

Is There a Link Between Acute Pain and Chronic Pain?

James P Rathmell, MD

Pain is a normal physiologic response to injury. The presence of pain signals impending tissue injury and signals the need to protect the injured area during healing. Under some circumstances, pain persists after all tissue has healed. We now have a detailed understanding of the physiologic mechanisms that are responsible for the initial perception of acute pain and the neuronal changes that rapidly lead to an increase in sensitivity of the injured region. At the same time, efforts to use combinations of analgesics and analgesic techniques including regional analgesia have been closely studied and shown to provide excellent pain relief. Despite our best efforts, some patients go on suffer from long-term chronic pain after the acute event. In this review, we will examine the basic physiologic mechanisms that lead to the perception of acute pain, our current understanding of the neuronal mechanisms that produce sensitization immediately after injury, and the risk factors that are associated with persistent pain after surgery. Our discussion will include an examination of the role for specific analgesic techniques in improving pain control in the immediate postoperative period and how we might identify those at greatest risk for persistent pain and develop analgesic regimens most likely to minimize the risk of persistent pain.

SENSITIZATION AND THE PROMISE OF PREEMPTIVE ANALGESIA

Pain is produced by physical, thermal, or chemical stimuli that can potentially induce tissue injury. Between the site of the stimulus and pain perception, a complex sequence of electrochemical events take place, which are collectively called nociception (Figure 1). Different stimuli can lead to the perception of pain. These include mechanical, thermal, and chemical stimuli. Mechanical forces, heat, and chemical changes result in increased firing in nerve terminals within tissue, this process is referred to as transduction. Afferent axons carry signals from the site of peripheral stimulation toward the spinal cord where the signals are relayed to higher centers within the central nervous system. This process is called transmission. The magnitude of incoming nociceptive traffic reaching the central nervous system can be modified before reaching higher centers, a process termed modulation. Stimulation of the periaqueductal gray region within the midbrain and the periventricular gray matter lateral to the hypothalamus produces profound analgesia in humans. These regions have been found to contain high concentrations of endogenous opioid neurotransmitters. The periventricular gray matter and the periaqueductal gray matter are interconnected and also connect anatomically with the rostroventral medulla. The rostroventral medulla sends descending projections via the dorsolateral funiculus to the dorsal horn of the spinal cord. Norepinephrine, serotonin, and systemically administered opioids all likely produce their nociceptive effects through activation of these descending inhibitory pathways.

Preclinical studies have demonstrated that peripheral injuries can trigger long-lasting increases in the excitability

of neurons, a process termed sensitization. This occurs both at the level of the primary afferent nociceptive peripheral neuron (peripheral sensitization) and the dorsal horn of the spinal cord (central sensitization). This is manifest as a reduction in the threshold for activation of nociceptive neurons; subsequently normally nonpainful stimuli are perceived as painful (allodynia) and minor painful stimuli now produce severe and long-lasting pain (hyperalgesia). This increase in gain in the nervous system, the sensitization, serves as a normal and protective response to injury. The sensitization is a reminder that the injured area needs to be protected to allow the tissue injury to proceed without interruption from repeated injury. In the absence of pain, like that seen in diabetics with loss of normal peripheral sensation who suffer from poorly healing ulcers in the extremities, recurrent injury goes unnoticed, healing is poor, and amputation of affected digits is common.

Under most circumstances, as injured tissue heals, sensitization gradually diminishes toward normal sensation. Nonetheless, persistent pain after injury is common. When pain persists along with the characteristics of sensitization after all tissue injury has healed, we call it neuropathic pain. The notion that the sudden barrage of incoming nociceptive traffic reaching the spinal cord is what leads to sensitization and that by applying an analgesic intervention before the traumatic event (surgical incision) we might reduce or even eliminate nociceptive traffic is what led to the concept of preemptive analgesia. We know when and where the surgical incision will take place. Can we reduce acute pain and maybe even prevent chronic pain from developing by giving an analgesic or performing a nerve block before the incision is made?

CLINICAL STUDIES OF PREEMPTIVE ANALGESIA

The term “preemptive preoperative analgesia” was coined in 1988 by Patrick Wall¹ and the road to using this concept of preemptive analgesia to reduce the magnitude and duration of postoperative pain was paved in 1983 by Clifford Woolf,² who showed evidence for a central component of postinjury pain hypersensitivity in experimental studies. It is now more than two decades since

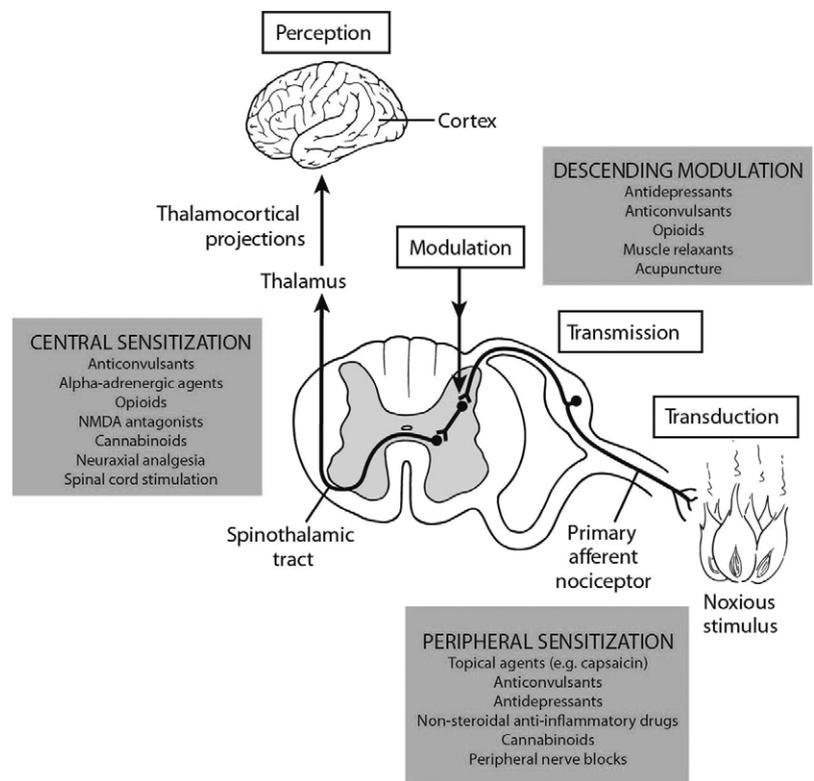
Accepted for publication April 30, 2013.

Conflict of Interest: Nothing to disclose.

Executive Vice Chair, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Henry Knowles Beecher Professor of Anaesthesia, Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts.

Copyright © 2013 International Anesthesia Research Society

Figure 1. Schematic representation of nociception: the normal physiologic processes that lead to pain perception. Sites where specific analgesics may modify normal pain perception and sensitized neuronal structures are shown.



the concept of preemptive analgesia was put forward; the concept has been tested with different analgesics across many types of surgery. The basic approach is simple: randomize patients undergoing a specific type of surgery to receive the analgesic either before incision or at some time after the incision is made and measure their overall pain experience by following self-reported pain scores and/or supplemental analgesic use in the postoperative period. There are now more than 100 such trials of preemptive analgesia and numerous reviews. Two meta-analyses that appeared toward the end of the decade-long international focus on preemptive analgesia attempted to summarize the findings and both came away with less than exuberant enthusiasm for this approach. The first meta-analysis appeared in 2002;³ this group identified 80 randomized clinical trials of preincisional versus postincisional analgesic regimens for postoperative pain control conducted in 3,761 patients in total. The studies included 20 trials of systemic nonsteroidal antiinflammatory drugs (NSAIDs), 8 trials of systemic opioids, 8 trials of systemic N-methyl-d-aspartate receptor antagonists, 24 trials of epidural, caudal, or intrathecal analgesia, and 20 trials of peripheral local anesthetic use (wound infiltration or nerve block) or combinations of treatment. They rigorously defined successful preemptive analgesia as a weighted mean difference in the total sum of pain scores during the first 24 hours after surgery and they also examined total supplemental analgesic use during the same time period. They concluded that statistical improvements in postoperative pain relief were observed in some parameters or time points in 24 of 80 (82 treatment arms) trials when preemptive analgesia was compared with postoperative analgesia. However, no evidence for preemptive treatment

with NSAIDs, IV opioids, IV ketamine, peripheral local anesthetics, and caudal analgesia to be of any benefit with respect to postoperative pain relief compared with a similar postincisional treatment. More than half of the trials of single-dose epidural treatment showed statistically significant but small and clinically unimportant improvements with preemptive analgesia.

A subsequent meta-analysis by Ong et al. appeared in 2005,⁴ examining much the same group of studies examined by Moniche et al. in their 2002 publication. Sixty-six studies with data from 3,261 patients were analyzed. Three primary outcome measures were analyzed by this group: pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption. In contrast to Moniche et al. who summed all pain scores during the first 24 postoperative hours, Ong et al. accepted reduction in a single pain scores at any point in time after surgery to represent significant preemptive analgesia. When the data from all three outcome measures were combined, they concluded that preemptive administration of epidural analgesia, local anesthetic wound infiltration, and NSAID administration all provided significant preemptive effects. Epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. Are these two major reviews at odds with one another? No, they simply defined a significant preemptive effect in differing ways: Moniche et al. used the more rigorous criteria of pain scores summed over the first 24 hours after surgery, perhaps a better measure of a truly meaningful clinical effect. While there may be statistically significant reductions in pain

scores and supplemental analgesic use after surgery with use of a preemptive analgesic approach, these differences are small and are unlikely to impact on the patient's overall pain experience. The largest differences appear early after emergence from anesthesia in the first few hours after surgery: if a preemptive approach was used, patients were more likely to emerge from anesthesia with good pain control. Perhaps the take-home message from this enormous body of work is simply that anesthesiologists should not wait until after emergence to begin, by whatever route is chosen, to administer analgesics.

Why doesn't preemptive analgesia work? In a recent review, Katz et al.⁵ take us through the history of preemptive analgesia and posit a number of reasons that the overly simplistic approach of administering a single analgesic just before surgical incision is so inadequate in improving postoperative analgesia and other outcomes. They tell us that the classic view of preemptive analgesia assumes that intraoperative painful stimuli contribute to postoperative pain more than postoperative stimuli. But, experimental studies demonstrate that sensitization is caused by factors other than the incision and subsequent intraoperative events alone. Our focus should shift to reducing the impact of noxious preoperative, intraoperative, and postoperative events.

PERSISTENT POSTSURGICAL PAIN: RISK FACTORS AND PREVENTION

When pain persists for more than 3 to 6 months after surgery, normal postsurgical healing is complete, and there is no alternate ongoing process (e.g. infection) to explain the ongoing pain, persistent postsurgical pain (PPP) is present.⁶ PPP is surprisingly common after many of the most frequently performed surgeries (Table 1).

We know much about the preoperative risk factors that are predictive of the appearance of PPP. Risk factors include the magnitude and location of the surgical insult, genetic susceptibility, preceding pain, psychosocial factors, age and gender. Indeed, recent studies clearly demonstrate that patients with specific single nucleotide polymorphisms have a genetically conferred resistance to both acute and chronic pain.⁷ Despite advances in our understanding of what leads to persistent pain after surgery and the ease with which we can identify those at greatest risk, it is unclear how best to approach the management of pain during the perioperative period in a way that will minimize the risk of persistent pain.

FROM PREEMPTIVE TO PREVENTATIVE ANALGESIA

The limited approach provided by preemptive analgesia, simply providing the analgesic before the incision is made, may minimally improve pain relief, but is unlikely to reduce the incidence of persistent pain after surgery. The concept of preventative analgesia has emerged during the past few years. The idea is to combine a number of different analgesics with mechanisms that differ and that may well impact directly on the mechanisms behind development of persistent pain in efforts to improve postoperative pain control and prevent the development of persistent pain.⁴ A few trials suggesting that such a preventative approach may be effective have appeared. Lavand'homme et al.⁸ randomized patients undergoing colectomy to receive a combination of analgesics including local anesthetics, opioids, and clonidine IV or via neuraxial administration and examined the effect on postoperative hyperalgesia surrounding the surgical incision as well as persistent pain as far as 12 months after surgery. The use of epidural analgesia as part of a multimodal regimen dramatically reduced the incidence of persistent pain at 12 months after surgery, suggesting that this multipronged, preventative approach might well improve on the original concept of preemptive analgesia. Subsequent clinical trials using the same approach have yielded conflicting results. Buvanendran et al.⁹ demonstrated that the use of oral pregabalin during the immediate perioperative period in patients undergoing total joint replacement reduced the incidence of persistent pain several months after surgery, again emphasizing that specific analgesics continued through the perioperative period might well reduce the long-term problem of PPP. These small, preliminary studies show promise, but need confirmation through large-scale, multicenter trials.

FUTURE DIRECTIONS

Major trials are now underway that incorporate prospective identification of risk factors into analgesic trials. If we identify high-risk patients through genetic screening or by specific characteristics known to correlate with the development of persistent pain after surgery, will we be able to modify the outcome? As anesthesiologists in practice today, we can do nothing more than design the very best analgesic regimens with the tools we have at hand (regional anesthesia, systemic opioids and adjuvant analgesics) and trust that our efforts will succeed. When our initial approach proves inadequate, we should rapidly shift gears and provide

Table 1. Estimated incidence of chronic postoperative pain and disability after selected surgical procedures (adapted with permission from Reference 6). †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	United States surgical volumes (1000s)†
Amputation	30 – 50%	5 – 10%	159 (lower limb only)
Breast surgery (mastectomy and lumpectomy)	20 – 30%	5 – 10%	479
Thoracotomy	30 – 40%	10%	Unknown
Inguinal hernia repair	10%	2 – 4%	609
Coronary artery bypass surgery	30 – 50%	5 – 10%	598
Cesarean delivery	10%	4%	220

analgesia through some alternate means; removing and replacing a nonfunctioning epidural promptly or switching to IV opioids as quickly as possible to avoid periods of prolonged inadequate analgesia. In the very near term, we are likely to gain a better understanding of how to take those identified as at high risk for a poor pain experience and combine our existing analgesic approaches into a tailor-fit prescription for each patient that will minimize the chances of poor analgesia and persistent pain.

REFERENCES

1. Wall PD. The prevention of postoperative pain. *Pain* 1988;33:289–90
2. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983;306:686–8
3. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002;96:725–41
4. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* 2005;100:757–73, table of contents
5. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? *Anesth Analg* 2011;113:1242–53
6. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618–25
7. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejm J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lötsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* 2006;12:1269–77
8. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* 2005;103:813–20
9. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010;110:199–207