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ABOUT COVER

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Abstract

Chronic postsurgical pain is a common surgical complication that severely reduces a patient's quality of life. Many perioperative interventions and management strategies have been developed for reducing and managing chronic postsurgical pain. Under the leadership of the Chinese Association for the Study of Pain, an editorial committee was formed for chronic postsurgical pain diagnosis and treatment by experts in relevant fields. The editorial committee composed the main content and framework of this consensus and established a working group. The working group conducted literature review (1989-2020) using key words such as "surgery", "post-surgical", "post-operative", "pain", "chronic", and "persistent" in different databases including MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. Only publications in the English language were included. The types of literature included systematic reviews, randomized controlled studies, cohort studies and case reports. This consensus was written based on clinical practice combined with literature evidence. The first draft of the consensus was rigorously reviewed and edited by all the editorial committee experts before being finalized. The level of evidence was assessed by methodological experts based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence. The strength of recommendation was evaluated by all editorial committee experts, and the opinions of most experts were adopted as the final decision. The recommendation level "strong" generally refers to recommendations based on high-level evidence and consistency between clinical behavior and expected results. The recommendation level "weak" generally refers to the uncertainty between clinical behavior and expected results based on low-level evidence.

Key Words: Chronic postsurgical pain; Treatment; Interventional; Prevention

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Core Tip: Chronic post-surgical pain (CPSP) is a common surgical complication. An editorial committee of experts in relevant fields was organized by the Chinese Association for the Study of Pain to draft this expert consensus. This expert consensus includes the definition, risk factors, pathogenesis, clinical manifestations, treatment and prevention of CPSP. It describes various treatments of CPSP with their associated recommendation levels, based on the clinical practice and literature references. This consensus also proposes the responsibilities and collaboration for surgeons, anesthesiologists and pain physicians in the management of CPSP, which will have significance in guiding the clinical practice.

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INTRODUCTION

Chronic post-surgical pain (CPSP) is one of the most common surgical-related complications despite continuous improvements in surgical procedures, more aggressive acute pain interventions and the use of multiple preventive measures. CPSP is defined as the presence of surgical-related pain for more than 3 mo post-surgery, not including pain caused by explicit reasons (such as chronic infection, recurrence of malignant tumor, etc.)^[1]. Some propose that pain lasting more than 2 mo after surgery be called persistent post-surgical pain. The incidence of CPSP varies with the type of operation: Thoracotomy (approximately 50%)^[2], mastectomy (20%-50%)^[3] and amputation (30%-80%)^[4]. Investigations have found that CPSP is common in major

surgeries as well as certain minor surgeries such as herniorrhaphy and cesarean section^[5,6]. Due to the lack of comprehensive understanding of its mechanisms and treatments, the negative effects of CPSP on a patient's postoperative quality of life are increasingly prominent. Surgical trauma like CPSP is a planned injury that should be minimized as much as possible, which requires more research in this area.

RISK FACTORS

The risk factors of CPSP include three broad aspects: preoperative factors, surgical factors and postoperative factors (Table 1)^[7-14]. Understanding and identifying these risk factors can help in the screening of high-risk patients, which would enable physicians to formulate a more specific perioperative pain management program. This, in turn, can help improve the postoperative analgesia and reduce the occurrence of CPSP.

PATHOGENESIS

The occurrence of CPSP is a complex process, including physiological, psychological, social and environmental factors. However, the pathogenesis of CPSP has not been fully understood. The general view is that surgically related tissue damage and its persistent inflammatory response eventually lead to sensitization of the peripheral and central nervous system, which facilitates the development of CPSP.

Peripheral sensitization

After tissue damage, sustained local stimulation causes a decrease in peripheral nociceptor threshold. Inflammatory factors, such as bradykinin, prostaglandin and substance P, are produced at the injury site. These inflammatory factors cause upregulation of the transient receptor potential vanillin subtype 1 receptor^[15], voltage-dependent sodium channels^[16] and voltage-dependent calcium channels^[17].

Central sensitization

Persistent signals from the peripheral nervous system cause central nervous system sensitization. Excitatory neurotransmitters (*e.g.*, substance P, glutamate) cause increased excitability in secondary neurons of the spinal dorsal horn. GABAergic interneurons reduce their inhibition of the endogenous analgesic descending inhibitory system^[18]. The inhibitory effect of the descending 5-hydroxytryptamine pathway on nociceptive signals in spinal cord processing becomes significantly reduced^[19]. Increased excitability of the gray matter region-medullary medulla ventral medial nucleus axis also takes place^[20].

MANIFESTATIONS AND DIAGNOSIS

CPSP is manifested as neuropathic pain, such as spontaneous pain, hyperalgesia and allodynia. However, its specific characteristics vary by surgery. CPSP after thoracotomy is manifested as pins and needles, burning or electric-like sensation in the surgical wound and corresponding area innervated by the intercostal nerve. It is also frequently accompanied by numbness, formication, feeling cold or hot and foreign body sensation. CPSP after mastectomy is characterized by persistent burning, pins and needles and electric-like sensation or bursting pain in the surgical area, lateral chest, armpit and anterior medial upper arm. It may be accompanied by numbness and hypoesthesia. After joint replacement, CPSP is typically characterized by joint soreness and faint pain. However, some patients may have dragging pain and joint stiffness, while a few patients may have the characteristics of neuropathic pain and sensory disturbances. Chronic pain after amputation can be categorized as stump pain and phantom limb pain. Stump pain usually occurs at the amputation site after the wound has been healed for a period time, and it has a major neuropathic component. Phantom limb pain is ongoing pain felt in parts of the body that have been amputated. It mostly occurs at the distal end of the limb. Sensations caused by phantom limb pain include electrical shock, cutting, bursting or burning.

CPSP can cause psychiatric dysfunctions, such as anxiety, depression and pain, catastrophizing in some patients. The existence of sleep disorders is also very

Table 1 Risk factors for chronic postsurgical pain^[7-14]

Risk factors for CPSP ^[7-14]	
Preoperative factors	Preoperative chronic pain; psychological factors (depression, anxiety, pain catastrophizing and fear of surgery); smoking; younger age; female gender; genetic susceptibility
Surgical factors	Type and site of surgery (amputation, breast cancer, thoracotomy, hysterectomy, inguinal hernia repair, cesarean section); surgical technique (open surgery > laparoscopy and thoracoscopy, traditional hernia repair > tension-free hernia repair); extensive use of electric knife; long operation time; infection on incision site; nerve damage or compression
Postoperative factors	Severe acute postoperative pain; opioid use (high doses of opioids can cause hyperalgesia and may be related to NMDA receptor activation); neuropathic pain (early postoperative neuropathic pain is prone to chronic); complication (cardiovascular, respiratory, renal/gastrointestinal, wound, thrombotic or neural)

CPSP: Chronic post-surgical pain; NMDA: N methyl D aspartate.

common, including difficulty falling asleep, waking up early, poor sleep quality and nightmares. Patients with severe symptoms also experience reduced work and social capacity.

The diagnosis of CPSP requires the following five criteria: (1) Appearance after surgical trauma; (2) Lasting for at least 3 mo; (3) Continuation of immediate or delayed acute pain after surgery; (4) Located on, but not limited to, the surgical area and/or the innervated area of the affected nerve; and (5) Exclusion of other causes, such as chronic infection, malignant tumor recurrence, *etc.* Neuroelectrophysiological examination can determine the location and extent of nerve injury and predict the prognosis early and accurately. Infrared thermography helps to evaluate pain severity and treatment outcomes.

TREATMENT

Medication

Most CPSP symptoms have neuropathic pain properties; therefore, pharmacotherapy for neuropathic pain is currently recommended. Common drugs included in its management are anticonvulsants, antidepressants and analgesics (Table 2)^[21].

Interventional therapy

Nerve block: Depending on the location of the pain, a nerve block in the corresponding innervation area may be possible. A mixture of local anesthetics and glucocorticoids is commonly used. Nerve block can stop the transmission of pain signals, inhibit neuroinflammation and promote neural function recovery.

Thoracic epidural block, thoracic paravertebral nerve block, erector spinae plane block, anterior serratus plane block, intercostal nerve block and local infiltration can relieve chronic pain after thoracotomy and breast surgery [Level (LE): 5; strength of recommendation (SR): Strong] (Table 3). Lumbar epidural block, lumbar paravertebral nerve block and posterior medial branch of spinal nerve block can relieve chronic pain after spinal surgery (LE: 5; SR: Strong). Transversus abdominis plane block can relieve chronic abdominal pain after open abdominal surgery and laparoscopic surgery^[22] (LE: 4; SR: Strong). Ilioinguinal/iliohypogastric nerve block can relieve chronic post-herniorrhaphy groin pain^[23] (LE: 3b; SR: Strong).

Nerve modulation: Nerve modulation promotes neural function recovery by regulating the central, peripheral or autonomic nervous system.

(1) Pulsed radiofrequency (PRF): PRF is one of the most commonly used neuro-modulation methods. A pulse current is transmitted to the peripheral nerve, which regulates the excitability of the affected neuron by changing the electromagnetic field. Parameters such as pulse frequency, pulse duration, voltage, tissue temperature and duration should be adjusted in the operation to achieve the best therapeutic effect.

PRF of stellate ganglion can alleviate chronic pain after breast surgery^[24] (LE: 1b; SR: Strong). PRF of the dorsal root ganglion of T2 and T3 can alleviate chronic pain after breast surgery^[25] (LE: 4; SR: Strong). PRF of thoracic dorsal root ganglion can alleviate chronic pain after thoracotomy^[26] (LE: 3b; SR: Strong). PRF of lumbar dorsal root ganglion can alleviate chronic post-amputation phantom pain and stump pain^[27,28] (LE: 4; SR: Strong). PRF of the ilioinguinal nerve and genital branch of the genitofemoral nerve can alleviate chronic post-surgical orchialgia caused by groin surgery^[29] (LE: 1b;

Table 2 Algorithm for pharmacotherapy of chronic post-surgical pain

Algorithm for pharmacotherapy of CPSP	
First-line therapy	Gabapentin; pregabalin; duloxetine; venlafaxine; tricyclic antidepressants
Second-line therapy	Capsaicin cream/patch; lidocaine cream/patch; tramadol; paracetamol dihydrocodeine
Third-line therapy	Strong opioids; botulinum toxin type A

CPSP: Chronic post-surgical pain.

Table 3 Oxford Centre for Evidence-Based Medicine levels of evidence

Level	Therapy/prevention, etiology/harm
1a	Systematic review of RCTs
1b	RCT
1c	"All-or-none"
2a	Systematic review of cohort studies
2b	Cohort study or poor RCT
2c	"Outcomes" research; ecological studies
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without critical appraisal, or based on physiology, bench research or "first principles"

RCT: Randomized controlled trial.

SR: Strong).

(2) Spinal cord stimulation (SCS): SCS can regulate pain-related signaling pathways and neurotransmitter balance and inflammation and pain-related neuropeptide levels. It can be considered for patients who have failed to respond to conventional drugs and physical, psychological and nerve block therapies.

SCS can be used to treat intractable chronic pain after lumbar surgery. High-frequency spinal cord stimulation is superior to traditional low-frequency stimulation. However, it is necessary to fully understand the indications and contraindications^[30] (LE: 1a; SR: Strong). For intractable chronic post-surgical abdominal wall pain, chronic post-amputation phantom pain or stump pain and chronic pain after limb fracture surgery, *etc.*, SCS can be considered if a temporary stimulation test is effective (LE: 5; SR: Weak).

(3) Intrathecal drug delivery systems: Continuous subarachnoid infusion of opioids, local anesthetics or clonidine has a definitive therapeutic effect on nociceptive pain as well as a good analgesic effect on intractable neuropathic pain. After full evaluation and comprehensive consideration, it can be used to treat intractable chronic pain after abdominal and limb surgery (LE: 5; SR: Weak).

(4) Others: Transcutaneous electrical nerve stimulation, repeated transcranial magnetic stimulation and transcranial direct current stimulation can improve pain to some extent. They can be used as adjuvant therapy for chronic pain after thoracotomy, breast surgery, joint replacement and limb surgery. For example, transcutaneous electrical nerve stimulation can relieve phantom limb pain for a short time^[31] (LE: 2b; SR: Weak).

Neurolysis: Neurolysis can be considered for intractable CPSP with clear nerve location and no pain relief after routine treatment. Common techniques include physical methods (radiofrequency thermocoagulation), chemical methods (alcohol, phenol) and surgical resection. However, nerve damage from neurolysis can lead to paresthesia or loss of the corresponding innervation area. At the same time, there is a risk of recurrence of CPSP and appearance of new pain after the procedure. Therefore, a cautious decision must be made after carefully weighing the advantages and

disadvantages.

Radiofrequency thermocoagulation of stellate ganglia can relieve chronic pain after breast surgery^[24] (LE: 1b; SR: Weak). Surgical intercostal neurolysis can relieve chronic pain after thoracotomy^[32] (LE: 4; SR: Weak).

Physical therapy/cognitive behavioral therapy

Physical therapy (manual therapy, rehabilitation exercise, myofascial trigger point therapy, extracorporeal shock wave therapy, ultrasound therapy, laser therapy, *etc.*) can reduce muscle spasms, improve blood circulation, regulate peripheral nerve activity and promote the restoration of mechanical balance. Cognitive behavioral therapy is the use of cognitive and behavioral techniques to change the patient's poor cognition and break the vicious cycle of psychological factors in order to significantly reduce pain and improve pain-related physical and emotional disorders^[33].

Cognitive behavioral-based physical therapy can promote the recovery of chronic pain after lumbar spine surgery^[34] (LE: 1b; SR: Strong). Myofascial trigger point therapy combined with rehabilitation exercise can relieve chronic pain after total knee arthroplasty^[35] (LE: 4; SR: Strong). Considering the universality of physical therapy and cognitive behavioral therapy, they can be used for the treatment of chronic pain after various surgeries when necessary (LE: 5; SR: Strong).

Traditional Chinese medicine

Acupuncture is a treasure in traditional Chinese medicine. It acts on the corresponding acupoints of the human body to regulate Yin and Yang, dredge the meridians and collaterals, promote blood circulation and remove blood stasis. Acupuncture can alleviate postoperative pain, reduce the use of opioids and promote a patient's functional recovery^[36]. Acupuncture can be used to treat chronic pain after thoracotomy, breast surgery, abdominal surgery, spinal surgery, arthroplasty and limb surgery (LE: 1a; SR: Strong).

PREVENTION

The high prevalence and long course of CPSP severely affect the postoperative quality of life for patients with this condition. Identifying high-risk patients for CPSP, conducting relevant psychological interventions and instituting effective preventative measures can lead to significant social and economic benefits. First, a comprehensive analysis of the patient's condition must be made to develop the optimum surgical plan and minimize neural tissue damage. Next, an individualized multimodal analgesic program, given the complexity of the pathogenesis of chronic pain, can be provided. If CPSP does occur, treatment from pain specialists should be performed as soon as possible.

Optimized surgical procedure

The surgeon should evaluate for an optimized surgical plan based on the benefits and risks for the patients and minimize intraoperative tissue and nerve damage. Compared with open surgery, laparoscopic surgery can reduce the occurrence of CPSP in inguinal hernia repair, and patients recover more quickly after surgery^[37] (LE: 1a; SR: Strong). Compared with open lobectomy, thoracoscopic lobectomy can significantly reduce the incidence of CPSP^[38] (LE: 4; SR: Strong).

Multimodal analgesia

Multimodal analgesia refers to the use of pharmacology and other forms of intervention that target the peripheral and central nervous systems to alleviate acute postoperative pain and reduce the use of opioids and related side effects. The concept of multimodal analgesia has been widely accepted, and most medical centers have developed their own plans for different surgeries.

Regional anesthesia can significantly reduce the incidence of CPSP: Thoracic epidural block can be used to prevent chronic pain after thoracotomy^[39] (LE: 1a; SR: Strong). Thoracic paravertebral nerve block does little to prevent chronic pain after breast surgery^[40]. It can be used as an effective analgesic measure during and after surgery, but it is inadequate as a preventive measure to reduce CPSP (LE: 1b; SR: Strong). Transversus abdominis plane block or quadratus lumborum block does little to prevent chronic pain after caesarean section^[41]. It can be used as an effective

analgesic measure during and after surgery, but it is inadequate as a preventive measure to reduce CPSP (LE: 3b; SR: Strong).

Preventive analgesia: The main drugs used are lidocaine, antidepressants and anticonvulsants, but conclusions appear heterogeneous. Intravenous infusion of lidocaine can be used to prevent chronic pain after breast surgery to some extent^[42]. Recommended dosage is 1.5 mg/kg bolus followed by 2 mg/kg/h (LE: 1a; SR: Strong). Venlafaxine (antidepressant) can be used to prevent chronic pain after breast surgery^[43]. Recommended dosage is 37.5 mg/d for 10 d starting the night before surgery (LE: 1b; SR: Weak). Increasing evidence suggests that prophylactic gabapentin and pregabalin (anticonvulsants) have little effect on CPSP prevention^[44,45]. Routine preventive use is not recommended, except in high-risk patients (LE: 1a; SR: Strong).

Psychological intervention

It is important to fully communicate with the patient about the surgical plan and expected results before surgery. For major operations, such as orthopedic surgery, thoracotomy and abdominal surgery, patients with psychological difficulties should be identified in time and provided with perioperative cognitive behavioral therapy and relaxation therapy to reduce the incidence of CPSP^[46] (LE: 1a; SR: Strong).

Rehabilitation

It is recommended to develop a customized postoperative rehabilitation training plan based on different surgical procedures. Active rehabilitation training after surgery can reduce swelling in the surgical area and surrounding tissues, reduce tissue adhesion, accelerate organ function recovery, improve joint mobility and thereby reduce the incidence of CPSP (LE: 5; SR: Strong).

DIVISION AND COOPERATION

The specialists who are closely involved in CPSP include surgeons, anesthesiologists and pain physicians. Cooperation between them can maximize the benefit to the patient. Because CPSP is a common complication associated with surgery, the surgeon is obliged to try to reduce its incidence by screening patients, optimizing the surgical plan and completing the operation carefully. However, most surgeons focus their clinical work on the management of the primary disease. Anesthesiologists and pain physicians are primarily responsible for managing pain, with the former providing perioperative analgesia and the latter providing postoperative chronic pain management. Postoperative acute pain chronicization is a continuous pathophysiological process, which requires continuous clinical attention and management. In practice, anesthesiologists and pain physicians perform their respective responsibilities, leaving a middle period unattended, which makes it impossible to effectively control CPSP in time. In order to seamlessly connect the work of surgeons, anesthesiologists and pain physicians to ensure the continuity of postoperative pain management, the division of labor and cooperation between these specialties needs to be clarified (Table 4).

CONCLUSION

Due to the complex nature of CPSP, preventive measures are not well established, though it is now known that CPSP cannot be prevented by a singular measure. The occurrence of CPSP can be reduced by actively managing postoperative acute pain through multimodal analgesia, targeted at peripheral and central mechanism accompanied by psychological intervention. When CPSP occurs, pain management should be performed at the earliest possible time. The close cooperation of anesthesiologists and pain physicians will likewise help reduce the incidence of CPSP. The key to effective management of CPSP is early detection coupled by early diagnosis and early treatment.

Table 4 Division and cooperation between surgeons, anesthesiologists and pain physicians

Division and cooperation between surgeons, anesthesiologists and pain physicians	
Surgeon	(1) Optimize surgical methods based on the principle of minimizing tissue trauma; (2) Communicate with the anesthesiologist before surgery to negotiate the best anesthesia plan; and (3) Provide preventive medication and necessary psychological intervention for patients at high risk of CPSP
Anesthesiologist	(1) Carefully evaluate the patient's medical history, including chronic pain, opioid use, drug abuse and mental illness. Screen for patients at high risk of CPSP; (2) Educate patients and their families. Inform them about the possible challenges of perioperative analgesia and the risks of CPSP; (3) Communicate with the surgeon before the operation to understand the surgical method and discuss the best anesthesia plan; (4) Establish perioperative pain management files; (5) Based on a comprehensive assessment of the patient's condition, an individualized multimodal analgesic plan is formulated; (6) Carefully evaluate and record the analgesic effect on the patient; (7) If the patient does not have good postoperative analgesia and uses high-dose opioids, the pain management file should be transferred to the pain physician 1 wk after the operation; and (8) Based on the follow-up results and the latest progress on research, continue to summarize and optimize the analgesia schemes for different surgical operations
Pain physician	(1) Review the perioperative pain management files after taking over the patient; (2) Carefully analyze the nature and source of pain and develop a corresponding treatment plan; (3) Establish a follow-up mechanism; (4) If CPSP occurs, provide pain management in time; and (5) Regularly discuss difficult cases of CPSP with surgeons and anesthesiologists. Summarize risk factors and feedback treatment effect. Discuss further optimization of perioperative analgesia plan and preventive measures

CPSP: Chronic post-surgical pain.

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