimulation that normally does not produce pain, and the hypersensitivity usually outlasts the duration of the initial injury.\textsuperscript{6,8,14}

Essentially, central sensitization involves a change in the way the spinal cord interprets noxious input leading to disturbances of sensory perception. To demonstrate that the CNS was involved, Lamotte et al\textsuperscript{12} injected capsaicin into an area of anesthetized skin on the forearm. Capsaicin is the algesic substance found in hot chili peppers. None of the subjects developed any hyperalgesia around the area of capsaicin injection within the anesthetized area. Subjects who received an injection of capsaicin in an unanesthetized area developed hyperalgesia surrounding the injection site. Since no area of hyperalgesia was produced in the anesthetized area, Lamotte et al believe that the neurons were sensitized in the CNS.\textsuperscript{12}

### Pain modulation

The central nervous system contains morphine-like neurotransmitters that are capable of reducing the perception of pain. These opioid-like substances include endorphin, met-enkephalin, leu-enkephalin, and dynorphin. They reduce both the brain’s transmission of pain impulses and the perception of these pain impulses. Receptors for these pain-inhibiting substances are located in the periaqueductal gray and periventricular areas of the brain near the third and fourth cerebral ventricles and in the substantia gelatinosa of the spinal cord (within the dorsal horn). Exogenous opioids, such as morphine, meperidine, and fentanyl, occupy these same receptors and produce substantial analgesia.

Transmission of pain impulses is also modified by inhibitory neurons descending from the brain. One such inhibitory pathway originates in the periaqueductal gray area and the reticular formation and descends to synapse with spinal interneurons to alter the transmission of noxious stimuli. Activation of this pathway inhibits the transmission of pain impulses through the dorsal horn of the spinal cord to the brain.

### Pathophysiology of pain

Postoperative pain has deleterious effects on the body and results in organ dysfunction when allowed to persist. Historically, pain management practices have too often resulted in inadequate postoperative pain relief.\textsuperscript{1,20} Patients have sometimes been apprehensive about asking for pain medication, and their expectations for pain relief have been low despite the fact that 75% have experienced moderate to severe pain.\textsuperscript{20}

- **Cardiovascular effects.** Severe pain is associated with an increase in sympathetic nervous system activity resulting in increases in heart rate, peripheral vascular resistance, blood pressure, and cardiac output. The resulting increase in myocardial oxygen demand causes myocardial ischemia in susceptible people.
Large epicardial coronary arteries have alpha receptors, and, in the presence of exaggerated sympathetic stimulation, such as occurs with severe pain, these arteries constrict. While this constriction serves a purpose in healthy hearts, in persons with coronary artery disease, epicardial coronary artery constriction greatly increases the risk of myocardial ischemia and infarction. Studies of patients with coronary artery disease who were experiencing pain have demonstrated unfavorable effects on the myocardial oxygen supply/demand ratio. Severe postoperative pain and sympathetic stimulation have also been associated with decreased venous return predisposing to thromboembolism.

- **Respiratory effects.** The pain that patients experience following upper abdominal and Thoracic surgery is sometimes severe enough to lead to respiratory dysfunction. Pain with breathing causes a reduction in the movement of the upper abdominal and thoracic musculature resulting in an increase in respiratory rate and a decrease in tidal volume, vital capacity, functional residual capacity, and alveolar ventilation. Hypoxemia may develop as a result. Splinting as the result of pain discourages the patient from coughing and clearing secretions. This contributes to a substantial increase in the incidence of postoperative atelectasis and pneumonia.

- **Gastrointestinal and genitourinary effects.** Pain causes an increase in intestinal secretions and sphincter tone, which often leads to the development of, or slows recovery from, paralytic ileus. Urinary retention is common postoperatively in part because increased sympathetic stimulation increases urinary sphincter tone.

- **Endocrine effects.** The effects of surgical stress on the endocrine system have been studied extensively. Numerous changes occur in the endocrine system as a result of the continuous noxious stimuli that is often associated with postoperative pain. Catabolism is enhanced by hormones, such as adrenocorticotrophic hormone (ACTH), cortisol, catecholamines, antidiuretic hormone, angiotensin II, aldosterone, and glucagon, the levels of which can be increased substantially by pain. Proteins and lipids are broken down, resulting in hyperglycemia. An increase in aldosterone and antidiuretic hormone results in water retention and a shift of water from the intracellular to the extracellular space. Hyperglycemia and increased cortisol levels increase the chances of postoperative infection and produce immunosuppression.

**Pain and postoperative complications**

Some postoperative complications can be reduced in magnitude or prevented if proper analgesia is provided. For example, in a study of 30 grossly obese patients who underwent gastroplasty, a comparison was made between epidural and intramuscular (IM) morphine for analgesia. Postoperative pulmonary function, the incidence of deep venous thrombosis, gastrointestinal motility, analgesia, and duration of hospital stay were observed. Peak expiratory flows were better in the epidural group. Only 3 patients, all from the IM morphine group, developed signs consistent with thrombosis in the calf and thigh area postoperatively. There was no evidence of deep venous thrombosis preoperatively in either group. Gastrointestinal motility improved more quickly in the epidural morphine group, and the time to first ambulation was shorter. An average total of 66.1 mg (± 6.4 mg) of IM morphine was used compared with 9.3 mg (± 1.2 mg) of epidural morphine (P<.001). The IM morphine group required a longer postoperative hospitalization than the epidural morphine group. Earlier recovery of peak expiratory flow and bowel function led to a decreased length of stay for patients in the epidural morphine group. These patients were also more mobile and had better pain control.

**Preemptive analgesia**

Under some circumstances, when an analgesic is administered before a painful stimulus, the subsequent perception of pain is prevented, delayed, or reduced to a greater extent than if the analgesic had been administered after the stimulus. This effect is termed **preemptive analgesia.**

Formalin injected subcutaneously into a rat’s paw produces a state of sensory hyperexcitability. In 1 group, opioids were administered intrathecally before the formalin injection, while in another group, they were administered after formalin injection. Rats pretreated with spinal opioids had a 70% inhibition of sensory nerve stimulation compared with the group that received spinal morphine after the formalin injection. In surgical terms, if the sensory hyperexcitability that follows surgical incision can be prevented with preemptive analgesia, postoperative pain may be reduced substantially. Woolf and Wall determined that treatment became less effective and more opioid was needed if sensory hyperexcitability was allowed to develop before treatment with opioids was begun. The dose of morphine needed to prevent central hypersensitivity is one tenth the dose needed to produce analgesia once the hypersensitivity is produced.

- **Efficacy of preemptive analgesia.** Opioids have been studied extensively for their preemptive analgesic effect by observing postoperative pain scores and by determining the amount of postoperative analgesics that patients require. The need to prevent or reduce both a peripheral and a central component of sensory hypersensitivity has been clearly identified.

Preemptive epidural morphine, compared with epidural morphine administered at the completion of
surgery, has been shown to prolong the time to first patient request for supplemental analgesics. In patients who underwent lumbar laminectomy, the first request for pain medicine averaged 19.9 ± 2.3 hours after surgery in those who received their epidural morphine preoperatively versus 8.5 ± 1 hour in those who had received it after operation (P<.05). This is especially interesting because intuitively, it would seem that analgesia would last longer in the group given morphine the latest. Other studies have yielded similar results with combinations of epidural morphine and ketamine.

Katz et al studied 30 patients scheduled for elective thoracic surgery. They compared epidural opioid administered before and after skin incision. Epidural fentanyl was administered to one group before incision, while the other group received epidural fentanyl 15 minutes after incision. Postoperative visual analog pain scores were lower in the group that received epidural fentanyl before incision compared with those in the postincision group (P<.05). The postincision group also required significantly more intravenous morphine as rescue medication, an average of 26.1 mg versus 11.7 mg (P<.008). Preemptive analgesia reduced the sensory hypersensitivity associated with incision and rib retraction. Epidural fentanyl was more effective in decreasing postoperative pain when given before skin incision.

Preemptive administration of both intravenous and intramuscular morphine has been shown to decrease postoperative pain and analgesic requirement. Sixty women undergoing total abdominal hysterectomy were divided into 3 groups. Group 1 received 10 mg of morphine IM 1 hour before surgery. Group 2 received 10 mg of morphine intravenously with the induction of general anesthesia. Group 3 received 10 mg of morphine intravenously during closure of the surgical wound. On average, a significantly lower dose of intravenous morphine was needed for postoperative analgesia in group 2 than in group 3 (38.4 mg versus 48.3 mg; P<.05). The intensity of postoperative pain experienced was significantly higher in group 3 patients than in patients in either group that received morphine before skin incision (P<.05). Preemptive analgesia with intravenous morphine reduced postoperative analgesic requirements and pain scores. Similar effects have been produced using preemptive ketamine in place of morphine.

Tverskoy et al hypothesized that when induction of general anesthesia included fentanyl or ketamine (a nonopioid anesthetic and analgesic) in addition to thiopental sodium, postoperative pain and wound hyperalgesia would be reduced compared with induction of general anesthesia with thiopental alone. Patients who received only thiopental required much more meperidine for postoperative analgesia (mean, 108 ± 14 mg) than those who received either fentanyl (50 ± 9 mg; P<.001) or ketamine (58 ± 8 mg; P<.003) in addition to thiopental for induction of general anesthesia. Patients who received fentanyl or ketamine at induction had a higher pain threshold compared with patients who received only thiopental. This suggests a preemptive analgesic effect for fentanyl and ketamine when administered at the induction of general anesthesia.

Conclusion

Painful invasive and diagnostic procedures initiate noxious afferent stimuli that sensitize both the peripheral nervous system and the CNS. This sensitization increases the perceived intensity of pain occurring after the event. There is evidence that preventing this neural sensitization reduces the pain experienced after the procedure. In effect, pain can be treated more effectively before it starts than after. Once begun, pain is an ongoing process and should be treated as long as the inflammatory process continues. Many studies using opioids preemptively have shown reductions in the magnitude of postoperative pain.

Opioids are, however, just one of many classes of drugs that have been studied for their preemptive analgesic effect. Local anesthetics, nonsteroidal anti-inflammatory drugs, and N-methyl-D-aspartate receptor antagonists have also been shown to produce preemptive analgesia.

A thorough knowledge of the many complex mechanisms involved in pain generation, perception, and treatment empowers anesthetists to develop and implement the most effective pain management strategies possible. Understanding and applying the concept of preemptive analgesia has the potential for improving the management of pain.

REFERENCES


AUTHORS
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