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Review

CHRONIC POSTOPERATIVE PAIN

Nebojša Ladjević[1,2], Maja Milinić[2], Vesna Jovanović[1,2], Jelena Jovičić[1,2], Ivana Likić[1,3] and Nikola Ladjević[4]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Center for Anesthesiology and Reanimatology, University Clinical Centre of Serbia, Belgrade, Serbia
[3]Clinic for Gyneacology and Obstetrics, University Clinical Centre of Serbia, Belgrade, Serbia
[4]Clinic for Urology, University Clinical Centre of Serbia, Belgrade, Serbia

SUMMARY – Chronic postoperative pain (CPOP) is a serious health issue that affects millions of patients every year. The incidence of CPOP is the highest after amputations, inguinal hernioplasty, thoracotomies, cardiac surgery and breast surgery. In addition to surgical factors, the other risk factors are: female gender, younger age, preoperative pain, psychological state and acute postoperative pain. The most common expression of CPOP is neuropathic pain after surgical trauma. The treatment of chronic postoperative neuropathic pain (CPNP) is difficult. Various methods have been recommended for its prevention, the most important being techniques that avoid nerve damage and adequate perioperative analgesia. The goal of this review was to discuss data from published studies examining the incidence, risk factors and mechanisms of CPOP, with a focus on surgery, the unique opportunity to implement pharmacological strategies for prevention of CPNP and current pharmacotherapy approaches for treatment of CPNP. Commonly used drugs to prevent and treat CPNP in the current clinical setting are: opioids, α2-adrenergic agonists, cyclooxygenase antagonists, gabapentin, pregabalin, steroids, N-methyl-D-aspartate receptor antagonists and local anesthetics.

Key words: *chronic postoperative pain; neuropathic pain; sensitization; microglia; pharmacotherapy; analgesia*

Introduction

Chronic pain is pain that persists or recurs for longer than 3 months[1], and whatever its etiology, is a pressing medical and socioeconomic problem[2,3]. Surgery is a frequent and important cause of chronic pain[4]. According an estimation of the global volume of surgery, between 187.2 and 281.2 million major surgical procedures were undertaken in 2004. Approximately, this is one surgery per every 25 persons[5]. It was estimated that between 266.2 and 359.5 million surgeries took place in 2012, and the number of surgical procedures increased by 33.6% over 8 years[6]. Additionally, it is estimated that 10-50% of patients who undergo surgery develop chronic postsurgical (postoperative) pain, and the pain is severe in 2-10%[7]. Only recently, chronic postoperative pain (CPOP) has been recognized as a significant problem in children[8]. Chronic postoperative pain is therefore a serious health issue that affects millions of patients every year and leads to disability and reduced quality of life in these patients[9,10]. Nevertheless, the first paper on CPOP was published by Crombie et al. only 20 years ago[4,11].

There were several problems that arose when investigating CPOP. The first was definition. CPOP was originally defined as pain that develops after a

Correspondence to:
Vesna Jovanović
Centre for Anesthesiology and Reanimatology
University Clinical Centre of Serbia, Belgrade, Serbia,
11000 Belgrade, Resavska 51.
Phone: +381628768938
Email: vantonijevicjov@gmail.com

surgical procedure, lasts at least 2 months, and other causes of pain (for example, infection) having been excluded[11]. More recently, the initial definition has been modified[12]. According to the first proposed definition of chronic pain classification for the International Classification of Diseases, 11th Revision (ICD-11), CPOP and posttraumatic pain form an entity that was defined as pain that develops after a surgical procedure or a tissue injury, persists at least 3 months, and all other causes of pain (infection, recurring malignancy) as well as the previous existence of a chronic pain condition should be excluded[13]. Most recently, CPOP has been defined as pain developing or increasing in intensity after the surgical procedure, persisting at least 3 months with a significant negative effect on the quality of life, is localized to the surgical field or to a referred area (e.g. innervation territory), occurs as a continuation of acute postoperative pain or may develop after an asymptomatic period and other causes for the pain have been excluded (e.g. infection). This updated definition of CPOP has been accepted by the International Association for the Study of Pain (IASP) Task Force on Chronic Pain and recommended to be included in the upcoming ICD-11[3]. Finally, the World Health Organization (WHO) released its new ICD-11 in June 2018, according to which CPOP is defined as chronic pain developed after a surgical procedure and persisting beyond the healing process, i.e., at least 3 months after surgery; pain is either localized to the surgical field, referred to a dermatome (after surgery/injury to deep somatic or visceral tissues) or projected to the innervation territory of a nerve situated in this area; it is necessary to exclude pain continuing from a pre-existing pain problem as well as other causes of pain (infection, malignancy, etc.)[1].

Breast surgery (mastectomy, cosmetic surgery), the amputation of a limb, herniotomy and thoracic surgery (including minimally invasive procedures) are the most frequent surgical procedures causing CPOP[1]. CPOP is often neuropathic pain. An average 30% of patients (with a range of 6% to 54% and above) develop neuropathic pain depending on the type of surgery[1,13]. According to the current definition proposed by the IASP Taxonomy Committee and accepted by the IASP, neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system[14-16]. Neuropathic pain caused by nerve injury is repeatedly cited as the main cause of CPOP[17]. Sensory abnormalities are present in a significant number of patients with CPOP, suggesting that CPOP often has a neuropathic component[7,18-20]. Pain that has a neuropathic component is usually more severe and more difficult to treat than nociceptive pain[13]. Neuropathic pain indicates the need for strong analgesic medications and requires a specific therapeutic approach[3,21]. Effective strategies for prevention and treatment of pain include clear differentiation of neuropathic from non-neuropathic causes of postsurgical pain[7]. Chronic neuropathic pain is associated with impairments in a wide range of health-related quality of life (HRQoL) domains: emotional, physical and social functioning[22].

CPOP occurs as a continuation of acute postoperative pain ormay develop after an asymptomatic pain-free period. CPOP develops in the skin or deep tissues of the surgical field, may be related to the course of the injured nerve or may be referred to characteristic areas due to viscerosomatic convergence[23]. The intensity and character of CPOP is variable. Approximately 1-15% of patients describe the CPOP as severe[7]. Neuropathic pain is often described like shooting, burning or tingling, but sometimes characteristics of somatic pain such as aching, squeezing or stabbing are also reported, especially when associated with joint arthroplasty[24,25].

The primary goal of this paper was to review current pharmacotherapy approaches for the prevention and treatment of chronic postoperative neuropathic pain (CPNP) as the most common expression of CPOP caused by the iatrogenic damage of the sensory nerve during surgery, especially NMDA receptor antagonists. To this end, we briefly summarize the incidence of CPOP and the risk factors for its development and have thoroughly examined existing knowledge and evidence on the transition from acute to chronic pain following surgery.

Chronic postoperative pain – incidence, risk factors, pathophysiological mechanisms

A large number of studies have examined the incidence of CPOP after various surgical procedures. One of the best-described examples of persistent postsurgical chronic pain syndrome is chronic phantom limb pain after amputation. The incidence of this condition based on the literature varies from 30% to 81%[26]. Over 60% of patients experience chronic pain after breast cancer surgery[27]. CPOP incidence after Caesarean section is at least 5.9%, and after vasectomy it occurs in up to 15% of patients[28,29]. Studies on CPOP

have shown that this condition was present in 39.5% of patients four months after hernioplasty[30].

Chronic pain after thoracotomy occurs in about 25% to 60% of cases[26]. Reviews of CPOP incidence after radical prostatectomy, hysterectomy, laparoscopic cholecystectomy and other surgical procedures have been provided in the studies by Kehlet et al. and Katz et al[7,19].

The risk factors for the development of CPOP are numerous. They can be classified into preoperative, intraoperative and early and late postoperative factors[31]. Because of the multidimensional nature of these factors, some researchers suggest a classification into different domains[24]. These domains include innate risk factors (genetic predisposition, pain history, demographic factors) as well as domains potentially amenable to interventions, such as psychological, medical comorbidities and surgical approaches. In addition to this proposed classification, risk factors for CPOP can be also classified as surgery-specific or patient-specific[31], and utilizing a combination of these factors offers the best risk assessment[32].

Preoperative factors are patient-specific factors that include the patient's condition and characteristics before surgery. These factors include gender, age, genetic predisposition, psychological conditions such as depression and a tendency to catastrophize and pre-existing pain[33].

- Demographics
- Psychosocial factors
- Pre-existing pain
- Pre-surgical pain sensitivity
- Pain genetics
- Pain epigenetics

Intraoperative factors are surgery-specific. Surgical trauma and nerve injury were identified as major risk factors in the development of chronic pain early on[4]. Other intraoperative risk factors were subsequently investigated: anesthetic technique, type of surgery, extent of surgery and anatomical site, especially ear-nose-throat surgery. It has been shown that prolonged operation time significantly affects the occurrence of CPOP, regardless of the type of surgery and whether the surgical approach is open or laparoscopic[31].

Postoperative factors. The transition of acute postoperative pain to CPOP largely depends on acute postoperative pain severity. If the intensity of acute pain is more severe, it is more likely to develop to CPOP. This indicates the great importance of effective perioperative analgesia in prevention strategies for the development of CPOP. Additionally, some postoperative treatments can enhance CPOP. For example, numerous radiotherapy treatments after surgery can cause neuropathic pain. Deployment of radiation to the axilla after mastectomy may cause brachial plexopathy and neuropathic pain. A study by Andersen et al. showed that radiation therapy is a risk factor for more intense chronic pain three months after breast cancer surgery[34].

Postoperative pain management after surgical patients leave the hospital has been insufficiently studied. A study by Apfelbaum et al. has shown that patients experienced more postoperative pain after discharge from the hospital[35]. The reviewed literature showed: 1) One of the most common causes of readmission after ambulatory surgery is pain; 2) Many studies have shown that patients have an increased incidence of pain at home; 3) Due to the presence of pain, patients cannot perform daily activities; 4) Pain is the most frequent reason for discharged postsurgical patients to contact their general practitioner. Few studies have investigated the presence of postoperative pain in patients discharged from the hospital. In their study, Chapman et al.[36] created a trajectory of postoperative pain. They tracked postoperative pain for each patient six days after elective surgery. Pain trajectory was represented as a linear combination of pain intensity and time. The trajectory had two characteristics: 1) the intercept or initial level of postoperative pain; and 2) the slope or rate of change in pain over a period of six days. The trial included 502 patients. 63% of the patients showed gradual pain resolution over several days, as expected. However, 25% of patients showed a flat trajectory over six days with no significant change in the intensity of pain they initially reported. 12% of patients had a persistent increase in pain during the six-day follow-up. The pain trajectory quantitatively showed the patient's postoperative pain level and the rate at which the patient resolved that pain. The pain trajectory may be a potentially valuable tool for studying the risk associated with postoperative pain control in patients who have risk factors for developing chronic pain.

Current pharmacotherapy for prevention of chronic postoperative neuropathic pain

The treatment of chronic postoperative neuropathic pain (CPNP) is difficult, so the emphasis should be

placed on prevention. The most important prevention measures are adequate perioperative analgesia and techniques that avoid nerve damage. In the current clinical setting to prevent and treat CPNP, the most commonly used drugs are: opioids, α2-adrenergic agonists, cyclooxygenase antagonists, gabapentin, pregabalin, steroids, N-methyl-D-aspartate receptor antagonists and local anesthetics.

Other interventions included exercise, spinal cord stimulation, postamputation limb liner, acupuncture, laser and magnetic therapy, mirror therapy and mindfulness-based stress reduction, but we will focusing on NMDA receptor antagonists[7].

N-methyl-D-aspartate (NMDA) receptor antagonists

N-methyl-D-aspartate (NMDA) receptors are the sub-group of ionotropic glutamate receptors which are excitatory receptors in neurons. They have a crucial role in neuronal development and synaptic plasticity and transmission. The amino acid glutamate, the primary excitatory neurotransmitter at almost all synapses in the central nervous system, acts on two different groups of receptors: ionotropic and metabotropic. Based on their pharmacological properties, ionotropic glutamate receptors are divided into different receptor sub-groups: GluA (AMPA, 2-amino-3-3-hydroxy-5-methyl-isoxazol-4-yl propanoic acid), GluD (δ), GluK (kainate) and the GluN (NMDA, N-Methyl-D-aspartic acid)[37,38]. In their structure, NMDA receptors are multisubunit heteromeric membrane proteins. They form heterotetrameric channels containing two obligatory glycine-binding NR1 subunits and two other subunits, either from the NR2 subfamily (2A, 2B, 2C, 2D) or the NR3 subfamily (3A or 3B). For activation, NMDA receptors require binding of glycine and glutamate to the NR1 and NR2 subunits, forming obligate heteromers of glycine-binding NR1, glutamate-binding NR2 and glycine-binding NR3 subunits. Other ionotropic glutamate receptors (named non-NMDA receptors), such as AMPA and kainate receptors, can form functional homotetrameric channels activated solely by glutamate[39].

Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is a non-competitive NMDA receptor antagonist. The active enantiomer S(+)-ketamine is the most potent NMDA receptor antagonist in clinical use, two times stronger than the racemic form, and four times stronger than the R(-)-ketamine isomer. Ketamine acts on glutamate binding sites, NMDA (N-Methyl-D-Aspartate), and non-NMDA receptors. After binding to the intra-channel location, it reduces the channel opening time. Ketamine also acts on non-NMDA glutamate, opioid and muscarinic cholinergic receptors. It facilitates GABA signaling and also has a local anesthetic effect. Additionally, ketamine binds to agonist sites on dopamine D2 receptors with great affinity.

Therefore, the clinical effects of ketamine manifest in different ways and are not only related to the effect on NMDAR[40].

Perioperative administered ketamine is the most studied drug with regard to CPOP. The impact of ketamine for the prevention of CPOP has been evaluated in three recent systematic reviews and meta-analyses[41-43]. A systematic review of the literature published in the Cochrane Database of Systematic Reviews[41] identified 14 studies evaluating the perioperative effectiveness of ketamine. Ketamine has been administered to patients in three ways: before the incision, as an intraoperative infusion and as a postoperative infusion.

In three studies, ketamine was administered in each of the perioperative periods; in two studies, ketamine was started as an intraoperative infusion and continued for the next two or three postoperative days; in seven clinical trials, ketamine was administered as an incisional loading dose plus intraoperative infusion; in two studies, ketamine use was limited to one of these three treatment periods; in one study, two different preincisional doses of ketamine were administered; in one study, ketamine was administered with morphine in the patient-controlled analgesia.

The patients were scheduled for thoracotomy, amputation and abdominal, breast and orthopedic surgery. The incidence of pain was analyzed at 3, 4, 6 and 12 months after surgery. Five studies reported the incidence of postoperative pain at 3 months, only one study reported the incidence of pain at 4 months, eight trials reported the incidence of pain at 6 months and two studies reported the incidence of pain at 12 months. The authors reported that no significant effect of ketamine compared to placebo was found at 3 months (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.45 to 1.23). However, the results were different for studies that evaluated ketamine use for more than 24 hours compared with studies that lasted less than

24 hours. These results showed a significant effect of ketamine compared with placebo (OR 0.37, 95% CI 0.14 to 0.98). One study investigated the incidence of postoperative pain at 4 months, and the results showed that there was no difference between the groups. The overall effectiveness risk ratio showed a significant effect of ketamine compared with placebo (OR 0.50, 95% CI 0.33 to 0.76). Furter analysis showed no significant effect of ketamine compared with placebo in those studies where ketamine was administered for longer than 24h. We can conclude that perioperatively administered ketamine had a significant effect in reducing the incidence of CPOP in the 6th month.

Another systematic review and meta-analysis[42] identified 17 studies evaluating the perioperative effectiveness of ketamine. These studies examined the influence of ketamine on the prevalence and severity of CPOP in adult patients. Both short-term and long-term side effects of ketamine use were also investigated. Most of these studies were identified in a previous systematic review published in 2013 by Chaparro et al[41]. All enrolled studies were placebo controlled. One study included an active gabapentin control group. In these studies, there were different perioperative periods when ketamine was administered, and the doses of ketamine were also different. The total number of patients who received ketamine was 1015, and 785 received placebo. A small number of patients withdrew from the studies before the start of the interventions. The dose of ketamine administered varied both within and between studies. In most studies, ketamine was administered as a bolus dose followed by a continuous infusion. Some studies used only a single bolus dose. Most often, a bolus dose was administered immediately before the start of the surgery, and then a continuous infusion of ketamine was continued for 72 hours. The routes of administration of ketamine were also different in the studies. The majority used the intravenous route. In two studies, ketamine was given epidurally as an adjunct to patient-controlled epidural analgesia.

One study used an intravenous infusion with the addition of ketamine as an intramuscular bolus. One study included separate arms receiving intravenous ketamine. Four studies administered S-ketamine intravenously or epidurally and showed that it was more potent than the racemic mixture. Sixteen studies reported CPOP prevalence data, and one study did not. In studies where more than one ketamine regimen was used, researchers chose the dose closest to those used in other studies. A subanalysis was performed at three time points: 3 months (one study used 4 months of data), 6 months and 1 year or later. The overall RR of developing CPOP when ketamine was intravenous and epidurally administered was 0.84 in the ketamine group vs. placebo, assessed at the first time point, i.e., at 3 months. This means a 16% relative reduction in the probability of developing CPOP, but this was not statistically significant. (P=0.06, 95% CI: 0.70-1.01). No single study demonstrated a statistically significant difference between ketamine and placebo when the risk of CPOP was examined.

Overall, at three months, 28% patients in the ketamine group reported CPOP versus 35% in the placebo group. In the other two time points (at 6 months and at 1 year or later) the overall RR was not statistically significant when ketamine was administered both intravenously and epidurally. At each time point, a decrease in the number of participants was reported. Only one study showed a statistically significant reduction in the risk of developing CPOP at 6 months. 142 patients who underwent hip replacement were included in the study. At the end of the study, 6 out of 72 patients receiving ketamine vs. 15 out of 70 patients receiving placebo reported CPOP (P=0.04). One study compared ketamine, placebo and gabapentin. The study showed that the prevalence of incisional pain was lower in those patients who received gabapentin, at three and six months. However, the authors did not present supporting data.

A recent systematic review with a metanalysis[43] that evaluated the impact of perioperative intravenous ketamine on the incidence of CPOP included 10 studies with a total of 784 patients. All of these studies had already been identified in the previous systematic review published in 2014 by McNicol et al[42]. However, this systematic review determined the outcomes differently from the two previous cited systematic reviews. While two previous reviews analyzed only the presence or absence of pain, Klat et al.[43] analyzed and the intensity of the pain measured by Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) of 0 to 10. The authors used the cut-off value 3 for the VAS/NRS, indicating that VAS/NRS measurements are classified as pain if they were greater than or equal to 3. They analyzed pain recorded 1, 3, 6 and 12 months after surgery at rest and in motion. The patients underwent thoracotomy, orthopedic surgery, breast surgery, rectal surgery, leg amputation and hemorrhoidectomy. All

studies were placebo-controlled. Positive outcomes related to CPOP were reported in three studies, with total of 303 patients. After summarizing the results, authors reported that a marginally significant reduction of CPOP due to ketamine administration was noted only by metanalysis of postoperative pain at rest after one month (RR 0.52 (95% CI, 0.27 to 0.97)). All other results of the metanalysis were not significantly different from the null hypothesis. Based on these results, the authors concluded that there was currently insufficient evidence that perioperative administration of ketamine affects the reduction of chronic postoperative pain[43].

Memantine

Memantine (hydrochloride, 1-amino-3,5-dimethyladamantane hydrochloride) is an oral non-competitive NMDA receptor antagonist with a specific mechanism of action. It inhibits prolonged influx of Ca^{2+} that is responsible for neuronal excitotoxicity. Because memantine maintains the physiological function of NMDAR, it does not lead to psychodysleptic adverse events. At high concentrations, it affects many CNS targets, including voltage-activated sodium channels, serotonin receptors (5HT3), nicotinic acetylcholine receptors (nAChRs), etc. However, it does not bind to receptors which are important for the development of psychiatric and neurological disorders: adrenergic, dopamine or GABA receptors, or voltage-dependent calcium, sodium or potassium channels. The drug has been available for Alzheimer's disease treatment in the form of capsules, tablets or solution since 2015, in various generic formulations. It is the only drug that is not an acetylcholinesterase inhibitor approved by the FDA for the treatment of Alzheimer's disease[44].

Memantine pharmacokinetics

This drug is available in the form of immediate-release or extended-release formulations.

After oral administration, it is completely absorbed and has absolute bioavailability, namely 100%. Peak plasma concentration is reached after between 3 and 8 hours. Mean distribution volume is 9 to 11 L/kg. Plasma protein binding is about 45%. Only 20% of the drug is changed during metabolism in humans. Metabolism via cytochrome P450 has not been described. Metabolites do not display any NMDAR antagonism. Memantine is mostly excreted in the urine as an unchanged drug[44,45].

Results of recent preclinical studies that evaluated the impact of preemptive memantine administration on the prevention CPNP are encouraging. Memantine administered a few days before surgery showed significant positive results. It has been shown to prevent the development of central sensitization and neuropathic pain and cognitive impairment in animals. However, memantine administered postoperatively did not show benefit when neuropathic pain had already occurred and when central sensitization mechanisms were initiated[46,47]. Unfortunately, the impact of perioperative memantine administration on the prevention of CPOP has been examined only in a very small number of clinical studies.

A small randomized, double-blind, placebo-controlled study (19 patients) investigated the impact of early postoperative treatment of memantine in combination with continuous brachial plexus blockade on the development of phantom pain in acute traumatic upper limb amputees. The results showed a significantly decreased prevalence of phantom limb pain (PLP) in the memantine group at 6 months follow-up (10% in the memantine group versus 38% in the control group) and 12 month follow up (18% in the memantine group versus 29% in the control group).

After 6 months of memantine treatment, a significant reduction in the intensity of PLP was observed. However, there was no significant difference in PLP intensity between the groups after 12 months[48].

A recent randomized, single-blind, placebo-controlled clinical trial that included 40 women undergoing mastectomy investigated the effect of memantine on the prevention of chronic pain after mastectomy. The treatment group included 20 patients. Each patient in this group received memantine in increasing doses for two weeks before mastectomy and maintained at 20 mg daily for two weeks after surgery. The control group of 20 women received placebo (lactose) at the same time. Patients who received memantine reported significantly lower NRS pain intensity 3 months after mastectomy compared with patients from placebo group. No significant difference was observed at 6 months post-mastectomy. Examining the occurrence of neuropathic pain caused by surgery, no significant difference was observed 3 months and 6 months after mastectomy between the two groups. In

the memantine group, 35% of patients developed neuropathic pain at 3 months after surgery (versus 45% of patients in the placebo group) and 35% of patients reported neuropathic pain at 6 months after surgery (versus 30% of patients in the placebo group). However, the features of chemotherapy-induced neuropathic pain were significantly reduced in the memantine group compared to the placebo group at 3 months (P=0.001) and 6 months post-mastectomy (P=0.009)[49]. To our knowledge, this is the first clinical study in the literature that has been shown that administration of memantine before surgery successfully prevented the development of CPOP and diminished neuropathic pain.

While these results are promising, future studies are needed with a larger number of patients in different surgical procedures in order to demonstrate the positive effect of memantine on the development of CPOP.

Conclusion

The treatment of CPOP is very difficult, and prevention measures are thus of crucial importance. There are many strategies for prevention, but it would appear that they are not sufficiently implemented in daily practice. That is why it is necessary to constantly emphasize the importance of CPOP and develop awareness of it among physicians.

Conflict of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations:

AMPA, 2-amino-3-3-hydroxy-5-methyl-isoxazol-4-yl propanoic acid; CI, confidence interval; CPOP, chronic postoperative pain; CPNP, chronic postoperative neuropathic pain; HRQoL, health-related quality of life; IASP, the International Association for the Study of Pain; ICD-11, International Classification of Diseases, 11th Revision; NMDA, N-methyl-D-aspartate; NRS, Numerical Rating Scale; RR, relative risk; OR, odds ratio; PCA, patient-controlled analgesia; PLP, phantom limb pain; VAS, Visual Analogue Scale; WHO, World Health Organization

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Sažetak

KRONIČNA POSTOPERATIVNA BOL

N. Ladjević, M. Milinić, V. Jovanović, J. Jovičić, I Likić i *N. Ladjević*

Kronična postoperativna bol (KPOB) predstavlja ozbiljan zdravstveni problem koji svake godine pogađa milione pacijenata, što dovodi do invaliditeta i direktno narušava kvalitet života oboljelih. Incidencija kronične postoperativne boli je najveća nakon amputacija, ingvinalne hernioplastike, torakotomije, kardiokirurških operacija i operacija dojke. Pored kirurških specijalnosti, drugi dokazani faktori rizika jesu: ženski spol, mlađa životna dob, postojanje prijoperacijske boli, psihološko stanje i akutna postoperativne boli. Neuropatska bol koji nastaje kao rezultat kirurške traume i dalje je najčešći oblik KPOB. Za njegovu prevenciju neophodna je adekvatna perioperativna analgezija, preporučuju se tehnike kojima se izbjegava oštećenje živaca, i treba ih koristiti kada god je to moguće jer je liječenje kronične poslijeoperativne neuropatske boli (KPNB) veoma teško. Cilj ovog preglednog rada je da se raspravi o podacima iz nedavno objavljenih studija koje ispituju incidenciju, faktore rizika, mehanizme KPOB, sa fokusom na kirurgiju, jedinstvenu priliku za primjenu farmakoloških strategija za prevenciju KNPB, i aktuelne farmakološke pristupe u njegovom liječenju. U trenutnoj kliničkoj praksi za prevenciju i lečenje KPNB najčešće korišteni lijekovi su opioidi, α2-adrenergički agonisti, antagonisti ciklooksigenaze, gabapentin, pregabalin, steroidi, N-methyl-D-aspartat receptor antagonisti i lokalni anestetici.

Ključne riječi: *kronična poslijeoperativna bol, neuropatska bol, senzitizacija, mikroglija, farmakoterapija, analgezija*