The Link Between Acute and Chronic Pain

James P. Rathmell, MD
Vice Chair and Chief, Division of Pain Medicine
Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital
Professor of Anaesthesia, Harvard Medical School
Boston, Massachusetts, USA

OVERVIEW
Pain is a normal response to injury. There are specific anatomic and physiologic changes that ensue immediately following tissue damage that remind us to protect the injured area until the injury has healed. Normally, these changes abate as the tissue heals. But these same changes persist in some individuals long after all healing has occurred in the form of chronic pain. It is clear that a period of acute pain always precedes the development of chronic pain. But it is unclear what leads to persistent pain after injury in some individuals and complete healing without residual pain in others. Initial attempts to reduce postoperative pain and lower the chance of chronic pain took the form of administering analgesics “preemptively”, prior to the anticipated surgical insult. This approach has been disappointing. At the same time, we have come to learn that persistent pain after surgery or other traumatic injuries is surprisingly common after most common types of surgery. We are now starting to see trials of specific analgesic regimens aimed at preventing the transition from acute to chronic pain, examining patients at long term follow up. This refresher course lecture will review our current understanding of the anatomy and physiology of pain, discuss the extensive evidence that suggests that a preemptive approach to providing analgesia has proven disappointing, detail the specific risk factors that are linked with the development of chronic pain after surgery, and examine the current trends toward employing specific agents in the peri-operative period aimed at reducing the incidence of chronic pain following surgery.

THE ANATOMY OF PHYSIOLOGY OF PAIN
Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”¹. Pain is a normal, protective, physiologic response. Without pain, we are subject to repeated injury allowing injured areas to heal poorly or not at all. Diabetics who gradually lose sensation in their feet as the diabetic neuropathy progresses often develop skin ulceration. These areas heal poorly without the normal protective reminder that pain provides, often leading to amputation. Poorly healing decubitus ulcers that occur in patients who have sustained spinal cord injury are another example of the importance of normal sensation and pain in reminding us to protect injured areas so that healing can proceed without recurrent injury. Congenital insensitivity to pain is a rare condition where the affected person cannot feel physical pain. Affected individuals often develop severe infections after injury, as the initial injury goes unnoticed, eventually losing digits to recurrent injury and being subject to recurrent infections.

Much has been learned about the specific neural mechanism underlying the perception of pain and the response of the nervous system after injury. The specific neural mechanisms that lead from a harmful or potentially harmful stimulus to the perception of pain are collectively termed nociception. Nociception can be divided in to discrete events that together lead to the perception of pain (Figure 1). First, the actual or potential damaging stimulus must be converted to electrical impulses, a process known as transduction. Heat, cold, mechanical distortion, and changes in tissue pH are all stimuli that are potentially damaging to tissue and are converted to electrical impulses that travel toward the central nervous system along pain fibers. The primary organ of pain perception is the free nerve ending in the periphery. The free nerve endings convert these specific stimuli to neuronal impulses through changes in activity in specific ion channels within peripheral nerves. Following transduction, nerve pain signals travel as neuronal impulses toward the central nervous system along pain fibers. The primary organ of pain perception is the free nerve ending in the periphery. Free nerve endings convert these specific stimuli to neuronal impulses through changes in activity in specific ion channels within peripheral nerves. Following transduction, nerve pain signals travel as neuronal impulses toward the central nervous system, largely along specific nerve fibers: poorly myelinated A-delta and unmyelinated C-fibers. These signals are transmitted to the neuronal cell body within the dorsal root ganglion and then

---

¹. International Association for the Study of Pain.
along the nerve’s central projection that synapses on a second order neuron within the dorsal horn of the spinal cord. The second order neuron, in turn, sends a projection across midline to join the spinothalamic tract in the anterolateral aspect of the spinal cord. Pain signals travel cephalad in the spinothalamic tracts to reach the thalamus, the relay station which sends projection to the primary somatosensory cortex as well as various other regions within the brain. Incoming pain signals can be modulated or dampened. The endogenous opioid system acts in just this way: opioid agonists bind to receptors within the rostroventral medulla and the periaqueductal gray area of the brainstem and lead to an increase in descending inhibitory neuronal traffic that reaches that reaches the dorsal horn and reduces the amplitude of incoming pain signals. Thus, at the level of the dorsal horn where incoming nociceptive neuronal traffic enters the central nervous system, pain impulses can be modified in various ways. This is the sum of the processes that lead to the normal perception of pain.

When a barrage of nociceptive neuronal impulses reaches the dorsal horn, the activity in a specific group of second order neurons changes. Second order neurons fire more rapidly with subsequent activation (termed spinal cord wind up) and new connections develop between neurons that normally carry non-painful stimuli and those that carry pain signals. These changes in the dorsal horn are collectively called central sensitization. The net result of central sensitization is that the injured area becomes sensitized. While this sounds complex, the actual sum effect of these neuronal changes is something that we understand intuitively. Place your hand on a hot stove and you will immediately and reflexively pull your hand away from the damaging heat. Almost instantaneously after the injury, touching the area even lightly will produce a painful sensation rather than the non-painful sensation of light touch that was produced by the same stimulus before the injury. This pain to normally non-painful stimuli is termed allodynia, and it reminds us to protect the injured area until the injury has healed; sensitization is the neuronal mechanism that underlies the development of allodynia. Normally, allodynia disappears as tissue heals. But, in some individuals and after some types of injury, this sensitization persists even after all tissue healing appears to be complete in the form of neuropathic pain.

THE RISE AND FALL OF PRE-EMPTIVE ANALGESIA

Soon after the first detailed descriptions of central sensitization came the idea that blocking the barrage of nociceptive input to the dorsal horn at the time of injury might reduce the subsequent magnitude of acute pain and perhaps even reduce the likelihood of developing chronic pain. In the case of elective surgery, the location and time of the damaging tissue injury is known in advance. Thus, administering an analgesic “preemptively” prior to the surgical insult is feasible and perhaps doing so would reduce or eliminate the subsequent central sensitization by reducing the magnitude of the nociceptive input to the dorsal horn. This concept has been tested in dozens of randomized trials. Many different analgesics have been tested in this way, including non-steroidal anti-inflammatory drugs, opioid analgesics, peripheral local anesthetic infiltration, peripheral nerve blocks, and neuraxial techniques. In many such well-conducted trials, the analgesic was administered either before the surgical incision or after the surgical incision was made and patients’ subsequent pain experience was catalogued. There have been two recent meta-analyses that present the sum experience with preemptive analgesia in detail. While these two reviews reach different conclusions, a careful look at the underlying assumptions in the two analyses will lead the reader to the same conclusions. Statistical improvements in postoperative pain relief by preemptive treatment were seen at some time points in about one third of the nearly 100 trials examined, however quantitative analysis of pain scores within 24 hours after surgery were in no case significant. Thus, there is lack of evidence for any robust preemptive analgesic effect across a wide range of different surgeries using many different analgesics and analgesic combinations. Indeed, the pain relief provided by a well-functioning epidural is just as good if the epidural is dosed at the conclusion of the surgery as compared with dosing the same epidural prior to the surgical incision. The authors of one of these articles suggested that future studies should redirect focus from timing to protective analgesia, aimed at preventing pain hypersensitivity, a concept that we will explore in some detail later in this review.

Table 1 – Estimated incidence of chronic postoperative pain and disability after selected surgical procedures* (Reproduced from permission from reference 5).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Estimated incidence of chronic pain (%)</th>
<th>Estimated chronic severe pain (&gt;5 out of score of 10)</th>
<th>US surgical volumes (1000s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30-50%</td>
<td>5-10%</td>
<td>159 (lower limb only)</td>
</tr>
<tr>
<td>Breast Surgery (lumpectomy and mastectomy)</td>
<td>20-30%</td>
<td>5-10%</td>
<td>479</td>
</tr>
<tr>
<td>Thoractomy</td>
<td>30-40%</td>
<td>10%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Inguional hernia repair</td>
<td>10%</td>
<td>2-4%</td>
<td>609</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>30-50%</td>
<td>5-10%</td>
<td>598</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10%</td>
<td>4%</td>
<td>220</td>
</tr>
</tbody>
</table>

*Rheuma surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders.

†National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC PAIN

Now let us turn for a moment to the other end of the healing process. Long after surgery, after all of the injured tissue appears to have healed completely, some patients are left with persistent pain. Numerous well-conducted population surveys are now available and
they point to a disturbing conclusion. Persistent pain after surgery is common and, in a significant proportion of affected patients, the pain remains severe and disabling for months or years after surgery (Table 1). With the realization that chronic pain is common after tissue injury following trauma or surgical intervention of any kind, investigation turned toward examination of the underlying risk factors. A number of specific risk factors have been identified; among them are the magnitude of tissue injury, genetic factors leading to susceptibility to chronic pain, preceding chronic pain in any anatomic location, psychosocial factors, and age and sex (Figure 2). Much attention has been focused on modifying surgical techniques to minimize the extent of tissue injury; a turn toward endoscopic techniques with natural orifice transluminal endoscopic surgery being perhaps the ultimate development in this trend. Indeed, recent evidence has demonstrated that the incidence of persistent postsurgical pain following inguinal hernia repair is significantly lower when an endoscopic technique is used rather than an open technique. Clear and convincing evidence of the link between specific single nucleotide genetic polymorphisms and pain susceptibility has emerged. Indeed, we can now identify specific individuals who have low likelihood of severe pain following surgery and these same individuals are less likely than those without the same genetic profile to develop chronic pain. What is less clear is how to use this new information. Can we use preoperative genetic screening to effectively identify patients at high risk and somehow modify their management to minimize postoperative pain and the risk of developing chronic pain? This question remains unanswered and is the subject of intensive ongoing study.

**FROM PREEMPTIVE TO PREVENTATIVE ANALGESIA**

Extensive clinical trials have made it clear that simply providing analgesia before the surgical insult will not be enough to improve post-operative pain control or reduce the incidence of chronic pain. Why is preemptive analgesia insufficient? The precise reasons that our current approaches to providing preemptive analgesia are inadequate are unclear, but several hypotheses have emerged. The first is readily apparent. None of the many different approaches to providing preemptive analgesia can completely eliminate the barrage of nociceptive input from reaching and sensitizing the central nervous system. In the clinical realm, this is obvious. For instance, when we employ continuous epidural analgesia, the postoperative infusion is most often low-dose local anesthetic and opioid in combination. This provides excellent analgesia, but spares patients dense sensory and motor blockade that would limit movement and put them at risk for injury to the anesthetized areas. These patients still experience mild to moderate pain during their recovery. Thus, the central nervous system is still receiving nociceptive input and the central sensitization that is the normal physiologic process to injury still ensues. Thus, it seems unreasonable to expect that the processes that link acute pain to chronic pain have been unlinked. The second observation is that tissue injury leads to the production of circulating humoral mediators which enter the bloodstream and lead to sensitization of the central nervous system even when there is no direct neural traffic reaching the dorsal horn. So how do we move from the failed concept of preemptive analgesia to the adoption of analgesic regimens that are directly targeted toward the neural mechanisms that lead to severe acute pain and the chronic neural changes associated with chronic pain? There have been a number of promising recent studies that employed specific analgesic agents...
or combinations of analgesic agents and followed patients for long intervals after surgery, cataloguing their pain experiences and the incidence of chronic. Lavand’homme and colleagues randomized 85 patients undergoing elective colon resection to receive a multi-modal regimen that included intra-operative ketamine, local anesthetic, clonidine, and opioid administered either intravenously or epidurally and then followed their postoperative course.\(^{10}\) Outcomes included long-term assessment of patients for persistent pain out to a year after surgery. None of the patients who had epidural analgesia intraoperatively had chronic pain requiring treatment at one year after surgery, while 12% of those who did not receive epidural analgesia had persistent pain requiring treatment at one year follow-up. In another well designed and conducted trial, Kumar and colleagues randomized 240 patients undergoing total knee arthroplasty to receive either placebo or oral pregabalin pre-operatively and for 14 days after surgery.\(^{11}\) None of those patients who received pregabalin reported chronic pain at 6 months after surgery, while 5.2% of those receiving placebo reported ongoing and significant pain at the surgical site. There are a number of other smaller, uncontrolled studies that also support the notion that short-term intervention in the perioperative period can impact the incidence of chronic pain, but these studies are nothing more than suggestive. What is clear from this work is that the impact of analgesic interventions must be assessed far beyond the postoperative period to assess their true value, and anesthesiologists are likely to be involved closely in these long-term outcome studies. The exact analgesic agents and the specific approaches to modifying the transition from acute to chronic pain will evolve swiftly in the years to come. Many risk factors are well-validated as predictors of the severity of acute pain following injury and the probability of chronic persistent pain. The challenge ahead is to determine what we can do to use this information to identify high-risk patients and modify their peri-operative treatment in ways that impact the development of chronic pain.

REFERENCES