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Chronic post-surgical pain after total knee arthroplasty: a narrative review

Dan Luo[1,2†], Zhidong Fan[1,2*†] and Wenqin Yin[3*†]

Abstract

Total knee arthroplasty (TKA) is an efficacious treatment for end-stage knee osteoarthritis, often accompanied by severe postoperative pain. In certain patients, this pain can persist for over 3 months and is referred to as chronic post-surgical pain (CPSP). Postoperative persistent pain has emerged as a significant and noteworthy issue impacting patient quality of life following TKA. The etiology of CPSP after TKA is multifaceted. Peripheral or central sensitizations resulting from inflammatory reactions, nerve injury, and neurobiological mechanisms are the primary mechanisms contributing to chronic persistent pain after TKA. Preoperative, intraoperative, and postoperative factors can induce pain sensitization. Once CPSP occurs after TKA, it significantly hampers patient recovery with challenging treatment options. Currently, among the preventive and therapeutic strategies for chronic pain after TKA, it is widely believed that early comprehensive preventive treatment to prevent acute to chronic pain transition can substantially reduce the incidence of CPSP following TKA. In recent years, studies have investigated perioperative strategies aimed at reducing the occurrence of persistent pain after TKA. This article provides an overview of advancements in understanding the pathogenesis, high-risk factors, and preventive measures for chronic pain following TKA. We hope that this review will guide future research directions on CPSP after TKA while contributing to clinical perioperative pain management.

Key points

What do we know about CPSP after TKA: CPSP after TKA is a key factor affecting the long-term quality of life and satisfaction of patients, and has always been a clinical concern. At present, the etiology and pathogenesis of CPSP after TKA are still not completely clear. Existing evidence shows that there are great clinical differences in the prevention and treatment of CPSP, and the results of researches are also quite heterogeneous.

What this review article can provide further: We hope that by summarizing the latest research progress, we can provide some references for perioperative analgesia of TKA, and point out the direction for the research of CPSP after TKA.

Keywords TKA, CPSP, Pathogenesis, High-risk factors, Prevention, Treatment

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Introduction

Knee osteoarthritis (KOA) is a pathological condition involving joint degeneration caused by local injury, inflammation, and chronic strain of the knee and is characterized by joint pain and dysfunction caused by degeneration and destruction of the articular cartilage (Glyn-Jones et al. 2015). Synovitis (inflammation of the synovial membrane), which is characterized by synovial hyperplasia, diffuse T and B lymphocytes, or perivascular infiltration, is considered a fundamental feature of KOA (Martel-Pelletier et al. 2016; Scanzello and Goldring 2012). Nearly 40% of people over the age of 65 are thought to have knee osteoarthritis, and the incidence is steadily increasing (Springer et al. 2020). Total knee arthroplasty (TKA) is an effective treatment for advanced KOA and has achieved remarkable results in improving patients' quality of life and relieving pain (Joice et al. 2017). However, patients who undergo TKA not only experience severe pain in the early stage after surgery, which leads to adverse events such as limited knee functional exercise and prolonged discharge time, but also approximately 20% of them experience long-term persistent pain (Liu et al. 2012; Kim et al. 2015). A study in the USA investigated the incidence of chronic pain 1 year after knee arthroplasty, which was found to be approximately 53% (Liu et al. 2012). Kim et al. reported that the incidence of chronic pain in female patients with knee osteoarthropathy 3 months after TKA was 16% (Liu et al. 2012; Kim et al. 2015). The International Association for Pain Research (IASP), in the new International Classification of Diseases (ICD) for Chronic Postoperative and Post-traumatic Pain (ICD-11), refers to this pain for more than 3 months as chronic post-surgical pain (CPSP) (Schug et al. 2019; Werner and Kongsgaard 2014). CPSP after TKA affects patients' quality of life and satisfaction with surgery, which is a clinical problem that has been widely studied by the medical community but has not been completely solved. For these patients, researchers have been trying to identify the causes of pain and explore effective prevention and treatment strategies.

This article reviews the latest research progress on the possible causes, mechanisms, risk factors, prevention, and treatment of persistent pain after TKA. We gathered evidence from clinical studies about CPSP after TKA in the past decade and provided low- to moderate-quality evidence to guide the perioperative and postdischarge pain management of patients undergoing TKA.

Mechanism of CPSP after TKA

The mechanism of CPSP after TKA is very complex. At present, the possible underlying mechanisms include inflammatory reactions, neuropathic injury, and neurobiological mechanisms (Chapman and Vierck 2017).

Inflammatory reactions

Peripheral sensitization

Peripheral inflammation plays an important role throughout the perioperative period. After TKA, the body will undergo a protective inflammatory reaction, which is an important part of innate immunity after injury and a necessary step in promoting wound repair (Ren and Dubner 2010). The release of substance P, calcitonin gene-related peptide (CGRP), and neurokinin A (NKA) from the knee during acute inflammation leads to acute pain, which is usually gradually relieved during wound healing. When the wound is poorly repaired, the chronic inflammation at the knee can persist, leading to the occurrence of CPSP (Rashiq and Dick 2014). Surgical trauma and the release of inflammatory mediators such as histamine, bradykinin, 5-HT, tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) are the main causes of CPSP.

Necrotic cells around the knee release adenosine triphosphate (ATP) and danger-associated molecular patterns (DAMPs) to activate mast cell surface receptors, leading to further release of vasoactive amines such as histamine and 5-hydroxytryptamine (5-HT), which can directly sensitize the injury-inducing sensory neurons. Moreover, several pro-inflammatory cytokines such as interleukin-1β and TNF-α are released around the knee (Deumens et al. 2013). In addition, DAMPs can cause macrophages to aggregate and activate and release chemokines such as CCL2 and CX3CL1 (Kiguchi et al. 2012). These pro-inflammatory cytokines can directly or indirectly activate protein kinase A, protein kinase C, mitogen-activated protein kinase (MAPK), and other complex signal transduction pathways in neurons, thereby reducing the excitation threshold of peripheral neurons and generating peripheral sensitization (Ellis and Bennett 2013).

Central sensitization

Although the specific mechanism of the central inflammatory response in CPSP is still unclear, previous studies have shown that the central inflammatory response can enhance the spinal cord nociceptive reflex arc and sensitize the body to nociceptive stimuli (Kiguchi et al. 2012; Ellis and Bennett 2013; Woolf 2011). When peripheral nociceptive receptors are sensitized by surgical injury, many abnormal excitatory electrical activities are transmitted to spinal cord posterior horn neurons, resulting in abnormal opening of calcium ion channels in the presynaptic membrane, significant enhancement of abnormal discharge, and increased release of inflammatory factors

such as substance P, CCL2, and ATP. This can promote the infiltration of many spinal dorsal horn glial cell (microglia and astrocytes) infiltration and further release IL-1β, cathepsin S, bone-derived growth factor (BDGF), and other inflammatory factors (Nadeau et al. 2011).

In addition to directly causing the sensitization of peripheral nociceptive receptors, IL-1β in the dorsal horn of the spinal cord can also indirectly play a pro-inflammatory role by mediating the increased synthesis of many other pro-inflammatory cytokines (such as IL-6 and TNF-α) (Gabayl et al. 2011). In addition, BDGF released by the presynaptic membrane and microglia binds to tropomyosin receptor kinase B (TrkB) in the postsynaptic membrane, depolarizes the postsynaptic membrane, increases electrical activity, and promotes central sensitization and neuronal remodeling (Clark et al. 2010). This further promotes the formation of CPSP.

Nerve injury

At present, it is believed that neuropathic pain caused by peripheral nerve injury leading to secondary nerve inflammation is one of the mechanisms of CPSP after TKA. Some patients who undergo TKA exhibit neuropathic pain, such as burning or electric shock-like pain, accompanied by hypersensitivity, hypoesthesia, dullness, and induced tenderness (Haroutiunian et al. 2013). After peripheral nerve injury, continuous spontaneous abnormal discharges of neurons in the injured area and dorsal root ganglion cause sensitization of the spinal cord, which leads to neuropathic pain. During TKA, the peripheral nerves of the knee, such as the infrapatellar branch of the sciatic nerve, are affected. Such peripheral nerve injury is one of the leading causes of the high incidence of CPSP after TKA (Steegers et al. 2008). All or part of nerve injury may lead to chronic postoperative pain, but not all intraoperative nerve injuries cause CPSP (Ivens et al. 1992). For example, injury to some skin nerve fibers is not associated with CPSP. Notably, patients who do not experience nerve injury during surgery are also likely to develop CPSP. Therefore, in addition to nerve injury, other influencing factors lead to the occurrence of CPSP after TKA (Katz and Seltzer 2009).

Neurobiological mechanism

The interaction between the nervous system and the immune system is an important factor in the development of CPSP. In the inflammatory cascade caused by nerve injury, the release of immunomodulatory and pro-inflammatory cytokines promotes the production of CPSP, in which neurogliocyte, chemokines, and toll-like receptors (TLRs) play important roles in the neuroimmune response (Skaper et al. 2012, 2014).

Neurogliocytes

When the body is stimulated, microglia are rapidly activated, and activated microglia migrate to the dorsal horn of the spinal cord, secrete pro-inflammatory substances, and rapidly proliferate. They are a major source of inflammatory mediators in the central nervous system (Skaper et al. 2012). Once activated, microglia remain activated, which may be important factors in central sensitization. Astrocytes, which maintain the blood–brain barrier and nourish neurons, interact with mast cells to produce inflammatory responses and aggravate central sensitization (Skaper et al. 2012, 2014).

Chemokines

Chemokines and their receptors mediate the interaction between spinal dorsal horn glial cells and neurons and play important roles in the occurrence of neuropathic pain induced by nerve injury (Kalliomäki et al. 2013). At present, the chemokines and their receptors related to CPSP are mainly CX3CL1/CX3CR1, CCL2/CCR2, etc. The expression of CX3CR1 in microglia is significantly upregulated when the peripheral nerve of the knee joint produces neuropathic pain. CX3CL1 promotes the recruitment of microglia by upregulating CX3CR1. Moreover, the combination of CX3CL1 and CX3CR1 causes the phosphorylation of p38 MAPK in microglia, activates the p38 MAPK signal transduction pathway, releases a variety of pro-inflammatory cytokines, and further sensitizes central neurons (Lee et al. 2010). Peripheral or central nerve injury can increase CCL2/CCR2 expression in microglia and astrocytes of the spinal cord and dorsal root ganglion (Clark et al. 2011). CCL2/CCR2 is involved in central sensitization and chronic pain regulation by mediating glial cell-neuron interactions during neuroinflammatory responses to surgically injured peripheral nerves (Steenwinckel et al. 2011).

Toll-like receptors (TLRs)

TLRs are pattern recognition receptors of the body's immune system that can sense injurious stimuli and transmit stimulus signals to other neurons and immune cells. Animal experiments have shown that TLR4 activates glial cells through a cascade of pro-inflammatory signals (Yang et al. 2015). Peirs and Seal suggested that the increase in TLR4 levels may be a marker of activated microglia, indicating that TLR4 may be an important indicator for predicting the occurrence of CPSP (Peirs and Seal 2015). Du et al. confirmed for the first time that the selective infiltration of CD4+α β T cells into the spinal nerve root capsule can lead to mechanical pain sensitization, and the spinal root capsule is the site where nerve immune cells play an important role after

peripheral nerve injury for the first time, which provides an anatomical basis for the study of the role of immune cells in chronic pain (Du et al. 2018). Notably, the situation of each patient is unique, and the mechanism of chronic pain may also be the result of a combination of factors.

Risk factors for CPSP after TKA

It is extremely important to predict the risk factors for CPSP after TKA, especially for those areas that can improve or improve in advance. Many risk factors are often not independent but interrelated (Glare et al. 2019; Schug and Bruce 2017). The following will summarize the risk factors for CPSP from three dimensions: preoperative, intraoperative, and postoperative.

Preoperative factors

The general features are shown in the following Table 1.

Pain catastrophizing

Pain catastrophizing (PC) is an exaggerated and negative form of pain (Sullivan et al. 1995). As one of the main negative psychological emotions related to pain, pain catastrophe can regulate the pain experience through a variety of mechanisms. However, there is no consensus on the effect of PC on the outcome of CPSP after TKA. Recent studies have shown that this may be an important risk factor leading to poor TKA outcomes. To clarify this effect, a systematic review reviewed the literature thus far on pain catastrophe as a prospective predictor of CPSP after TKA, but in five assessed studies, pain catastrophe was identified as an important predictor of chronic pain lasting more than 3 months after TKA (Burns et al. 2015). However, in a 1-year longitudinal study of 71 TKA patients, Høvik et al. found that the score of catastrophic thinking gradually decreased with decreasing degree of pain at 8 weeks and 1 year after the surgery. Therefore, the authors question the view of PC as a stable predictor (Kalliomäki et al. 2013). In addition, different studies have different sets of classification thresholds for PCs. Therefore, the current findings concerning the association between PC and CPSP after TKA need to be further verified.

Gene polymorphisms

With increasing genetic research, polymorphisms of gene loci may be related to pain, and genetic factors may provide important information and facilitate the exploration of new pain treatment strategies. Current research is focused on genetic variation, in which these genes encode proteins involved in nerve conduction, transmission, opioid receptor signaling, and inflammatory processes (Wieskopf et al. 2015; Langford et al. 2015). A retrospective study of 311 Caucasian patients who underwent total knee replacement revealed that eight KCNJ6 SNPs were significantly associated with medication order. KCNJ6 (GIRK2) encodes an ATP-sensitive inward recirculating potassium channel controlled by G protein, and the G protein-gated inward recirculating potassium channel is an important effector that determines the degree of opioid inhibition when the opioid receptor is activated (Hibino et al. 2010). Therefore, variations in genes associated with GIRK provide another potential opioid-related pathway through which pain responses may be genetically influenced. A genome-wide association study was conducted in Germany on neuropathic pain after total joint replacement in 613 patients (Warner et al. 2017). The first four candidate genes detected were replicated in 1220 patients with osteoarthritis and total joint replacement surgery, and three SNPs had the same GWAS results in two repeat cohorts. Meta-analysis revealed that the most relevant mutation was the protein kinase Cα rs887797 locus. This gene encodes protein kinase Cα, which is involved in the nervous system and may promote central sensitization of dorsal horn neurons.

Intraoperative factors

Surgery-related factors have a great impact on CPSP. Different surgical methods, different types of implants, and different degrees of surgical failure can affect the

Table 1 Currently identified risk factors for CPSP after TKA

Obesity (BMI ≥ 28 kg/m^2)	Elevated BMI is a risk factor for poor joint function recovery after TKA (Guo et al. 2022).
Psychological status	Preoperative mental state (including anxiety and depression) may increase the risk of CPSP (Kim et al. 2018).
Age and sex	Relatively young patients are more sensitive to pain and may feel knee pain more easily, and female TKA patients may be more likely to report CPSP than male patients (Singh et al. 2008).
History of knee surgery	The incidence of CPSP after TKA revision surgery and/or with other knee surgery history was greater than that after primary TKA (Skou et al. 2013; Petersen et al. 2015).
Preoperative moderate to severe pain	Patients with severe knee pain (NRS ≥ 4) and limited range of motion before TKA were more likely to experience moderate or severe pain 6 months after TKA (Noiseux et al. 2014; Ghoshal et al. 2023; Sun et al. 2021).
Fibromyalgia syndrome (FMS)	FMS is a group of syndromes characterized by extensive pain and tenderness throughout the body (Clauw 2014). Patients with FMS have increased the incidence of CPSP after TKA can reach 44% (D'Apuzzo et al. 2012).

occurrence of chronic pain. For example, there are many surgical approaches for total knee arthroplasty, but in recent years, the medial parapatellar approach has become the most common choice (Rand and Ilstrup 1991). The medial parapatellar approach has a wide field of vision, convenient operation, and high accuracy, but it easily damages the quadriceps tendon, thus aggravating postoperative pain. Because of this pain, some scholars have introduced the minimally invasive technique to the TKA operation and have chosen the medial vastus muscle approach for surgery, which can effectively reduce postoperative pain and achieve faster functional recovery of the knee joint. It is difficult for patients in remission to adhere to rehabilitation training, so this training seriously affects patient prognosis (Bong and Dicesare 2004). Moreover, the type and location of implants—inappropriate selection or placement—may increase the risk of CPSP.

Postoperative factors

Acute postoperative pain (APSP)

The potential pathophysiology of the transition from acute pain to chronic pain is complex and multifactorial (Glare et al. 2019; Fregoso et al. 2019). In several existing animal studies, evidence of the molecular pathological mechanism and correlation leading to the transformation from acute to chronic pain has been reported (Basbaum et al. 2009; Denk et al. 2014; Descalzi et al. 2015). Studies on the transition from acute pain to chronic pain in patients with TKA have focused on biochemical and pathophysiological changes in the peripheral and central nervous system pain pathways (Cazzaniga et al. 2024). Several studies of correlation analysis have also suggested that early postoperative pain is associated with CPSP (Liu et al. 2012; Grosu et al. 2016; Thomazeau et al. 2016; Lavand'homme et al. 2014). Notably, there are differences in the evaluation period, evaluation tools, and evaluation indicators (mean or maximum) of APSP in these studies, and the anesthesia methods and analgesia programs adopted in different studies differ.

Inadequate analgesic measures

The concept of multimodal analgesia for the treatment of perioperative pain has been widely accepted, and many institutions have adopted standard multimodal analgesia protocols tailored to TKA (Joshi and Jagadeesh 2013). However, RCTs that examine TKA-related multimodal regimens versus placebo and follow patients for preventive analgesic effects are limited. We identified only one trial comparing spinal anesthesia to general anesthesia with femoral block in the published literature, and spinal anesthesia demonstrated positive preventive effects at 3 months and 6 months following TKA (Sciberras et al. 2022). Multimodal analgesia protocols, including gabapentin, NSAIDs, acetaminophen, and regional anesthesia, are effective in controlling perioperative pain and reducing perioperative opioid use after arthroplasty surgery (Clarke et al. 2009; Horlocker et al. 2006).

Postoperative knee function

The outcomes of early postoperative knee function and CPSP after TKA have not been determined. However, a study has shown that worse functional outcomes and knee flexion at 3 months after TKA are effective predictors of dissatisfaction at 12 months after TKA (Williams et al. 2013).

Other factors

Sleep disorders

A systematic review and meta-analysis revealed that preoperative sleep disorders had a negative effect on the occurrence and development of CPSP; early detection of sleep disorders in patients undergoing elective surgery contributed to more targeted intervention, better pain management, and reduced use of painkillers (Varallo et al. 2022).

Post-traumatic stress disorder (PTSD)

According to the DSM-5 definition, PTSD refers to a more common negative psychological reaction after trauma, which mainly refers to sudden threatening or catastrophic and other life events that cause the delayed appearance of individual symptoms (Foa et al. 2016). Two studies conducted by Cremean-Smith et al. used the IES to assess the impact of surgery as a stress factor on the joint function of patients 1 and 3 months after surgery, and the results revealed that PTSD symptoms were significantly correlated with knee joint function after TKA (Cremeans-Smith et al. 2011, 2015).

Prevention of CPSP after TKA

The prevention of CPSP after TKA lasted throughout the perioperative period. At present, regarding the prevention and treatment of CPSP after TKA, experts believe that early identification of high-risk factors and intervention for high-risk patients can often achieve good results (Voscopoulos and Lema 2010). A variety of drugs, analgesic methods, and analgesic concepts are comprehensively applied for the prevention and treatment of CPSP.

Preoperative strategy

Pain information

To provide patients with detailed information about the surgical process, postoperative recovery, and expected results, and to help patients set reasonable recovery expectations, the psychological state of patients can be

improved to reduce preoperative anxiety and improve postoperative satisfaction (Moreira et al. 2024).

Psychological evaluation and support

Patients' psychological status, such as anxiety and depression, should be evaluated, psychological support or intervention should be provided if necessary, and positive beliefs should be provided. Studies have shown that psychological factors have an important effect on the occurrence and persistence of CPSP. Cognitive behavioral therapy and other psychological interventions can help patients better manage pain, which has been proven to be beneficial for improving CPSP (Kazarian et al. 2021).

Preventive analgesia treatment

The use of drugs (such as gabapentin, pregabalin, high-dose dexamethasone, and ketamine) before surgery to reduce chronic inflammation or pain and the perioperative use of pregabalin can reduce the incidence of chronic neuropathic pain after surgery (Buvanendran et al. 2010). (1) At present, the efficacy of adding gabapentin or pregabalin to multimodal analgesia is uncertain. One meta-analysis supported the view that perioperative administration of gabapentin was effective in reducing the incidence of CPSP (Clarke et al. 2012). However, in a recent study outside of the 1-year literature update, gabapentin failed to reduce the incidence or intensity of CPSP compared with placebo 3 months after TKA (Clarke et al. 2014). Buvanendran et al. reported a reduction in the incidence of CPSP 6 months following TKA in patients who were randomized to receive a 300-mg preoperative dose of pregabalin followed by a 14-day twice-a-day (BID) regimen of pregabalin (50–150 mg) or placebo (Buvanendran et al. 2010). (2) Ketamine is believed to reduce pain and analgesic consumption through the prevention of NMDA-mediated sensitization of spinal cord dorsal horn neurons. Chaparro et al. reported that at 6 months following surgery, there was an overall significant decrease in the incidence of CPSP in patients receiving ketamine compared with those receiving a placebo (Chaparro et al. 2013). (3) Duloxetine is a type of 5-HT and norepinephrine reuptake inhibitor (SNRI) that has a clinical effect on CPSP. Several studies have confirmed the analgesic effect and safety of duloxetine in TKA (Kouhestani et al. 2023). (4) In recent years, several studies have shown an additional analgesic benefit of perioperative glucocorticoids (Xu et al. 2018; Nielsen et al. 2023). Nielsen et al. have found that preoperative high-dose dexamethasone (1 mg/kg) reduced moderate to severe pain 24 h after TKA (Nielsen et al. 2023). However, its effects on CPSP are rarely reported.

The formulation of individualized comprehensive strategies (such as distinguishing between low-risk and high-risk groups), preoperative risk assessment to identify risk groups, targeted optimization of preoperative risk factors, and identification and early intervention to solve the problem of CPSP after TKA is very important to optimize the prognosis of patients (Dembek and Bicket 2023).

Intraoperative strategy

Optimization of surgery

The precision of surgical techniques and the selection of indications for artificial joints are the keys to reducing CPSP. Minimally invasive surgical techniques should be used to reduce tissue injury and pain; at the same time, the correct placement and fixation of the prosthesis should be ensured to reduce mechanical problems. To avoid nerve injury, intraoperative nerve injury is the main cause of CPSP (Haroutiunian et al. 2013).

Anesthesia

Anesthesia included optimal analgesia, minimal side effects, and strategies to avoid postoperative pain hypersensitivity, including peripheral nerve block (PNB) and local anesthesia (LA) (such as cocktail therapy). LA at the incision site is beneficial for pain management after TKA. LA is an effective method of intraoperative analgesia that can significantly reduce postoperative pain and the need for analgesics. It is achieved by injecting anesthetics into the surgical area. Studies have shown that LA via incisions can reduce the use of postoperative opioids and pain scores (Wylde et al. 2015). PNBs, such as traditional femoral nerve block, anterior femoral cutaneous nerve block, and sciatic nerve block, as well as modern adductor canal block and infiltration between the popliteal artery and posterior capsular of the knee (iPACK), have been shown to provide effective early pain control after TKA, but long-term pain observations and randomized controlled trials to verify the efficacy of these methods in treating CPSP are lacking (Ohgoshi et al. 2019; Kim et al. 2019; Kampitak et al. 2023). It was found that LA and PNB provided similar effects, both in terms of analgesic efficacy, opioid sparing, and health economic benefits (Tong et al. 2018; Borck et al. 2022). Gradually, people have begun to pay attention to the effect of their combination. Indeed, the combination of LA and PNB appeared to lower pain scores better, but these reductions did not necessarily reach minimal clinical significance. Therefore, considering the consumption of more hospitalization costs, routine combination use is not recommended at present (Luo et al. 2022; Kampitak et al. 2019; Tang et al. 2023).

In recent years, some studies have investigated the effect of local anesthesia/peripheral nerve block on CPSP, but due to the limited sample size and other reasons, no benefits have been reported for CPSP, which is very rare in TKA (Albi-Feldzer et al. 2013, 2021). However, in terms of effective control of acute postoperative pain, the efficacy of local anesthesia/peripheral nerve block in CPSP after TKA is worth further exploration.

Postoperative strategy

Optimal analgesia

(i) Multimodal analgesia: In recent years, multimodal pain management has become the mainstream strategy for pain control after TKA. This combines different types of drugs and treatments to minimize pain (Dembek and Bicket 2023).

(i) In addition, to reduce the risk of side effects and dependence on opioids, we explored other drugs, such as non-opioid analgesics and new analgesics. Compared with traditional local anesthetics, the liposome bupivacaine, a new local anesthetic, is a recently developed continuous release local anesthetic that can increase the duration of anesthesia (Malige et al. 2022).

Establishment of transitional pain services

Transitional pain clinics aim to overcome the discontinuity between ward-based acute postoperative pain management and outpatient chronic pain management (Glare et al. 2019). Regular follow-up and examination of patients after discharge are very important for early detection of CPSP risk factors, management of these conditions, regular assessment of the degree of pain and functional recovery, and adjustment of the treatment plan as needed (Clay et al. 2012). This includes regular exercise, strength training, and joint flexibility exercises, complemented by more refined pain assessment tools and ongoing pain monitoring to more effectively adjust pain management strategies.

Optimized rehabilitation strategy

An effective postoperative rehabilitation plan and physiotherapy are very important for the prevention of CPSP. Early exercise and functional recovery not only contribute to pain control but also accelerate the overall recovery of patients. Studies have shown that active postoperative rehabilitation programs can assist in pain management and promote faster recovery. In one study in which 86 participants were randomized to walking guidance and training from postoperative day 2 or no intervention further to standard rehabilitation reported at 6 months, those receiving intervention had lower VAS scores and HSS scores than controls (Li et al. 2017).

The prevention and treatment of complications, such as infection and thrombosis, may increase pain or delay recovery. A Study has shown that effective perioperative intervention can reduce the incidence of CPSP after TKA (Beswick et al. 2019).

Treatment after CPSP in patients with TKA

Drug therapy

Drug therapy is a common method for reducing CPSP after TKA. In the past, commonly used drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and muscle relaxants, were still suitable for most CPSP patients. However, long-term use may cause side effects. Therefore, attention should be given to controlling the dose and course of treatment when drugs are used. In recent years, targeted inhibitors have emerged as a new direction for the treatment of CPSP (Kehlet et al. 2006). For example, the α2 and δ-1 calcium channel subunits associated with gabapentin and pregabalin and the N-type calcium channel Cav2·2 blocker ziconotide have been widely used to treat chronic neuropathic pain, but their effects are different, and more research is needed to understand which subgroups of CPSP patients are most likely to benefit (Kehlet et al. 2006; Finnerup et al. 2015; Wermeling 2005).

Radiofrequency therapy of the knee

There is hot and cold radiofrequency therapy, and conventional thermal radiofrequency and cold radiofrequency therapy can reduce the degree of pain experienced by osteoarthritis patients and CPSP patients. Although a preliminary study did not reveal a statistically significant difference, more than 50% of patients experienced a reduction in pain (Vanneste et al. 2023). Radiofrequency ablation of the knee joint nerve (GNRFA) is a minimally invasive treatment for patients with chronic knee pain (CKP) for whom conservative treatment is ineffective. Both t-RFA and c-RFA effectively reduced the NRS pain score of most CKP patients during the 1-year follow-up period. In the tendency score matching of CKP patients, compared with c-RFA, knee nerve t-RFA had a greater treatment success rate and greater pain relief at 1 month after the operation (Wu et al. 2022). However, owing to the poor quality of the available data, no definite recommendations can be made (Dworkin et al. 2013).

Neuroregulatory technology

Neuroregulatory technology, including transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), and nerve block, is a new treatment method that relieves pain by stimulating or regulating the nervous system. These techniques can relieve pain by stimulating or regulating the nervous system. At present,

neuroregulatory techniques such as electrical stimulation of the spinal cord have shown potential in the treatment of CPSP. These methods are expected to provide solutions for refractory pain by directly acting on the nervous system. Recently, neuroregulatory techniques such as spinal cord electrical stimulation have been studied for the treatment of CPSP. For example, transcutaneous electrical stimulation and spinal cord electrical stimulation have achieved good results in some patients (Rupp et al. 2022).

Psychological intervention

Psychological interventions, including cognitive behavioral therapy, psychological counseling, and relaxation training, can help patients change their cognition and coping style with respect to CPSP and reduce pain (Weinrib et al. 2017). A randomized clinical trial conducted by Garland et al. revealed that mindfulness-oriented recovery and enhancement therapy can reduce the incidence of CPSP and the use of opioids in veterans and military personnel who receive long-term opioid therapy (Garland et al. 2024).

Individualized treatment

Individualized treatment involves developing a personalized treatment plan according to the specific situation of the patient. By means of genetic testing, imaging evaluation, and clinical evaluation, doctors can more accurately understand the patient's condition and pain mechanism to formulate a targeted treatment plan. One of the challenges of successful pain control is that there is a large individual difference between the efficacy of painkillers and adverse drug events. Pharmacogenomics is a new and affordable tool. Understanding this difference through genetic detection is helpful for the rational use of opioids to improve postoperative pain and reduce the occurrence of side effects (Agulló et al. 2023). It is not clear whether preoperative drug genome testing is worthwhile for TKA patients, and future studies may focus on high-risk groups, such as patients with chronic pain or those undergoing complex and painful surgeries, to test whether pharmacogenomic results are beneficial in some cases (Kraus et al. 2023).

Biological therapy

Biological therapy is a method that uses biomaterials or cells to promote tissue repair and regeneration. For example, technologies such as stem cell therapy and bioactive substance injection have shown potential in some studies and can be expected to reduce CPSP and promote joint function recovery in the future (Yang et al. 2023). The above treatments are still in the research stage and need further clinical verification and long-term follow-up.

Conclusions and prospects

In general, comprehensive prevention and treatment methods, including improvements in surgical techniques, prevention and treatment of complications, rehabilitation exercise, and drug treatment, can effectively reduce the pain of TKA patients in the acute stage and prevent acute pain from turning into chronic pain. Notably, the situation of each patient is unique, and the mechanism of CPSP may be the result of a combination of factors. Therefore, when carrying out targeted prevention and treatment of CPSP, it is necessary to comprehensively consider the specific conditions of the patients, including the degree of pain, duration, and course, that affect quality of life. Therefore, the treatment plan should be adjusted according to the specific conditions of the patients, and individualized treatment plans should be developed. It also requires the joint efforts of orthopedic surgeons, pain surgeons, rehabilitators, and patients to achieve the best treatment results. Future research should focus on acute and subacute postoperative periods as well as early pharmacological and non-pharmacological interventions that may reduce the incidence of CPSP in TKA. The reported CPSP studies need to elucidate the best future management of patients experiencing CPSP. Moreover, relevant treatments aimed at improving quality of life and function may be appropriate.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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