

## Expanding our Horizons

### Transition of Acute Postoperative Pain to Persistent Pain and Establishment of Chronic Postsurgical Pain Services

*Editor's Note:* This is the third in a series of four Editorial Views on long-term outcomes after anesthesia and surgery. This series adds to other recent Editorial Views in ANESTHESIOLOGY and includes a discussion of broadening our research outside of the operating room to prevention of wound infections, cancer spread, cardiovascular morbidity and mortality, chronic postsurgical pain, and rare complications. ANESTHESIOLOGY will sponsor special sessions in 2010 on the topic of long-term outcomes at annual meetings of the Japanese Society of Anesthesiologists, the European Society of Anesthesiology, and the American Society of Anesthesiologists.

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ACUTE postoperative pain should not be considered simply an uncomfortable symptom that disappears when surgical wounds heal. Instead, pain reflects a complex constellation of evolving effects at peripheral, spinal, and cerebral levels involving several neurotransmitters and modulators, including the immune system. Although most patients expect to experience pain after surgery, the pain experience in this setting can be exaggerated by psychologic and pharmacologic factors. For example, level of anxiety is known to correlate with severity of pain from nociceptive stimuli, and days or weeks before the surgical procedure, patients may be mentally stressed by impending anesthesia and surgery, with their potential for adverse outcomes. In addition, surgical tissue injury occurs during anesthesia, which may be important because anesthetic drugs interfere with sensory perception, but their effects on pain processing are not necessarily unidirectional. For example, potent opioids produce both antinociception and hyperalgesia.<sup>1</sup> Halogenated vapors, given to produce unconsciousness and amnesia, also activate peripheral pronociceptive ionic channels, thereby augmenting neurogenic inflammation.<sup>2</sup>

Postoperative pain is an association of somatic, inflammatory, neuropathic, and — at times — visceral pain. Postoperative pain results not only from local tissue injury, leading to spontaneous firing of nociceptors and their increased sensitivity to stimuli (primary hyperalgesia), but also from central nervous system changes resulting in sensitization and pain from a wider area (secondary hyperalgesia).

In the last decade, secondary hyperalgesia has prompted particular attention for several reasons. First, secondary

hyperalgesia reflects transformations within the central nervous system that augment pain perception from injured and surrounding areas. Interestingly, this phenomenon, which has been primarily studied in the spinal cord, reflects neuroplastic changes, which share many features of mechanisms of memory at supraspinal sites. Second, most of the medications used to alleviate postoperative pain have minor effects on this secondary hyperalgesia, possibly explaining why large series still report insufficient postoperative pain relief.<sup>3</sup> Finally, secondary hyperalgesia is thought to be a basis for chronic postsurgical pain (CPSP).<sup>4</sup>

The criteria for the diagnosis of CPSP were defined by the International Association for the Study of Pain 10 yr ago. CPSP is a pain syndrome that develops postoperatively and lasts at least 2 months with other causes for pain (*e.g.*, recurrence of malignancy, chronic infection, *etc.*) being excluded; pain continuing from a preexisting disease is also an exclusion.<sup>5</sup> CPSP is not restricted to major surgeries (cardiac, thoracic, abdominal, and orthopedic) and amputations; it is also observed after simple procedures such as inguinal hernia repairs, mastectomies, and Cesarean deliveries.

Anesthesiologists are just now realizing the high estimated incidence of CPSP and how we might attempt to prevent it. About 30% of patients are reported to suffer moderate-to-severe CPSP after specific types of major surgery. Even after minor procedures, approximately 5% of patients suffer severe CPSP.<sup>6</sup> Although the reported prevalence is high, most anesthesiologists are unaware of this problem because they don't see large numbers of patients with CPSP in their practice. How can we explain this discrepancy? The most likely possibility is that the follow-up of these patients is lost for the anesthesiologists in charge. Patients suffering persistent pain weeks or months after sur-

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gery are cared for by their surgeon or primary caregiver rather than by their anesthesiologist.

Several predictive factors for CPSP have been identified, related to both patient and surgical factors. Factors linked to the patients include female gender, young age, obesity, preoperative anxiety and/or catastrophizing, and preexisting pain. Part of the interindividual variability in pain sensitivity is caused by genetic polymorphisms of genes involved in endogenous pain control. In this regard, some protective genotypes (homozygous carriers of a GTP cyclohydrolase 1 haplotype) or phenotypes (children born of mothers with a familial history of hypertension) have been isolated.<sup>7,8</sup> Nevertheless, according to the complexity of the mechanisms involved in pain perception, the recently isolated favorable haplotypes are not necessarily protective against all types of hyperalgesia (*e.g.*, somatic *vs.* visceral).<sup>9</sup> At the present time, the development of this area of study is inadequate to allow systematic genotype screening to discriminate populations at risk of developing CPSP. Another way to predict CPSP is by testing preoperative experimental pain. In this regard, psychophysical measures exploring “static” pain parameters (pain thresholds, magnitude estimation of suprathreshold nociceptive stimuli, and tolerance) have been regularly reported to predict the intensity of acute postoperative pain in the early phase after surgery.<sup>10</sup> Nevertheless, these measures of response to an acute, phasic, experimental stimulus are less indicative of the complex pain modulation process that occurs after surgery. Some aspects of such modulation can be quantified by using the “dynamic” psychophysical measures of temporal summation and evocation of diffuse noxious inhibitory control, a measure recently reported to predict the risk of CPSP after thoracotomy.<sup>11</sup>

Factors linked to surgery include invasive procedures: redo interventions, surgery in a previously injured area, and particular surgical techniques.<sup>12</sup> Most of these factors also predict the intensity of acute postoperative pain; however, acute pain intensity *per se* is a strong predictor for development of CPSP.<sup>6</sup> Although, adequate treatment of acute postoperative pain is mandatory, there is no consistent evidence in large series of patients that it necessarily prevents the development of CPSP.

Once established, CPSP of neuropathic or inflammatory origin is difficult to treat; CPSP is thus an important cause for referral to chronic pain facilities.<sup>13</sup> Anesthesiologists have therefore adapted various strategies aimed at reducing the intensity of acute postoperative pain and therefore perhaps the incidence of CPSP. The critical question, of course, is whether anesthetic technique significantly influences development of CPSP. Divergent opinions are found in the literature. Some investigators are convinced that surgery, by cutting nerves or initiating prolonged inflammatory reactions, is the major determinant.<sup>14</sup> Consistent with this theory, some investigators have demonstrated in limited series of patients that

potent analgesia combined with antihyperalgesic medications influences the incidence of CPSP.<sup>15</sup> However, no large prospective trial has confirmed that any specific anesthetic intervention reduces the risk of CPSP.

A better understanding of the determinants of CPSP might be obtained by considering the physiologic role of pain, a concept often ignored in the setting of perioperative care. Pain is part of an extraordinary sensory modality that serves not only to detect threats (including imperceptible ones such as viral invasion) but also to promote survival, learning, and memory. Given that hyperalgesia and nociceptive inhibitory systems are part of a natural perception process, why do some patients develop CPSP and the majority do not?

An explanation may be found in the “generalized hypervigilance” hypothesis which some believe to be a mechanism leading to fibromyalgia. These patients show robust perceptual amplification that is not restricted to pain perception, but is also observed with other sensory modalities.<sup>16</sup> The consequence of a hypervigilant state is dysregulation in the mechanism of discrimination. Interestingly, fibromyalgia patients share many common characteristics with patients at risk of developing important acute postoperative pain and CPSP (female gender, anxiety, catastrophisation, *etc.*). Moreover, a history of trauma (including surgery) is frequently reported as a precipitating factor of this disease.<sup>17</sup> In this regard, CPSP may be part of a hypervigilant disease initiated in vulnerable population by the preoperative stress or by surgery itself.

In summary, CPSP is a relatively recently recognized entity, and precise distinctions between physiologic and pathologic contributions remains unclear. Large-scale prospective studies including careful enquiries concerning preoperative pain and risk factors are required to determine its exact incidence and the respective role of surgery and anesthetic techniques. Large prospective studies will similarly be needed to determine which, if any, anesthetic interventions reduce the risk of CPSP.

Just as anesthesiologists responded to patients’ need for better management of acute postoperative pain by the establishment of acute postoperative pain services, the time is right for us to consider establishing specifically dedicated facilities to take care of CPSP patients. Doing so, surgeons or the other medical practitioners could directly refer their patients instead of entrust them to one or other unrelated pain clinic. These new “CPSP services” would certainly help to more accurately determine the true incidence of this phenomenon, to uncover the populations at risk, and to provide early treatment strategies. Such a service would also provide an ideal venue to monitor the link between perioperative analgesic management and CPSP development. The need is clearly there for our patients, and who better to treat and eventually prevent CPSP than us?

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