Medicinski podmladak

Medical Youth

Mini review article

CHRONIC POST-SURGICAL PAIN AFTER TOTAL KNEE ARTHROPLASTY - RISK FACTORS AND PREVENTION

HRONIČNI POSTHIRURŠKI BOL POSLE UGRADNJE TOTALNE PROTEZE KOLENA - FAKTORI RIZIKA I PREVENCIJA

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Abstract

Chronic post-surgical pain (CPSP) is one of the frequent complications affecting patients' quality of life which additionally increases economic and healthcare burdens after surgery. The incidence of CPSP depends on the type of surgery with wide variability among surgeries. Chronic diseases, lifestyle changes, and increased life span lead to increasing surgeries performed worldwide, especially in orthopedics. Total knee arthroplasty (TKA) is a standard orthopedic procedure performed in end-stage knee osteoarthritis to improve the quality of life and decrease pain. Different pain management strategies are suggested to provide adequate analgesia and prevent chronic pain after TKA. Chronic post-surgical pain (CPSP) after TKA is an almost three-fold risk compared with other surgeries and the prevalence is also higher than after total hip arthroplasty. The prevention and treatment of CPSP after TKA are crucial not only because affecting the quality of life and causing dissatisfaction but becoming one of the reasons for revision surgery. The early identification of risk factors for CPSP after TKA is important to guide the development of preventive treatment strategies that may also improve post-surgical outcomes.

Keywords:
chronic pain,
risk factors,
total knee arthroplasty

The authors declare no conflicts of interest.

doi:10.5937/mp75-46867
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Sažetak

Hronični posthirurški bol (HPHB) jedna je od čestih komplikacija koja utiče na kvalitet života pacijenata, povećavajući dodatno ekonomska i zdravstvena opterećenja nakon operacije. Njegova incidencija zavisi od vrste operacije i razlikuje se u odnosu na tip hirurgije. Hronične bolesti, promenjen način života i produženi životni vek doprinose povećanju broja hirurških intervencija koje se izvode širom sveta, posebno u ortopedskoj hirurgiji. Totalna artroplastika kolena (TAK) standardna je ortopedska procedura koja se izvodi u završnoj fazi osteoartritisa kolena u cilju poboljšanja kvaliteta života i smanjenja bola. Posle ove intervencije primenjuju se različiti terapijski modaliteti u cilju obezbeđivanja adekvatne analgezije i sprečavanja nastanka hroničnog bola. Rizik za pojavu hroničnog bola posle ugradnje totalne proteze kolena je skoro tri puta veći u poređenju sa drugim hirurgijama, ali i u odnosu na totalnu artroplastiku kuka. Prevencija i lečenje HPHB posle TAK-a od presudnog su značaja, ne samo zbog uticaja na kvalitet života i nezadovoljstvo pacijenata nego i zato što HPHB postaje jedan od razloga za revizionu hirurgiju. Rana identifikacija faktora rizika za HPHB nakon TAK-a je važna za razvoj strategija preventivnog lečenja koje takođe mogu poboljšati i posthirurške ishode.

Ključne reči:
hronični bol,
faktori rizika,
totalna artroplastika kolena

Introduction

Chronic post-surgical pain (CPSP) is one of the frequent complications after surgery affecting quality of life and productivity. Difficulty in its treatment additionally increases the healthcare burden (1). One year after surgery 20 - 30% of patients report persistent pain of varying severity depending on the type of surgery (2,3). Chronic diseases, lifestyle changes, and increased life span lead to increasing surgeries performed worldwide, especially in orthopedics (1).

Total knee arthroplasty (TKA) is a standard orthopedic procedure performed in end-stage knee osteoarthritis to improve the quality of life and decrease pain (4). Postoperatively, it is associated with significant pain, especially in the first 24 hours. Different pain management strategies are suggested to provide adequate analgesia and prevent chronic pain after TKA (4). TKA relieves pain in most patients, but the prevalence of CPSP is higher than hip arthroplasty and has an almost three-fold risk compared with other surgeries (5,6). The prevention and treatment of CPSP after TKA are crucial not only because it affects the quality of life and causes dissatisfaction but becoming one of the reasons for revision surgery (7,8). The etiology of CPSP is multifactorial. Many studies have examined different preoperative risk factors with a priority on a limited number of variables. Factors identification allows their evaluation and implementation of preventive strategies. Also, this understanding enables a multidisciplinary approach and individually adjusted treatments. This means combining different treatments matched to the patient's needs (7-11). Lack of evidence in recommendations about optimal management of CPSP after TKA also exists in the current literature. Recommendations primarily focus on perioperative pain control instead of the therapy of chronic pain. However, prevention and treatment of CPSP are limited, and further research is needed to improve outcomes.

This article summaries current knowledge of potentially risk factors and prevention of CPSP after TKA.

Definition of chronic post-surgical pain

According to the International Classification of Disease Eleventh revision (ICD-11), chronic post-surgical pain is defined as:

Pain that persists ≥ 3 months after a surgical procedure, with localization at the surgical area, with excluded other causes of pain (infection, pre-existing pain, malignancy). It can show characteristics of neuropathic pain (2).

Mechanisms and characteristics

The mechanisms of CPSP are complex and remain poorly understood. Pathophysiology changes lead to peripheral (at the site of surgery) and central (spinal and supraspinal) sensitization (7,9). Surgical insult triggers multiple mechanisms leading to transcriptional and posttranslational changes, expression of nerve growth factor, local cytokines activity, and changes in inotropic channel expression, that occur in the primary sensory neurons in the dorsal root ganglia (9). These mechanisms, as results of the inflammatory and immune response, are responsible for the development of acute postoperative pain. At the same time changes in brain network connectivity and descending pain modulation, cause central sensitization. Central sensitization is the result of the release of neurotransmitters in the spinal cord and microglial activation. These changes could increase pain sensitivity outside of the area of surgery (secondary hyperalgesia) (9,10). Molecular mechanisms of CPSP include the release of different classes of neurotransmitters that mediate the transmission of impulses across the synapse. Its binding to the receptors on postsynaptic neurons influences pain transmission in either way, an inhibitory or excitatory. Also, microglia and astrocytes, contribute to the development and maintenance of chronic pain by releasing different neurotransmitters (9,10). Neuropeptides as the class of neurotransmitters play important roles not only in the formation, transmission, and modulation but also in the perception of different

types of pain. Glutamate, an excitatory neurotransmitter, is involved in neurotransmission and plasticity at the level of the spinal cord, and in the storage and generation of long-term memories (10). Activation of glutamate receptors is responsible for developing pain hypersensitivity after incision, while NMDA receptors play a substantial role in formulating long-term pain vulnerability (10). Endogenous opioid peptides, enkephalin, and dynorphin belong to the neuropeptides family that bind to opioid receptors. Their release decreased pain sensation by inhibition of excitatory neurotransmitters from afferent pathways. In chronic pain expression of opioid receptors can be decreased, changing brain regions' capacity to respond to endogenous or exogenous opioids (10, 11).

Mechanisms of CPSP after TKA are complex and result of tissue injury, inflammatory response and neuroplastic pain. Neuropathic CPSP is result of direct nerve injury during surgery. It is less likely after this surgery with early detection and more intensity (10, 11).

Risk factors

The early identification of risk factors for CPSP after TKA is essential for implementation of preventive treatment strategies that may also improve post-surgical outcomes (7, 8).

Chronic post-surgical pain is complex and progressive process caused by a multitude of different factors present before surgery, intraoperatively, and postoperatively. These risk factors can be divided into a few groups: patient-related, surgery and anesthesia-related, and pain-related **(figure 1)** (7, 8, 12, 13). Preventive strategies based only to understanding and identification of modifiable factors.

Lower education level, psychological factors such as fear/anxiety, depression and pain catastrophizing are identified as preoperative risk factors for CPSP after TKA (14-21). Multiple comorbidities are also risk factors, but without any specific comorbidity as risk factors (14). The existence of high intensity-pain preoperatively in the knee for surgery and in another place in the body contributes to long-term pain after surgery (15-19).

Patient-related risk factors can be considered biological, psychological, and socioeconomic factors. Several single gene mutations have been identified as possible risk factors for increased sensitivity but without strong predictive value for CPSP. Biological characteristics usually include age and sex, where younger adults and female sex patients are more prone to developing CPSP. Also, patients with increased BMI and persistent comorbidities are at greater risk (13-20). Psychological factors that could have a greater impact on the development of CPSP include depression, sleep disorders, fear of undergoing surgery, anxiety, and a tendency to exaggerate surgery outcomes. Socioeconomic factors usually include lower education levels, marital status, where unmarried patients are at greater risk, smoking, and unemployment (13-20).

Surgical risk factors for CPSP are types and duration of interventions, complications during the procedure, number of previous surgeries, possible complications during the procedure, and a type of tissue injury that occurs during surgery. Patients undergoing abdominal, orthopedic, and thoracal surgery are at increased risk of developing CPSP. Although the laparoscopic approach can reduce risk in surgeries, advantages are only confirmed in hernia and cholecystectomy (13-20).

Postoperatively, the presence and intensity of acute pain, accompanied by the development of hyperalgesia and allodynia at the site of surgery, is one of the most important factors for the development of CPSP. Patients on chronic opioid therapy require higher doses of opioids in the postoperative course, which may also be one of the precipitating factors for CPSP (21, 22). In patients who received opioid therapy before thoracotomy, chronic

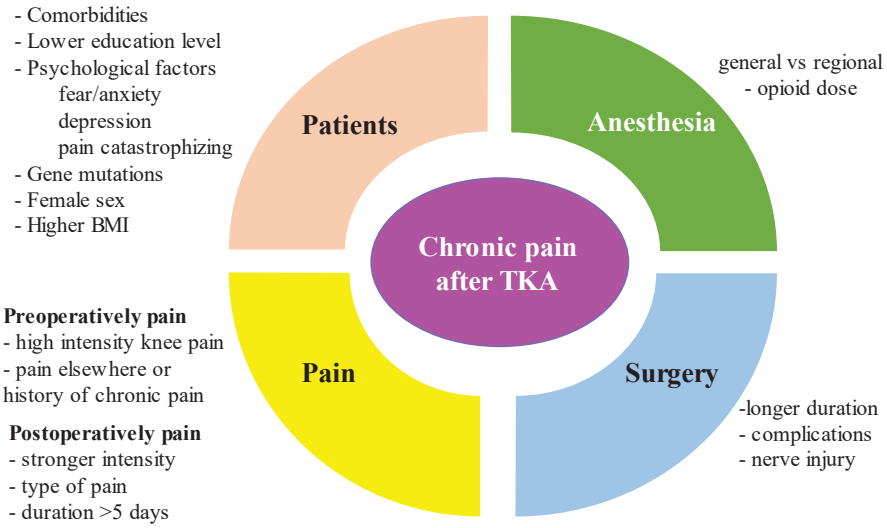

Figure 1. Risk factors for chronic post-surgical pain after total knee arthroplasty. TKA - total knee arthroplasty.

post-surgical pain occurred in 48% of patients compared to 5% in patients who did not receive opioids (21, 22).

Several studies have also pointed to the importance of increased use of opioids intraoperatively. High doses of opioids may lead to the activation of NMDA receptors, and consequently to the onset of acute hyperalgesia and increased use of opioids in the postoperative period, resulting in the development of CPSP. An increased incidence of chronic pain a year after cardiac surgery and after thoracic surgery was in patients who intraoperatively received high doses of remifentanil (9, 10, 14-17).

Immune system function can also play an important role in the etiology of CPSP. Correlation between inflammation, immune response, and clinical recovery parameters has been shown. The inflammatory response caused by monocyte activation is associated with poor patient outcomes, which can lead to complications that can result in chronic postoperative pain (9, 10).

Prediction and prevention of CPSP

Preventive treatment strategies aimed to early identified patients with risk for CPSP. Different risk models/tools have been development to predict individual risk (21).

In a 2017, Meretoja and colleagues singled out preoperative pain in the operative region, high BMI, axillary lymph node dissection, and intense pain at the site of surgery on the 7th postoperative day as predictive risk factors for breast carcinoma surgery (23). Montes and colleagues in 2020 investigated more than 30 potential risk factors in four different surgical procedures (inguinal hernia surgery, abdominal or vaginal hysterectomy, and thoracotomy). They singled out six items which included type of procedure, age, physical status, mental status, preoperative pain in the surgical field and preoperative pain in other areas (24).

It is important to note that the risk factors for CPSP are not independent but act cumulatively, and individualized prevention of CPSP is necessary (6, 7).

Quantitative sensory testing (QST) has been used to define individual somatosensory profile before surgery. It can evaluate the status of the peripheral and central nervous system and therefore serve as a predictive tool in the prevention of CPSP. Promising initial results of QST needs further clinical investigations and confirmation (7).

Different non-pharmacological and pharmacological strategies have been investigated in the prevention of the occurrence of postoperative pain. Several methods can be applied (13-18).

High-risk patients of developing chronic pain are advised to avoid surgical treatment, especially in elective procedures, if there is a possibility of some alternative treatment methods. From a surgical point of view, it is desirable to avoid extensive surgical tissue trauma and resort to minimally invasive procedures. Enabling early rehabilitation of patients by preventing the occurrence of acute postoperative pain, thus reducing the possibility of peripheral and central sensitization (13-18).

Numerous pharmacological strategies have been investigated for different drugs in preventive strategies for the development of CPSP. However recent meta-analysis did not confirm beneficial clinical results due to different methodological deficiencies. Also, the studies investigating the preventive effects of regional anesthesia on CPSP have the same such as including not only patients at risk, short duration of treatment, and no standardized assessment of outcomes (13-20).

Nerve blocks, an anesthetics technique, can reduce the transmission of nociceptive stimuli to the central nervous system, and reduce neuronal inflammation. Thus, lead to reduced opioid consumption and the risk of opioid hyperalgesia. However, beneficial effects of epidural anesthesia, peripheral nerve blocks, and wound infiltration are still debated due to a limited number of studies (13-20). Studies showed that epidural anesthesia can be effective only when used intra and postoperatively with no data on how long it should be used to have an impact on CPSP development. As regards peripheral nerve blocks as well as local infiltration of the operating site, it is still impossible to draw a definitive conclusion on whether these methods have an effect in preventing CPSP (13-20).

Ketamine with its effect on NMDA receptors can reduce the consumption of opioid analgesics intraoperatively and the intensity of acute pain postoperatively. It can also be used in patients in the preoperative period who are on high doses of opioid analgesics. The role of ketamine in the prevention of CPSP is still unknown. In the last systematic review, the authors concluded that there is currently insufficient evidence in the literature to support the claim that ketamine does indeed reduce the risk of chronic postoperative pain (13-20, 25).

Nitrous oxide and dextromethorphan, also with effect on NMDA receptors, could be used in reducing acute pain. However, currently, there are no data of their possible role in preventing chronic postoperative pain (13-20).

An increase in the use of opioid analgesics both preoperatively and intraoperatively may be a risk factor for CPSP. Reducing opioid consumption by combining with higher doses of IV anesthetics such as ketamine or propofol or regional anesthesia techniques could potentially work preventively. Reducing opioids by 50% in the preoperative period showed better outcomes 6 - 12 months after knee surgery. Both NSAIDs and acetaminophen can be used as a multimodal analgesia method to reduce opioid consumption. However, there is currently no evidence that these drugs alone play a significant role in chronic pain development (13-20, 26).

Lidocaine has been examined in CPSP prevention, but no significant effects have been confirmed so far (26).

The role of gabapentin and pregabalin and their effectiveness in the treatment of chronic neuropathic pain is already known. By blocking the calcium channels, they participate in the process of central sensitization but also reduce the consumption of opioids as well as the intensity of pain. Their use in the prevention of CPSP is still under

debate. In the case of gabapentin, studies have failed to demonstrate a decrease in CPSP formation in patients after amputations, thoracotomy, cesarean section, cardiovascular surgery, or breast surgery for 3 - 6 months postoperatively (12, 27, 28). On the other hand, studies have shown that pregabalin can reduce the incidence of CPSP in patients after cardiovascular surgery, spinal surgery, thyroid, and knee surgeries for 3 months postoperatively, but not 6 - 12 months postoperatively (26-28).

Few studies evaluated the effects of α2 agonists, such as clonidine and dexmedetomidine, but failed to provide evidence of whether these drugs affect the prevention of CPSP (12, 27).

Conclusion

Chronic post-surgical pain is a significant problem, both medically and socioeconomically. The difficulty in controlling and treating this pain remains an important factor that significantly reduces the quality of the patient's life. Further studies are needed to evaluate all potential risk factors and preoperatively identify patients for higher risk of CPSP after TKA. This is important to guide the development of preventive treatment strategies that may also improve post-surgical outcomes.

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