



Mechanisms of Acute Pain: An Update

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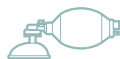
ABSTRACT

Dentists are faced with human suffering generated by dental diseases and their treatments on a daily basis. This exposure to suffering has resulted in the dental practitioner's constant pursuit of more efficacious ways to decrease their patient's acute pain experience. Expertise in the administration of local anesthetics and the use of nitrous oxide/oxygen inhalation sedation were born from this pursuit. Advances in the management of acute pain will follow an improved understanding of the physiology of acute pain, the physiology of the immune system and their interaction. Indeed, their interaction has become a productive area of investigation. This article reports on promising new developments in acute pain research. Our current understanding offers a few new recommendations and a vision of a less painful experience associated with dental diseases and their treatments.

Many may remember the introduction of Melzack and Wall's groundbreaking theory that the brain could modulate incoming pain perception, the so-called "gate control" theory.¹ Because of that well-known article published in 1965, general interest as well as directed research into pain increased through the next four decades. Research funding organizations increased their focus on the treatment of acute pain even more after the Agency for Healthcare Policy and Research, publicized its clinical practice guidelines in 1992.² The American Society of Anesthesiologists, a large organization of physician anesthesiologists, also played a leadership role by developing, publishing, and later revising practice guidelines for acute pain management.³ In 2001, the Joint Commission on Accreditation of Healthcare Organizations, stipulated that all health care institutions seeking future accreditation would be required to have an acute pain management program.⁴ Thus, JACHO provided a major stimulus for clinical programs, as well as research interest and funding. As part of the new accreditation standards, JCAHO established patient satisfaction as a major goal for health care institutions.



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Declarations of the patient preferences in pain management and a postoperative patient evaluation protocol have now been incorporated into hospital policies. Reprioritization of the patient's pain experience in the perioperative period and the associated data collection have dramatically increased institutional interest in generating a positive patient surgical/recovery experience.

Advances in Our Understanding of Pain

Several advances in the understanding of the physiology of pain are helping to optimize the treatment of acute pain and have suggested an expansion of research into pain. These advances are so fundamental they require changes in the teaching of physiology and pharmacology in dental and medical education.

Peripheral Sensitization

Any surgery can be presumed to be a planned injury to the body. The injury may actually be secondary to the use of lasers, electrocautery, heat from dental drills, cutting of tissues, suturing, and retraction at the surgical site. When any injury is inflicted, free nerve endings and nonspecific receptors (nociceptors) are stimulated. The injury also causes the local release of inflammatory agents, as well as local sympathetic amines that have the ability to lower the threshold of stimulation and shorten the latency of activation of those free nerve endings and nociceptors initially stimulated by the injury. Some of the inflammatory agents stimulate and sensitize, while others only stimulate. The clinical outcome is that one may see an exaggerated pain response to a repeated pain

stimulus, or even spontaneous pain with no obvious stimulus at all.

Peripheral sensitization helps one understand why the light touching of a healing wound can elicit a very painful response (primary hyperalgesia). Also, it helps one understand why a painful response can be elicited by touching apparently normal tissue adjacent to a wound (secondary hyperalgesia). Another consequence of peripheral sensitization is the recruitment of nerves to pain conduction that are not normally used to send pain signals to the central nervous system. Some of these nerves do not pass through the parts of the spinal cord (i.e., specific laminae of the dorsal horn) that modulate pain. Hence, the central nervous system receives even more pain signals from the periphery; and central sensitization may ensue.⁵

Nociceptor activation in the perioral tissues is not conducted to the dorsal horn of the spinal cord. Rather, the transmission of pain is primarily to the medulla of the brainstem (i.e., nucleus caudalis) with nociception conducted in afferent portions of the trigeminal nerve with some additional afferent activity occurring in the seventh, ninth and 10th cranial nerves. Once in the brainstem, the noxious information is treated similarly to that received by the dorsal horn of the spinal cord.⁶

Central Sensitization

Acute peripheral pain signals cause changes in the brain and spinal cord (i.e., central nervous system) referred to as central sensitization, also known as "wind-up." When repetitive noxious stimuli generated by peripheral injury are received at the dorsal horn of the spinal cord, it causes a "conditioning"

of the central nervous system such that there is enhanced pain responsiveness to future noxious or painful stimuli. It is believed that central sensitization can long outlast the original peripheral pain stimulus. It is interesting to note that general anesthesia does not inhibit central sensitization.⁵

Pain and Surgical Outcomes

Processing of peripheral pain stimulation in the central nervous system provokes spinal reflex activity, such as muscle spasm and sympathetic nervous system activity. In addition, supraspinal reflexes appear to initiate something called the Surgical Stress Response, SSR, that peaks in the postoperative period. It is generally felt that this stress response can cause or contribute to many, sometimes serious, postsurgical complications. It has a negative impact on the cardiac, coagulation, and immune systems. When the SSR is avoided as it can be by utilizing the acute pain management concepts discussed in this article, patients have fewer complications and are discharged from the hospital earlier.^{7,8}

It is interesting that placement of local anesthetics in the area of surgery does not inhibit the stress-related mediators from being released into the bloodstream. However, despite the release of the pain mediators into the bloodstream, using local anesthetics to block pain stimuli from the site of surgery appears to reduce or eliminate central sensitization and the SSR. In summary, acute postoperative pain can cause recovery complications associated with the cardiovascular, pulmonary, renal, endocrine, immune, and gastrointestinal systems, and thereby delay release from the hospital and prolong recovery.⁵

LIDOCAINE WAS ALSO DISCOVERED TO REDUCE CARDIAC ARRHYTHMIAS LONG AFTER ITS INTRODUCTION AS A LOCAL ANESTHETIC.

Lidocaine: A Local Anesthetic or an Anti-inflammatory?

Both! One of the striking pharmacologic discoveries in recent years is that the group of drugs known as local anesthetics also have important anti-inflammatory properties.^{9,10} The way that local anesthetics produce anti-inflammatory effects is not clear. They appear to decrease the movement of leukocytes from the blood to the site of injury. More specifically, local anesthetics decrease leukocyte adhesion to the endothelium of blood vessels, as well as the ability of the leukocytes to cross the endothelium of blood vessels.¹⁰ Local anesthetics have also been found to reduce vascular permeability and thus, fluid losses in the obstructed bowel and in experimentally induced lung injury. However, intravenous application has been less efficacious than topical application. We will have to wait for future studies of local anesthetics as anti-inflammatory agents to realize their mechanism of action and their possible therapeutic applications. It is interesting to note that lidocaine was also discovered to reduce cardiac arrhythmias long after its introduction as a local anesthetic.

Evidence That NSAIDs Act in the Spinal Cord

Aspirin, although a nonsteroidal anti-inflammatory agent, is frequently excluded from the large group of recently discovered and marketed NSAIDs (e.g. ibuprofen) due to its higher incidence of side effects, which include epigastric distress, nausea, ulceration of the stomach and vomiting. In addition, the non-aspirin NSAIDs appear to be more efficacious as pain relievers than aspirin.⁶ In this discussion, aspirin has been excluded from the group of NSAIDs.

It has been widely believed that the NSAIDs acted only on receptors that were located in the periphery. The NSAIDs reduce the synthesis of prostaglandins, which sensitized peripheral nociceptors.⁶ It is now known that the so-called COX-1 receptors for NSAIDs are also located in the spinal cord, and effective analgesia of NSAIDs in that location has been documented. In fact, it is not only believed that the NSAIDs work in the spinal cord, but that this site of action may be more clinically significant than the peripheral sites of action.¹¹ In the future, NSAIDs may also be used in epidurals and spinals as are opioids and local anesthetics.

Opioid Receptors in the Peripheral Nervous System

Opioid receptor distribution has been thought of as limited to the central nervous system and some have believed only in the brain. It is now known that opioid receptors also exist in the peripheral nervous system on sensory afferent neurons.¹² There is an increasing body of literature that supports the injection or infiltration of opioids at a surgical site to achieve clinically significant analgesia.¹³ Peripheral nerve opioid receptors are up-regulated in the presence of inflammation. Up-regulation takes place by axonal transport to the periphery of opioid receptors synthesized in the dorsal root ganglia.¹²

Immune Cells Synthesize Opioids

Endogenous opioid synthesis (only peptide opioids are synthesized in the body) has historically been attributed to parts of the brain or brainstem. One of the more intriguing discoveries is that circulating immune cells that migrate to sites of injury can synthesize and release opioid peptides.^{12,14} It

is noteworthy that peripherally synthesized peptide opioids appear to be devoid of the side effects of centrally acting exogenous opioids (e.g., nausea/vomiting, respiratory depression, constipation and sedation).

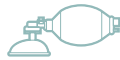
Opioid receptors are also found on immune cells. Opioid modulation of the proliferation of these immune cells and their functions has been reported.¹² These actions may be stimulatory or inhibitory. The role and importance of these findings to pain physiology has not yet been established. We can look forward to research into the therapeutic use of peptide opioids because they are unable to cross the blood-brain barrier and therefore may not have the well-known side effects of currently used opioids.

Clinical Implications of Our Current Understanding of Pain Mechanisms

When a patient arrives at the dental office with pain of dental origin, the practitioner must first decide whether the pain is associated with an infection. If so, the patient needs an appropriate antibiotic and acute pain therapy. An anti-inflammatory analgesic would be appropriate in light of the inflammation that accompanies infections, and a narcotic can be added if pain is judged to be moderate to severe. If the pain is solely of an inflammatory nature (e.g., a recent tooth fracture not involving the pulp), then an NSAID would be the drug of choice in order to reduce developing inflammation. However, the optimal time to implement acute pain management occurs before pain has started (as we encounter in postoperative pain).

Routine Nonsurgical Dental Treatments

Oral NSAIDs are the first choice of therapy for post-treatment pain



of nonsurgical origin assuming no contraindication.⁶ Most pain generated by procedures in this group will be adequately managed without the addition of other agents. Using an NSAID that can be given twice a day rather than the 4 to 5 times a day for some agents may improve patient compliance and thereby the result. It is optimum to take the medication before pain begins to minimize peripheral sensitization and avoid central sensitization. Therefore, taking the NSAID just before a short (one-half hour or less) procedure or just after a longer procedure is simply good planning to obtain the blood level of the NSAID when it is needed. Other analgesics (acetaminophen and opioids) should be used only as an added rescue analgesic or when NSAIDs are contraindicated.⁶

Routine Dental Procedures and General Anesthesia

If general anesthesia is to be employed as in treating the handicapped patient, a single administration of intramuscular ketorolac may be preferred because the immediate need for patient cooperation is obviated. The patient can be started on oral NSAIDs (if they will comply) six hours after surgery.

Surgical Procedures Causing Moderate to Severe Postoperative Pain

In the patient that is having surgery that is expected to cause moderate to severe postoperative pain, the infiltration of local anesthetics into the surgical site at the beginning of treatment (to provide anti-inflammatory effects) as well as a conventional regional block (e.g. an inferior alveolar block if appropriate) with a long-acting local anesthetic can provide a decreased pain

experience for days.⁶ If the procedure is long enough, infiltration and block may need to be repeated. The local anesthetic management is indicated whether or not general anesthesia is utilized during the treatment. Upon completion of surgery, an NSAID regimen should be instituted as soon as possible before the patient experiences pain. If general anesthesia is utilized, a single intramuscular dose of ketorolac may obviate the need for patient compliance and then the practitioner can institute a regimen of orally administered NSAIDs.

In order to be optimally prepared to minimize the pain and suffering from dental disease and dental treatments, dentists need to monitor future developments in acute pain control as well as developments in the management of inflammation.

Summary

We now know that advances in acute pain management will require a better understanding of the physiology of acute pain as well as a better understanding of the physiology of the immune system. Pain and inflammation are observed after tissue injury secondary to both disease and surgery. Our understanding of pain physiology and immune system physiology is growing at a rapid pace. Novel and more efficacious approaches to the treatment of acute pain will surely follow. ■■■■

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