Acute Pain Pathophysiology

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As anesthesiology expands its role perioperative medicine, our knowledge in acute pain management is highly regarded. In order to continue to in the front of acute pain management, mechanisms of acute pain must be explored and new analgesic drugs must be evaluated.

Although many new discoveries are being made in pain research, the ability to translate these directly to perioperative pain management must be established. For this summary, we will evaluate studies on clinical acute pain mechanisms and new analgesic drugs tested in preclinical models. By summarizing the literature on incisional pain mechanisms, it is our hope that the clinician will begin to understand the basic science of acute postoperative pain. [1]

Sensitization and hyperalgesia

It is well recognized that injury causes two changes in the responsiveness of the nociceptive system, peripheral sensitization and central sensitization [2] and together, these changes in the processing of nociceptive and non-nociceptive information are hypothesized to contribute to acute postoperative pain and hyperalgesia after surgery. Peripheral sensitization involves the primary afferent fibers and is characterized by lowering of response threshold, an increase in response magnitude to suprathreshold stimuli, and an increase in spontaneous activity. [**Figure 1**]

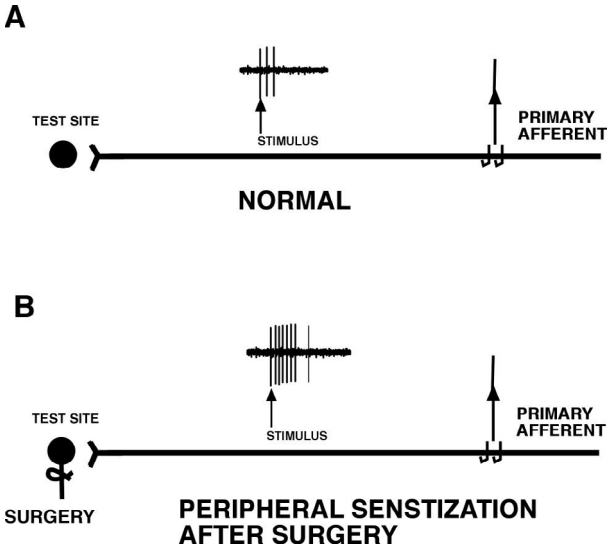

Figure 1 Peripheral sensitization. **A**: Responses of primary afferent fibers showing action potentials (top) and the receptive field at the fiber terminal in normal tissue. **B**: Model of primary afferent (peripheral) sensitization after surgery increased responsiveness. Adapted from[1].

However, nociceptive input can enhance the responses of pain transmission neurons in the central nervous system (Fig. 2A-B). This phenomenon is termed central sensitization. One example of central sensitization is increased pain responses evoked in dorsal horn neurons by stimuli from outside the area of injury. [**Figure 2]**

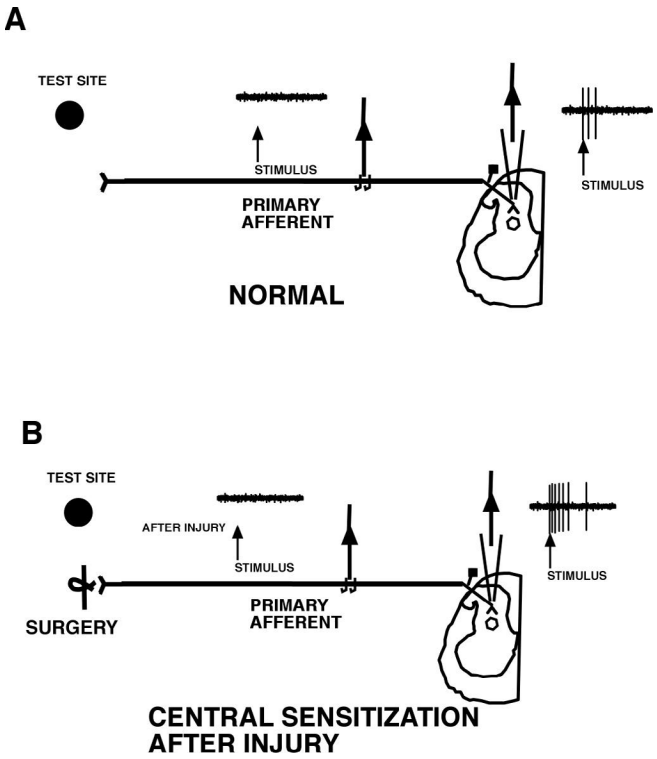

Figure 2. Central sensitization. **A**: Responses of primary afferent fibers and dorsal horn neurons showing action potentials (top) in normal tissue. The test site is located outside the area of injury. **B**: Model of secondary hyperalgesia and central sensitization after injury. The responses of the primary afferents are unchanged but the response in the dorsal horn is greater. Adapted from [1].

Quantifying clinical postoperative pain

Pain at rest

We use a variety of measurements to quantify pain generated after surgery. One nearly universal measurement is pain at rest or nonevoked pain using a visual analogue scale (VAS) or a verbal score. Recovery room nurses and floor nurses assessment use these scores to quantify acute pain. Upon awakening, nearly all adult can report a verbal analogue pain score using a range of "0" for no pain and "100" as the worst pain imaginable. In some cases, a VAS at rest may be the only relevant pain score as in major head and neck surgery in which patients are not required to perform any functional activity limited by the surgery. Physiologic correlates to pain at rest are activation of nociceptors and dorsal horn pain transmitting neurons producing increases in ongoing activity.

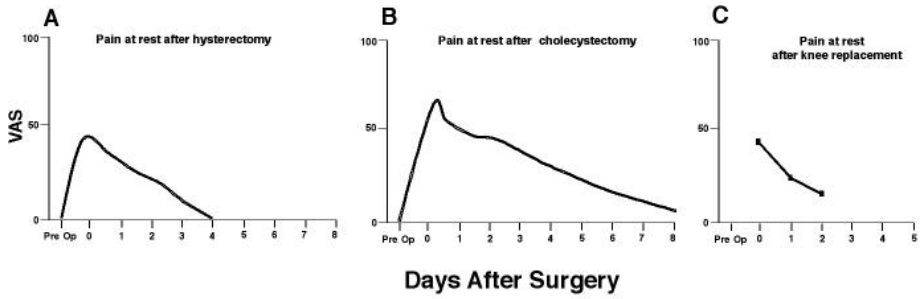

Fig. 3 Schematic of pain at rest after hysterectomy (A), cholecystectomy (B) and knee replacement (C), adapted from [3-5].

Pain during activities

The second most common pain measurement after surgery is evoked pain or pain with activities. Within the last 10 years it is recognized that a goal of perioperative medicine is early, improved functional capacity; this particular function measured depends upon the type of surgery. For example, after tonsillectomy, pain may occur at rest and during swallowing; improved pain with swallowing may permit earlier oral intake. Physiologic correlates to pain with activities are increased responses of nociceptors and dorsal horn neurons to abrupt, evoked responses.

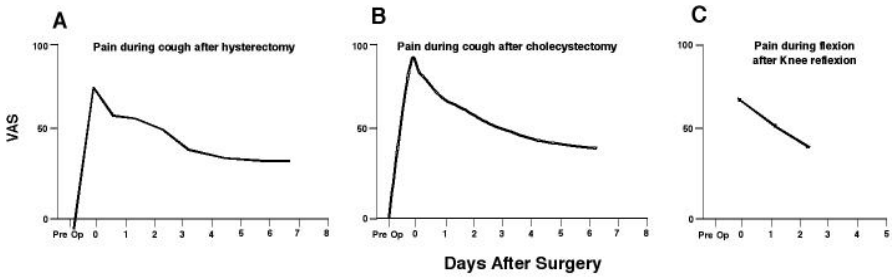

Fig. 4 Schematic of pain with activities after hysterectomy (A), cholecystectomy (B) and knee replacement (C) adapted from [3-5].

After thoracic surgery, we typically obtain pain scores at rest and during cough; improved pain control during cough may diminish pulmonary complications in this at risk group. Similarly, after abdominal surgery, we obtain pain scores at rest, with ambulation and perhaps during cough. Pain measurements at rest and during flexion are measured after total knee replacement and greater range of motion in the first few days after surgery is associated with improved function weeks later. In other patients, joints may be immobilized after surgery (e.g. ankle fusion) and evoked pain is not relevant. A problem with most evoked pain measures like pain during cough is the difficulty in standardizing effort.

After nearly all surgeries, pain with activities is much greater than at rest; for example, a VAS pain rating at rest may be 2 but pain with coughing can be rated a 7. Also, pain with activities persist much longer after most surgery than pain at rest. One possibility is pain at rest and pain with activities may simply represent an intensity dependent difference with pain during activities a stronger stimulus than pain at rest. Alternatively, pain with activities may have a different mechanism(s) than pain at rest resulting in a different pattern of pain transmission.

Hyperalgesia after surgery

Other tests have been explored in patients to understand postoperative pain mechanisms in preclinical models. Many tests have been developed in animal models to evaluate pain hyeralgesia-like responses. Table 1 summarizes clinical pain measurements after a variety of surgeries and the surrogates for pain in models that was reviewed.[6] The animal models provide important information on pain mechanisms but do not perfectly substitute for human pain reports.

Table 1: Methods to measure pain in patients after surgery and pain-like responses in postoperative models.

Clinical Postoperative Pain [6]	***Postoperative Pain Models*** [6]
Pain at rest	Heat withdrawal latency
Pain during activities	Primary mechanical withdrawal threshold
Pain during activities: Ambulation	Secondary mechanical withdrawal threshold
Pain during activities: Cough, Spirometry	Guarding
Pain during activities: Knee flexion/extension	Weight bearing
Pressure pain threshold	General Activity
Area of mechanical hyperalgesia	Conditioned responses
Flexion response to mechanical stimuli	Primary mechanical allodynia
	Secondary mechanical allodynia
	Graded hyperalgesia
	Graded allodynia

Acute Pain Mechanisms and Postoperative Therapies

Immediately after surgery, opioids like morphine are titrated to pain at rest. After intermediate and major surgeries, opioids rarely eliminate pain at rest, unless significant side effects like sedation occur.[7] Even in the first few days after surgery, pain at rest is rarely zero even when opioids are optimized, and pain with activities may remain moderate or severe.[8]

There has been an emphasis on sufficient opioid dosing in acute postoperative pain. Through the last 10 years, data indicate opioid dosing is generally optimized. When opioid dosing for major surgical procedures is liberalized but carefully administered, pain at rest at the first 24 hours after surgery averages 30-40 on a scale of 0 to 100. Additional opioid dosing produced no greater decrease in pain, only an increase in side effects. When opioid dosing is optimized, pain with activities is approximately 60. The amount of increase in the VAS from the score at

rest to that during activities is generally constant, an increase of 30 to 40 on the VAS scale. These data suggest that the amount of increase in the VAS with activities is not affected by optimizing opioid dosing, rather the baseline from which the pain with activities is only lowered. From data like this, many conclude that pain with activities is relatively insensitive to opioids.

Prostaglandins and postoperative pain

Cyclooxygenase (COX) inhibitors have been recognized as adjuncts to opioids in the treatment of acute postoperative pain. In clinical studies, their analgesic efficacy is measured in their "opioid sparing" effects or less common a decrease in both pain and opioid consumption. Two isoenzymes for COX have been identified and both selective COX-1 (constitutive) and COX-2 (inducible) inhibitors produce opioid sparing effects in postoperative pain patients.

Prostaglandins not only cause pain due to sensitization in the periphery but could theoretically contribute to postoperative pain through an action in the central nervous system. [9,10] The importance of the central nervous system actions of parenterally administered COX-1 and COX-2 inhibitors in postoperative pain is not yet understood although evidence is accumulating that some COX inhibitors do penetrate into the CNS [11] and decrease central prostaglandin production in postoperative patients.

Antihyperalgesic drugs, gabapentin and ketamine

Increased interest in the perioperative use of ketamine hydrochloride as an analgesic agent has occurred because one of its mechanisms of action is blockade of N-methyl-D-aspartate (NMDA) receptors.[12] The NMDA receptor ahs been implicated in plasticity and pain memory; this has stimulated a variety of studies on the perioperative use of ketamine for acute pain management. Small doses of ketamine that may not be analgesic but are antihyperalgesic may be useful in postoperative pain management when employed as adjuncts to opioids.[13] It is suggested that parenteral ketamine influences persistent pain after colectomy, perhaps a short term treatment with long term consequences.[14]

Gabapentin was originally developed for the treatment of epilepsy. However, gabapentin has been demonstrated to have antihyperalgesic properties in human pain models. Recent studies indicate gabepentin binds to the alpha$_2$delta subunit of voltage-dependent calcium channels (VDCC). There has been a recent surge in trials of gabapentin in acute postoperative pain. [15] Treatment with gabapentin produces both opioid-sparing effects and in some cases decreases in pain at rest and pain with activities. Surprisingly, side effects like dizziness, frequent in chronic pain patients, are not outstanding in postoperative patients.

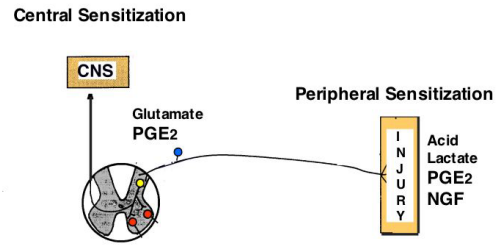

Fig. 6 Model for peripheral sensitization caused by surgery. Evidence suggests low pH[16], lactate, PGE_2[17] and nerve growth factor (NGF) [18] may contribute to peripheral sensitization in incisions. In the central nervous system, glutamate [19,20] and prostaglandins [9,10,21,22] contribute to central sensitization.

Other antihyperalgesic receptors for postoperative pain

Novel analgesic treatments will arise from basic science studies on the mechanisms for incisional pain. In the periphery, prostaglandins,[17] acid,[16] lactate and nerve growth factor[23] likely contribute to acute incisional pain. The receptors for these factors include TRPV1, ASIC3, EP1 and TrkA. These and other undiscovered sensitizing chemicals and their receptors will likely represent future sites for therapies affecting peripheral sensitization. In the central nervous system, prostaglandins, glutamate and VDCC have a role in central sensitization after incisions. The receptor antagonists that will have antihyperalgesic properties include the NMDA, AMPA, EP1 and VDCC, which interfere with central sensitization.

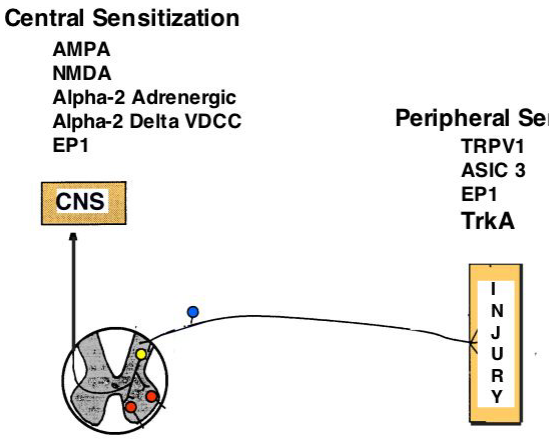

Fig. 7 Receptors for peripheral and central sensitization. In the incision, the capsaicin receptor (TRPV1),[24,25] acid sensing ion channel (ASIC3) [26], prostaglandin receptor EP1[17], and the NGF receptor (TrkA) [18,23]. In the CNS, glutamate receptors (AMPA and NMDA), [14,20] adrenergic, voltage dependent calcium channels,[27,28] and prostaglandin receptor EP1 [21] contribute to postoperative pain.

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