Review Article

A Conceptual Framework for Prevention of Chronic Postsurgical Pain

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Chronic postsurgical pain is one of the most common adverse events of surgery. The pain characteristics can occur as nociceptive pain and neuropathic pain or mixed, creating long-term suffering for patients. At present, there are no techniques for the prevention of this pain. However, anticipation of this condition must be done based on predictive concepts to control the risk factors, such as careful preoperative assessment, adequate perioperative pain management, adjusting surgical techniques that reduce tissue destruction, psychological support, improving physical function, and a multidisciplinary team working. Moreover, patient care needs to be considered individually in conjunction with formulating a patient care plan for each type of surgery. In particular, the International Association for the Study of Pain and the World Health Organization collaborated by establishing a definition of chronic postoperative pain and implemented it in the International Classification of Disease-11 for guidance in the study of prevalence and clinical symptoms. It will improve the strategy for the prevention and treatment of this condition.

Keywords: Prevention; Chronic pain; Persistent; Postsurgical pain

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The Lancet Commission on Global Surgery Report estimated that 313 million surgical procedures are undertaken worldwide each year[1]. Postoperative morbidity and mortality are vital as a marker to the success of the surgery. Consequently, morbidity and mortality are commonly used to measure the surgical outcome in studies. However, a potential adverse effect from surgery is chronic pain. Approximately 10% of patients suffered from chronic pain after surgery[2-4]. Chronic postsurgical pain (CPSP) affects the long-term quality of life. Therefore, there have been studies on causes and prevention methods for more than 20 years[4]. An observational study of CPSP in Europe presented that the incidence of moderate to severe CPSP at 12 months was 11.8%. Moreover, postoperative functional impairment was associated with the severity of CPSP[5]. Therefore, CPSP is a problem that affects a wide range of factors, such as increasing health costs, reduced performance, absence from work, psychological distress, and impact on family, and health system[6-8].

Previous studies on the prevention of CPSP are limited by an incomplete understanding of the pathophysiology and mechanism of the disease. Furthermore, the understanding is based on study design, type of operation, mode of pain management, outcome measurement, and unclear term definition. To improve the treatments for CPSP patients, the co-operation of the International Association for the Study of Pain (IASP) with representatives of the World Health Organization (WHO) generated a systematic classification of chronic pain by including CPSP in the current International Classification of Diseases (ICD-11)[9]. Now, medical technology is developing rapidly to keep patients safer while and it Enhanced Recovery After Surgery (ERAS). Advanced minimally invasive surgery (MIS) has less postoperative pain than extensive surgery, but the incidence of CPSP has not decreased. The transition from acute postoperative pain to CPSP is often unpredictable. This present review aimed to synthesize the updated evidence and present the conceptual framework for CPSP prevention.

The ICD-11 of CPSP

Macrae and Davies first stated CPSP in 1999[4]

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Table 1. Prevalence of chronic postsurgical pain in common surgeries[12]

	Any intensity (%)	Moderate-severe intensity (%)	Prevalence (%); prevalence (%) if restricted to a severe pain rating
Amputation of limb	30 to 85	5 to 10	Up to 85
Arthroplasty, knee	13 to 44	15	44; 15
Cesarean section	6 to 55	5 to 10	Up to 12
Cholecystectomy	3 to 50	Not reported	Not reported
Craniotomy	0 to 65	25	12 to 16
Hip replacement	27	6	27; 15
Inguinal hernia repair	5 to 63	2 to 4	6 to 29
Laminectomy and spinal fusion	10 to 40	4 to 6	5 to 36
Mastectomy	11 to 57	5 to 10	22
Coronary artery bypass graft	30 to 50	5 to 10	28; 4
Thoracotomy	5 to 65	10	48

Adapted from Glare P, et al. 2019[12]

and subsequently, it was refined by Werner and Kongsgaard[10]. However, CPSP remained underrecognized, undertreated, and limited in the epidemiological studies on the usefulness of the individual surgical procedure. The taskforce IASP and WHO proposed a CPSP definition in the ICD-11 as pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, which is a minimum of three months after surgery. The pain must be localized to the surgical site or referred to the dermatome area. Other causes of pain, such as pre-existing pain conditions, infections, or malignancy, were excluded[11]. For the diagnosis of CPSP, the ICD-11 is categorized according to a type of surgery, including chronic pain after amputation, spinal surgery, thoracotomy, breast surgery, herniotomy, hysterectomy, arthroplasty, and other specified CPSP[11].

Incidence and prevalence of CPSP

Collecting statistics on CPSP remains problematic because most studies were conducted within a single institution. Furthermore, those studies were for only one type of surgery, small sample sizes, or a retrospective study. There are also standardized limitations of pain assessment tools, including emotional, mental, performance, pain perception, and overall quality of life. Moreover, epidemiological data were also collected in these patients in the context of differences in ethnicity, language, culture, and beliefs. However, the incidence and prevalence of CPSP are consistent that they can be found in all types of surgeries. Paul et al[12] compiled the study of CPSP prevalence in the United States that showed that surgeries with an exceptionally high prevalence of severe pain, or greater than 20%, are limb amputation, thoracotomy, mastectomy, herniorrhaphy, laminectomy with spinal fusion, knee arthroplasty, and hip replacement (Table 1)[12].

Simon et al[13] conducted a systematic review of 281 studies that covered 11 types of chronic postoperative pain. Thoracic and breast surgery had similar incidences of neuropathic pain, at 66.0% and 66.7%, respectively, because it carries a high risk of nerve injury. However, knee and hip replacement surgery had a high incidence of CPSP, but the pain characteristics were more minor neuropathic pain, and caused by a chronic inflammatory pain. MIS is an option to decrease the risk of tissue injury, such as laparoscopic surgery. However, the incidence of chronic pain was not reduced[14,15].

Clinical feature of CPSP

Patients had difficulty explaining the characteristics of pain associated with CPSP, but aching pain is the most commonly described[14,16]. However, surgery may cause tissue and nerve damage. Therefore, neuropathic pain such as hyperalgesia, dysesthesia, and allodynia are frequently presented[17]. Like other chronic pain conditions, CPSP affects quality of life, especially psychological distress, sleep disturbance, and social relationships impairment[18]. Cancer patients who undergo surgery may also present with CPSP. Differential diagnosis should be ruled out for cancer recurrence or spreading to other sites.

Mechanisms of transition from acute to CPSP

The mechanism of transition from acute postoperative pain to CPSP is complex and poorly

understood. However, molecular mechanisms in animal models demonstrated the pathophysiology of these processes[19-24]. Nociceptors are sensory receptors that are activated by noxious stimuli. After an incision, nociceptive inputs produce local molecular changes by releasing many neuronal mediators from inflammatory cells such as adenosine triphosphate (ATP), K^+ and H^+ ions, bradykinin, histamine, serotonin (5-HT), prostaglandin E2 (PE2), interleukin-1β (IL-1β), interleukin-6 (IL-6), nerve growth factor (NGF), and tumor necrosis factor-alpha (TNF-α), which is referred to as an "inflammatory soup" at the site of injury[25-28]. All mediators result in activating intracellular secondary messenger systems such as protein kinase C (PKC) and protein kinase A (PKA), leading to phosphorylation and altered activity of transducer and voltage-gated ion channels[27]. Furthermore, at the dorsal root ganglia (DRG) of primary sensory neurons also increased expression of acid-sensing ion channels 3 (ASICS3), transient receptor potential cation channel subfamily V member 1 (TRPV1), and mechanistic target of rapamycin (mTOR) that develops the peripheral sensitization[28]. Peripheral changes may facilitate sustained nociceptive inputs into the dorsal horn of the spinal cord and release the neurotransmitter glutamate that acts at α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs), and trigger calcium influx, which cause neuronal membrane excitability[26]. Here, if the NMDARs continue insults from noxious stimulation or nerve injury, it will lead to neuroplasticity and glia cell activation that cause central sensitization[26,27]. Subsequently, noxious signals are passed to ascending pathway to the thalamus and then project to the corticolimbic area. After ascending projection, the descending inhibitory pain pathway projects from the periaqueductal grey (PAG) to the rostral ventromedial medulla (RVM) and sends the descending inputs directly to nociceptive neurons in the dorsal horn of the spinal cord[29]. Studies demonstrated that descending pathway plays a vital role in inhibiting and facilitating responses to noxious stimulation, which explains the cause of pre-existing pain patients risk developing CPSP[29-31]. Additionally, noxious stimulation contributes to corticolimbic plasticity, or changes in structure, activity, or connectivity, that result in psychological and behavioral change[21].

Predictive factors for CPSP

Identifying and assessing the risk factors for the potential for CPSP is essential because certain risk factors can be planned to lessen or prevent this condition. Risk factors can be divided into six domains, demographic, clinical, surgical-related, pain, psychosocial, and physical functioning as summarized in Table 2[12,32-34]. Studies have shown that demographic factors, such as females, young age, less education, seeking compensation, and smokers, are risk factors for the disease. In addition, other aspects of the patient's risks, including medical comorbidities, pain interfered with the physical function, and psychological distress, are the main risk factors for developing CPSP. There still needs to be further study for the genetics and epigenetics factors. However, the analyses of gene mutation of catechol-O-methyltransferase (COMT), opioid receptor mu 1 (OPRM1), and guanosine-5'-triphosphate cyclohydrolase 1 (GCH1) are associated with the increasing risk of chronic pain[35,36]. Studies have confirmed the importance of surgical-related factors and perioperative pain management associated with the transition from acute to CPSP[12,32-34]. From the basic knowledge of pathophysiology for pain, inadequate pain control leads to peripheral and central sensitization, disturbed sleep, and cognitive, and physical function. However, the use of high-dose or long-term opioids in the perioperative periods may result in the risk of CPSP. Opioid-induced hyperalgesia (OIH) is the primary clinical state of neuronal hypersensitivity and neuroplasticity in the central nervous system. Likewise, prolonged opioid use leads to adverse effects, addiction, and trigger or worsen symptoms of CPSP[12]. As mentioned above, the CPSP is caused by surgery that generates an inflammatory process or nerve injury. Therefore, surgical factors such as extensive surgery, long duration of operation, and complications are relevant to developing CPSP[12,32-34].

Preventing of CPSP

Because the pathophysiological studies on the mechanism of CPSP are limited, it is unclear how to prevent these states. In addition, CPSP risk factors cannot be controlled, such as genetic, gender, age, co-morbidity, or disability. However, healthcare professionals need to be knowledgeable in planning preventative strategies to reduce the risk of CPSP as some risk factors can be modified, including body mass index, preoperative pain, psychological factors, and education.

With advanced surgical techniques, MIS can reduce tissue or nerve injuries and allow the patient

Table 2. Predictive factors for chronic postsurgical pain[12]

	Subgroup with worse CPSP	Consistency of evidence
Demographic		
Age	Younger adults	Consistent
Sex	Female	Mixed
Marital status or living arrangements	Single or living alone	Mixed
Education level	Less educated	Consistent
Employment status	Unemployed	Mixed
Compensation status	Seeking compensation	Consistent
Lifestyle	Smokers	Consistent
Gene mutations	Various single gene candidates (e.g., COMT, OPRM1, GCH1)	Few data
Clinical		
Medical comorbidities	More	Consistent
Body-mass index	Higher	Mixed
Prior disability	Greater	Consistent
Surgery related		
Duration of surgery	Longer	Consistent
Surgical technique	Nerve injury	Mixed
Analgesia regimen	Systemic, reactive vs. spinal, pre-emptive	Mixed
Anesthesia	General vs. regional	Mixed
Complications	More	Consistent
Pain		
Preoperative	Present	Consistent
Postoperative, intensity	Stronger	Consistent
Postoperative, duration	>5 days	Consistent
Psychological		
Fear or anxiety	Greater	Consistent
Depression	Greater	Consistent
Pain catastrophizing	Greater	Consistent
Other psychological issues (e.g., vulnerability factors)	Present	Few data
Physical functioning		
Pain interference	Worse	Consistent

CPSP=chronic postsurgical pain; COMT=catechol-O-methyltransferase; OPRM1=opioid receptor mu 1; GCH1=guanosine-5'-triphosphate cyclohydrolase 1
Adapted from Glare P et al 2019[12]

to recover faster with less pain. However, there are inconclusive data on the prevention of CPSP definitively. A study established that 10% increase in the percentage of time in severe pain was associated with a 30% increase of CPSP incidence at 12 months[5]. Therefore, whether the surgery is a minimal or extensive incision, there is a need for adequate pain management in the perioperative phase to reduce the development of peripheral and central sensitization according to the preventive analgesia. Currently, there are studies on methods to reduce the risk.

Modification of surgical approach

MIS and laparoscopic procedures are advanced surgical techniques and have become the standard in routine operations, including robotic surgery, endoscopic surgery, and laparoscopic surgery. These techniques allow surgeons to perform safe, precise, and minor tissue damage. The other benefits of minimally invasive procedures are faster recovery after surgery, an earlier return to work, and increased patient satisfaction. MIS has been demonstrated to reduce the severity of postoperative pain. However, there is no substantial evidence that it significantly prevents the occurrence of CPSP. A retrospective study of open thoracotomy surgery (OTS) indicates that persistent thoracotomy pain syndrome (PTPS) has a significantly more common and higher chance when compared with video-assisted thoracoscopic surgery (VATS). The incidence of PTPS was 35%

and 54% (aOR 0.33; 95% CI 0.13 to 0.86) and the percentage of neuropathic pain was 18% and 48% (aOR 0.18; 95% CI 0.04 to 0.85) with VATS and OTS respectively[37]. The present study pointed out that VATS has less tissue injury but remains a significant potential for PTPS. This was confirmed with other studies that VATS is associated with a prevalence of PTSP after surgery[38,39].

The less extensive surgery for intraoperative nerve identification of the iliohypogastric, ilioinguinal, and genitofemoral nerves during inguinal hernia repair was not different in risk of development of CPSP (16%) in patients with non-identification of these nerves at six months follow-up[40]. Studies demonstrated that chronic postsurgical inguinodynia was seen in 6% in the ilioinguinal nerve-excision and 21% in the ilioinguinal nerve-preservation undergoing anterior inguinal hernia mesh repair[41,42]. One systematic review and meta-analysis provided evidence that the identification rates of the inguinal nerve were low, especially, it hardly identified the genital branch of the genitofemoral nerve[43].

In breast cancer surgery, nerve injury is the main factor in persistent postoperative pain after axillary lymph node dissection (ALND). ALND may cause damage to the branches of the intercostal nerves and the intercostobrachial nerve (ICBN). In a meta-analysis of randomized controlled trials (RCTs), preservation of the ICBN in axillary dissection is associated with significantly less sensory disturbance, especially hyposensitivity but not hypersensitivity[44].

Arthroscopy surgery of the shoulder, hip, and knee can also lead to persistent pain due to factors such as revision arthroscopy, psychological distress, preoperative pain and analgesic use, poor postoperative pain control and rehabilitation, and nerve injury[45-47].

However, MIS or less extensive surgery still has negligible impact on the prevalence of CPSP, but it significantly impacts the intensity of postoperative pain. Therefore, adequate perioperative pain management is recommended for all types of surgery.

Modification of perioperative analgesia

Based on the current understanding of the pain mechanism and pathway involved in the nociceptive and neuropathic pain, there are options for clinicians to manage pain effectively, including pharmacological and non-pharmacological intervention. Multimodal analgesia is a strategy that uses several agents or techniques, each acting at different sites of the pain pathway. The most common medication regimen includes the combinations of local or regional analgesia techniques and non-opioid analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase (COX)-2-specific inhibitors, and analgesic adjuncts such as ketamine, dexamethasone, gabapentinoids, and lidocaine. The achieved goals of perioperative pain management are to alleviate suffering, minimize adverse effects, enhance recovery after surgery, reduce the length of hospital stay, achieve patient satisfaction, and reduce the incidence of CPSP.

Modification of preoperative pain management: Preoperative patient-specific risk factors are predictors of CPSP and opioid use after surgery, especially preoperative pain at the future surgical site, which is associated with delayed pain discontinuance (HR 0.93; 95% CI 0.87 to 1.00)[48]. Moreover, both preoperative opioid use (HR 0.60; 95% CI 0.39 to 0.92) and preoperative pain outside of the surgical site (HR 0.94; 95% CI 0.89 to 1.00) are associated with delayed opioid cessation[48].

Modification of anesthetic technique:

• *Regional or neuraxial analgesia*:

From Cochrane systematic reviews, Weinstein et al found that regional anesthesia was beneficial in preventing CPSP in thoracotomy, breast surgery, cesarean section, and open abdominal surgery[49].

Performing epidural anesthesia in open thoracotomy was associated with a reduction in the incidence of CPSP at 3 to 18 months compared to systemic analgesia (OR 0.52; 95% CI 0.32 to 0.84)[49]. In a pooled 18 RCT for breast surgery, the regional anesthesia can significantly reduce chronic pain after surgery at 3 to 12 months compared with systemic analgesia (OR 0.43; 95% CI 0.28 to 0.68)[49]. Significantly, the paravertebral block is more effective for breast cancer surgery (OR 0.61; 95% CI 0.39 to 0.97). For obstetrics surgery, four RCTs were included with Cesarean Section, regional anesthesia with spinal or epidural anesthesia could reduce the risk of CPSP at 3 to 8 months after surgery (OR 0.46; 95% CI 0.28 to 0.78)[49], and spinal anesthesia would reduce the risk of CPSP better than general anesthesia[50].

In the case of limb amputation, preoperative epidural anesthesia may help reduce the incidence of CPSP, but there is still limited evidence. However, a study showed that applying perioperative epidural anesthesia can reduce the severity of phantom limb pain at 12 months[51,52]. Following open abdominal surgery, CPSP occurred significantly. Perioperative epidural analgesia is associated with a reduced incidence of CPSP after surgery at 6 to 12 months[53,54].

At present, there is insufficient evidence for the timing of epidural prior to incision or post incision for preventing CPSP. Nevertheless, earlier administration of epidural may serve more benefit[55]. There are still restrictions on the number of participants and study design on regional anesthesia for other surgeries[49].

• *Local anesthetic infiltration*:

The systematic review and meta-analysis of Weinstein et al found that local anesthetic infiltration (LAI) can reduce CPSP for breast surgery (OR 0.29; 95% CI 0.12 to 0.73) and iliac crest bone graft harvesting (OR 0.1; 95% CI 0.01 to 0.59) at 3 to 12 months[49]. However, LAI for other surgeries is not available to prevent CPSP, such as knee and hip surgeries[56].

Modification of pharmacotherapy:

• *Opioids*:

Intravenous opioid is commonly used in the perioperative for moderate to severe pain. At present, using opioids to prevent CPSP has limited support. Studies reported that intravenous patient-controlled analgesia of fentanyl reduced phantom limb pain intensity, prevalence, and frequency six months after amputation if starting 48 hours before and lasting for 48 hours after the lower-limb amputation. However, it was not significant for preventing residual limb pain[52]. Remifentanil is a short-acting strong opioid that results in hyperalgesia if using the high-dose intraoperative phase, associated with CPSP[57,58]. Nevertheless, opioids remain used for postoperative pain, but long-term use may induce opioid-related adverse events (ORAEs) such as respiratory depression, dependence, tolerance, or addiction. Therefore, opioid stewardship strategies should contribute to the perioperative program by a multifaceted team-based approach with maximizing non-pharmacologic interventions, multimodal analgesics, providing decision-support for the discreet use of opioids, and including alleviation strategies for ORAEs[59].

• *Ketamine*:

Ketamine is a non-competitive channel blocker of N-methyl-D-aspartate (NMDA) receptors at the central nervous system. It demonstrated a potent dissociative anesthetic that produced analgesia and amnesia. Ketamine has a role in perioperative pain management, which prevents wind-up in the spinal cord neurons from becoming sensitized to painful stimuli. A sub-anesthetic dose of ketamine was also studied to prevent CPSP from surgery.

Cochrane Review in 2013 found that peri-operative ketamine could reduce the incidence of any pain at 3 to 6 months if administered more than 24 hours after surgery, such as amputation, thoracotomy, abdominal surgery, breast surgery, and orthopedic surgery. Ketamine significantly decreased the incidence of moderate-to-severe pain at six months. However, most trials of perioperative ketamine were small, which could lead to the overestimation of treatment[60].

In 2021, Meg et al reported an updated systematic review and meta-analysis that identified the studies of perioperative ketamine between 2013 and 2019. It showed no effect on the prevalence of any pain at six months when administered for less than 24 hours in a risk ratio of 0.62 (95% CI 0.36 to 1.07) or more than 24 hours in a risk ratio of 0.91 (95% CI 0.74 to 1.12)[61]. Additionally, patients often reported various unusual symptoms when using ketamine, including dizziness, diplopia, delusions, hallucinations, delirium, and confusion. However, perioperative low-dose ketamine administration significantly improves pain scores and reduced opioid consumption in a wide range of surgery[62].

• *Gabapentinoids*:

Pregabalin and gabapentin are also antagonists of voltage-gated calcium channels on the presynaptic neuron, which works by binding to the alpha-2-delta subunit. These medications result in analgesic actions significantly alleviating the symptoms of neuropathic pain such as spontaneous pain, hyperalgesia, and allodynia. Neuropathic pain may also develop secondary to other pathological conditions, including CPSP.

The systematic review and meta-analysis of Meg et al[61] in 2021, which included 26 studies between 2013 and 2019, evaluated pregabalin. The study showed no treatment effects of any pain at 3, 6, or 12 months when pregabalin administration was 24 hours or less or more than 24 hours for surgery. However, the prevalence of moderate to severe pain at 3 and 6 months showed a significant overall effectiveness risk ratio if pregabalin was administered for more than 24 hours. Nevertheless, it may induce adverse effects, including dizziness, nausea, vomiting, sedation, diplopia, somnolence, visual disturbances, fainting, fatigue, constipation, and allergic reaction[63-67]. In addition, gabapentin was evaluated in 18 studies that showed no treatment effects of any pain and did not reduce the prevalence of moderate to severe pain at 3 or 6 months. Moreover, it may produce adverse effects such as sedation, dizziness, nausea, syncope, paresthesia of the legs, and elevated serum creatinine[68,69].

• *Systemic lidocaine*:

Lidocaine is an amino-amide-type local anesthetic, passing through the blood-brain barrier via passive diffusion. When used as a local anesthetic, lidocaine has a primary mechanism of action through the blockade of voltage-gated sodium channels (VGSCs).

Intravenous lidocaine infusions have shown antinociceptive in both acute and chronic pain states, especially in acute postoperative and chronic neuropathic pain, but its mechanisms are still elusive. Meg et al[61] reported a subgroup analysis of breast surgery where systemic lidocaine was found to reduce the incidence of any pain at six months statistically when lidocaine was administered for 24 hours or less, but it had no treatment effects for the prevalence of moderate to severe pain both 3 and 6 months. Therefore, systemic lidocaine for preventing CPSP should follow the new evidence.

• *Nonsteroidal anti-inflammatory drugs*:

NSAIDs are commonly used for perioperative pain management. The primary mechanism of action involves the peripheral and central inhibition of cyclooxygenase (COX) and the reduced production of prostaglandins from arachidonic acid. Perioperative NSAIDs can decrease opioid consumption and decrease adverse events related to opioids. However, the systematic review and meta-analysis by Meg et al[61] showed NSAIDs did not have an effect for preventing CPSP and did not reduce the prevalence of moderate to severe pain at 3, 6, and 12 months from surgery whether the administration of NSAIDs was less than 24 hours or more than 24 hours.

• *Corticosteroids*:

Six studies in the systematic review and meta-analysis by Meg et al[61] evaluated the use of dexamethasone and methylprednisolone for perioperative pain management. The result showed the heterogeneity of timing of outcome assessment. However, it found that administration of corticosteroids for 24 hours or less resulted in no treatment effect and could not reduce the prevalence of moderate to severe pain at 3, 6, and 12 months.

• *Nefopam*:

Nefopam is a non-opioid, non-steroidal, centrally acting analgesic drug. The recently discovered analgesic mechanisms of action are descending pain modulation by triple neurotransmitters, which are serotonin, norepinephrine, and dopamine, and reuptake inhibitors, and inhibition of long-term potentiation mediated by NMDA from the inhibition of calcium influx or blockade of voltage-sensitive sodium channels like carbamazepine. This mechanism may use nefopam as a therapeutic agent to treat neuropathic pain[70]. However, Christophe et al[71] found that using nefopam for total knee arthroplasty did not reduce the incidence of chronic pain at one year. In contrast, Hyo-Seok et al[72] used nefopam 20 mg for breast surgery and showed a statistically significant pain reduction in 24 hours and a significant reduction in chronic pain at three months with 36.6% nefopam group and 59.5% placebo group ($p<0.04$), but it was a small size trial.

• *Antidepressants*:

Antidepressants work by selective inhibitors of both serotonin (5-HT) and norepinephrine (NE) reuptake involved in descending inhibition of pain. This mechanism results in an increased activation threshold necessary to transmit painful stimuli to the brain and effective pain relief, particularly in neuropathic pain. In 2014, Karen et al[73] included 15 studies that evaluated the results of antidepressants for perioperative pain. They found insufficient evidence to support the clinical use of antidepressants to treat acute or prevent CPSP. Studies need to assess the risk-benefit ratio of antidepressants in postoperative pain management and should optimize dosing, timing, and duration of treatment.

Modification of multidisciplinary team approach

A multifaceted team-based approach plays a vital role in promoting the effectiveness of perioperative pain management. The healthcare team working process begins before admission and continues after discharge by providing the collaboration of clinical practice and process improvement with sharing goals and outcomes. Standardized perioperative strategies should maximize multimodal analgesics and non-pharmacologic therapies and cover preventive management. Collaborative practice models have now been developed to ensure that there is no gap between the management of acute pain after surgery by setting the transitional pain clinic that approaches the prevention of CPSP. The transitional pain service of Toronto General Hospital has demonstrated three-stage to reducing CPSP and monitor opioids in the long-term by using a preoperative and postoperative approach in the hospital and postoperative for the outpatient setting[7,74]. Thus, it is possible to identify the patients at risk of CPSP and opioid dependence. CPSP patients will be followed up by chronic pain service after discharge within 6 to 12 weeks and referred to a multidisciplinary team including rehabilitation, mental health service, and addiction

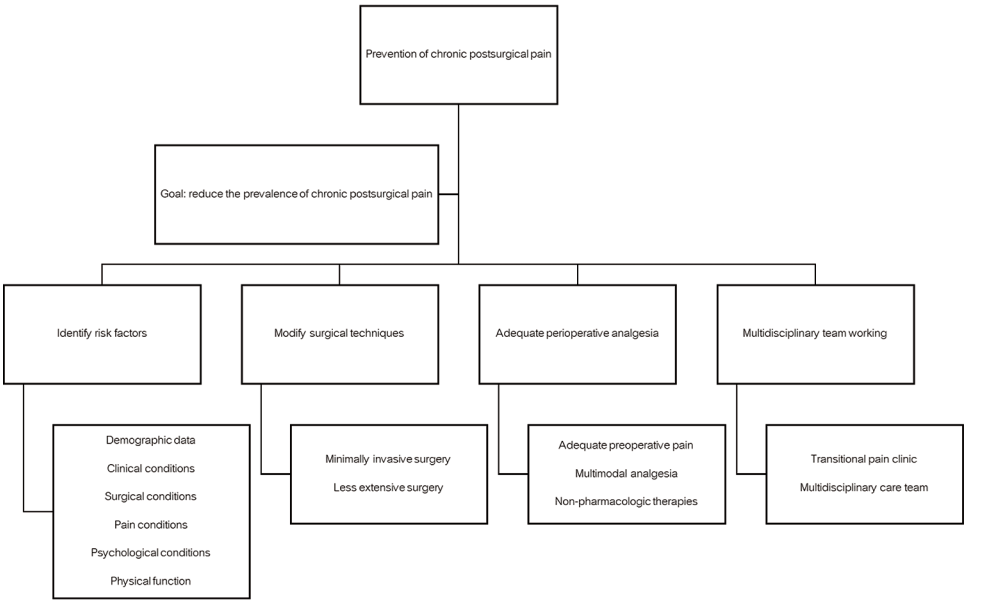

Figure 1. A conceptual framework for prevention of chronic postsurgical pain.

medicine if indicated[74]. Therefore, the transitional pain clinic can provide rapid pain management in these CPSP patients, reducing medical costs, unplanned readmissions, long-term disability, and failure to return to work.

A conceptual framework for prevention of CPSP

Although the development of CPSP has causative factors and its mechanism of action is still unknown, it is essential to note that the development of CPSP has been linked to pathogenic factors. This preventive and predictive approach can reduce the incidence of the disease. It also reduces the long-term use of opioids, increases the overall quality of life, and reduces healthcare costs. As shown in Figure 1, caring for patients undergoing surgery requires a conceptual framework to prevent this condition.

Conclusion

CPSP is a significant problem and more common from the increase in the aging population, resulting in significant growth in the demand for surgical services. At present, the mechanism is not yet known clearly. Furthermore, no medications or techniques have been found from studies to prevent the incidence of CPSP. However, adequate perioperative pain management is essential in reducing the risk of developing this condition. An analgesic method must be chosen according to the individual patient and the type of surgery.

What is already known on this topic?

CPSP is a significant problem and affects patients' overall quality of life. Preventive approaches have been demonstrated to reduce the incidence of CPSP, but it is unclear how to prevent it effectively.

What this study adds?

No single technique approach is superior to others that can prevent CPSP. The concept for reducing chronic pain after surgery consists of proper patient assessment before and after surgery, selecting a surgical technique that minimizes the tissue injury, giving adequate perioperative pain management, and providing patient care from a multidisciplinary team.

Conflicts of interest

The authors declare no conflict of interest.

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