

Consequences of Inadequate Postoperative Pain Relief and Chronic Persistent Postoperative Pain

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Postoperative pain is still inadequately relieved despite substantial improvements in the knowledge of the mechanisms and treatment of pain [1]. Evidence suggests that inadequate relief of postoperative pain may result in harmful physiologic and psychologic consequences that lead to significant morbidity and mortality [2], which may delay recovery and the return to daily living [3]. In addition, the presence of postoperative symptoms, including pain, significantly contributes to patients' dissatisfaction with their anesthesia and surgical experience [4]. Most importantly, it has been recognized that inadequately treated postoperative pain may lead to chronic pain, which is often misdiagnosed and neglected [5,6]. This article reviews the physiologic and psychologic consequences of inadequate pain relief, with an emphasis on chronic persistent postoperative pain.

Physiologic consequences

Inadequately treated pain, particularly acute pain, is associated with physiologic changes caused by endocrine, metabolic, and inflammatory responses (Table 1). This stress response activates the autonomic system, which may have adverse effects on various organ systems [2]. The somatic pathway stimulation

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Table 1
Consequences of unrelieved pain

Organ systems	Physiologic responses
Cardiovascular	Increased heart rate, peripheral vascular resistance, arterial blood pressure, and myocardial contractility resulting in increased cardiac work, myocardial ischemia and infarction
Pulmonary	Respiratory and abdominal muscle spasm (splinting), diaphragmatic dysfunction, decreased vital capacity, impaired ventilation and ability to cough, atelectasis, increased ventilation/perfusion mismatch, hypoventilation, hypoxemia, hypercarbia, increased postoperative pulmonary infection
Gastrointestinal	Increased gastrointestinal secretions and smooth muscle sphincter tone, reduced intestinal motility, ileus, nausea, and vomiting
Renal	Oliguria, increased urinary sphincter tone, urinary retention
Coagulation	Increased platelet aggregation, venostasis, increased deep vein thrombosis, thromboembolism
Immunologic	Impaired immune function, increased infection, tumor spread or recurrence
Muscular	Muscle weakness, limitation of movement, muscle atrophy, fatigue
Psychological	Anxiety, fear, anger, depression, reduced patient satisfaction
Overall recovery	Delayed recovery, increased need for hospitalization, delayed return to normal daily living, increased health care resource utilization, increased health care costs

caused by surgical injury increases the secretion of hypothalamic-releasing hormones, which in turn stimulates the secretion of the anterior and posterior pituitary gland [2]. The autonomic overactivity results in an increased heart rate, peripheral vascular resistance, increased arterial blood pressure, and myocardial contractility, which all culminate in increased myocardial oxygen consumption from increased cardiac work [7]. In addition, intense sympathetic stimulation may also produce coronary vasoconstriction as well as atherosclerotic plaque rupture and, subsequently, decrease myocardial oxygen supply. The combination of increased myocardial oxygen demand and decreased oxygen supply can be detrimental in patients with coronary artery disease and may lead to myocardial ischemia, anginal pain, and myocardial infarction.

Inadequate pain relief, particularly after thoracic and upper abdominal surgery, may cause pulmonary dysfunction and an increase in postoperative pulmonary complications [8]. Involuntary spinal reflex responses to the noxious stimulus from the injured area result in reflex muscle spasm in the immediate region of the injury as well as the surrounding muscle groups, which prevents movement in this area (ie, splinting), with subsequent hypoventilation and hypoxemia. In addition, pain can cause diaphragmatic dysfunction, which further impairs ventilation [9]. After upper abdominal surgery, vital capacity decreases by 40% to 60%, with a greater decline in the elderly than in younger patients [9].

Increased sympathetic activity from severe pain increases gastrointestinal secretions and smooth muscle sphincter tone while also decreasing intestinal motility [10]. This partly accounts for the gastric stasis and paralytic ileus, particularly after abdominal surgery. In addition, opioid analgesics may also

contribute to the decreased intestinal motility. Therefore, local anesthetic epidural blockade but not epidural opioid reduces pain-related impairment of intestinal motility [11]. Unrelieved pain can increase the incidence of postoperative nausea and vomiting. Chia et al [12] evaluated the risk factors of postoperative emesis in patients who underwent lower abdominal gynecologic surgery and received morphine intravenous patient-controlled analgesia (IV-PCA). They found that patients with postoperative emesis had significantly higher pain scores at rest and during coughing than those without emesis, even though the opioid consumption was similar. Logistical regression analysis further validated the fact that pain intensity is a sensitive predictor of postoperative emesis. Similar results have been documented in other studies [13,14]. Interestingly, one study [14] reported that the incidence of moderate to severe nausea was reduced from 37% to 23% with the increased use of opioids and assumed improved pain relief. It is hypothesized that the sympathetic activation caused by pain results in increased firing of the area postrema, leading to emesis [15].

The increase in sympathetic activity can also lead to increased urinary sphincter tone, reflex inhibition of urinary bladder tone, and subsequent urinary retention. The metabolic response to surgical stress also leads to a hypercoagulable state, venous stasis, and the increased risk of deep vein thrombosis and thromboembolism, which may be further exaggerated by reduced physical activity from inadequate pain relief [16]. In addition, the immune function may also be decreased, resulting in an increased incidence of infection and tumor spread or recurrence. Inadequately treated pain can also cause increased postoperative fatigue. The limitation of movement caused by pain may cause a marked impairment of muscle metabolism, muscle atrophy, muscle weakness, and delayed return to normal muscle function [17].

Psychologic and behavioral consequences

The psychologic factor related most to high levels of pain is anxiety [18]. Severe pain causes individual behavioral changes including increased sensitivity to external stimuli such as light and sound, withdrawal from interpersonal contact, and increased self-absorption and self-concern. Patients experience a loss of control over their environment if acute pain is unrelieved for prolonged periods, culminating in depression and helplessness. Prolonged and unrelieved pain can lead to the expression of anger and resentment, especially when it is believed that treatment is being withheld [19]. Premorbid tendencies for anxiety, hostility, depression, or preoccupation with health are exacerbated by severe and unrelieved acute pain. An acute psychotic reaction may occasionally result [20].

Postoperative pain has been found to be an important cause for long-lasting postoperative temper tantrums and untoward behavioral changes in children. In a prospective multicenter study, Kotiniemi et al [21] evaluated behavioral changes in children during the first month after surgery and assessed the

significance of some patient-related factors on the incidence of behavioral changes. Pain on the day of surgery was found to predict the occurrence of behavioral problems up to the fourth week, which was longer than the duration of the pain itself [21].

Recovery and health care use

Uncontrolled pain has also been shown to prolong a patient's stay in the postanesthesia care unit and the hospital and to delay discharge and increase the incidence of unanticipated hospital admissions after ambulatory surgery [22–26]. Inadequate management of pain after ambulatory surgery has significant consequences (Box 1). Pavlin et al [25] reported that the three most common medical causes of delayed discharge after ambulatory surgery were pain, drowsiness, and nausea and vomiting. In a later study, Pavlin et al [26] found that pain was the most common cause of postanesthesia care unit delays, affecting 24% of patients overall. It was also a significant independent predictor of the duration of total recovery [26].

Unfortunately, after the patients are discharged, home pain management seems to be commonly ignored [27]. Numerous investigators [28–31] have reported an increased incidence of pain at home. In an analysis of studies related to postdischarge symptoms after outpatient surgery, Wu et al [31] found that the overall incidence of postdischarge pain after outpatient surgery was approximately 45%. Pain was one of the most common causes for readmission after outpatient surgery [31–34]. Poorly controlled postoperative pain may increase the incidence of postoperative delirium and cognitive dysfunction [35]. Overall pain and its consequences reduce the health-related quality of life and also delay return to normal daily activities [3,23,36,37]. Inadequate postoperative pain control was also the most frequent reason for patients to contact their family practitioner after discharge from the hospital [38].

Because pain was among the top five most undesirable outcomes after surgery [39], inadequate treatment of pain can reduce patient satisfaction [4]. A

Box 1. Consequences of inadequate pain management after ambulatory surgery

- Increased postanesthesia care unit stay
- Increased Phase II unit stay
- Delayed discharge home
- Unanticipated hospital admission
- Increased contact with family practitioner
- Delayed return to daily living function
- Decreased patient satisfaction

survey [23] intended to determine the significance of pain and other symptoms on the recovery process found that pain and analgesic side effects significantly contributed to patient dissatisfaction, distress, and delayed return to normal activity after discharge from ambulatory surgery. Inadequately treated pain may also increase the use of health care resources [3,31,40]. The economic impact of delayed recovery and delayed return to normal activities of daily living as well as unanticipated hospital admission, readmission, or lost employment time may increase health care costs [31,40].

Persistent postoperative pain

Recently, persistent pain after surgery, also referred to as chronic postsurgical pain syndrome, has been recognized as a major factor in delaying recovery and return to normal daily living [5,6]. Long-lasting pain has been reported after numerous surgical procedures including thoracotomy, mastectomy, hernia repair, and limb amputation [5,6]. Of note, all surgical procedures have the potential to develop persistent postoperative pain. The devastating consequences of persistent postoperative pain (eg, distress and disability) have led to an increased interest in its prevention [41]. With an estimated 3 million general surgical procedures performed in the United States [42], if even a small percentage of these patients develop chronic pain, it would be a significant problem. A more detailed review of the transition from acute to chronic pain has been published recently [43].

Definition

The definition of persistent postoperative pain remains controversial because it may be difficult to determine whether the pain is merely a continuum of the preoperative condition or has developed after the surgical procedure. Although chronic pain has been defined as the presence of pain that persists for longer than 3 months after surgery, such a simplistic definition has been criticized [6]. It has been suggested that the criteria for the diagnosis of persistent postoperative pain should include pain lasting for at least 2 months after a surgical procedure, with other causes for the pain excluded (Box 2). Furthermore, it is necessary to exclude the preoperative condition as the cause for persistent pain, because surgery may simply exacerbate a pre-existing painful condition [6].

Incidence

The exact incidence of persistent postoperative pain is not known. In 1992, a survey [44] of patients attending pain clinics in Scotland and northern England demonstrated that 20% of patients implicated surgery as one of the causes of their chronic pain, and in approximately half of these patients, it was the sole cause. The overall incidence varies significantly from 5% to 80% and is related

Box 2. Criteria for the diagnosis of chronic persistent postoperative pain

- Pain developed after a surgical procedure
Preoperative condition as the cause of postoperative persistent pain is excluded
- Pain is of at least 2 months' duration
Assessment of spontaneous pain intensity is not adequate
Characteristics of chronic neuropathic pain are present
- Other causes for the pain are excluded (eg, continuing malignancy or chronic infection)
Onset of pain from radiotherapy or infiltration is usually delayed

Modified from Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001;87:88–98; with permission.

to the type of surgical procedure [5,6,45–51]. A study [52] evaluating the incidence of persistent pain after total knee replacement surgery found that 42% of patients met the International Association on Study of Pain criteria for complex regional pain syndrome (CRPS) at 4 weeks and 3 months, whereas 19% of patients met the criteria at 6 months after surgery. Approximately 14% of patients had significant pain before surgery, including allodynia, edema, and temperature, color, and sweating asymmetry [52]. The incidence of CRPS after various orthopedic surgeries varies between 0.8% and 40% [53]. However, earlier studies had serious methodological flaws such as variable definitions of persistent pain.

Predictors of persistent postoperative pain

The predictors of chronic persistent postoperative pain can be divided into preoperative, intraoperative, and postoperative factors (Box 3). Preoperative factors include pre-existing pain at the operative site, previous surgery, and psychologic and genetic factors as well as the presence of conditions such as irritable bowel syndrome, migraine headache, fibromyalgia, and Raynaud's disease [5,6]. Preoperative pain that predicts persistent postoperative pain tends to be continuous pain of 1 month or longer [5]. The probability of phantom limb pain is increased in the presence of severe preoperative pain [54,55]. Although preoperative breast pain predicts phantom breast pain [48], preoperative breast pain did not predict chronic pain after breast surgery when evaluated prospectively [56]. Long-standing symptoms, including pain, predict chronic pain after cholecystectomy [57]. Preoperative pain sensitivity as measured by

Box 3. Predictors of chronic persistent postoperative pain

- Preoperative factors

Presence of preoperative pain

Repeat surgery

Psychological vulnerability (eg, neuroticism)

Work-related injury

- Surgical factors

Type of surgical procedure

Surgical approach with risk of nerve damage (eg, nerve identification, nerve

trans-section, repair technique)

- Postoperative factors

Intensity of early postoperative pain

Postoperative radiation therapy or chemotherapy

Psychologic vulnerability (eg, neuroticism)

Modified from Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. *Anesthesiology* 2000; 93:1123–33; with permission.

pressure algometry did not predict either the severity of acute pain or the probability of chronic pain after thoracotomy [45]. In contrast, Werner et al [58] observed a correlation between pain after anterior cruciate ligament reconstruction and pain during an experimental first-degree burn 6 days preoperatively. The authors did not find a correlation between postoperative pain and the extent of secondary hyperalgesia or changes in pain threshold from mechanical or thermal stimuli. However, this was a small study, and patients were not followed to evaluate the development of chronic pain.

Intraoperative factors include the type of surgical procedure performed and the probability that certain types of surgical procedures are more likely to develop chronic persistent postoperative pain. For example, patients undergoing limb amputation, thoracotomy, sternotomy, and mastectomy have a high prevalence of chronic persistent postsurgical pain. Surgical technique and incisional approach also play important roles in predicting persistent postoperative pain. The extent of tissue damage appears to be a predictor of chronic pain and the extent of acute pain (eg, phantom limb pain appears to be more common after

the amputation of a leg than after toe amputation) [5]. Thoracotomy performed using a posterolateral approach is more likely to result in chronic pain than that performed using an anterolateral approach [59,60]. Similarly, chronic pain is more common after chest wall resection [61,62]. Mastectomy combined with the implantation of a prosthesis results in a higher prevalence of pain than mastectomy alone [63]. Nerve injury such as intercostobrachial nerve injury during breast surgery or intercostal nerve injury during thoracotomy also contributes to chronic pain [5,6,49,60].

Postoperative factors include the severity of postoperative pain, radiotherapy, and neurotoxic chemotherapy as well as psychologic vulnerability. Patients with a significantly greater severity of postoperative pain (particularly movement-evoked pain) are more likely to develop chronic pain [45,49,50]. However, the link between early postoperative pain and chronic pain does not necessarily imply causality. Nevertheless, adequate pain relief, particularly movement-evoked pain relief, may reduce the risk of persistent postoperative pain and deserves further investigation. There is a suggestion that certain patient personality factors may also play a role in the development of chronic pain. Psychologic vulnerability, as evaluated by a questionnaire, which appears to correlate with neuroticism and possibly somatization, has been shown to predict the post-cholecystectomy syndrome [64,65]. This contrasts with a lack of predictive power for psychologic parameters such as depression and anxiety for the development of chronic pain [45,48].

Mechanisms involved in the transition from acute to persistent postoperative pain

It has been suggested that persistent pain should be considered a disease state of the nervous system, not merely a symptom of some other disease condition [66]. Peripheral and central sensitization of the nervous system has been implicated in the development of intractable pain that potentially can become chronic. Repeated and prolonged noxious stimuli after tissue or nerve injury induce alterations in function, chemical profile, and even structure of neurons, which may increase the sensitivity to pain. Peripheral sensitization of nociceptors and the subsequent barrage of nerve impulses entering the spinal cord results in hyperexcitability in dorsal horn neurons and central sensitization (ie, metabolic activation and hyperexcitability of spinal nociceptive neurons, expansion of sensory receptive fields, and alterations in the processing of innocuous stimuli), leading to a reduced pain threshold and the amplification of the pain response. These postoperative neuroplastic changes underlie the development of "pathologic" pain, which is characterized by hyperalgesia (an increased response to a stimulus that is normally painful) and allodynia (pain caused by a stimulus that does not normally provoke pain).

De Kock et al [67] demonstrated that reducing the area of hyperalgesia after colectomy did not greatly reduce acute pain but was associated with a decrease in the number of patients who developed residual pain as late as 6 months after

colectomy. Therefore, the area of secondary hyperalgesia (hyperalgesia outside of the injured area), one measure of central sensitization, could perhaps predict that patients are likely to develop persistent pain after surgery. Kawamata et al [68] subjected volunteers to a small incision in the volar forearm and mapped the area of hyperalgesia surrounding the incision. The authors noted that there was a large area of hyperalgesia, which did not develop when a local anesthetic injection was administered before the incision. Therefore, a neural blockade should significantly diminish central sensitization.

In addition to the use of local anesthetic techniques, an improved understanding of the role of cyclooxygenase (COX)-2 in pain sensitization suggests that COX-2 inhibitors should be an important consideration as a part of multimodal analgesic therapy. Recent research has advanced our understanding of the role of COX-2 and prostanoids in neural plasticity and pain sensitization [69]. Tissue injury is associated with an increased prostanoid (prostaglandin) synthesis and increased sensitivity of nociceptors (or peripheral sensitization). Peripheral inflammation also increases central prostanoid levels, which mediates more widespread changes in pain perception. Nitric oxide (NO) also has a possible role in the development and persistence of hyperalgesia [70]. Proposed mechanisms for the role of NO-induced nociceptor sensitization include enhancement of the release of an algescic substance (prostaglandin E₂), inhibition of the action of an endogenous antinociceptive substance acting on peripheral nociceptors, and a direct action of NO on nociceptors [71]. In addition, central sensitization may be partially mediated by the activation of *N*-methyl-D-aspartate (NMDA) receptors with subsequent NO production. Recent animal research suggests that in the periphery, NO modulates the response to a noxious stimulus. A new class of NO-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) is being developed that releases nitric oxide in relatively small amounts over a prolonged period of time (6–12 h) [70]. Furthermore, the plasma concentration of stable NO products may be a useful predictor of subsequent development of chronic postoperative pain.

Prevention of persistent postoperative pain

The first step in prevention is to recognize that pain can occur after surgery. Of the number of interventions that have been identified to reduce chronic pain after surgery, the surgical approach is of great importance. A surgical approach that minimizes tissue and nerve damage should be used whenever possible. Because the classical posterolateral approach for thoracotomy is associated with greater tissue damage and a higher probability of nerve injury resulting in greater acute pain and a higher probability of chronic pain, it should be avoided, and an anterolateral approach should be used instead. The skill or finesse of the surgical team appears to be critical, as suggested by a low prevalence of chronic pain in specialized surgical centers [5,72–74]. The type of anesthesia (ie, general versus regional) by itself does not appear to be a significant factor.

Recent evidence suggests that achieving pain relief only at rest is not adequate and that movement-evoked (dynamic) pain relief is necessary to prevent postoperative physiologic impairment. It seems that the specific modality of pain relief is not as important as the degree of dynamic pain relief achieved. The use of multimodal analgesia techniques, which has been shown to provide optimal dynamic pain relief with minimal side effects, may prevent persistent postoperative pain. Although opioids have potent analgesic effects for spontaneous pain, they are inadequate for the treatment of movement-evoked pain. Thus, opioids may have only minimal effects in modifying neuronal plasticity and reversing established central sensitization. In contrast, local anesthetic techniques, COX-2 inhibitors, α_2 agonists, and NMDA receptor antagonists may be important for controlling movement-evoked pain and preventing central sensitization.

Conduction blockade with local anesthetics (eg, epidural analgesia and continuous peripheral nerve blockade) provides superior dynamic pain relief. When appropriate, the use of an epidural anesthesia with local anesthetics (both intraoperatively and postoperatively) may be beneficial. Because it has been theorized that persistent postsurgical pain results from sensitization, the blockade of sensitization may help with prevention. Obata et al [75] reported a significantly reduced incidence of post-thoracotomy pain at 6 months (67%–33%) when epidural analgesia with local anesthetics was administered both during and after surgery. Senturk et al [76] compared the effects of thoracic epidural analgesia with bupivacaine and morphine (initiated either preoperatively or postoperatively) or IV-PCA morphine. Patients receiving preoperative thoracic epidural analgesia experienced a significantly lower incidence of pain at 6 months (78% versus 45%) compared with IV-PCA. However, randomized controlled trials have not validated these reports [54,77,78].

Although regional analgesic techniques form the basis of postoperative pain management, current evidence suggests that combining them with COX-2 inhibitors (ie, NSAIDs and COX-2-specific inhibitors) may be more effective [79]. A combination of NSAIDs with preoperative opioids, preincisional regional block, and postoperative continuous paravertebral block or epidural block has been promoted as ideal for nearly total analgesia [60]. Several studies [80] have suggested that small doses of ketamine (an NMDA antagonist) enhance opioid analgesia, prevent tolerance to opioids, and improve pain relief as well as reduce hyperalgesia. However, at this time, the treatment recommendations are nonspecific. It is also suggested that the early use of tricyclics and anticonvulsants may be of benefit in the prevention of the neuropathic component of chronic pain. Recent studies [81] have suggested that gabapentin and pregabalin reduce postoperative morphine requirements and movement-related pain and thus may provide a “protective” effect that may diminish the hyperalgesic response to surgery. Recently, Reuben [53] reviewed various novel therapies for the prevention and treatment of chronic persistent postoperative pain, with an emphasis on CRPS. These therapies include free radical scavengers such as dimethylsulfoxide [82–86], *N*-acetylcysteine [86], vita-

min C [87,88], mannitol [89], and carnitine [90], with only dimethylsulfoxide and *N*-acetylcysteine showing some promise. The basis for the trial of these free radical scavengers is that CRPS is induced by an exaggerated inflammatory response to tissue injury caused by excessive toxic oxygen radical production [87,88]. Calcitonin [91,92] and kentanserin [93,94] have also been tried with variable but marginal success.

Summary

It is now well accepted that inadequately treated pain and associated stress response have significant physiologic and psychologic consequences, which may lead to organ dysfunction and increase postoperative mortality and morbidity. In addition, unrelieved postoperative pain reduces the ability to participate in rehabilitation programs, leading to poor postoperative outcomes. Furthermore, poorly controlled pain can potentially increase the incidence of chronic persistent postoperative pain. Thus, pain delays recovery and discharge home and reduces quality of life and patient satisfaction. Overall, inadequately treated pain increases resource use and health care costs. Therefore, an improvement in perioperative analgesia is not only desirable for humanitarian reasons but is also essential for the potential reduction in postoperative morbidity, improved health-related quality of life, and reduced health care costs.

Chronic persistent postoperative pain is common but often under-recognized or misdiagnosed. The first step in preventing persistent postoperative pain is to accept that it can occur after surgery. Despite numerous reports of persistent postoperative pain resulting in distress and disability, it has been ignored. The prevalence of chronic persistent postoperative pain appears to vary with the type of surgery as well as the surgical approach. Therefore, the use of a surgical approach that minimizes tissue trauma is crucial. However, it is not clear why some patients develop persistent pain, whereas others undergoing the same surgical procedure do not. Other risk factors include pre-existing pain, the extent of acute pain, and certain personality factors (psychologic vulnerability).

It appears that the intensity of acute postoperative pain (particularly movement-evoked pain) is an important predictor of persistent postoperative pain. Therefore, it is necessary to provide effective and rational early interventions, which reduce postoperative pain not only at rest but also on movement. Multimodal analgesia techniques, including regional analgesia (epidural analgesia or continuous peripheral nerve blocks), COX-2 inhibitors (NSAIDs and COX-2 specific inhibitors), and opioids have been recommended for providing dynamic pain relief with a lower incidence of side effects. In addition, NMDA antagonists (eg, ketamine), α_2 agonists (eg, clonidine and dexmedetomidine), and anticonvulsants (eg, gabapentin and pregabalin) have been investigated. However, the use of these adjunct analgesics remains controversial and needs to be evaluated in larger studies.

It is imperative that future acute pain studies collect appropriate data, including preoperative pain intensity and physiologic and psychologic risk factors. In addition, data regarding the location and length of surgical incisions and handling of nerves and muscles should also be obtained. Furthermore, postoperative follow-up, including quantitative and descriptive pain assessment, patient function, and physical signs and symptoms as well as postoperative interventions (eg, radiation therapy and chemotherapy), should be collected for at least 1 year. Areas of interest include identifying high-risk individuals, because focused interventions may be beneficial for these patient populations. In addition, the determination and adoption of surgical techniques that will minimize the incidence of chronic postoperative pain are imperative. It is necessary to assess the relationship between the intensity and time course of postoperative pain and the occurrence of persistent postoperative pain. Finally, prospective randomized, controlled studies are needed to determine how different pain management strategies influence the incidence of persistent postoperative pain.

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