Prevention of Chronic Postsurgical Pain: The Effect of Preventive and Multimodal Analgesia

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Chronic post-surgical pain (CPSP) is a chronic pain condition, affecting many people who have undergone surgery. The development of CPSP is complex and the treatment options are limited; therefore, postsurgical pain management is crucial for satisfactory pain relief and prevention of CPSP development. In this review, we analyzed the existing treatment modalities for patients with CPSP. The treatments include opioids, acetaminophen, N-methyl-D-aspartate (NMDA) receptor antagonists, anticonvulsants, and local anesthesia. All treatments had significant effect on CPSP and opioid-sparing effect; moreover, preventive analgesic treatment is important for improving quality of postoperative pain management. However, since most of the studies had limitations, further research on determining effective combinations and treatment modalities is required.

Keywords: chronic post-surgical pain (CPSP), enhanced recovery after surgery (ERAS), multimodal analgesia (MMA), preventive analgesia, opioids

In Taiwan, total operations were approximately four million in 2015.³ Many procedures are likely to be associated with chronic post-surgical pain (CPSP), if the postoperative pain is not managed properly. CPSP is defined as persistent pain of longer than 2 months’ duration after the surgical procedure, excluding other causes of pain such as malignancy, infection, and pre-existing pain problem.² The incidence rate of CPSP differs by surgery. In addition to the surgery type, numerous other risk factors may contribute to CPSP, including psychosocial factors, demographics, genetic predisposition, and pre-existing pain (Table 1).²

Most studies have focused on amputation, breast surgery, thoracotomies, and inguinal hernia repair because these operations are considered to be associated with a combination of nociceptive and neuropathic symptoms and show high incidence of CPSP.¹ The estimated incidence of CPSP following amputation is around 30%. Systematic reviews have summarized the frequency of CPSP after amputation; the latest published review that included data from five randomized controlled trials reported that moderate to severe chronic pain may occur in 80% of cases up to 20 years after amputation.⁴ Moreover, the incidence of persistent pain following mastectomy were reported to range from 13% to 69%.⁵ Post-mastectomy pain syndrome is attributable to surgical injury to the major peripheral nerves in the axilla during lymph node dissection.⁶,⁷ A recent prospective study found that breast implant and adjuvant radiotherapy were associated with increased CPSP.⁸ The incidence of chronic pain at 3- and 6-month post-thoracotomy was 57% and 47%, respectively.⁹ In a retrospective study, Pluimjs and colleagues found an association between the severity of CPSP and extent of surgery.¹⁰ A recent
trial showed that video-assisted thoracic surgery, with less nerve damage, had a lower incidence of CPSP and pain-related functional impairment. In a review by Aasvang, moderate-to-severe chronic groin pain and discomfort were reported in 10–12% of patients. Moreover, Bugada and colleagues found that in patients undergoing open inguinal hernia repair, CPSP was correlated with preoperative arterial hypertension.

This article reviews the most recent literature on pathophysiology of CPSP and highlights the current understanding of etiologies and treatment options for perioperative management of postoperative pain.

Preemptive and Multimodal Analgesia (MMA)

Unrelieved CPSP is linked to adverse physiological changes that increase morbidity and mortality. To improve CPSP management, several concepts have been proposed, including preemptive analgesia and MMA. Central and peripheral sensitizations are the major causes of hypersensitivity to pain after injury. Wall proposed the concept of preemptive analgesia, whereby, preoperative local anesthesia and morphine block the induction of central sensitization, thus decreasing the incidence of hyperalgesia and postoperative pain intensity. However, in a review article, Moiniche et al. suggested that there was no superiority of preemptive analgesia administered before skin incision. Moreover, several randomized clinical trials comparing postoperative pain scores and total analgesic consumption, reported no significant effect in all outcome measures.

The aim of preventive analgesia is to decrease sensitization associated with noxious stimuli in the perioperative period; moreover, duration and efficacy of perioperative analgesic regimen are more important than preemptive timing of analgesic intervention (Fig. 1). Enhanced perioperative anesthesia protocols and use of peripheral nerve blocks were reported to improve patient satisfaction after hip arthroplasty and early postoperative rehabilitation.

MMA is defined as administration of two or more analgesics or modalities through different mechanisms for postoperative analgesia. It improves postoperative pain management, has shorter duration hospital stay, and is an important management practice for enhanced recovery after surgery (ERAS). The American Society of Anesthesiologists and the American Pain Society recommend use of multimodal approach for postoperative pain control. The regimen may include a combination of opioids, acetaminophen, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitor selective NSAIDs (COX-2 inhibitors), α-2 agonists (clonidine and dexametomidine), anticonvulsants (gabapentin and pregabalin), and local anesthetic techniques during the perioperative period via various routes. In this article, we review common analgesics and techniques for postoperative pain management, as well as prevention of CPSP.

Central neuraxial routes include epidural and spinal analgesia: co-administration of local anesthetic with opioid as single bolus dose or continuous administration via epidural catheter. Evidence supports epidural analgesia as standard procedure for major thoracic and abdominal procedures with satisfactory

### Table 1. Perioperative risk factors of chronic postsurgical pain

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<tr>
<th>Preoperative factors</th>
<th>Intraoperative factors</th>
<th>Postoperative factors</th>
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<tr>
<td>Preoperative moderate to severe chronic pain</td>
<td>Surgical procedures with risk of nerve damage</td>
<td>Inadequate post-operative pain management</td>
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<td>Repeat surgery</td>
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<td>Psychological vulnerability</td>
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<td>Psychological vulnerability</td>
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<td>Preoperative anxiety</td>
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<td>Genetic predisposition</td>
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<td>Radiation therapy to area</td>
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<td>Female gender</td>
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Table 1.
The overall mortality was reduced by approximately one-third in patients who received neuraxial blockade for postoperative pain management with reduced cardiac and renal complications. Recently, a different mode for epidural analgesia was introduced. Capogna et al. reported that programmed intermittent epidural anesthetic bolus (PIEB) had less total local anesthetic consumption, fewer manual bolus doses for breakthrough pain, and greater patient satisfaction as compared to continuous epidural infusion (CEI). However, recent meta-analyses showed no reduction in patients’ mortality with perioperative epidural analgesia as compared with general anesthesia and systemic opioids for postoperative pain management. Moreover, contraindications and limitations were reported, such as spinal hematoma, epidural abscess, and technical complications, particularly in elderly patients with frequent antiplatelet treatment.

Regional ultrasound-guided peripheral nerve blocks are increasingly incorporated into MMA regimens for post-surgical pain management. TAP blocks are reported to significantly reduce morphine requirement and pain compared with placebo after abdominal surgery. Moreover, TAP block provides effective analgesia in patients in whom spinal anesthesia is contraindicated and reduces morphine consumption during the first 24 hours after surgery. A randomized triple-blind study reported that combined ilioinguinal-TAP block provided superior analgesia and reduced patient-controlled analgesia (PCA)-fentanyl dose and pain score.

Surgical site infiltration with local anesthetics provides simple, effective, and inexpensive MMA. Systematic review of RCTs reported that continuous catheter-infusion of local anesthesia into the wound improved analgesia, reduced opioid consumption and related side effects, increased patient satisfaction, and reduced hospital stay; the action mechanism involved direct blocking of pain transmission in nociceptive afferents from the wound. Intra-articular analgesic infiltration also reduced pain and opioid consumption.
after orthopedic procedures. In one study on patients with breast cancer, the wound infiltration group showed decreased CPSP and no indication for analgesia at 3- and 6-month follow-up. However, the risks associated with use of local anesthetics, including effects on the cardiac and central nervous system should be considered.

**Pharmacology of Analgesics**

Opioids are currently a major component in multimodal regimen. Intravenous or intramuscular administration of opioids has traditionally been used in management of moderate-to-severe pain. Intravenous PCA with opioid is widely used for postoperative analgesia. A recent Cochrane review reported benefits of lower visual analog score (VAS) of pain symptom and increased patient satisfaction under PCA versus non-PCA. Studies showed that continuous basal infusion of opioid in naive patients may increase the likelihood of opioid-induced respiratory depression; however, it is unclear whether the continuous infusion is a significant risk factor for respiratory depression. The disadvantages of opioids include side effects such as confusion, sedation, hypotension, constipation, dizziness, pruritus, headache, nausea, vomiting, and respiratory depression. However, acute opioid tolerance and opioid-induced hyperalgesia (OIH) have been reported in the clinical use of opioids for anesthesia and postoperative pain management. Among possible action mechanisms, increased presynaptic glutamate release and postsynaptic N-methyl-D-aspartate (NMDA) receptor activation were suggested. A recent meta-analysis, including 1,494 patients, reported that high-dose intraoperative remifentanil was associated with development of OIH and high morphine requirement at > 1 day postoperatively. Therefore, selection of opioids should be based on pharmacological profile.

Nalbuphine is a semi-synthetic opioid used for moderate to severe pain relief, with agonist action on the κ-opioid receptor, as well as antagonist action on the μ-opioid receptor. The effect of low-dose nalbuphine may be similar to that of ultra-low-dose naloxone: inhibiting morphine-μ-opioid receptor interaction-induced side effects via Gi-protein signaling. Clinical-dose nalbuphine may inhibit morphine-induced side effects while maintaining analgesic effect through κ-opioid receptor agonism; moreover, at low dose, it may enhance the analgesic effect of morphine via Gs-protein, similar to ultra-low-dose naloxone. Nalbuphine showed same potency as that of morphine with few effects on cardiovascular hemodynamics in patients without cardiac disease; in addition, it provided safe and effective treatment for prehospital conditions. Yeh and colleagues reported that combined morphine and nalbuphine in PCA decreased the incidence of pruritus. Moreover, low-dose nalbuphine combined with NSAID had superior efficacy in elderly patients undergoing elective open gastrointestinal surgery in terms of postoperative analgesia and decreased severity of postoperative nausea and vomiting (PONV). In a current meta-analysis, the analgesic efficacy of nalbuphine provided a better safety profile than morphine in the aspect of certain side effects. Recently, naldebain, a slow-release nalbuphine prodrug with long duration of action, was newly introduced in Taiwan; it delivers and maintains an effective blood level for approximately 6 days. Naldebain intramuscularly at 24-hour preoperative is recommended for attaining peak plasma concentration and shows effective postoperative pain reduction. This regimen provides preemptive analgesia and continuous postoperative pain control for at least another 5 days. It shows potential as an ideal analgesic, providing preemptive analgesia, global perioperative pain processing coverage, and may be used in combination with either morphine or NSAID for management of minor-to-moderate postoperative pain and inhibition of CPSP development.

Acetaminophen is most widely used for postoperative pain with an opioid-sparing effect of approximately 20% for mild-to-moderate pain. Previous studies have demonstrated the effectiveness of intravenous acetaminophen in decreasing postoperative pain in patients undergoing various surgical procedures. A recent Cochrane review, including 75 studies, reported that intravenous acetaminophen offered at least 50% pain relief. Nonselective NSAID and selective COX-2 inhibitors decreased inflammation by diminishing cyclooxygenase activity and provided 30–50% opioid-sparing effect. Perioperative administration of ketorolac and COX-2 inhibitors significantly decreased the required dosage of intravenous opioid, shortened the gastrointestinal recovery, and reduced the patients’ hospital stay after gastric surgery.

NMDA receptor antagonist ketamine and dextromethorphan, reduce neuroplasticity through inhibition of NMDA receptors. A systemic review reported sig-
significant reduction of CPSP at 3- and 6-months postoperatively, including thoracotomy, mastectomy, hysterectomy, and various orthopedic surgeries. However, Grady et al. reported that ketamine had no effect in improving postoperative analgesia or opioid-related side effects in patients who underwent abdominal hysterectomy. Gabapentinoids gabapentin and pregabalin, are anticonvulsants commonly used to treat neuropathic pain or fibromyalgia. The agents modulate central pain pathways through interactions with the α-2-delta subunit of voltage-dependent calcium channels. Evidence suggested that perioperative administration of gabapentin effectively reduced the incidence of CPSP. A meta-analysis confirmed that administration of pregabalin was associated with significant reduction of opioid consumption and neuropathic pain, but side effects of increased sedation, dizziness, and visual disturbance were reported.

α-2 agonist dexmedetomidine, exerted antinociceptive effect through modulation of brain-derived neurotrophic factor (BDNF) located in the central nervous system and spinal cord. Systematic review and meta-analysis confirmed that intrathecal or epidural dexmedetomidine provided postoperative and neuropathic pain relief. A randomized controlled study indicated that addition of dexmedetomidine prolonged the action duration of interscalene brachial plexus block in arthroscopic shoulder surgery; however, it was associated with increased risk of hypotension and bradycardia. Dexmedetomidine is indicated for use in anesthesia induction and intraoperative infusion; however, it is not recommended in postoperative pain management regimen. In addition, in a recent study, intraoperative dexmedetomidine infusion effectively improved analgesia during and after elective laparoscopic cholecystectomy; it also significantly reduced postoperative morphine consumption and patient with severe postoperative pain and prolonged first rescue analgesic time.

Melatonin-mediated analgesic effect possibly involves the β-endorphins, γ-aminobutyric acid (GABA) receptor, opioid receptors, and nitric oxide-arginine pathway. Early clinical trials suggested correlation between melatonin and chronic pain. Patients with chronic pain had significantly lowered melatonin levels in the blood and urine. Melatonin is also known to facilitate sleep. Particularly, pathological sleep disorder associated with sleep disturbance was reported in patients with chronic pain. Thus, melatonin has a potential role in postoperative pain management. A recent systematic meta-analysis suggested that melatonin could reduce oxidative stress and requirement of anesthetics. Likewise, our previous study showed that melatonin restored the antinoceptive effect of morphine through inhibition of spinal microglia activation in morphine-tolerant rats.

Conclusions

Chronic pain after surgery is a common occurrence. Improved management of acute postoperative pain is important to prevent development of CPSP. Preemptive analgesia is reported to have significant analgesic benefit in animal models. Therefore, its timing of administration should be based upon pharmacokinetics and type of surgery. MMA and preemptive analgesia have advantages in terms of improving postoperative pain control, and minimizing opioid consumption. However, treatment of all patients with perioperative drugs under expectation of preventing conversion to chronic pain is impractical. Researchers are faced with the challenge to predict occurrence of CPSP and identify patients at risk for its development. Further research is needed to determine the modality, analgesic regimen, and timing and duration of perioperative pain management required for prevention of CPSP.

References

Preventive Analgesia and MMA for CPSP


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