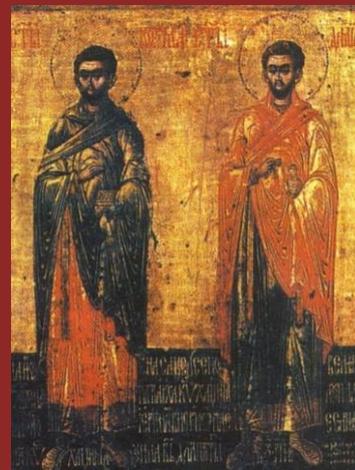


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Medicinskog fakulteta Univerziteta u Nišu i  
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Bol u teoriji i praksi / Pain in theory and practice



Scientific Journal of the University of Niš Faculty of Medicine  
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Medicinski fakultet Univerziteta u Novom Sadu



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**SAŽECI / ABSTRACTS**

## COVID 19: IMPLICATIONS FOR PAIN SERVICES AND ANALGESIC DRUGS

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The COVID-19 pandemic has had impacts on all aspects of life and society throughout the world and will have impacts on individuals and health services for many years to come.

The use of some analgesics has not been without controversy during the pandemic. Early in the pandemic preliminary findings suggested that NSAIDs may exacerbate COVID-19 symptoms and should not be used. However, subsequent studies have comprehensively proved their safety. Corticosteroids were initially not recommended by the WHO as a treatment for COVID-19, but numerous randomized trials have now demonstrated that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen. There have been fewer publications on other analgesic drugs. Expert or consensus recommendations suggested opioids should be used with caution as due to their respiratory depressant and immunosuppressive effects. Epidemiological evidence suggests patients prescribed long-term opioids with COVID-19 were at higher risk of increased morbidity, mortality and healthcare utilisation.

As the pandemic has evolved, we have since found ourselves asking different questions. The successful development and mass roll-out of vaccines led to questions around timing of corticosteroid injections. Longer-term consequences of the COVID-19 pandemic are also becoming evident with more people being prescribed opioids whilst awaiting hip and knee replacement surgery.

There has also been interest in repurposing of some analgesic drugs, including tramadol, cannabidiol and SSRI antidepressants, as potential treatments for COVID-19 infection, although the evidence for many of these has been contested.

The presentation will conclude by briefly considering how EFIC has responded to the COVID-19 pandemic, from highlighting initial recommendations about NSAIDs in acute COVID-19 infection, to surveys about impacts on clinical practice and continuing to curate a resource of clinical and scientific evidence relevant to the pain community.

**Key words:** *COVID-19; analgesics; Adrenal Cortex Hormones; Anti-Inflammatory Agents, Non-Steroidal; Analgesics, Opioid*

## COVID 19: IMPLIKACIJE USLUGA U ZBRINJAVANJU BOLA I ANALGETIKA

**Roger Knaggs**

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Pandemija COVID-19 uticala je širom sveta na sve aspekte života i društvo u celini, a uticaće i na pojedince i zdravstvenu zaštitu i u godinama koje dolaze.

Tokom ove pandemije, korišćenje nekih od analgetika izazivalo je kontroverze. Rano tokom pandemije, preliminarni nalazi ukazivali su na to da NSAIL lekovi mogu pogoršati simptome COVID-19 i da ih ne treba koristiti. Ipak, naknadne studije sveobuhvatno su dokazale njihovu bezbednost. SZO u početku nije preporučivala kortikosteroide za tretiranje COVID-19, ali su brojni randomizovani trajali pokazali da sistemska kortikosteroidna terapija poboljšava kliničke ishode i smanjuje mortalitet hospitalizovanih pacijenata sa COVID-19 koji zahtevaju potpurnu terapiju kiseonikom. O ostalim analgeticima bilo je manje publikacija. Stručne ili preporuke donete konsenzusom ukazivale su na to da opioide treba koristiti oprezno zbog efekata koji se odnose na depresiju respiracije i imunosupresiju. Epidemiološki podaci pokazuju da su pacijenti sa COVID-19 kojima je bila propisana opioidna terapija u dužem trajanju bili izloženi većem riziku morbiditeta, mortaliteta i u većoj meri su koristili zdravstvene resurse.

Sa evolucijom pandemije, našli smo se u situaciji da sebi postavljamo različita pitanja. Uspešan razvoj i masovna proizvodnja vakcina vodili su pitanjima o tajmingu injekcija kortikosteroida. Postaju očigledne i dugoročne posledice COVID-19 pandemije, sa povećanim brojem osoba kojima se propisuju opiodi dok čekaju operacije ugradnje zgloba kuka i kolena.

Takođe, zabeležen je interes za prenamenu nekih od analgetika, uključujući tramadol, kanabidiol i SSRI antidepresive, kao potencijalnih agenasa za tretman COVID-19 infekcije, mada su za mnoge od ovih lekova predstavljeni i dokazi protiv takve prenamene.

U zaključku, u prezentaciji će ukratko biti razmotren odgovor EFIC na pandemiju COVID-19, od inicijalnih preporuka o NSAIL agensima kod akutne COVID-19 infekcije, do pregleda uticaja na kliničku praksu i nastavka brige o resursima kliničkih i naučnih dokaza relevantnih za zajednicu profesionalaca koji se bave bolom.

***Ključne reči:*** COVID-19; hormoni kore nadbubrega; antiinflamatorni agensi, nesteroidni; analgetici, opiodi

## RATIONAL USE OF OPIOIDS

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Opioids are commonly and increasingly used for the treatment of moderate to severe pain. While they are a cornerstone for the treatment of cancer pain, there has been an increasing concern about the use of opioids for the management of chronic non-cancer pain. Their use in the management of acute pain has a tendency to be minimized as well.

There is good quality evidence showing the harms/risks which can occur in people with chronic non-cancer pain who use opioids for longer than two weeks. Adherence to the guidelines for opioid use in chronic non-cancer patients and integration of harm reduction measures can ensure rational use of opioids. Opioids should only be used for some selected chronic non-cancer pain syndromes if the established non-pharmacological and pharmacological treatment options have failed, as a part of a comprehensive, multi-modal, multi-disciplinary approach to treatment, and under supervision.

Pain remains a serious consequence of cancer and its treatment. A safe and effective opioid use requires the knowledge of their pharmacokinetics and pharmacodynamics, and understanding the mechanism of their action together with the insight into the clinical status of each patient. This leads to an appropriate selection, dosing, titration, rotation and application route, and a recognition and management of side effect. As opioid adverse effects occur often, the goal is to prevent and manage constipation, nausea, sedation and neurotoxicity. Recognizing the risk factors of overuse along with the key components of universal precautions will promote the safe use of opioids. The most frequent errors in opioid prescriptions are in omission and miscalculation of rotated and rescue doses, and overdosing due to disregard for patient's clinical status which undergoes changes over the course of their illness.

Rational use of opioids includes the assessment of pain and adherence to the recommendations for opioid use in cancer and non-cancer patients. Safe and rational use of opioids for patients with chronic non-cancer pain requires an appropriate choice of patient, the use of the minimal recommended doses in the expected duration of treatment, and regular assessment and reassessments of efficacy and appearance of side effects. Rational and effective use of opioids in patients with cancer requires balance and skill.

**Key words:** *opioids, rational use, non-cancer pain, cancer pain*

## PRAVILNA UPOTREBA OPIOIDA

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Opioidi se uobičajeno i često upotrebljavaju za lečenje srednje jakog i jakog bola. Dok su osnova za lečenje kancerskog bola, njihova upotreba za lečenje hroničnog nekancerskog bola predstavlja sve veću zabrinutost. Tendencija je da se sve manje upotrebljavaju za lečenje akutnog bola.

Kvalitetni naučno utemeljeni podaci govore o koristi i šteti koja se može pojaviti kod ljudi koji opioide upotrebljavaju za lečenje nekancerskog bola u trajanju više od dve nedelje. Racionalnu upotrebu opioida za lečenje nekancerskog bola možemo sprovesti uz preporuke za lečenje i mere za suzbijanje štete. Opioidi se preporučuju za lečenje kroničnog nekancerskog bola samo za izabrane sindrome bola, kada je nefarmakološko i farmakološko lečenje neuspešno i u sklopu komprehenzivnog multi-disciplinarnog multimodalnog pristupa uz nadgledanje stanja bolesnika.

Bol ostaje ozbiljna posledica kancerske bolesti i lečenja. Za bezbednu i delotvornu upotrebu opioida potrebno je znanje o njihovoj farmakokinetici i farmakodinamici, razumevanje mehanizma njihovog delovanja, zajedno sa poznavanjem statusa svakog pojedinog bolesnika. Na osnovi toga, moguće je napraviti pravilan izbor, doziranje, titraciju, rotaciju, način aplikacije, kao i prepoznavanje i upravljanje neželjenim efektima. Budući da se nuspojave često pojavljuju, moramo znati kako preduprediti zatvor, mučninu, sedaciju i nervnu toksičnost. Uz opšte mere opreza i prepoznavanja rizičnih faktora za predoziranje, možemo obezbediti racionalnu upotrebu opioida. Najčešće greške u prepisivanju opioida su izostavljanje i pogrešno izračunavanje rotiranih i spasilačkih doza i predoziranje zbog zanemarivanja kliničkog statusa pacijenta koji se menja u toku bolesti.

Racionalna upotreba opioida temelji se na oceni bola i poštovanju preporuka za upotrebu kod bolesnika sa i bez karcinoma. Bezbedna i racionalna upotreba opioida za hronični bol kod bolesnika bez karcinoma zasniva se na pravilnom izboru bolesnika, upotrebi minimalnih i preporučenih doza u predviđenom trajanju, zajedno sa redovnim ocenjivanjem uspešnosti lečenja i nuspojava. Za racionalnu i uspešnu upotrebu opioida kod bolesnika sa karcinomom moramo biti vešti i znati kako balansirati lečenje.

***Ključne reči:*** *opioidi, racionalna upotreba, nekancerski bol, kancerski bol,*

## REGENERATIVE MEDICINE FOR CHRONIC PAIN – WHERE DO WE STAND?

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Regenerative medicine is broadly based on the body's essential ability to heal itself, by supplementing the innate repair mechanisms with homologous or autologous biologic agents. Regenerative therapy shows a great amount of promise in improving musculoskeletal conditions and providing patients with an effective treatment option for their chronic pain.

One such biologic agent is platelet-rich plasma (PRP), a concentrate made from whole blood centrifuged to remove red blood cells, which contains a variety of growth factors. Four types of PRP can be formulated, depending on the white blood cell counts and fibrin architecture. PRP has demonstrated the most efficacy in treating inflammatory states, such as arthritic conditions.

Mesenchymal stem cells (MSCs) are another currently available biologic agent. MSCs are unspecialized progenitor cells, capable of division and self-renewal for long period of time, and can give rise to specialized cell lines. Their medicinal potential is based on their ability to secrete bioactive factors that promote tissue healing, and ability to induce endogenous stem cell activity. The differentiation of MSCs is susceptible to local paracrine influence, and low levels of inflammation are necessary to achieve desired anabolic regenerative effects. As a result, MSCs are most effective in degenerative diseases, such as repair of bone and cartilage in discogenic disease and osteoarthritis.

Current literature establishes biologic agents as a cost-effective approach, more beneficial than standard, non-interventional care, and guidelines suggest they be considered upon initial failure of conservative therapy. Several contraindications are known, and must be acknowledged, including blood dyscrasias, infections and malignancy. Potential adverse events include infection, tissue rejection, and transient worsening of the pain. Interventional pain guidelines specifically have recommended that it be used independently or in conjunction with other treatment modalities, following diagnostic evidence of a need for biologic therapy.

**Key words:** *Regenerative medicine, Platelet-rich plasma, Mesenchymal stem cells, Chronic pain, Inflammation, Arthritis, Degenerative disease*

## REGENERATIVNA MEDICINA ZA HRONIČNI BOL – GDE SMO?

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Regenerativna medicina se u velikoj meri zasniva na suštinskoj sposobnosti tela da se izleči, korišćenjem unutrašnjih mehanizama popravke homolognim ili autolognim biološkim agensima. Regenerativna terapija je veoma obećavajuća u poboljšanju hroničnog bola kod pacijenata sa poremećajima mišićno-skeletnog sistema.

Jedan takav biološki agens je plazma bogata trombocitima (PRP), koncentrat napravljen od krvi centrifugirane za uklanjanje crvenih krvnih zrnaca, koja sadrži razne faktore rasta. Mogu se formulisati četiri tipa PRP, u zavisnosti od broja belih krvnih zrnaca i arhitekture fibrina. PRP je pokazao najveću efikasnost u lečenju inflamatornih stanja, kao što su artritična oboljenja.

Mezenhimalne matične ćelije (MSC) su još jedan trenutno dostupan biološki agens. MSC su nespecializovane progenitorske ćelije, sposobne za deobu i samoobnavljanje tokom dužeg vremenskog perioda, i mogu dovesti do specijalizovanih ćelijskih linija. Njihov medicinski potencijal zasniva se na sposobnosti da luče bioaktivne faktore koji promovišu zarastanje tkiva i sposobnosti da indukuju aktivnost endogenih matičnih ćelija. Diferencijacija MSC-a je podložna lokalnom parakrinom uticaju, a niski nivoi zapaljenja su neophodni da bi se postigli željeni anabolički regenerativni efekti. Kao rezultat toga, MSC su najefikasniji kod dege-nerativnih bolesti, kao što su popravka kostiju i hrskavice kod diskogenih bolesti i osteoartritisa.

Trenutna literatura utvrđuje da li su biološki agensi isplativ pristup, korisniji od standardne, neinterventne nege, a smernice sugerišu da se oni razmatraju nakon početnog neuspeha konzervativne terapije. Nekoliko kontraindikacija je poznato i moraju se imati na umu kod ove terapije, uključujući krvne diskrazije, infekcije i malignitet. Potencijalni neželjeni efekti uključuju infekciju, odbacivanje tkiva i prolazno pogoršanje bola. Smernice posebno preporučuju da se koriste samostalno ili u kombinaciji sa drugim modalitetima lečenja, nakon dijagnostičkih dokaza o potrebi za biološkom terapijom.

***Ključne reči:*** *regenerativna medicina, plazma bogata trombocitima, mezenhimalne matične ćelije, hronični bol, zapaljenje, artritis, degenerativna bolest*

## TRANSFERRING PAIN KNOWLEDGE INTO PRACTISE: LOST IN TRANSLATION OF NEUROPATHIC PAIN

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Preclinical and clinical pain related science have since long suffered from lack of joint ventures that, as securely as possible, have approached problems that are relevant for the understanding of clinical pain phenomenologies and treatment (Yeziarski & Hansson, 2018), the core of translational pain medicine. The uncoupling of the two has led to loss of momentum and few novel efficacious treatment remedies where needed the most, that is, in long-term pain states. Here, the area of translational pain medicine is craving for a road map so that preclinical and clinical scientists can walk hand in hand into the future with a common agenda on how to approach the search for much needed improved treatment strategies. Perhaps it would be timely to make a full stop to get peer agreement on guidelines recommending how to move on regarding choice of animal models, relevant testing procedures, etc., to optimally explore neuropathic pain conditions for the benefit of the pain suffering patients. To keep doing what has been largely unsuccessful for decades seems to be a waste of animal lives, funding and hard labour by dedicated colleagues. To create a novel and hopefully more successful approach in agreement between academia and industry is not wishful thinking for the future; it is an immediate demand by the suffering patients.

**Key words:** *pain knowledge, practise, neuropathic pain*

## PRENOŠENJE ZNANJA O BOLU U PRAKSU: IZGUBLJENO U PREVODU NEUROPATSKOG BOLA

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Pretkliničku i kliničku nauka u vezi sa bolom dugo je pratio nedostatak zajedničkih poduhvata koji bi, što je moguće sigurnije, pristupili problemima relevantnim za razumevanje kliničkih fenomenologija bola i lečenja (Jeziarski & Hanson, 2018), što je srž lečenja translacionog bola. Razdvajanje ovo dvoje dovelo je do slabijeg napretka i nekoliko novih efikasnih lekova za lečenje tamo gde je bilo najpotrebnije, to jest, kod dugotrajnih stanja bola. Ovde oblast translacione medicine bola žudi za smernicama kako bi pretklinički i klinički naučnici mogli da hodaju ruku pod ruku u budućnost sa zajedničkim planom o tome kako pristupiti traženju prekopotrebnih poboljšanih strategija lečenja. Možda bi pravovremeno postizanje saglasnost oko smernica koje se preporučuju kako da se krene dalje u pogledu izbora modela životinja, relevantnih procedura testiranja, itd. Kako bi se optimalno istražila stanja neuropatskog bola u korist bolesnika. Nastaviti sa tim što je decenijama bilo uglavnom neuspešno predstavlja gubljenje života životinja, uzaludnog finansiranja i teškog rada predanih kolega. Stvaranje novog i nadamo se uspešnijeg pristupa, u dogovoru između akademske zajednice i industrije, nije želja za budućnost, to je neposredan zahtev pacijenata koji pate.

***Ključne reči:*** *znanje o bolu, praksa, neuropatski bol*

## PAIN IN RHEUMATOLOGY – FROM NOCICEPTION TO PERCEPTION

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Nociplastic pain was introduced as a new term for describing nociceptive pain and neuropathic pain. Persistent nociceptive pain is a risk factor for nociplastic pain, which can often occur in isolation or in combination with other types of pain, most often in patients with chronic rheumatic diseases (osteoarthritis, lumbar and cervical syndrome, fibromyalgia, rheumatoid arthritis, complex regional pain syndrome, tendinopathy and similar). Nociplastic pain arises from altered nociception with central sensitization mechanism. It is manifested through an increased sensitivity outside the primary area of tissue injury or damage, or beyond the innervation territory of lesioned or diseased nervous structures (fibromyalgia, osteoarthritis, Ehlers-Danlos syndrome, and rheumatoid arthritis). Often, there are discrepancies between the degree of inflammation and structural damage and pain in patients suffering from rheumatic disease. Different underlying pathophysiological mechanisms in different patients can manifest as the same central sensitization phenotype. Nearly half of the patients with rheumatoid arthritis have moderate to high amounts of pain, fatigue, pain catastrophizing, and sleep disturbance, but with minimal signs of peripheral inflammation, thereby indicative of the widespread pain syndrome, whereas a third of patients also fulfill the fibromyalgia syndrome criteria. Patients with rheumatoid arthritis without other painful comorbidities had hyperalgesia and abnormal cerebral nociceptive processing during noxious stimulation of inflamed joints, but not during the stimulation of healthy tissues, thereby indicating peripheral or spinal sensitization. Some of the pain conditions with features of central sensitization are characterized by peripheral inflammation (eg, rheumatoid arthritis and osteoarthritis). Neuroinflammation in the CNS is a potential contributor to the pain and other symptoms in rheumatological diseases. Aberrant glial activation, shown in patients with chronic non-specific low back pain and fibromyalgia can explain the establishment, maintenance, or both, of central sensitization in at least a subset of patients. Although central sensitization can predict poor treatment outcomes in some patient groups, there are both pharmacological and non-pharmacological treatments available that show the capacity to attenuate central sensitization.

**Key words:** *pain, rheumatic diseases, nociceptive, nociplastic, neuropathic*

**BOL U REUMATOLOGIJI – OD NOCICEPCIJE DO PERCEPCIJE**

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Nociplastični bol je uveden kao novi deskriptor za nociceptivni bol i neuropatski bol. Stalni nociceptivni bol je faktor rizika za nastanak nociplastičnog bola, koji se često može javljati izolovano ili udruženo sa drugim tipovima bola, najčešće kod bolesnika sa hroničnim reumatskim bolestima (osteoartritis, lumbalni i cervikalni sindrom, fibromijalgija, reumatoidni artritis, kompleksni regionalni bolni sindrom, tendinopatije i slično). Predstavljena je povećanom osetljivošću izvan primarnog područja povrede ili oštećenja tkiva, ili izvan teritorije inervacije oštećenih ili obolelih nervnih struktura (npr. fibromijalgija, osteoartritis, Ehlers-Danlosov sindrom i reumatoidni artritis). Često postoji diskrepanca između stepena inflamacije, strukturnog oštećenja i bola kod pacijenata sa reumatskim oboljenjima. Različiti patofiziološki mehanizmi kod različitih bolesnika mogu izraziti isti fenotip centralne senzitivizacije. Skoro polovina od ukupog broja bolesnika sa reumatoidnim artritisom ima bol umerenog do jakog intenziteta, umor, poremećaj sna, ali sa minimalnim znacima periferne upale, što ukazuje na rasprostranjeni sindrom bola, dok trećina bolesnika takođe ispunjava kriterijume sindroma fibromijalgije. Bolesnici sa reumatoidnim artritisom bez drugih bolnih komorbiditeta imali su hiperalgeziju i abnormalni cerebralni nociceptivni process tokom štetne stimulacije upaljenih zglobova, ali ne i tokom stimulacije zdravih tkiva, što ukazuje na perifernu ili spinalnu senzitivizaciju. Neka od stanja bola sa karakteristikama centralne senzitivizacije karakteriše periferna upala (npr. reumatoidni artritis i osteoartritis). Neuroinflamacija u centralnom nervnom sistemu potencijalno doprinosi bolu i drugim simptomima kod reumatoloških oboljenja. Aberantna glijalna aktivacija, prikazana kod bolesnika sa hroničnim nespecifičnim bolom u donjem delu leđa i fibromijalgijom, može objasniti uspostavljanje i/ili održavanje centralne senzitivizacije kod najmanjeg broja bolesnika. Iako centralna senzitivizacija može predvideti loše ishode lečenja kod nekih grupa bolesnika, dostupni su farmakološki i nefarmakološki tretmani koji pokazuju sposobnost da ublaže efekte centralne senzitivizacije.

***Ključne reči:*** *bol, reumatske bolesti, nociceptivni, nociplastični, neuropatski*

## KETAMINE FOR CHRONIC PAIN – CURRENT VIEW

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Chronic pain is one of leading causes of suffering and disability worldwide. Its prevalence is estimated to be 25% to 30%. Socio-economic burden as a result of chronic pain is huge and cannot be underestimated. Chronic pain is still resistant to conventional treatment. In the recent years, ketamine has gathered an enormous interest and we have been faced with marked increase in its clinical use despite the fact that ketamine has been clinically available for about 50 years. Ketamine has multiple actions as an analgesic, antihyperalgesic, antidepressant, antiinflammatory agent, and it also has opioid sparing effects. These complex mechanisms of action make it difficult to understand its safety and effectiveness for the treatment of chronic pain conditions. In low doses intravenous ketamine (0.1-0.5 mg/kg) produces analgesia and sedation, whereas in high doses it causes general anesthesia. For single-dose infusions, ketamine was significantly better than placebo in the short term (24-48 hours), but the pain relief was not sustained. For a multi-day infusion regimen, the long-term effects of repeated treatments are uncertain. Limited evidence indicates that ketamine could establish pain relief for up to two weeks in patients with chronic pain. Moderate evidence suggests that patients with CRPS have experienced a reduction in pain which was sustained for up to three months. There is insufficient evidence for the benefits of ketamine as a routine treatment for chronic pain and it should not be considered as a first line treatment for chronic pain. However, there are some cases where ketamine may be considered, including failure to respond to first-line treatment, a need to reduce opioid consumption in patients with limited options for managing chronic pain, and a need to reduce opioid use after surgery. In all these cases, personalized approach and monitored ketamine infusions may provide safe and effective pain relief in the short term. Perioperative low-dose ketamine infusions have demonstrated opioid-sparing effects. In contrast, for patients experiencing chronic pain and using high doses of opioids, there is insufficient evidence to support the use of ketamine infusions for management of pain and reduction of opioid use over the long term. Contraindications for ketamine iv infusions are: uncontrolled cardiovascular disease, hepatic impairment, elevated intracranial and intraocular pressure, psychosis, pregnancy.

Determining the effectiveness of ketamine for chronic pain in different studies was also obstructed by: different types of pain, different routes of administrations, different dosing protocols, small sample sizes, lack of appropriate control groups, and an inadequate follow up period.

**Key words:** *chronic pain treatment, ketamine*

## KETAMIN ZA HRONIČNI BOL – SADAŠNJI STAV

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Hronični bol jedan je od vodećih uzroka patnje i invaliditeta širom sveta. Njegova prevalencija je procenjena na 25% do 30%. Socioekonomski teret uzrokovan hroničnim bolom je ogroman i ne može se potcenjivati. Hronični bol je još uvek refraktoran na konvencionalne tretmane. Poslednjih godina, ketamin je izazvao ogromno interesovanje, te smo suočeni sa značajno povećanom upotrebom ketamina u kliničkoj praksi i pored činjenice da je klinički dostupan već oko 50 godina. Ketamin ima višestruko dejstvo: analgetik, antihiperalgezik, antidepressiv, antiinflamatorni agens, kao i efekt opioidne štednje. Ovi kompleksni mehanizmi delovanja otežavaju razumevanje njegove bezbednosti i efektivnosti u tretmanu hroničnih bolnih stanja. Niske doze intravenskog ketamina (0,1-0,5 mg/kg) izazivaju analgeziju i sedaciju, dok visoke doze uzrokuju opštu anesteziju. U pojedinačnoj kratkoročnoj infuziji ketamin je bio signifikantno bolji u kratkom periodu (24-48 hours) nego placebo, otklanjanje bola nije duže održano. U višednevnom infuzionom režimu dugotrajni efekti ponavljanih tretmana su neizvesni. Ograničeni su dokazi da ketamin otklanja bol tokom dve nedelje kod bolesnika sa hroničnim bolom. Umeren dokaz sugerise da bolesnici sa KRBS doživljavaju smanjenje bola koje se održava do tri meseca. Nema dokaza da je ketamin koristan kao rutinski tretman za hronični bol i ne treba ga razmatrati kao prvu liniju tretmana. Međutim, postoje neki slučajevi kada se ketamin može razmotriti: neuspešan odgovor na prvu terapijsku liniju, potreba smanjenja potrošnje opioida kod bolesnika sa ograničenim opcijama za zbrinjavanje hroničnog bola, kao i potreba da se smanji upotreba opioida posle operacije. Kod svih slučajeva, personalizovani pristup i monitoring infuzija mogu obezbediti sigurno i efektivno kratkoročno otklanjanje bola. Perioperativne niske doze infuzija ketamina pokazuju poštene efekte opioida. Nasuprot tome, kod bolesnika koji doživljavaju hronični bol i upotrebljavaju visoke doze opioida, nedovoljno je dokaza da podrže infuzije ketamina za zbrinjavanje bola i smanjenje dugoročne upotrebe opioida. Kontraindikacije za intravenske infuzije su: loše kontrolisana kardiovaskularna bolest, oštećenje jetre, povišen intrakranijalni i intraokularni pritisak, psihoza, trudnoća.

Utvrđivanje efektivnosti ketamina za hronični bol u različitim studijama je ometeno i zbog različitih tipova bola, različitih puteva davanja, različitih protokola doziranja, male veličine uzorka, nedostatka kontrolnih grupa, neadekvatnim periodom praćenja.

**Ključne reči:** *tretman hroničnog bola, ketamin*

## PERIPHERAL POLYNEUROPATHY IN PROLONGED COVID-19

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause long-term disability (prolonged COVID) with neurological manifestations even after mild infections. Reports of peripheral neuropathy and polyneuropathy include Guillain-Barré syndrome, mononeuritis multiplex, brachial plexitis, cranial neuropathies, and orthostatic intolerance. Various prolonged symptoms of COVID overlap with symptoms of small fiber polyneuropathy. Recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears to be exponential, with patients reporting a variety of long-term symptoms of COVID, including unexplained fatigue/exertion intolerance and dysautonomic and sensory problems. Indirect evidence links long-term COVID with incident polyneuropathy affecting small fiber (sensory/autonomic) axons.

Cross-sectional and longitudinal data were analyzed from patients with long COVID, as defined by World Health Organization (WHO), without a previous history of neuropathy or a clinical presentation suggestive of peripheral neuropathy. Standardized symptoms were diagnosed, clinical examination, neurodiagnostic tests and outcomes were performed.

Research and monitoring of symptoms lasted for a year.

A prospective study examined 68 patients (mean age 43.5 years, 79% of females), 59% had  $\geq 1$  test results confirming neuropathy. This included 50% of autonomic function tests. Three patients were diagnosed with critical illness axonal neuropathy. While one patient was diagnosed with multifocal demyelinating neuropathy 3 weeks after mild COVID,  $\geq 20$  were diagnosed with small fiber neuropathy. Longitudinal improvement averaged 72%, although no one reported complete resolution. In 85% of patients, immunotherapy (corticosteroids and/or IV immunoglobulins) was administered.

Among evaluated patients with long-term COVID-19 after mild SARS-CoV-2 infection, prolonged, often disabling small-fiber polyneuropathy was most common, starting as early as month after the onset of COVID-19 infection.

**Key words:** *COVID-19, SARS-CoV-2, peripheral neuropathy, neurological symptoms, pain, post-viral*

## PERIFERNA POLINEUROPATIJA KOD PROLONGIRANOG COVID-19

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Teški akutni respiratorni sindrom koronavirus 2 (SARS-CoV-2) može izazvati dugotrajni invaliditet (prolongirani COVID) sa neurološkim manifestacijama čak i nakon blagih infekcija. Izveštaji o perifernoj neuropatiji i polineuropatiji uključuju Gilen Bareov sindrom, mon-neuritis multiplex, brahijalni pleksitis, kranijalne neuropatije i ortostatsku netoleranciju. Različiti prolongirani simptomi COVID-a preklapaju se sa simptomima polineuropatije malih vlakana. Oporavak od infekcije virusom korona 2 (SARS-CoV-2) teškog akutnog respiratornog sindroma izgleda eksponencijalno, gde bolesnici prijavljuju različite dugotrajne simptome COVID-a, uključujući neobjašnjiv umor/netoleranciju na napor i disautonomne i senzorne probleme. Indirektni dokazi povezuju dugi COVID sa incidentnom polineuropatijom koja utiče na aksone malih vlakana (senzorne/autonomne).

Analizirani su poprečni i longitudinalni podaci bolesnika sa dugim COVID-om koji je definisala Svetska zdravstvena organizacija (SZO) bez prethodne istorije neuropatije ili kliničke slike koja ukazuje na perifernu neuropatiju. Dijagnostikovani su standardizovani simptomi, urađen je klinički pregled, neurodijagnostički testovi i ishodi. Istraživanje i praćenje simptoma trajalo je godinu dana.

Prospektivnom studijom ispitano je 68 bolesnika (srednja starost 43,5 godina, 79% žena), 59% je imalo  $\geq 1$  rezultate testa koji potvrđuje neuropatiju. Ovo je uključivalo i 50% testova autonomne funkcije. Trojici pacijenata dijagnostikovana je kritična bolest aksonske neuropatije. Dok je jednom pacijentu dijagnostikovana multifokalna demijelinizirajuća neuropatija tri nedelje nakon blagog COVID-a, a  $\geq 20$  dobilo je dijagnozu neuropatije malih vlakana. Longitudinalno poboljšanje je u proseku iznosilo 72%, iako niko nije prijavio potpunu rezoluciju. Za lečenje, 85% je dobilo imunoterapiju (kortikosteroide i/ili IV imunoglobuline).

Među evaluiranim bolesnicima sa dugotrajnim COVID-om, produžena, često onesposobljavajuća polineuropatija malih vlakana nakon blagog SARS-CoV-2 bila je najčešća, počevši već u roku od jednog meseca, od nastanka infekcije COVID-19.

***Ključne reči:*** COVID-19, SARS-CoV-2, periferna neuropatija, neurološki simptomi, bol, postvirusno

## HEADACHES ASSOCIATED WITH COVID-19

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A headache is the most common neurological symptom in patients with COVID-19 infection, which can be associated with other symptoms or present as the first manifestation of the illness. On average, it is twice as frequent in patients with COVID-19 compared to other viral infections. It has been observed that newly-onset headache related to coronaviral infection begins suddenly, and it has different characteristics than previous headaches.

There are several hypotheses related to the etiology of headaches in COVID-19, such as the direct invasion of coronavirus, which can activate the peripheral trigeminal system. It has been confirmed that trigeminal ganglion has angiotensin-like activity, and hypothetically the viral invasion can disrupt renin-angiotensin-aldosterone system activity. This increases the levels of peptides related to the calcitonin gene, a potent peptide vasodilator important in pain transmission. Furthermore, SARS-COV-2 can ascend to the brain via cranial nerves. Besides direct invasion of olfactory and gustatory nerves in the oral and nasal mucosa, the trigeminal nerve endings can be infected too. The headache is more frequent in patients with anosmia and ageusia as well. Trans-synaptic viral spread to the central nervous system for some coronaviruses is well documented, and for SARS-COV-2, it remains plausible, albeit not proven yet. COVID-19 infection can affect the gut-brain axis by acting directly on gut microbiota, production of neural transmitters, and invasion of the vagus nerve, provoking recurrent gastrointestinal symptoms and headaches.

As the pandemic progresses and the population of recovered patients grows, it has become evident that a headache in the acute stages of COVID-19 infection can last indefinitely. A headache can present as a post-COVID manifestation too.

The COVID-19 pandemic has had numerous influences on the manifestation of headaches. A newly-onset headache and worsening of the existing one require further and detailed exploration.

**Key words:** *headache, COVID-19, trigeminovascular system*

## GLAVOBOLJE U VEZI SA COVID-19

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Glavobolja je najčešći neurološki simptom koji se javlja kod pacijenata sa koronavirusnom bolešću 2019 (COVID-19). Često se javlja zajedno sa drugim simptomima infekcije, ali može biti i prvi simptom bolesti. Glavobolja je prosečno dva puta češća kod obolelih od COVID-19 infekcije, od glavobolje kod drugih virusnih infekcija. Klinički je zapaženo da novonastala glavobolja koja je u vezi sa infekcijom korona virusom naglo nastaje i drugačijih je karakteristika od ranije glavobolje. Postoji više hipoteza u vezi sa glavoboljom kod COVID-19. Direktna invazija virusa može aktivirati periferni trigeminalni sistem. S obzirom na to da je potvrđeno da trigeminalni ganglion ima angiotenzinsku aktivnost, hipotetički invazija virusa može poremetiti aktivnost sistema renin-angiotenzin-aldosteron, što može povećati nivo peptida povezanog sa kalcitoninskim genom, koji je potentni peptidni vazodilatator, značajan u transmisiji bola. Takođe, virus pokazuje neurotropizam, te se putem kranijalnih nerava može preneti na mozak. Pored direktne invazije olfaktornih i gustativnih nerava u usnoj i nosnoj sluznici dolazi i do invazije trigeminalnih nervnih završetaka. Zbog toga je glavobolja češće prisutna kod bolesnika kod kojih se u kliničkom ispoljavanju infekcije javlja anosmija i ageuzija. Za neke koronavirusne je dokazan, a za SARS-COV-2 je vrlo verovatan, ali za sada nije dovoljno dokumentovan transinaptički prenos virusa u centralni nervni sistem. Udružena pojava gastrointestinalnih simptoma i glavobolje takođe je učestala. Delujući na mikrobiom creva, produkciju neurotransmitera i invazijom vagusnog nerva, COVID-19 infekcija može uticati na funkcionisanje osovine creva – mozak, te učestaliju pojavu gastrointestinalnih simptoma i glavobolje. Kako pandemija napreduje i populacija koja se oporavlja od COVID-19 raste, postaje očigledno da glavobolja prisutna u akutnom stadijumu infekcije može trajati neodređeni period. Glavobolja se može javiti i kao postkovid manifestacija.

COVID-19 pandemija ima višestruki uticaj na glavobolju. Novonastala glavobolja i pogoršanje postojeće glavobolje zahtevaju detaljnu eksploraciju.

***Ključne reči:*** glavobolja, COVID-19, trigeminovaskularni sistem

## ANALGOSEDATION IN CRITICALLY ILL PATIENTS

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Analgo sedation has a role in facilitating therapeutic and diagnostic procedures and reducing patient distress. Indications for analgo sedation are anxiolysis, amnesia, pain relief, control of agitation, reduction of intracranial pressure, reduction of patient discomfort and increase of therapeutic effect. The selection of a pharmacological agent is made individually according to the needs and condition of the patient, according to the expected length of treatment and previous response to therapy. The advantages are enabling synchronization with mechanical ventilation, reducing work of breathing, and reducing pain, stress and oxygen consumption. Adverse effects are the possible need for prolonged mechanical ventilation, longer patient recovery, hypotension, myopathy, delirium, and increased risk of pneumonia, ileus and thrombosis. The ideal agent has a sedative, analgesic and anxiolytic effect, minimal cardiovascular and respiratory side effects, early onset and cessation of action, is cheap, does not interact with other drugs and does not accumulate in liver and kidney failure. Intravenous anesthetics, opioids, benzodiazepines,  $\alpha 2$ -agonists, barbiturates, and neuroleptics are used for analgo sedation. Recently, inhalational anesthetics have been used more often. *Richmond Agitation-Sedation Scale*, *Riker Sedation-Agitation Scale* and *Ramsay Sedation Scale* are most commonly used to assess agitation and sedation.

**Key words:** *analgesia, hypnotics and sedatives, critical illness, critical care*

## ANALGOSEDACIJA KRITIČNO OBOLELIH

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Analgo sedacija ima ulogu u olakšavanju terapijskih i dijagnostičkih procedura i smanjenju distresa bolesnika. Indikacije za analgo sedaciju su anksioliza, amnezija, olakšavanje bola, kontrola agitacije, smanjenje intrakranijalnog pritiska, smanjenje nelagodnosti bolesnika i povećanje učinka terapije. Odabir farmakološkog sredstva vrši se individualno prema potrebama i stanju bolesnika, prema očekivanoj dužini terapije i na osnovu prethodnog odgovora na terapiju. Prednosti su omogućavanje sinhronizacije sa mehaničkom ventilacijom pluća, smanjenje disajnog rada, bolova, stresa i potrošnje kiseonika. Neželjena dejstva su moguća potreba za produženom mehaničkom ventilacijom pluća, produžena sedacija, hipotenzija, miopatije, delirijum, povećan rizik od pneumonija, ileusa i tromboza. Idealno sredstvo ima sedativni, analgetski i anksiolitički efekat, minimalna kardiovaskularna i respiratorna neželjena dejstva, rano nastupanje i prekid dejstva, jeftino je, nema interakcija sa drugim lekovima i ne nakuplja se u organizmu u jetrenoj i bubrežnoj insuficijenciji. Za analgo sedaciju koriste se intravenski anestetici, opioidi, benzodijazepini,  $\alpha 2$ -agonisti, barbiturati, neuroleptici. U poslednje vreme češće se koriste i inhalacioni anestetici. Za procenu agitacije i sedacije najčešće se koriste *Richmond Agitation-Sedation Scale*, *Riker Sedation-Agitation Scale* i *Ramsay Sedation Scale*.

**Ključne reči:** analgezija, hipnotici i sedativi, kritična bolest, nega kritično obolelih

## POSSIBILITIES OF TREATING PAIN IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES

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Pain in inflammatory rheumatic diseases is caused by chronic destructive synovitis and the existence of multisystemic dysfunction. The sensitivity threshold is hereditary and is linked to GCH-1, a gene on chromosome 7. About one quarter of people in the world have a special type of this gene, which is responsible for protection against pain. Unlike acute nociceptive pain in inflammatory rheumatic diseases, which is short-lived and has a protective role, chronic pain lasts longer than 3 months, is accompanied by physical and psycho-social changes, reduces the quality of life and represents a separate clinical entity. Pain therapy in inflammatory rheumatic diseases is complex and requires a clear idea of the cause of pain and the mechanisms of its occurrence. Nociceptive inflammatory pain is most often treated with DMARDs, anti-inflammatory drugs and analgesics. Chronic pain, however, is much more difficult to treat and often requires a multidisciplinary approach. The treatment usually starts with medication (csDMARDs, bDMARDs, tsDMARDs, anti-inflammatory drugs, analgesics, co-analgesics), but those are not a long-term effective solution, due to the numerous side effects. Recently, the influence of the multifunctional protein regulator of G protein signaling 4 (RGS4) on the maintenance and modulation of chronic pain in the brain has been discovered. The role of RGS4 helps to relieve pain and sensory symptoms, and these findings open the possibility of exploring new therapeutic modalities. The use of drugs in the treatment of pain in rheumatic patients is long-term, but it can also be uncritical with numerous adverse reactions. A multimodal approach to treatment can achieve an analgesic effect and minimize unwanted consequences. The importance of physical agents (laser therapy, magnetotherapy, transcutaneous electrostimulation, diadynamic currents, interference currents, galvanic current, electrophoresis, ultrasound, sonophoresis) in the treatment of chronic pain is great because it reduces the need to take drugs, and there are no unwanted side effects. Various alternative methods are available that can also be helpful: tai chi exercise, yoga, acupuncture, music and art therapy, pet therapy, psychotherapy, massage, meditation... In addition to nociceptive, inflammatory pain therapy, early discovery of neuropathic pain (using PainDetect and DN4 questionnaire) is very important for a successful treatment outcome. Effective drugs for this type of pain are drugs that stabilize or modulate CNS functions, tricyclic antidepressants (TCAs) or anticonvulsants. The most commonly used drugs in this group are pregabalin, carbamazepine, phenytoin, valproic acid, clonazepam and gabapentin. After using TCAs and anticonvulsants, local anesthetics are given in the third line. Multimodal treatment includes a pharmacological approach, regular exercise, physical therapy, adequate nutrition, psychotherapy, functional neurosurgery, and various surgical techniques. In addition to treating the underlying disease, pain in inflammatory rheumatic diseases requires an individual approach. Physical pain is related to emotional pain, so mastering emotional skills can affect stress, which is related to the health condition. Pain in inflammatory rheumatic diseases requires an individual approach. Physical pain is related to emotional pain, so mastering emotional skills can affect stress, which is related to a health condition.

**Key words:** *inflammatory rheumatic diseases, pain, treatment*

## MOGUĆNOSTI LEČENJA BOLA KOD BOLESNIKA SA ZAPALJENSKIM REUMATSKIM BOLESTIMA

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Bol kod zapaljenskih reumatskih oboljenja uzrokovan je hroničnim destruktivnim sinovitisom i postojanjem multisistemske disfunkcije. Prag senzibiliteta je nasledan i vezuje se za GCH-1, gen hromozoma 7. Oko jedne četvrtine ljudi na svetu ima poseban tip ovog gena koji je zadužen da štiti od bola. Za razliku od akutnog nociceptivnog bola u zapaljenskim reumatskim bolestima, koji je kratkotrajan i ima zaštitnu ulogu, hronični bol traje duže od tri meseca, praćen je fizičkim i psihosocijalnom promenama, umanjuje kvalitet života i predstavlja poseban klinički entitet. Terapija bola u zapaljenskim reumatskim bolestima je kompleksna i zahteva jasnu predstavu o uzroku bola i mehanizmima njegovog nastanka. Nociceptivni inflamatorni bol se najčešće leči DMARDs, antiinflamatornim lekovima i analgeticima. Hronični bol je, međutim, mnogo teži za lečenje i često zahteva multidisciplinarni pristup bolesti. Lečenje se obično započinje medikamentima (csDMARDs, bDMARDs, tsDMARDs, antiinflamatorni lekovi, analgetici, koanalgetici) ali nisu dugoročno efikasno rešenje, zbog brojnih neželjenih efekata. Nedavno je otkriven uticaj multifunkcionalnog protein regulatora signalizacije G proteina 4 (RGS4) na održavanje i modulaciju hroničnog bola u mozgu. Uloga RGS4 pomaže u uklanjanju bola i senzornih simptoma, a ova saznanja otvaraju mogućnosti istraživanja novih terapijskih modaliteta. Primena lekova u terapiji bola reumatskih bolesnika je dugotrajna ali može biti i nekritična sa brojnim neželjenim reakcijama. Multimodalnim pristupom lečenju može se postići analgetički efekat i minimizirati neželjene posledice. Značaj fizikalnih agenasa (laseroterapija, magnetoterapija, transkutana elektrostimulacija, diadinamičke struje, interferentne struje, galvanska struja, elektroforeza, ultrazvuk, sonoforeza) u terapiji hroničnog bola je veliki zbog toga što smanjuje potrebu za uzimanjem lekova, a nema nikakvih neželjenih nuspojava. Na raspolaganju su i različite alternativne metode koje takođe mogu biti od pomoći: tai či vežbanje, joga, akupuntura, terapija muzikom i umetnošću, terapija kućnim ljubimcima, psihoterapija, masaža, meditacija... Pored terapije nociceptivnog, inflamatornog bola, za uspešan ishod lečenja veoma je važno rano prepoznavanje neuropatskog bola (korišćenjem Pain Detecti DN4 upitnika). Efikasni lekovi za ovu vrstu bolova su lekovi koji stabilizuju ili moduliraju funkcije CNS-a, triciklički antidepresivi (TCA) ili antikonvulzivi. Najčešće korišćeni lekovi u ovoj grupi su pregabalin, karbamazepin, fenitoin, valproinska kiselina, klonazepam i gabapentin. Nakon korišćenja TCA i antikonvulziva, lokalni anestetici se daju u trećoj liniji. Multimodalno lečenje podrazumeva vafarmakološki pristup, redovno vežbanje, fizikalnu terapiju, adekvatnu ishranu, psihoterapiju, funkcionalnu neurohirurgiju, različite hirurške tehnike. Pored lečenja osnovnog oboljenja, bol u zapaljenskim reumatskim bolestima zahteva i individualan pristup. Fizički bol je povezan sa emocionalnim bolom, tako da se savladavanjem emocionalnih veština može uticati na stres, koji je povezan sa zdravstvenim stanjem.

**Ključne reči:** *zapaljenske reumatske bolesti, bol, lečenje*

## CONDITIONED PAIN MODULATION – EVALUATION AND POTENTIAL CLINICAL IMPLICATIONS

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Pain perception is a complicated process and depends both on ascending pathways that convey nociceptive information to the central nervous system and descending pathways through which nociceptive information can be modulated. There are two ways of nociceptive input modulation: inhibition and facilitation. One inhibitory system is diffuse noxious inhibitory control and conditioned pain modulation (CPM) is the new term for this paradigm in humans. CPM tests are based on the theory that "pain inhibits pain". One painful stimulus (conditioning stimulus) can modulate another painful stimulus (test stimulus). CPM effects can be evaluated by measuring the difference between pain induced by a test stimulus (TS) before, and pain during or after the administration of a painful conditioning stimulus (CS) in the remote body region. Efficient CPM represents inhibition of pain induced by the TS as a response to the CS. In certain chronic painful conditions (e.g. fibromyalgia, low back pain, temporomandibular disorders, irritable bowel syndrome, etc.) deranged CPM is frequently seen. In addition, it has been shown that efficacy of the descending pain inhibition could be a significant factor in the advancement of acute to chronic pain. Therefore, the interest in protocols that investigate CPM in a clinical setting is rising. Various TS and CS are used in existing CPM protocols. Mechanical, thermal, and electrical stimuli are the most frequently used modalities as a TS, while cold pressure test, contact heat and cuff pressure are the most frequently used as a CS. However, the gold standard for the CPM testing has not been reached yet. Although development of the clinically useful test for evaluation of the CPM is challenging, designing of such a test would be valuable for determination of the individual pain modulation profile and for designing the most efficient pain treatment.

**Key words:** *conditioned pain modulation, pain, pain modulation profile*

## USLOVNA MODULACIJA BOLA – EVALUACIJA I MOGUĆNOSTI KLINIČKE PRIMENE

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Percepcija bola je kompleksan proces koji zavisi kako od ascedentnih puteva koji prenose nociceptivne informacije do centralnog nervnog sistema tako i od descendentnih puteva preko kojih nociceptivna informacija može biti modulirana. Postoje dva načina modulacije nociceptivnog stimulusa: inhibicija i facilitacija. Jedan od inhibitornih sistema je difuzni inhibitorni sistem štetnih stimulusa, a uslovna modulacija bola (CPM) je novi termin za ovu paradigmu kod ljudi. Testovi za CPM su bazirani na tome da „bol inhibiše bol”. Jedan bolni stimulus (uslovni stimulus – CS) može modulirati drugi bolni stimulus (test stimulus – TS). Efekti CPM mogu biti evaluirani merenjem razlike između bola indukovanog test stimulusom pre i nakon primene bolnog uslovljavajućeg stimulusa (CS) na udaljenom delu tela. Efikasna CPM se odlikuje inhibicijom bola indukovanog TS kao odgovor na CS. U određenim hroničnim bolnim stanjima (npr. fibromijalgija, bol u donjem delu leđa, temporomandibularna oboljenja, sindrom iritabilnog kolona itd.) poremećena CPM je često prisutna. Dodatno, pokazano je da efikasnost nishodne inhibicije bola može biti važan faktor prelaska akutnog u hronični bol. Stoga, raste interes za protokole koji se bave CPM u kliničkom radu. Različiti TS i CS koriste se u postojećim CPM protokolima. Mehanički, toplotni i električni stimulusi su najviše upotrebljavani modaliteti kao TS, dok su test potapanja u hladnu vodu, kontaktna toplota i pritisak manžete najviše upotrebljavani kao CS. Zlatni standard za testiranje CPM nije utvrđen. Iako dizajniranje testova za CPM, koji bi se koristili u kliničkim uslovima, predstavlja izazov, razvoj takvog testa bi bio koristan za određivanje individualnog profila modulacije bola i utvrđivanje najefikasnije terapije bola.

***Ključne reči:*** uslovna modulacija bola, bol, profil modulacije bola

## FROM STIMULUS TO BRAIN CORTEX – ARE WE CLOSER TO UNDERSTANDING THE MYSTERY?

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The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or an experience described in the context of such damage". Nociceptors (pain receptors) are free nerve endings (A- $\delta$  (thick myelinated) and C (thin unmyelinated) nerve fibers). The mechanism of the formation of the sensation of pain arises from the integration of four physiological processes: transduction, transmission, perception and modulation. Transduction is the process of converting mechanical, thermal or chemical stimuli into an electrical stimulus. That is, algogenic substances change the permeability of the membrane of nociceptive endings for ions, there is a depolarization of the membrane and the formation of a receptor and later an action potential. Pain transmission is the process of transmitting painful impulses, i.e. generated action potentials from nociceptors to the spinal cord and brain. Transmission refers to the transmission of pain from irritated nociceptors to the primary and secondary somatosensory fields in the cerebral cortex and limbic system. Pain perception is the subjective experience of pain. The primary and secondary somatosensory cortex are responsible for the conscious perception and characteristics of pain in the form of its localization, intensity and duration of pain. The limbic system is involved in the emotional-affective component of pain perception. The perception of pain is actually the result of the neural activity of different centers in the brain that participate in the localization, processing and interpretation of painful sensations. Through perception, pain becomes a conscious experience and acquires an affective-motivational, emotional and behavioral component. In this process, the degree of attention, anxiety, fear, previous experience of the individual and expectations play a significant role. Threshold of pain receptor stimulation and pain tolerance are important for pain perception. Pain modulation is an activity that controls the process of pain signal transmission. Pain modulation refers to the inhibitory effect of descending pathways of pain control on neurons of the posterior horns of the spinal cord. The endogenous analgesia system modulates pain, which consequently affects the perception of pain.

**Key words:** *pain, stimulus, cerebral cortex, nociceptors*

**OD STIMULUSA DO KORTEKSA – DA LI SMO BLIZU REŠAVANJU MISTERIJE?****Dejan M. Nešić**Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku fiziologiju Kliničkog centra Srbije,  
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Međunarodna asocijacija za proučavanje bola (International Association for the Study of Pain) definiše bol kao „neprijatno senzorno i emocionalno iskustvo povezano sa stvarnim ili potencijalnim oštećenjem tkiva ili iskustvo opisano u kontekstu takvog oštećenja”. Nociceptori (receptori za bol) su slobodni nervni završeci (A- $\delta$  (debeli mijelinizovani) i C (tanki nemijelinizovani) nervna vlakna). Mehanizam formiranja osećaja bola nastaje integracijom četiri fiziološka procesa: transdukcije, transmisije, percepcije i modulacije. Transdukcija je proces konverzije mehaničkih, termičkih ili hemijskih nadražaja u električni stimulus. Odnosno, algogene supstance menjaju propustljivost membrane nociceptivnih završetaka za jone, dolazi do depolarizacije membrane i nastanka receptorskog, a kasnije i akcionog potencijala. Transmisija bola je proces prenosa bolnih impulsa, tj. generisanih akcionih potencijala iz nociceptora u kičmenu moždinu i mozak. Transmisija se odnosi na prenos bola od nadražanih nociceptora do primarnog i sekundarnog somatosenzornog polja u kori velikog mozga i limbičkog sistema. Percepcija bola je subjektivni doživljaj bola. Primarni i sekundarni somatosenzorni korteks su odgovorni za svesnu percepciju i karakteristike bola u vidu njegove lokalizacije, intenziteta i dužine trajanja bola. Limbički sistem uključen je u emocionalno-afektivnu komponentu percepcije bola. Percepcija bola zapravo predstavlja rezultat dejstva neuronske aktivnosti različitih centara u mozgu koji učestvuju u lokalizaciji, procesiranju i interpretaciji bolnih senzacija. Percepcijom bol postaje svesno iskustvo i dobija afektivno-motivacionu, emocionalnu i bihevioralnu komponentu. U ovom procesu značajnu ulogu imaju stepen pažnje, anksioznost, strah, prethodno iskustvo pojedinca i očekivanja. Za percepciju bola važni su prag nadražaja receptora za bol i tolerancija bola. Modulacija bola je aktivnost koja kontroliše proces transmisije bolnih signala. Modulacija bola se odnosi na inhibitorno dejstvo nishodnih puteva kontrole bola na neurone zadnjih rogova kičmene moždine. Endogeni analgezijski sistem vrši modulaciju bola, što posledično utiče na percepciju bola.

***Ključne reči:*** *bol, stimulacija, cerebralni korteks, nociceptori*

## COMPLEMENTARY METHODS IN THE TREATMENT OF PAIN

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Complementary medicine methods have been used increasingly to treat painful conditions such as neck and back pain, joint pain, headaches, and myofascial pain. The methods are used both in acute and chronic conditions. Pharmacological approaches may be unavailable for individual patients because of the adverse effects or precautions due to interactions with drugs used to treat comorbid conditions. Recent research also shows the possibility of complementary medicine methods acting on the hyperexcitability of different nervous system structures. The most important feature of these methods is safety in use. In this regard, the professional public's interest in integrative strategies for treating pain has grown in recent years. An electronic search of *PubMed*, *The Cochrane Library*, *EMBASE*, *Google Scholar*, and *Science Citation Index Expanded* databases was conducted with the following keywords: pain, alternative medicine, and complementary medicine. The methods used are relaxation, yoga, tai chi, manipulative techniques, and acupuncture. The literature review indicates a varying degree of effectiveness of the methods and methodological shortcomings of research in this area. Generally speaking, positive evidence for applying yoga, relaxation methods, tai chi, and manipulative techniques is still weak. However, the results from a systematic review of the literature indicates significant evidence for using acupuncture to treat painful conditions. Research also suggests that the degree of recommendation by the professional public for the application of complementary medicine is still weak, despite the appearance of recommendations in the specific guides for the treatment of painful conditions. There is also a noticeable trend of multimodal application of complementary medicine methods in treating pain.

**Key words:** *pain, alternative medicine, complementary medicine*

## KOMPLEMENTARNE METODE U LEČENJU BOLA

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Metode komplementarne medicine se sve češće koriste u lečenju bolnih stanja poput bolova u vratu i leđima, bolova u zglobovima, glavobolje i miofascijalnog bola. Metode se koriste kako u akutnim tako i hroničnim stanjima. Farmakološki pristupi mogu biti nedostupni za pojedine bolesnike zbog neželjenih efekata ili interakcija sa lekovima koji se koriste u lečenju komorbiditenih stanja. Takođe, novija istraživanja pokazuju mogućnost delovanja metoda komplementarne medicine na hiper-erkscitabilnost različitih struktura nervnog sistema. Kao najznačajnija odlika ovih metoda smatra se bezbednost pri upotrebi. U tom smislu, poslednjih godina je porastao interes stručne javnosti za integrativne strategije u lečenju bola. Srovedeno je elektronsko pretraživanje baza podataka *PubMed*, *The Cochrane Library*, *EMBASE*, *Google Scholar*, *Science Citation Index Expanded* sa sledećim ključnim rečima: bol, alternativna medicina, komplementarna medicina. Metode koje se koriste su metode relaksacije, joga, tai chi, manipulativne tehnike i akupunktura. Pregled literature ukazuje na različit stepen efektivnost metoda, ali i na metodološke nedostatke istraživanja u ovoj oblasti. Uopšteno govoreći i dalje su slabi pozitivni dokazi za primenu joge, metode relaksacije, tai chi i manipulativnih tehnika. Međutim, rezultati sistemskog pregleda literature ukazuju na značajne dokaze za primenu akupunkture u lečenju bolnih stanja. Istraživanja ukazuju i da je stepen preporuke od strane stručne javnosti za primenu komplementarne medicine i dalje veoma slab i pored pojave preporuka u pojedinim vodičima za tretman bolnih stanja. Takođe je primetan trend multimodalne primene metoda komplementarne medicine u lečenju bola.

**Ključne reči:** *bol, alternativna medicina, komplementarna medicina*

## CLINICAL MANIFESTATIONS OF PAINFUL DIABETIC NEUROPATHIES: DIAGNOSTIC AND DIFFERENTIAL DIAGNOSTIC CRITERIA

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According to the International Federation of Diabetes Mellitus (DM), it is estimated that this disease affects about 415 million adults worldwide (8.8% of the adult population), with this number predicted to increase to over 600 million by 2040. DM is associated with numerous chronic complications, among which diabetic neuropathy (DN) is one of the most common. Complications of DM on the peripheral nervous system are responsible for the most common form of neuropathy in the Western countries. DN shows a wide spectrum of clinical manifestations, with distal symmetrical sensorimotor polyneuropathy (DSPN) being the most common clinical form. Twenty five percent of patients with DN develop symptoms in the form of neuropathic pain. Painful diabetic neuropathy (BDN) is associated with increased stress, poorer quality of life and reduced work productivity, compared to non-painful DN and the general population. BDN can be manifested in the form of different clinical entities that sometimes represent a serious differential diagnostic problem in relation to other painful neurological and/or internal medicine conditions. Recognition and diagnosis of DN, especially rare and atypical forms, is important for the timely application of appropriate therapeutic procedures. An optimal treatment involves good glycoregulation, control of symptoms, especially pain, and adequate foot care. Poor effectiveness of the current therapeutic procedures may be related to the fact that most of the trials were conducted with patients with already established neuropathy. Therefore, it is assumed that early diagnosis and timely application of therapy would further improve results. This may provide an impetus to rekindle the interest of both neurologists and physicians in the primary health care system in the diagnosis and treatment of diabetic neuropathy.

**Key words:** *diabetes mellitus, diabetic neuropathy, neuropathic pain*

## KLINIČKO ISPOLJAVANJE BOLNIH DIJABETESNIH NEUROPATIJA: DIJAGNOSTIČKI I DIFERENCIJALNO DIJAGNOSTIČKI KRITERIJUMI

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Prema Međunarodnoj federaciji za dijabetes melitus (DM) procenjuje se da ovo oboljenje pogađa oko 415 miliona odraslih osoba širom sveta (8,8% odrasle populacije), sa predviđanjem da taj broj poraste na preko 600 miliona do 2040. godine. Dijabetes melitus je povezan sa brojnim hroničnim komplikacijama, među kojima je i dijabetička neuropatija (DN) kao jedna od najčešćih. Komplikacije DM na perifernom nervnom sistemu odgovorne su za najučestaliji oblik neuropatije u zemljama zapadne civilizacije. DN pokazuje širok spektar kliničkog ispoljavanja, gde distalna simetrična senzomotorna polineuropatija (DSPN) predstavlja najčešću kliničku formu. Kod 25% bolesnika sa DN razviju se simptomi u vidu neuropatskog bola. Bolna dijabetička neuropatija (BDN) povezana je sa povećanim stresom, lošijim kvalitetom života i smanjenom produktivnošću na poslu u poređenju sa nebolnom DN i opštom populacijom. BDN se može ispoljiti u vidu različitih kliničkih entiteta, koji nekada predstavljaju ozbiljan diferencijalno-dijagnostički problem u odnosu na druga bolna neurološka i/ili internistička stanja. Prepoznavanje i dijagnostikovanje DN, posebno ređih i atipičnih formi, važno je za blagovremenu primenu odgovarajućih terapijskih procedura. Optimalni tretman podrazumeva dobru glikoregulaciju, kontrolu simptoma, pre svega bola i adekvatnu negu stopala. Slaba efikasnost dosadašnjih terapijskih procedura može biti povezana sa činjenicom da je većina ispitivanja vršena kod bolesnika sa već razvijenom neuropatijom. Stoga se pretpostavlja da bi rana dijagnoza i blagovremena primena terapije dala bolje rezultate. Ovo može dati podsticaj da se ponovo pojača interesovanje, kako neurologa tako i lekara u primarnom zdravstvenom sistemu, za dijagnostiku i lečenje dijabetičke neuropatije.

**Ključne reči:** šećerna bolest, dijabetička neuropatija, neuropatski bol

## SPINAL CORD STIMULATION IN THE TREATMENT OF CHRONIC PAIN IN REFERENCE TO PAINFUL DIABETIC POLYNEUROPATHY

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Spinal cord stimulation (SCS) is a neuromodulation technique that reduces pain by electrical stimulation of the dorsal horns of the spinal cord. One of the four main indications for SCS implantation is painful diabetic polyneuropathy (DPN). In the period from February 2018 to June 2021, ten SCS systems were installed in the Institute for Physical Medicine and Rehabilitation "Dr. Miroslav Zotović", one of which was installed in a patient with painful DPN. The aim of the study is to demonstrate the effectiveness of the SCS system in a patient with painful DPN.

Male, 57 years old, treated for diabetes mellitus for the past 15 years, uses an insulin pump. EMNG verified severe sensorimotor polyneuropathy with superimposed L5 radiculopathy bilaterally. Before the implantation of the SCS system, there was pain in the lumbar segment, with propagation down both lower extremities (far left), *pain detect* 27, VAS 9. In June 2021, a *Prime Advanced* neurostimulator with a rechargeable battery and with surgical electrodes at the Th level 9/10 was implanted. After the acute postoperative pain subsided, the system was programmed. At discharge VAS 3 with a functionally satisfactory status, with the recommendation to use paracetamol 1 g, 3 times a day as needed. After 15 months from the system implantation, due to an enormous spike in glycemia, the pain in all levels of the spinal column intensified (suspicious of diabetic radiculopathy) and it was difficult to differentiate the value of the pain covered by the system. After switching off the system, the patient reports an increase in pain intensity in the LS segment and lower extremities by 30 to 40%. Analgesic therapy is included for pain at other spinal levels.

The SCS system proved to be effective in reducing pain in painful DPN.

**Key words:** *electric stimulation therapy, diabetic polyneuropathy, treatment outcome*

## STIMULACIJA KIČMENE MOŽDINE U LIJEČENJU HRONIČNOG BOLA SA OSVRTOM NA BOLNU DIJABETIČKU POLINEUROPATIJU

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Stimulacija kičmene moždine (SCS) je neuromodulaciona tehnika koja redukuje bol električnom stimulacijom dorzalnih rogova kičmene moždine. Jedna od četiri glavne indikacije za ugradnju SCS je bolna dijabetička polineuropatija (DPN). U periodu od februara 2018. godine do juna 2021. godine u Zavodu za fizikalnu medicinu i rehabilitaciju „Dr Miroslav Zotović“ ugrađeno je deset sistema za SCS, od toga je jedan sistem ugrađen kod bolesnika sa bolnom DPN. Cilj rada bio je prikazati efikasnost sistema za SCS kod bolesnika sa bolnom DPN.

Muškarac, starosti 57 godina, unazad 15 godina liječen od dijabetesa melitusa, koristi insulinsku pumpu. EMNG-om verifikovana senzomotorna polineuropatija teškog stepena sa superponiranom radikulopatijom L5 obostrano. Prije ugradnje sistema za SCS postojala je bol u slabinskom segmentu, sa propagacijom niz oba donja ekstremiteta (više lijevo), *pain detect* 27, VAS 9. U junu mjesecu 2021.godine ugrađen je *Prime Advanced* neurostimulator sa punjivom baterijom sa hirurškim elektrodama na nivou Th 9/10. Po smirivanju akutnog postoperativnog bola izvršeno je programiranje sistema. Na otpustu VAS 3, uz funkcionalno zadovoljavajući status, uz preporuku korišćenja paracetamola 1 g, tri puta dnevno po potrebi. Nakon 15 mjeseci od ugradnje sistema zbog enormnog skoka glikemije intenzivirali su se bolovi u svim nivoima kičmenog stuba (suspektno na dijabetičke radikulopatije) i teško je bilo izdiferencirati vrijednost bola koji pokriva sistem. Po isključenju sistema bolesnik navodi povećanje intenziteta bola u LS segmentu i donjim ekstremitetima za 30 do 40%. Zbog bola na ostalim nivoima kičmenog stuba uključena je analgetska terapija

Sistem za SCS se pokazao efikasnim u redukciji bola kod bolne DPN.

**Ključne reči:** električna stimulaciona terapija, dijabetesna polineuropatija, ishod terapije

## POST-STROKE PAIN: CHARACTERISTICS AND IMPACT ON FUNCTIONAL OUTCOME OF REHABILITATION TREATMENT - A CROSS-SECTIONAL STUDY

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Pain remains one of the most common medical problems in rehabilitation, and it is one of the most clinically challenging complications that occurs after a stroke. Post-Stroke Pain (PSP) often decreases patients' functional status and it can negatively affect the rehabilitation outcome.

To quantify and characterize pain in a sample of post-stroke patients undergoing rehabilitation and to investigate the impact of pain on patient' functional status.

This single center cross-sectional study included 56 inpatients with subacute and chronic stroke who were treated at Medical rehabilitation department, Clinical Centre of Vojvodina from 01.01.2021. to 31.12.2021. Pain intensity was measured with the *Numerical Rating Scale* (NRS). Furthermore, pain characteristics were assessed with the *Douleur Neuropathique en 4 Questions* (DN4), and *Neuropathic Pain Symptom Inventory* (NPSI) questionnaires. Functional outcome was measured with *Barthel index* (BI). A clinical assessment on pain occurrence, impact, and management was administered by the physician in charge of the patients.

About half of the patients (49.2%) reported pain occurrence after the stroke. Most of them had moderate to severe pain (NRS  $\geq 3$ ) – 76.3%. It was found that in 48.3% of patients the pain had neuropathic components (DN4  $\geq 4$ ). Significantly higher neuropathic pain scores were found in patients with hypoesthesia than in patients with a normal sensory function. Regarding functional outcome, we found that patients with higher neuropathic pain had lower functional outcome measures compared to the patients with no pain detected.

The results from the study show that neuropathic pain can negatively influence the functional outcome after a stroke. Pain in post-stroke patients should be carefully evaluated both in regards to intensity and its neuropathic components. Individually designed pharmacological and physical therapy for treatment and prevention of pain might improve patients' functional outcome and add quality to the rehabilitation process.

**Key words:** *stroke, pain, rehabilitation, functional outcome*

## BOL NAKON MOŽDANOG UDARA: KARAKTERISTIKE I UTICAJ NA FUNKCIONALNI ISHOD REHABILITACIONOG TRETMANA – STUDIJA PRESEKA

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Bol je jedan od najčešćih medicinskih problema u rehabilitaciji, i predstavlja klinički najizazovnije komplikaciju koja se javlja nakon moždanog udara. Bol nakon moždanog udara (PSP) često usporava funkcionalni oporavak bolesnika i može negativno uticati na ishod rehabilitacije.

Cilj rada bio je kvantifikovati i okarakterisati bol u uzorku bolesnika na stacionarnoj rehabilitaciji nakon moždanog udara i istražiti uticaj bola na funkcionalni status bolesnika.

Ovom studijom preseka obuhvaćeno je 56 stacionarno lečenih bolesnika sa subakutnim i hroničnim moždanim udarom. Bolesnici su lečeni na Kilinici za medicinsku rehabilitaciju Kliničkog centra Vojvodine od 01.01.2021. do 31.12.2021. Intenzitet bola je meren pomoću numeričke skale – *Numerical Rating Scale* (NRS). Štaviše, karakteristike bola su procenjene pomoću upitnika *Douleur Neuropathique en 4 Questions* (DN4) i *Neuropathic Pain Symptom Inventory* (NPSI). Funkcionalni ishod je meren pomoću *Barthel indeksa* (BI). Nadležni lekar je načinio kliničku procenu pojave bola, kreirao rehabilitacioni tretman za svakog bolesnika i uveo adekvatnu medikamentoznu terapiju.

Oko polovine od ukupnog broja bolesnika (49,2%) prijavilo je pojavu bola nakon moždanog udara. Većina njih je imala umeren do jak bol (NRS  $\geq 3$ ) – 76,3%. Neuropatska komponenta bola pronađena je kod 48,3% bolesnika (DN4  $\geq 4$ ). Značajno viši skorovi neuropatskog bola pronađeni su kod bolesnika sa hipoestezijom nego kod onih sa normalnom senzornom funkcijom. Što se tiče funkcionalnog ishoda, otkrili smo da bolesnici sa izraženijim neuropatskim bolom imaju niže vrednosti funkcionalnog ishoda u poređenju sa bolesnicima kod kojih bol nije otkriven.

Rezultati studije pokazuju da neuropatski bol može negativno uticati na funkcionalni ishod nakon moždanog udara. Bol kod bolesnika nakon moždanog udara treba pažljivo proceniti kako u pogledu intenziteta tako i u pogledu neuropatske komponente. Individualno dizajnirana farmakološka i fizikalna terapija, za lečenje i prevenciju bola, može poboljšati funkcionalni ishod i povećati kvalitet procesa rehabilitacije.

**Ključne reči:** *moždani udar, bol, rehabilitacija, funkcionalni ishod*

## POSTOPERATIVE PAIN AFTER LUMBAR MICRODISCECTOMY

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After lumbar microdiscectomy, different psychological factors can influence the postoperative back pain, including depression and pessimism.

The aim of the study was to determine the correlation between pain intensity and functional disability in patients after lumbar microdiscectomy.

The research was conducted on 198 patients at Clinical Centre of Vojvodina, Medical Rehabilitation Clinic Novi Sad, Serbia, with a permit from the Ethics Committee of Clinical Centre of Vojvodina. Four administered and validated questionnaires were utilised to obtain information about pain and its intensity and character, presence and degree of functional disability and depression, as well as personal expectations (pessimistic/optimistic) about the treatment results after microdiscectomy. These assessments were carried out after lumbar microdiscectomy in four time slots: just before rehabilitation treatment, and 1, 3 and 6 months after microdiscectomy.

Patients with a high degree of current and general anxiety and with clinically pronounced depression had pain of greater intensity. Significantly lower pain intensity, if any pain was present at all, was in patients who were not anxious or depressed and who were optimistically oriented. The mentioned differences in pain intensities, in all periods of the examination, were statistically highly significant ( $p < 0.01$ ).

Pain and functional disability of the patients after lumbar microdiscectomy are notably related to gender, depression and pessimism. The sensation of the pain was higher in women, while men had a greater degree of functional disability. Intensity of pain and functional disability were significantly greater in patients with a higher degree of depression and pessimism and by registering mentioned factors it is possible to predict the postoperative results.

**Key words:** *low back pain, lumbar microdiscectomy, pain, functional disability, gender, depression, pessimism*

## POSTOPERATIVNI BOL NAKON LUMBALNE MIKRODISSEKTOMIJE

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Nakon lumbalne mikrodisektomije na postoperativni bol u leđima mogu uticati različiti psihološki faktori, uključujući depresivnost i pesimizam.

Cilj rada bio je da se utvrde korelacije intenziteta bola i funkcionalnog stanja bolesnika posle lumbalne mikrodisektomije.

Istraživanje je sprovedeno na 198 bolesnika u Kliničkom centru Vojvodine, Klinike za medicinsku rehabilitaciju Novi Sad, uz dozvolu Etičkog komiteta Kliničkog centra Vojvodine. Korišćena su četiri primenjena i validirana upitnika za dobijanje informacija o bolu i njegovom intenzitetu i karakteru, prisustvu i stepenu funkcionalnog invaliditeta i depresije, kao i ličnim očekivanjima (pesimističkim/optimističnim) o rezultatima lečenja nakon mikrodisektomije. Ove procene su sprovedene nakon lumbalne mikrodisektomije u četiri vremenska intervala: neposredno pre rehabilitacionog tretmana, 1, 3 i 6 meseci nakon mikrodisektomije.

Prisutan bol sa većim intenzitetom imali su bolesnici sa visokim stepenom trenutne i opšte anksioznosti i sa klinički izraženom depresijom. Značajno niži intenzitet bola, ako je on bio prisutan, bio je kod bolesnika koji nisu bili anksiozni ili depresivni i koji su bili optimistički orijentisani, s tim da su pomenute razlike u intenzitetima bola, u svim terminima ispitivanja, bile statistički visoko značajne ( $p < 0,01$ ).

Bol i funkcionalni invaliditet bolesnika posle lumbalne mikrodisektomije su u značajnoj vezi sa polom, depresivnošću i pesimizmom. Osećaj bola bio je veći kod žena, dok su muškarci imali veći stepen funkcionalnog invaliditeta. Intenzitet bola i funkcionalna onesposobljenost bili su značajno veći kod bolesnika sa višim stepenom depresivnosti i pesimizma, a registrovanjem navedenih faktora moguće je predvideti postoperativne rezultate.

***Ključne reči:*** bol, lumbalna mikrodisektomija, invaliditet, pol, depresivnost, pesimizam

## PERCUTANEOUS LASER DISC DECOMPRESSION FOR LUMBAR RADICULAR PAIN: A SYSTEMATIC REVIEW OF PUBMED FOR THE LAST FIVE YEARS

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Lumbar disc herniation is the most common cause of lumbosacral radicular syndrome. It affects 1-2% of the general population, burdening health services and the economy worldwide.

The intravertebral disc has the properties of a narrow hydraulic space: the nucleus pulposus is surrounded by a relatively inelastic fibrous ring and the solid ends of the vertebrae. A slight increase in volume will regularly result in a significant increase in pressure and vice versa. Percutaneous laser disc decompression (PLDD) is a minimally invasive procedure in which thermal energy produced by a LASER probe is used to reduce intervertebral disc herniation. Evaporation of a small volume in a closed hydraulic space (*nucleus pulposus*) leads to decreased intradiscal pressure. It implies a thermal "shrinkage effect" with the retreat of the herniated disc and the nerve root's decompression, which reduces lumbar radicular pain. Pressure changes drastically in healthy discs but only slightly in degenerative discs. The photochemical effects of laser light also lead to the destruction of cytokines and neurokinins such as phospholipase A2, NO, TNF- $\alpha$ , IL-1 $\alpha$  and substance P, which play an essential role in inflammation and pain.

Previous research has shown an effective reduction of pain after PLDD and a small number of complications of the procedure itself. PLDD is a safe and effective procedure in well-selected patients. Unfortunately, there are still no extensive, randomised prospective studies on PLDD in lumbar radicular pain, and the studies mentioned above are needed in the future to confirm or dispute the results so far.

**Key words:** *percutaneous laser disc decompression, discectomy, lumbar radicular pain, disc protrusion*

## PERKUTANA LASERSKA DEKOMPRESIJA DISKA ZBOG LUMBALNE RADIKULARNE BOLI: SISTEMSKI PREGLED PUBMED ZADNJIH PET GODINA

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Lumbalna hernija intravertebralnog diska najčešći je uzrok lumbosakralnog radikularnog sindroma i pogađa 1 – 2% opšte populacije, stavlajući značajan teret na zdravstvene usluge i gospodarstvo u cijelom svijetu.

Intravertebralni disk ima svojstva uskog hidrauličkog prostora: nukleus pulposus okružen je relativno neelastičnim fibroznom prstenom i čvrstim krajevima kralježaka. Mali porast volumena redovito će rezultirati velikim porastom tlaka i obrnuto.

Perkutana laserska dekompresija diska (PLDD) je vrsta minimalno invazivnog zahvata u kojem se toplinska energija proizvedena LASER sondom koristi za smanjenje hernije intervertebralnog diska. Isparavanje malog volumena u zatvorenom hidrauličkom prostoru (*nucleus pulposus*) dovodi do smanjenja intradiskalnog tlaka i implicira termički učinak skupljanja sa povlačenjem hernije diska i dekompresiju živčanog korijena, što ima za posljedicu smanjenje lumbalne radikularne boli. Tlak se drastično mijenja u zdravim diskovima, ali samo neznatno u degenerativnim diskovima. Fotokemijski učinci laserskog svjetla također dovode do uništavanja citokina i neurokinina kao što su fosfolipaza A2, NO, TNF-a, IL-1a i tvar P, koji igraju ulogu ključnu ulogu kod upale i boli.

Dosadašnja istraživanja pokazala su učinkovito smanjenje boli poslije PLDD, te mali broj komplikacija samog zahvata. PLDD je siguran i djelotvoran zahvat kod dobro probranih bolesnika. Nažalost, ne postoje još velike, randomizirane prospektivne studije iz PLDD kod lumbalne radikularne boli, te su potrebna nova istraživanja kako bi potvrdila ili osporila dosadašnje rezultate.

***Ključne reči:*** *perkutana laserska dekompresija diska, disektomija, lumbalna radikularna bol, protruzija diska*

## PAIN AND GENETICS

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There is growing evidence that a number of genes play a critical role in determining pain sensitivity, pain reporting and susceptibility to developing chronic pain and their response to surgical outcomes, primarily the pain.

Genomic variations influence basal pain sensitivity and the likelihood of developing chronic pain so it is logical that the future of medicine is to provide more focused treatment based on a person's genetic code.

The completion of the human genome project in 2003 has provided a better understanding of why patients may experience pain syndromes.

Pain has diverse etiologies, mechanisms, and characteristics, and causes variable responses that are interpreted differently among individuals. Genomic variations influencing basal pain sensitivity and the likelihood of developing chronic pain diseases have been noted and continue to be studied.

Epigenetic mechanisms have also been implicated in the transition from acute to chronic pain, as well as its role in the development of chronic post-surgical neuropathic pain. Epigenetic, as well as genetic, mechanisms have been implicated in diverse pain conditions like "human bladder pain syndrome", as well as primary headaches, migraine and cluster headache.

For the pain states, no robust genetic markers have been identified so far.

Better understanding of pain-related genetic influences will provide important insights into the mechanisms of pain and may identify new targets for pharmacologic and other therapies. The selection of pain phenotype could substantially influence the nature and magnitude of any genetic association.

It is inevitable that multiple genes, each with a small individual effect, interact among themselves and with a variety of environmental factors, to influence pain sensitivity and the expression of chronic pain conditions.

Several studies have shown that polymorphisms in genes affecting the function of both catecholaminergic and serotonergic systems may be associated with chronic pain disorders

Better understanding of pain-related genetic influences will provide important insights into pain mechanisms and may identify new targets for pharmacologic and other therapies.

***Key words:*** *pain, genetics*

## BOL I GENETIKA

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Sve je više dokaza o tome da određeni broj gena igra ključnu ulogu u određivanju osetljivosti na bol, izveštavanju o bolu i podložnosti razvoju hroničnog bola i njihovom odgovoru na hirurške ishode, prvenstveno na bol.

Genomske varijacije utiču na bazalnu osetljivost na bol i verovatnoću razvoja hroničnog bola, tako da je logično da je budućnost medicine u pružanju fokusiranijeg lečenja zasnovanog na genetskom kodu osobe.

Završetak projekta ljudskog genoma 2003. godine omogućio je bolje razumevanje zašto bolesnici mogu iskusiti sindrome bola.

Bol ima različite etiologije, mehanizme i karakteristike i izaziva različite reakcije koje se različito tumače među pojedincima. Genomske varijacije koje utiču na bazalnu osetljivost na bol i verovatnoću razvoja hroničnih bolesti zabeležene su i nastavljaju da se proučavaju.

Epigenetski mehanizmi su takođe uključeni u prelazak sa akutnog na hronični bol, kao i njegovu ulogu u razvoju hroničnog posthirurškog neuropatskog bola. Epigenetski, kao i genetski, mehanizmi su uključeni u različita stanja bola, kao što je „sindrom bola u ljudskoj bešici“, kao i primarne glavobolje, migrene i klaster glavobolje.

Za stanja bola do sada nisu identifikovani robusni genetski markeri.

Bolje razumevanje genetskih uticaja povezanih sa bolom pružiće važan uvid u mehanizme bola i može identifikovati nove mete za farmakološke i druge terapije. izbor fenotipa bola bi mogao značajno uticati na prirodu i veličinu bilo koje genetske asocijacije.

Neizbežno je da više gena, svaki sa malim individualnim efektom, interaguju među sobom i sa različitim faktorima okoline, da utiču na osetljivost na bol i izražavanje stanja hroničnog bola.

Nekoliko studija je pokazalo da polimorfizmi u genima koji utiču na funkciju i kateholaminergičkog i serotonergičkog sistema mogu biti povezani sa hroničnim poremećajima bola.

Bolje razumevanje genetskih uticaja povezanih sa bolom pružiće važan uvid u mehanizme bola i može identifikovati nove mete za farmakološke i druge terapije.

***Ključne reči:*** bol, genetika

## NON-PHARMACOLOGICAL MANAGEMENT OF CANCER PAIN

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Pain is the most common symptom found in patients diagnosed with a malignant disease, at an estimated prevalence of 50-60%, with the prevalence starting at 33% during malignant disease treatment and progressing up to 70% at the advanced stages of the disease.

Cancer pain can manifest after surgery, during and after completed chemotherapy (chemotherapy-induced peripheral neuropathy), during and after completed radiotherapy (mononeuropathy, plexopathy, lymphedema), during hormonal therapy and immune checkpoint inhibitor therapy (arthralgia, myalgia).

The WHO's recommendation for treating cancer-related pain is a combination of pharmacological and non-pharmacological therapy. Non-pharmacological therapy involves the application of physical modalities, cognitive-behavioral therapy and other therapies (e.g. complementary therapy). Research has shown that cognitive-behavioral therapy has almost the same effectiveness in reducing the experience of pain as some other pharmacological methods of treatment, such as various drugs.

Physical modalities in treating cancer pain are defined through 4 groups: modalities that modulate nociception, modalities that stabilize or unload painful structures, modalities that influence local physiological processes and modalities that reduce pain arising from muscles and connective tissues.

For the above-mentioned purposes the following can be applied: exercise (aerobic, stretching and strength training, movement therapy), thermotherapy (topical therapy with hot or cold compresses or packs), acupuncture, transcutaneous electrical nerve stimulation, massage, positioning, assistive devices and orthotics, scrambler therapy with the proof of efficiency yet to be confirmed, as well as LLLT (*low-level laser therapy*) with the uncertain safety-in-use.

**Key words:** *cancer pain, non-pharmacological therapy, physical modalities, cognitive-behavioral therapy*

## NEFARMAKOLOŠKA TERAPIJA KANCERSKOG BOLA

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Bol je najčešći simptom kod obolelih od malignih bolesti, sa procenjenom prevalencijom od 50 do 60%, a prevalencija varira od 33%, tokom terapije maligne bolesti, do više od 70% kod uznapredovale bolesti.

Bolni sindrom se manifestuje nakon operacije, tokom i nakon završene hemioterapije (polineuropatija izazvana hemioterapeuticima), tokom i nakon završene radioterapije (mononeuropatija, pleksopatija, limfedem), tokom hormonske terapije i terapije imunocheckpoint inhibitorima (artralgije, mialgije).

Preporuka Svetske zdravstvene organizacije u terapiji kancerskog bola je kombinacija farmakološke i nefarmakološke terapije. Nefarmakološka terapija podrazumeva primenu fizikalnih modaliteta, kognitivno-bihejvioralne terapije i druge terapije (komplementarna terapija). U istraživanjima se pokazalo da kognitivno-bihejvioralna terapija ima gotovo jednaku efikasnost u smanjenju doživljaja bola kao i neke druge farmakološke metode lečenja, poput različitih lekova.

Fizikalni modaliteti u terapiji kancerskog bola definišu se u četiri grupe: modaliteti sa modulacijom nocicepcije; modaliteti koji rasterećuju ili stabilišu bolne strukture; modaliteti koji utiču na lokalne fiziološke procese i modaliteti koji redukuju bol poreklom iz mišićnog i vezivnog tkiva.

U navedene svrhe se primenjuju: vežbe (aerobne, vežbe istezanja i snage, terapija pokretom), primena termoterapije (topikalna primena hladnih ili toplih kompresa, pakovanja), akupunktura, transkutana elektronervna stimulacija, masaža, pozicioniranje, primena adaptivnih sredstava i ortoza, i još nedovoljno dokaza o efikasnosti scrambler terapije i bezbednoj primeni terapije laserom - LLLT (*low-level laser therapy*).

***Ključne reči:*** kancerski bol, nefarmakološka terapija, fizikalni modaliteti, kognitivno-bihejvioralna terapija

## CANNABIS – DRUG OR MEDICINE?

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Cannabis sativa-marijuana is a plant which, in the recent decades, has raised numerous questions and controversies, both among experts and the general public. Should it be legalized or even more strictly prohibited? Is it medicine or a drug?

For centuries, cannabis has been widely used in the industry as well as in medicine. The most well-known is the industrial, with about 0.3% and Indian with  $\geq 6\%$  of delta-9-THC(delta-9-tetrahydrocannabinol).

Delta-9-THC is one of the first discovered cannabinoids (exo- or phytocannabinoids) from cannabis and has a high psychoactive effect. Today we know over 100 different cannabinoids with various effects – antioxidant, anti-inflammatory, analgesic, immunomodulatory – which may or may not have the psychoactive effect. Numerous studies have shown that these cannabinoids can be used for the treatment of numerous conditions and diseases, which are accompanied by nausea, vomiting, anxiety, anorexia and chronic, resistant pain. Those are, above all, chronic cancer pain, MS pain, pain after a stroke, spinal cord injury, HIV...

Endocannabinoids are created in human cells, and there are cannabinoid receptors (CBR) on the cell membrane, to which endo-, exo-, and synthetic cannabinoids bind and form the CBR:cannabinoid complex, which is the basis of the action of these substances.

There is a lack of large, controlled studies that would show whether and how cannabis affects, first of all, the course of the malignant disease itself. Nevertheless, the application of an adequately formulated pharmaceutical preparation, according to strict indications, would certainly find its application in the treatment of chronic cancer pain, but also pain in other serious, chronic diseases, resistant to all applied drugs.

Should cannabinoids be used for medicinal purposes? Definitely yes, but only when there are clear indications. Should we legalize the use of marijuana on the whole? Definitely not, because that would mean that the psychoactive drugs have entered into our daily lives "through the small door".

**Key words:** *cannabis, exocannabinoids, endocannabinoids, endocannabinoid system, cannabinoid receptors*

## KANABIS – DROGA ILI LEK?

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Cannabis sativa-marihuana, biljka koja poslednjih decenija pokreće brojna pitanja i kontroverze, kako stručne tako i široke javnosti. Da li je legalizovati ili još strože zabraniti? Da li je lek ili droga?

Kanabis je vekovima unazad nalazio široku primenu u industriji, ali i u medicini. Najpoznatija je industrijska, sa oko 0,3% i indijska sa  $\geq 6\%$  delta-9-THC (delta-9-tetrahidrokanabidiol).

Delta-9-THC je jedan od prvih otkrivenih kanabinoida (egzo- ili fitokanabinoid) iz kanabisa i ima visoko psihoaktivno dejstvo. Danas poznajemo preko 100 različitih kanabinoida, koji imaju različita dejstva: antioksidativno, antiinflamatorno, analgetsko, imunomodulatorno i mogu, ali i ne moraju, imati psihoaktivno dejstvo. Brojne studije su pokazale da se ovi kanabinoidi mogu primeniti za tretman brojnih stanja i bolesti, koje su praćene mukom, povraćanjem, anksioznošću, anoreksijom i hroničnim, rezistentnim, bolom. To je, pre svega, kod hroničnog kancerskog bola, bola kod MS, bola nakon šloga, povreda kičmene moždine, HIV-a...

U ljudskim ćelijama se stvaraju endokanabinoidi, a postoje i kanabinoidni receptori (CBR), na ćelijskoj membrani, za koje se vežu endo-, egzo- ali i sintetski kanabinoidi i formiraju kompleks CBR: kanabinoid, na čemu se zasniva dejstvo ovih supstanci.

Nedostaju velike, kontrolisane studije koje bi pokazale da li i kako kanabis deluje, pre svega na sam tok maligne bolesti. Ipak, adekvatno formulisani farmaceutski preparat, prema strogim indikacijama, sigurno bi našao svoju primenu u tretmanu hroničnog kancerskog bola, ali i bola kod drugih teških, hroničnih bolesti, rezistentnog na sve primenjene lekove.

Da li primenjivati kanabinoide u medicinske svrhe? Definitivno da, ali kada postoje jasne indikacije. Da li legalizovati primenu marihuane kao cele biljke? Definitivno ne, jer bi to predstavljalo ulazak droge u naše živote na „mala vrata“.

**Ključne reči:** *kanabis, egzokanabinoidi, endokanabinoidi, endokanabinoidni sistem, kanabinoidni receptori*

## NEURAL PROLOTHERAPY – A NEW APPROACH IN THE TREATMENT OF PAINFUL CONDITIONS

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The most common cause of chronic pain is changes in the musculoskeletal system. Dr. John Lyfgot, the founder of Neural Prolotherapy, hypothesized that chronic pain may also arise as a result of reduced glucose levels in thin unmyelinated fibers and called this phenomenon neuroglycopenia. Neural prolotherapy is palpation-guided injection of a 5% glucose solution along the sensitive nerves in order to treat chronic neuropathic pain that responds to glucose. The procedure lasts 15-30 minutes, 4-6 procedures are recommended at intervals of 7-10 days. The success rate of the procedure is over 85%. The results of the studies that examined the connection between reduced glucose levels and pain indicated that specific sensorineural mechanisms and neuroinflammation are responsible for the occurrence of pain with reduced glucose levels in nervous tissue. Examination of the connection between neuroglycopenia and pain showed that: the release of inflammatory factors affects both GLUT3 and TrpV1 receptors, which leads to the modulation of glucose transport in nerve tissues; perineural glycopenia leads to progressive depolarization and hyperexcitability of nociceptive nerve fibers, most likely due to reduced efficiency of the ATP pump; neuroglycopenia lowers the level of adenosine monophosphate protein kinase, the level of which is correlated with chronic neuropathic pain; increasing extracellular dextrose levels by dextrose injection leads to nerve hyperpolarization via the Na/K pump by increasing K<sup>+</sup> conductance and decreasing excitability; direct application of 5% glucose along the affected nerve pathway leads to inhibition of the TrpV1 receptor, which further modulates the inflammatory response and helps restore normal nerve function.

Indications for the use of neural prolotherapy are: cervical and lumbar syndrome, tendinopathies, CRPS, carpal tunnel sy., frozen shoulder, Morton's neuroma, plantar fasciitis, trigeminal neuralgia, paresis/paralysis n. facialis, restless legs syndrome, headaches, temporomandibular pain, etc. Contraindications for the use of neural prolotherapy: There are no contraindications for the use of Neural Prolotherapy. Care should be taken in patients with diabetes mellitus.

Neural prolotherapy is an innovative injection procedure whose primary therapeutic effect is on glucose homeostasis in the tissues, and secondary on neuropathic pain. It has been shown to be used in almost all painful conditions of musculoskeletal origin. An almost immediate analgesic effect, simple to perform, a minimal number of side effects, no contraindications and the return of patients to the social and working environment immediately after the therapy are great advantages compared to all the currently known analgesic therapeutic procedures in use.

**Key words:** *neural prolotherapy, neuroglycopenia, neuropathic pain*

## NEURALNA PROLOTERAPIJA – NOVI PRISTUP U TRETMANU BOLNIH STANJA

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Najčešći uzrok razvoja hroničnog bola su promene muskulo-skeletnog sistema. *Dr John Lyfgot*, osnivač neuralne proloterapije, pretpostavio je da hronični bol može nastati i kao posledica smanjenog nivoa glukoze u tankim nemijelinskim vlaknima i ovaj fenomen nazvao neuroglikopenija.

Neuralna proloterapija predstavlja injekcionu palpatorno vođenu administraciju rastvora 5% glukoze duž senzitivnih nerava u cilju tretiranja hroničnog neuropatskog bola koji reaguje na glukozu. Procedura traje 15-30 minuta, preporučeno je 4-6 procedura u razmaku 7-10 дана. Uspešnost procedure je preko 85%.

Rezultati studija koje su ispitivale povezanost smanjenog nivoa glukoze i bola ukazale su da su za pojavu bola kod smanjenog nivo glukoze u nervnom tkivu zaduženi specifični senzorno-neuralni mehanizmi i neuroinflamacija. Ispitivanje povezanosti neuroglikopenie i bola je pokazala da: oslobađanje faktora zapaljenja utiče i na GLUT3 i TrpV1 receptore, što dovodi do modulacije transporta glukoze u nervna tkiva; perineuralna glikopenija dovodi do progresivne depolarizacije i hiper-ekscitabilnosti nociceptivnih nervnih vlakana, najverovatnije zbog smanjene efikasnosti ATP pumpe; neuroglikopenia snižava nivo adenozin monofosfat protein kinazu, čiji je nivo u korelaciji sa hroničnim neuroaptskim bolom; povećanje nivoa ekstracelularne dekstroze injekcijom dekstroze dovodi do hiperpolarizacije nerva preko Na/K pumpe povećanjem K<sup>+</sup> provodljivosti i smanjenjem ekscitabilnost; direktna primena 5% glukoze duž zahvaćenog nervnog puta dovodi do inhibicije TrpV1 receptora, što dalje modulira inflamatornu reakciju i pomaže u obnavljanju normalne nervne funkcije.

Indikacije za primenu neuralne proloterapije su: cervikalni i lumbalni sindrom, tendinopatije, CRPS, *Carpal Tunels Sy*, smrznuto rame, Morton neurom, plantarni fascitis, trigeminalna neurlagija, pareza/paraliza n. facialis sindrom nemirnih nogu, glavobolje, temporo-mandibularni bol itd.

Kontraindikacija za primenu neuralne proloterapije nema Potrebno je biti obazriv kod pacijenata sa dijabetesom melitusom.

Neuralna proloterapija predstavlja inovativnu injekcionu proceduru čiji je primarni terapijski efekat na homeostazu glukoze u tkivima, a sekundarni na neuropatski bol našao primenu u skoro svim bolnim stanjima muskulo-skeletnog porekla. Skoro trenutni analgetski efekat, jednostavna za izvođenje, minimalni broj neželjenih efekata, bez kontraindikacija i povratak pacijenata u socijalnu i radnu sredinu odmah nakon sprovedene terapije su velike prednosti u odnosu na sve do sada poznate analgetske terapijske procedure koje su u primeni.

**Ključne reči:** neuralna proloterapija, neuroglikopenija, neuropatski bol

## CHARACTERISTICS AND TREATMENT OF SPINAL PAIN IN INFLAMMATORY RHEUMATIC DISEASES

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Inflammatory rheumatic diseases are a special group of diseases, in which inflammation is the essential process on the peripheral joints and spine. When we talk about the characteristics of pain in these diseases, we should certainly emphasize the chronicity and intensity of pain, which separate this type from mechanical pain, which is caused by chronic use or injury, trauma to the joint.

Inflammatory back pain is localized in the axial spine and sacroiliac joints; it has a chronic course and differs from mechanical pain on the basis of various characteristics: back pain is more often localized in the lumbar spine and can be associated with pain in the buttock which moves from one side to the other. Chronicity, intensity and progression of the pain distinguish this kind of pain from other types of pain. Typical inflammatory back pain in rheumatology is associated with ankylosing spondylitis, although it can also be present in other diseases from the group of spondyloarthritides: it can occur in psoriatic, enteropathic spondyloarthritis and reactive arthritis.

Persistence, chronicity of inflammation, which is caused by the effect of proinflammatory cytokines, especially IL 17 and TNF alpha, results in structural changes, which are diagnostically recognized based on the fusion of the bones of the vertebrae, which is especially seen in ankylosing spondylitis. This suggests the need for research with the purpose of choosing an adequate therapeutic approach in the treatment of inflammation, inflammatory pain and damage, caused by a chronic and persistent inflammatory process. The modalities of therapy are reduced to the use of drugs that suppress pain and block the mentioned cytokines and the cascade of other signaling pathways that participate in the pathogenesis of inflammation and thus in the onset of inflammatory pain in inflammatory rheumatic diseases.

**Key words:** *inflammatory pain, spine, inflammatory rheumatic diseases*

## KARAKTERISTIKE I TRETMAN BOLA U KIČMENOM STUBU U ZAPALJENSKIM REUMATSKIM BOLESTIMA

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Zapaljenske reumatske bolesti su posebna grupa oboljenja u kojima dominira inflamacija, odnosno zapaljenski proces na perifernim zglobovima i kičmenom stubu. Kada govorimo o karakteristikama bola u ovim bolestima, svakako treba istaći hronicitet i intenzitet bola, koji odvajaju ovu vrstu od mehaničkog bola, koji nastaje hroničnom upotrebom ili povredom, traumom zgloba.

Inflamatorni bol u leđima lokalizovan je na aksijalnoj kičmi i sakroilijačnim zglobovima, ima hroničan tok i razlikuje se od mehaničkog bola na osnovu različitih karakteristika: bol u leđima je češće lokalizovan na lumbalnoj kičmi i može biti povezan sa bolom u zadnjici koji je šetajućeg karaktera, prenosi se sa jedne strane na drugu i hronicitet; intenzivnost i napredovanje bola izdvajaju ovakvu od druge vrste bola. Tipičan inflamatorni bol u leđima u reumatologiji povezan je sa ankilozirajućim spondilitisom, mada može biti prisutan i u drugim bolestima unutar grupe spondiloartritisa: može se javiti u psorijaznom, enteropatijskom spondiloartritisu i reaktivnom artritisu.

Perzistentnost, hronicitet inflamacije, koja je izazvana dejstvom proinflamatornih citokina, naročito IL 17 i TNF alfa, rezultuje strukturnim promenama, koje se dijagnostički prepoznaju na osnovu fuzije kosti pršljenova, što se posebno vidi kod ankilozirajućeg spondilitisa. Ovo sugeriše potrebu istraživanja u pravcu izbora adekvatnog terapijskog pristupa u lečenju inflamacije, inflamatornog bola i oštećenja koje je nastalo usled hroničnog i perzistentnog zapaljenskog procesa. Modaliteti terapije svode se na primenu lekova koji suprimiraju bol i blokiraju napred navedene citokine i kaskadu drugih signalnih puteva koji učestvuju u patogenezi zapaljenja, samim tim i nastanku inflamatornog bola u zapaljenskim reumatskim bolestima.

***Ključne reči:*** inflamatorni bol, zapaljenske reumatske bolesti

## MODERN PHARMACOTHERAPEUTIC APPROACHES IN THE TREATMENT OF CHRONIC CANCER PAIN: OUR EXPERIENCES

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The modern pharmacotherapeutic approaches to the treatment of chronic cancer pain involve the individualization of the therapy plan for each patient due to the extent of the primary disease, an adequate history of pain, assessment of the quality of pain, other comorbidities and other therapies for that patient. To assess the intensity of pain, the Numerical Pain Scale is still the most used, on the basis of which analgesics are prescribed in accordance with the analgesic ladder of the World Health Organization. To assess the share of the neuropathic component of pain in the so-called mixed pain, the painDETECT questionnaire, which has been validated and translated into Serbian, is the most widely used in our country. In addition to the standard step-by-step therapeutic approach on the analgesic ladder depending on the intensity of the pain, the system of using the analgesic elevator in daily clinical work is widespread today as well. In the pharmacotherapy of chronic cancer pain, in addition to the use of conventional analgesics (non-steroidal anti-inflammatory drugs, long-acting formulations of opioid analgesics, fast-acting formulations of opioid analgesics), the use of coanalgesics such as corticosteroids, anti-convulsants (primarily gabapentionoids), antidepressant drugs (primarily selective serotonin and noradrenaline uptake inhibitors), bisphosphonates is imperative. In addition, it is necessary to take into account the possible side effects of opioids that should be prevented (as far as possible) and treated symptomatically during the treatment period. The further course of the lecture presented the treatment experiences of our institution related to two oncology patients with chronic cancer pain. Chronic cancer pain is present in more than half of oncological patients and represents an indispensable segment in their entire treatment, which should be approached in a team and multidisciplinary manner.

**Key words:** *pharmacotherapy, chronic cancer pain, opioid analgesics, coanalgesics*

## SAVREMENI FARMAKOTERAPIJSKI PRISTUPI U LEČENJU HRONIČNOG KANCERSKOG BOLA – NAŠA ISKUSTVA

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Savremeni farmakoterapijski pristupi lečenju hroničnog kancerskog bola podrazumevaju individualizaciju plana lečenja svakog bolesnika ponaosob usled proširenosti osnovne bolesti, adekvatno uzetu anamnezu bola, procenu kvaliteta bola i ostalih komorbiditeta i druge terapije tog pacijenta. Za procenu intenziteta bola i dalje je najviše upotrebljavana Numerička skala bola na osnovu koje se analgetici ordiniraju u skladu sa analgetskim lestvicama Svetske zdravstvene organizacije. Za procenu udela neuropatske komponente bola u tzv. mešovitom bolu, kod nas, najčešće u upotrebi PainDetect upitnik koji je validizovan i preveden na srpski jezik. Pored standardnog terapijskog pristupa stepenik po stepenik na analgetskim lestvicama zavisno od intenziteta bola, danas je široko raspostranjen i sistem korišćenja analgetskog lifta u svakodnevnom kliničkom radu. Imeprativ u farmakoterapiji hroničnog kancerskog bola, pored korišćenja konvencionalnih analgetika (nesteroidnih antiinflamatornih lekova, dugodelujućih formulacija opioidnih analgetika, brzodelujućih formulacija opioidnih analgetika), predstavlja i upotreba koanalgetika kao što su: kortikosteroidi, antikonvulzivi (prvenstveno gabapentionoidi), antidepressivni lekovi (prvenstveno selektivni inhibitori preuzimanja serotonina i noradrenalina), bisfosfonati. Takođe, neophodno je voditi računa o mogućim neželjenim efektima opioida koje treba prevenirati (koliko je to moguće) i simptomatski rešavati tokom samog perioda lečenja. Dalji tok predavanja prikazao je iskustva lečenja dva onkološka pacijenta sa hroničnim kancerskim bolom u klinici za onkologiju Univerzitetskog kliničkog centra u Nišu. Hronični kancerski bol je prisutan kod više od polovine onkoloških pacijenata i predstavlja neizostavan segment u celokupnom njihovom lečenju, kome treba pristupiti timski i multidisciplinarno.

**Ključne reči:** farmakoterapija, hronični kancerski bol, opioidni analgetici, koanalgetici

## MULTIMODAL ANALGESIA IN THE TREATMENT OF ACUTE CANCER PAIN

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Cancer pain is a complex phenomenon, one of the most common and disturbing symptoms of malignancy. Malignant pain management is a major challenge and it is in the central position in the overall care of patients, due to its widespread and harmful impact on the general condition of the patient. Pain prevalence in patients with malignancy varies from 52% to 77%. Complexity and high prevalence led to the emergence of the term "acute painful syndrome", which includes various etiologies responsible for pain.

Acute pain often occurs during diagnostic procedures, while on painkillers, and during pharmacotherapy (chemotherapy, immunotherapy, hormonal therapy) and non-pharmacological (surgical, and radiotherapy) treatment. The proliferation of tumors in the organs of the body, which involves pathologic fracture and microfracture, spinal cord or nerve compression, and obstruction of visceral organs, can also lead to acute pain. It can be nociceptive, neuropathic or a combination of the two, with a sudden onset, sometimes with an acute exacerbation as the background for the chronic pain. The most common conditions in acute pain are acute painful crises, piercing pain, post-operative/procedural pain, acute bone pain, malignant bowel obstruction, mucositis, and neuropathy caused by chemotherapy or radiotherapy.

The severity of these painful syndromes depends on the location and size of the tumor mass. Prevention, timely treatment and an aggressive treatment approach on the first onset of pain are crucial because, regardless of the origin, any kind of acute pain causes remodeling and sensitization of neurons which can eventually turn it into chronic pain. These syndromes have complex outcomes which include physiological, emotional, cognitive, social, and environmental factors.

Acute cancer pain treatment requires a holistic and multidisciplinary approach.

Modern guidelines for the treatment of cancer pain specifically emphasize the importance of improving and maintaining the quality of life which can be achieved only through multimodal treatment, including personalized pharmacological, interventional, physical, psychological, rehabilitation and alternative modalities, which are planned and performed for each patient individually.

**Key words:** *cancer, acute pain, multimodal therapy*

## MULTIMODALNA ANALGEZIJA U LEČENJU AKUTNOG KANCERSKOG BOLA

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Kancerski bol je složen fenomen, jedan od najučestalijih i uznemirujućih simptoma maligniteta. Upravljanje malignim bolom je veliki izazov i predstavlja centralno mesto u celokupnoj nezi obolelih, zbog velike rasprostranjenosti i štetnog uticaja na opšte stanje bolesnika. Prevalencija bola kod bolesnika sa malignitetom varira od 52% do 77%. Složenost i visoka prevalencija su dovele do nastanka terminologije „akutnog bolnog sindroma“ koji obuhvata različite etiologije odgovorne za bol.

Akutni bol se često javlja u toku dijagnostičkih procedura, analgetičkih intervencija, farmakoloških/ hemioterapija, imunoterapija, hormonalna terapija/ i nefarmakoloških terapija/ hirurška, radioterapija/. Širenje tumora u telesne organe takođe može da dovede do akutnog bola, kao što su patološke i mikrofrakture, kompresija kičmene moždine ili nerava, opstrukcija visceralnih organa. Može biti nociceptivan, neuropatski ili mešovite prirode, sa naglim iznenadnim početkom, ponekad je moguća akutna egzacerbacija u pozadini hroničnog bola ili se javlja u vidu prolaznog probojnog bola. Najčešća stanja akutnog bola: akutne bolne krize, probojni bol, postoperativni/proceduralni bol, akutni bol zbog zahvatanja kostiju, maligna opstrukcija creva, mukozitis i neuropatije izazvane hemoterapijom ili radioterapijom.

Ozbiljnost ovih bolnih sindroma zavisi od mesta i obima tumorske mase. Prevencija i pravovremena terapija, agresivno upravljanje na početku pojavljivanja, od ključnog su značaja, jer bez obzira na poreklo, bilo koja vrsta akutnog bola izaziva remodeliranje i senzibilizaciju neurona, što se konačno može pretvoriti u hronični bol. Ovi sindromi imaju složen ishod, uključuju fiziološke, emocionalne, kognitivne, društvene i faktore sredine.

Terapija akutnim malignim bolom zahteva holistički i multidisciplinarni pristup.

U savremenim vodičima za tretman kancerskog bola posebno se ističe značaj održavanja i poboljšanja kvaliteta života, što se postiže jedino multimodalnim lečenjem, uključujući farmakološke, interventne, fizičke, psihološke, rehabilitacione i alternativne modalitete koji se planiraju i izvode za svakog pacijenta ponaosob, odnosno personalizovano.

***Ključne reči:*** *kancer, akutni bol, multimodalna terapija*

## POSTOPERATIVE PAIN IN THE REHABILITATION OF PATIENTS AFTER KNEE ARTHROPLASTY

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Postoperative pain often worries surgeons and physiatrists in conditions after total knee arthroplasty (TKA). Pain after TKA is a serious problem given the increase of the use of TKA as well as the aspect of population aging. The presence of postoperative pain follows immediate and early postoperative period and therefore it is one of the main goals of physiatric interventions, in addition to the prevention of thromboembolic complications and edema control in the first 6 weeks after surgery. The pain caused by TKA is of a nociceptive nature due to the activation of peripheral nociceptors, as a consequence of mechanical or other trauma. Postoperative pain after TKA can negatively affect postoperative recovery. Data from the literature indicate that effective pain management leads to a better and earlier functional recovery after hip or knee arthroplasty and thereby prevent chronic pain. Intensive post-surgical rehabilitation, which plays a fundamental role in recovery and maintenance of the patient's complete movement abilities, can be hindered when adequate analgesia is not delivered to the patient and result in decreased patient's satisfaction with the surgery, worse locomotion with frequent occurrence of stiff knee. In addition, the risks of thromboembolic complications and infection can increase because the patient moves less due to the pain, which leads to a longer stay of the patient in hospital and consequently increases health care costs.

**Key words:** *endoprosthesis, rehabilitation, postoperative pain*

## POSTOPERATIVNA BOL U REHABILITACIJI PACIJENATA NAKON IMPLANTACIJE ENDOPROTEZE KOLJENA

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Postoperativna bol često zadaje brige hirurzima i fizijatrima u stanjima nakon totalne artroplastike koljena (TKA). Bol nakon TKA predstavlja ozbiljan problem s obzirom na povećanje upotrebe TKA kao i aspekt starenja populacije. Prisustvo postoperativne boli prati neposredni i rani postoperativni period, te je jedan od glavnih ciljeva fizijatrijske intervencije, pored prevencije tromboembolijskih komplikacija i kontrola otoka prvih 6 nedjelja od operativnog zahvata. Bol koja nastaje usljed TKA je nociceptivne prirode zbog aktivacije perifernih nociceptora, a kao posljedica mehaničke ili druge traume. Postoperativna bol nakon TKA može negativno uticati na postoperativni oporavak. Podaci iz literature ukazuju da efikasno upravljanje bolom dovodi do boljeg i ranijeg funkcionalnog oporavka poslije artroplastične hirurgije kuka ili koljena, i na taj način se sprečava hronični bol. Intenzivna posthirurška rehabilitacija, koja ima fundamentalnu ulogu u oporavku i održavanju kompletnih sposobnosti kretanja pacijenata, može biti ometena kada se bolesniku ne obezbijedi odgovarajuća analgezija, što za posljedicu ima lošije zadovoljstvo bolesnika operativnom intervencijom, lošiju lokomociju sa mogućom pojavom stiff koljena. Kao dodatna posljedica, rizici od tromboembolijskih komplikacija i infekcije mogu se pojačati jer se zbog boli bolesnik manje kreće, što dovodi do dužeg boravka u bolnici, te ima za posljedicu i povećanje troškova zdravstvene zaštite.

***Ključne reči:*** endoproteza koljena, rehabilitacija, postoperativna bol

## CHRONIC IMMUNE-MEDIATED NEUROPATHIES IN WHICH NEUROPATHIC PAIN IS THE FIRST OR LEADING SYMPTOM

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variants, paraproteinemic neuropathies, multifocal motor neuropathy (MMN), and vasculitic neuropathies are a part of a larger group of chronic immune-mediated neuropathies. These neuropathies are caused by an immune response against peripheral nerve antigens (mainly myelin components and proteins located at the node of Ranvier). In many of these neuropathies, disease-associated autoantibodies have not yet been identified. Corticosteroids, plasma exchange (PTE), intravenous immunoglobulins (IVIg), and monoclonal antibodies are therapy strategies that are fully or partially successful in these diseases. Pure motor chronic immune-mediated neuropathies are not followed by pain. In small-fiber neuropathies (SFN), thinly myelinated A $\delta$  and unmyelinated C fibers are affected. Immune-mediated neuropathies, such as CIDP (especially sensory variants), paraproteinemic, and vasculitic neuropathies are commonly connected with damage to these nerve fibers, which is clinically presented as neuropathic pain and autonomic symptoms. In CIDP patients, pain was reported in more than 60% of patients. Pain severity varied from moderate to severe intensity. This pain could be nociceptive, neuropathic (NP), or combined. NP was found in 30% of CIDP patients. Vasculitic neuropathies are clinically presented as mononeuritis multiplex which is characterized by painful sensorimotor mononeuropathies. Pain should be evaluated (neuropathic, nociceptive, or combined pain) and adequately treated if it is present in immune-mediated neuropathies. In these patients, besides immunomodulatory therapy, there is a need for adequate symptomatic treatment (neuropathic pain medications, non-steroid antiinflammatory drugs, opioids, or nonpharmacological measures...).

**Key words:** *immune-mediated neuropathies, neuropathic pain, vasculitis*

## HRONIČNE IMUNOPOSREDOVANE NEUROPATIJE U KOJIMA JE BOL NEUROPATSKE PRIRODE PRVI ILI VODEĆI SIMPTOM

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Hronična inflamatorna demijelinizirajuća poliradikuloneuropatija (CIDP) i njene varijante, paraproteinemijske neuropatije, multifokalna motorna neuropatija (MMN) i vaskulitične neuropatije deo su veće grupe hroničnih imunoposredovanih neuropatija. Ove neuropatije su uzrokovane imunim odgovorom protiv perifernog nervnog sistema (uglavnom mijelinski omotač i proteini locirani na Ranvijerovom čvoru). Specifična autoantitela nisu identifikovana za sve poremećaje. Kortikosteroidi, terapijska izmena plazme, intravenski imunoglobulini i monoklonska antitela spadaju u terapijske strategije koje su parcijalno ili potpuno uspešne u lečenju ovih oboljenja. Čisto motorne hronične imunoposredovane neuropatije nisu praćene bolom kao simptomom. Neuropatije malih vlakana (SFN) su poremećaj tanko mijelinizovanih A $\delta$  i nemijelinizovanih C vlakana. Kod CIDP (pogotovo senzornih varijanti), paraproteinemijske i vaskulitične neuropatije uobičajeno je zahvatanje ovih vlakana, što se klinički ispoljava neuropatskim bolom i autonomnim poremećajima. Kod bolesnika sa CIDP bol je prijavljen kod više od 60% bolesnika. Uglavnom je umerenog i jakog intenziteta. Karakteristike bola ukazuju na neuropatski, nocicpetivni ili kombinovani bol. Neuropatski bol je evidentiran kod oko 30% slučajeva. Vaskulitične neuropatije se klinički prezentuju kao mononeuritis multiplex koji karakterišu bolne senzomotorne mononeuropatije. Bol treba proceniti (neuropatski, nociceptivni ili kombinovani bol) i pravilno lečiti ako je prisutan kod imunoposredovanih neuropatija. Kod ovih bolesnika, osim primene imunomodulatorne terapije, postoji potreba za uvođenjem adekvatne simptomatske terapije (lekovi za neuropatski bol, nesteroidni antiinflamatorni lekovi, opioidi, nefarmakološke mere lečenja...).

***Ključne reči:*** *imunoposredovane neuropatije, neuropatski bol, vaskulitis*

## PHARMACOLOGICAL CHARACTERISTICS IN THE ELDERLY POPULATION

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The elderly are the fastest increasing population with multiple comorbidities and polypharmacy. They are especially prone to pain, both chronic and neuropathic, and treatment in the geriatric context should be based on balancing between benefits and risks.

The process of aging includes multiple changes in the structure, neurochemistry and function of the nociceptive pathways, and also a significant reduction in the functioning of the endogenous inhibitory analgesic pathway.

Because of the comorbidities, the elderly often use multiple drugs and in the context of changed physiology, especially pharmacokinetics, there is a big risk factor for side effects.

Holistic geriatric assessment is a useful tool in the prevention of circulus vitiosus in the pharmacotherapy of pain. Generally the conclusion is that analgetics which are used in the younger adult population are useful in the elderly as well, but the ratio between risks and benefit should be carefully evaluated. Recommendations for pharmacological treatment of pain in this vulnerable population are based on safety rather than efficacy.

**Key words:** *elderly, pain, pharmacology*

## FARMAKOLOŠKE KARAKTERISTIKE STARIJIH BOLESNIKA

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Stariji ljudi su najbrže rastući dio populacije bolesnika s čestim multimorbiditetom i polifarmacijom. Osobito su osjetljivi na bol, posebno kroničnu i neuropatsku, a liječenje u gerijatrijskom kontekstu treba počivati na pažljivom balansu dobrobiti i rizika.

Proces starenja uključuje multiple promjene u strukturi, neurokemiji i funkciji nociceptivnih puteva, te značajno smanjenje učinkovitosti inhibitornog endogenog analgetskog sustava.

Zbog komorbiditeta stariji bolesnici često koriste konkurentne farmakološke pripravke koji u kontekstu promijenjene fiziologije, osobito farmakokinetike, predstavljaju veliki rizik u nastanku neželjenih štetnih događaja.

Polifarmacijska preskripcija potencijalno neprikladnih lijekova često dovodi do tzv. Preskripcijske kaskade – novih jatrogenih neželjenih nuspojava.

Cjelovita gerijatrijska procjena koristan je alat u prevenciji često začaranog kruga farmakoterapije boli. Općenito se može reći da su analgetici koji se koriste u mlađoj odrasloj populaciji učinkoviti i u starijih, ali se omjer rizika i koristi treba pažljivo i trajno evaluirati.

Preporuke o farmakološkom liječenju boli u ovoj vulnerabilnoj populaciji više se temelje na sigurnosti nego učinkovitosti.

***Ključne reči:*** stariji, bol, farmakologija

## DIFFERENCES IN PAIN THRESHOLDS FOR HEAT, COLD AND PRESSURE BETWEEN PATIENTS WITH PAINFUL LUMBOSACRAL RADICULOPATHY AND HEALTHY SUBJECTS

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In localized pain syndromes, it is expected that there is hyperalgesia in the regions that are painful. However, it remains unclear whether hyperalgesia is present in pain-free regions that are distant from the location where patients feel pain.

The aim of this study was to determine whether there are differences in pain thresholds in patients with neuropathic pain due to lumbosacral radiculopathy (LSR) and a control group of healthy subjects in regions where patients feel pain as well as in regions remote from painful regions where there is no pain.

This cross-sectional study included 26 subjects with painful LSR and 26 healthy subjects. The pressure pain threshold (PPT), heat pain threshold (HPT) and cold pain threshold (CPT) were tested on the paraspinal musculature of the lumbar spine and on opposite forearm.

In the LSR group, significantly lower PPT values were registered in both tested regions ( $p < 0.001$ ), HPT values were significantly lower in the forearm area ( $p = 0.002$ ) and in the lower back area ( $p = 0.021$ ). CPT values were significantly lower in the forearm region ( $p = 0.017$ ), but there was no significant difference in the lower back ( $p = 0.124$ ).

Subjects with painful LSR show signs of generalized hyperalgesia since, in addition to the expected lower PPT and HPT in the lower back (where they experience pain), they also have lower PPT and HPT in remote regions (where they do not feel pain) compared to healthy subjects.

**Key words:** *lumbosacral radiculopathy, pain threshold, neuropathic pain, hyperalgesia, central sensitization*

## RAZLIKE U PRAGOVIMA BOLA ZA TOPLO, HLADNO I PRITISAK IZMEĐU BOLESNIKA SA BOLNOM LUMBOSAKRALNOM RADIKULOPATIJOM I ZDRAVIH ISPITANIKA

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Kod lokalizovanih bolnih sindroma očekivano je da postoji hiperalgezija u regijama koje su bolne. Međutim, ostaje nejasno da li je hiperalgezija prisutna i u bezbolnim regijama koje su udaljene od lokacije gde bolesnici osećaju bol.

Cilj ove studije bio je da se utvrdi da li postoje razlike u pragovima bola kod bolesnika sa neuropatskim bolom usled lumbosakralne radikulopatije (LSR) i kontrolne grupe zdravih ispitanika u regijama gde bolesnici osećaju bol, kao i u regijama koje su udaljene od bolnih regija i gde nema bola.

Ova studija preseka obuhvatila je 26 ispitanika sa bolnom LSR i 26 zdravih ispitanika. Prag bola na pritisak (engl. *pressure pain threshold*-PPT), prag bola na toplo (engl. *heat pain threshold*-HPT) i prag bola na hladno (engl. *Cold Pain Threshold*-CPT) ispitivani su na paraspinalnoj muskulaturi lumbalnog dela kičme i na suprotnoj podlaktici.

U grupi sa LSR registrovane su značajno niže vrednosti PPT u oba testirana regiona ( $p < 0,001$ ), vrednosti HPT bile su značajno niže u predelu podlaktice ( $p = 0,002$ ) i u predelu donjeg dela leđa ( $p = 0,021$ ). Vrednosti CPT-a značajno su bile niže u regiji podlaktice ( $p = 0,017$ ), ali nije bilo značajne razlike u donjem delu leđa ( $p = 0,124$ ).

Ispitanici sa bolnom LSR pokazuju znake generalizovane hiperalgezije pošto, pored očekivanih nižih PPT i HPT u donjem delu leđa (gde imaju bolove), imaju i niže PPT i HPT u udaljenim regijama (gde ne osećaju bol) u odnosu na zdrave ispitanike.

**Ključne reči:** lumbosakralna radikulopatija, prag bola, neuropatski bol, hiperalgezija, centralna senzitivizacija

## THE DEGREE OF EXPRESSION OF CENTRAL SENSITIZATION AND EMOTIONAL STATUS IN PATIENTS WITH NEUROPATHIC PAIN COMPARED TO HEALTHY SUBJECTS

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It is believed that emotional factors as well as central sensitization are very important for the onset and maintenance of chronic pain.

The aim of this research was to examine whether there are significant differences in the expression of central sensitization, degree of anxiety, depression and stress between healthy subjects and subjects with neuropathic pain due to lumbosacral radiculopathy.

This study included 33 subjects with painful lumbosacral radiculopathy (mean age  $54.12 \pm 9.43$  years, 6 (18.2%) women) and 30 healthy subjects (mean age  $50.87 \pm 5.64$  years, 12 (40%) women). The Serbian version of the Central Sensitization Inventory (CSI) was used to examine the degree of central sensitization symptoms. In order to evaluate the emotional status, we used the Serbian version of the Depression, Anxiety, Stress Scale (DASS 21).

The obtained results showed a significantly higher value of the CSI score in subjects with neuropathic pain ( $t = -7.690$ ,  $p = 0.000$ ). There were statistically significantly worse DASS 21 values in subjects with neuropathic pain in all 3 subscales: depression subscale ( $t = -2.437$ ,  $p = 0.018$ ), anxiety subscale ( $t = -3.597$ ,  $p = 0.001$ ), stress subscale ( $t = -3.982$ ,  $p = 0.000$ ).

The degree of expression of symptoms of central sensitization determined on the basis of the CSI, as well as the degree of anxiety, depression and stress determined on the basis of the DASS 21 scale, are significantly higher in subjects with neuropathic pain compared to the group of healthy subjects. This should be kept in mind when designing a treatment plan for individuals with painful lumbosacral radiculopathy.

**Key words:** *neuropathic pain, central sensitization, anxiety, depression, stress*

## STEPEN IZRAŽENOSTI CENTRALNE SENZITIZACIJE I EMOCIONALNOG STATUSA KOD BOLESNIKA SA NEUROPATSKIM BOLOM U ODNOSU NA ZDRAVE ISPITANIKE

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Smatra se da su za nastanak i održavanje hroničnog bola veoma važni emocionalni faktori kao i centralna senzitivizacija.

Cilj ovog istraživanja bio je da se ispita da li postoje značajne razlike u izraženosti centralne senzitivizacije, stepenu anksioznosti, depresivnosti i stresa između zdravih i ispitanika sa neuropatskim bolom usled lumbosakralne radikulopatije.

Ova studija obuhvatila je 33 ispitanika sa bolnom lumbosakralnom radikulopatijom (prosečne starosti  $54,12 \pm 9,43$  godina, 6 (18,2%) žena) i 30 zdravih ispitanika (prosečne starosti  $50,87 \pm 5,64$  godina, 12 (40%) žena). Za ispitivanje stepena izraženosti simptoma centralne senzitivizacije korišćena je srpska verzija Skale centralne senzitivizacije (engl. *Central Sensitization Inventory* – CSI). Kako bismo izvršili evaluaciju emocionalnog statusa koristili smo srpsku verziju Skale depresije, anksioznosti i stresa (engl. *Depression, Anxiety, Stress Scale* – DASS 21).

Dobijeni rezultati pokazali su značajno više vrednosti skora CSI kod ispitanika sa neuropatskim bolom ( $t = -7,690$ ,  $p = 0,000$ ). Statistički značajno lošije vrednosti DASS 21 kod ispitanika sa neuropatskim bolom u sve tri podskale: podskala depresivnosti ( $t = -2,437$ ,  $p = 0,018$ ), podskala anksioznosti ( $t = -3,597$ ,  $p = 0,001$ ), podskala stresa ( $t = -3,982$ ,  $p = 0,000$ ).

Stepen izraženosti simptoma centralne senzitivizacije utvrđen na osnovu CSI, kao i stepen anksioznosti, depresije i stresa utvrđen na osnovu DASS 21 skale, značajno je veći kod ispitanika sa neuropatskim bolom u odnosu na grupu zdravih ispitanika. Ovo treba imati na umu prilikom dizajniranja plana lečenja osoba sa bolnom lumbosakralnom radikulopatijom.

**Ključne reči:** neuropatski bol, centralna senzitivizacija, anksioznost, depresija, stres