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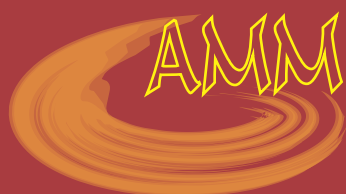


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CORTICAL STIMULATION FOR CHRONIC PAIN: FROM ANECDOTE TO EVIDENCE

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Epidural stimulation of the motor cortex (eMCS) was devised in the 1990s, and has now largely supplanted thalamic stimulation for neuropathic pain relief. Its mechanisms of action involve the activation of multiple cortico-subcortical areas initiated in the thalamus, with the involvement of endogenous opioids and descending inhibition toward the spinal cord. Evidence for clinical efficacy is now supported by at least seven randomized clinical trials (RCTs); benefits may persist up to 10 years and can be reasonably predicted by preoperative use of non-invasive repetitive magnetic stimulation (rTMS). rTMS was first developed as a means of predicting the efficacy of epidural procedures, then as an analgesic method on its own right. Reasonable evidence from at least six well-conducted RCTs favours a significant analgesic effect of high-frequency rTMS of the motor cortex in neuropathic pain (NP), and less consistently in widespread fibromyalgic pain. Stimulation of the dorsolateral frontal cortex (DLPFC) has not proven efficacious for pain so far. The posterior operculo-insular cortex is a new and attractive target but evidence remains inconsistent. Transcranial direct current stimulation (tDCS) is applied upon similar targets as rTMS and electrical motor cortex stimulation (eMCS); it does not elicit action potentials but modulates the neuronal resting membrane state. tDCS presents practical advantages including low cost, few safety issues, and possibility of home-based protocols. However, the limited quality of most published reports entails a low level of evidence. Patients responsive to tDCS may differ from those treated by rTMS, and in both cases repeated sessions over a long time may be required to achieve clinically significant relief. Both invasive and non-invasive procedures exert their effects through multiple distributed brain networks influencing the sensory, affective and cognitive aspects of chronic pain. Their effects are mainly exerted upon abnormally sensitised pathways rather than on acute physiological pain. Extending the duration of long-term benefits remains a challenge, for which different strategies will be discussed.

Key words: motor cortex stimulation, neuromodulation, neuropathic pain, insula, rRMS, tDCS

KORTIKALNA STIMULACIJA KOD HRONIČNOG BOLA: OD ANEGDOTE DO DOKAZA

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Epiduralna stimulacija motoričkog korteksa (eMCS) osmišljena je devedesetih godina prošlog veka i u velikoj meri je potisnula talamičku stimulaciju za ublažavanje neuropatskog bola. Njeni mehanizmi delovanja uključuju aktivaciju višestrukih kortiko-subkortikalnih područja, započetu u talamusu, uz uključivanje endogenih opioda i silaznu inhibiciju prema kičmenoj moždini. Dokaze o kliničkoj efikasnosti sada podržava najmanje sedam randomizovanih ključnih studija (RCTs); koristi mogu trajati do 10 godina i mogu se razumno predvideti preoperativnom upotrebom repetitivne transkranijalne magnetne stimulacije (rTMS). rTMS je prvo razvijena kao sredstvo za predviđanje efikasnosti epiduralnih procedura, a potom i kao samostalna metoda za lečenje bola. Značajni dokazi iz najmanje šest dobro sprovedenih randomizovanih kliničkih studija favorizuju važan analgetski efekat visokofrekventne rTMS motoričkog korteksa kod neuropatskog bola (NP), što je manje dosledno kod rasprostranjenog fibromijalgičnog bola. Stimulacija dorzolateralnog frontalnog korteksa (DLPFC) do sada se nije pokazala efikasnom u lečenju bola. Posteriorni operkulo-insularni korteks je nova i atraktivna tema, ali su dokazi nedosledni. Transkranijalna stimulacija jednosmernom strujom (tDCS) primenjuje se u sličnim situacijama, kao i rTMS i eMCS; ne izaziva akcione potencijale, već modulira stanje membrane u mirovanju neurona. tDCS uvodi praktične prednosti uključujući nisku cenu, mali broj pitanja o bezbednosti i mogućnost protokola koji se izvode kod kuće. Međutim, ograničeni kvalitet većine objavljenih izveštaja podrazumeva nizak nivo dokaza. Pacijenti koji reaguju na tDCS mogu se razlikovati od onih kod kojih je uključena rTMS i u oba slučaja ponovljene sesije tokom dužeg vremena mogu biti neophodne da bi se postiglo klinički značajno olakšanje. I invazivne i neinvazivne procedure ispoljavaju svoje efekte kroz višestruke distribuirane moždane mreže utičući na senzorne, afektivne i kognitivne aspekte hroničnog bola. Njihovi efekti uglavnom deluju na abnormalno senzitivizovane puteve, pre nego na akutni fiziološki bol. Produženje trajanja dugoročnih benefita ostaje izazov, što će biti predmet budućih strategija.

Ključne reči: stimulacija motoričkog korteksa, neuromodilacija, neuropatski bol, insula, rRMS, tDCS

MAGIC PILL OR MAGIC INJECTION

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The prevalence of chronic pain in the last few years in the U.S. population of adults is above 20%. The cost for treating chronic pain is estimated to be about \$560 billion per year including the indirect cost for the loss of productivity and missed days of work. Furthermore, pain is one of the main reasons for getting disability benefits, and taking into consideration that it is mainly measured by subjective rating scales makes this healthcare issue more complicated.

Most of the studies dealing with the correlation between chronic pain, depression, and anxiety have shown that more than 50% of the people with chronic pain have these comorbidities. Even though physicians of many specialties such as anesthesiologists, physical medicine and rehabilitation, neurologists, surgeons, etc. treat these patients and the majority of guidelines suggest a multidisciplinary approach in treating chronic pain, mental healthcare professionals are rarely included as part of these teams. However, if patients have anxiety, depression, or other mental health issues, treating the pain without treating these issues will not resolve the problem. These patients tend to be repeated visitors of the pain clinic, increase their healthcare expenditures, and utilize more sick leaves.

Early discovery of these comorbidities and training pain physicians to use a more integrative pain management approach could be helpful when there are not enough available mental health resources.

Key words: *regenerative medicine, platelet-rich plasma, mesenchymal stem cells, chronic pain, inflammation, arthritis, degenerative disease*

MAGIČNA TABLETA ILI MAGIČNA INJEKCIJA

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Prevalencija hroničnog bola u poslednjih nekoliko godina u populaciji odraslih u SAD jeste iznad 20%. Troškovi lečenja hroničnog bola procenjuju se na oko 560 milijardi dolara godišnje, uključujući indirektno troškove za gubitak produktivnosti i propuštene dane rada. Štaviše, bol je jedan od glavnih razloga za dobijanje invalidnine, a činjenica da se uglavnom meri subjektivnim skalama ocenjivanja ovo pitanje zdravstvene zaštite čini još komplikovanim.

Većina studija koje se bave korelacijom hroničnog bola, depresije i anksioznosti pokazala je da više od 50% ljudi sa hroničnim bolom ima ove komorbiditete. Iako lekari mnogih specijalnosti, kao što su anesteziolozi, specijalisti fizikalne medicine i rehabilitacije, neurolozi, hirurzi itd., leče ove pacijente i većina smernica sugeriše multidisciplinarni pristup u lečenju hroničnog bola, stručnjaci za mentalno zdravlje retko su uključeni u ove timove. Međutim, ako pacijenti imaju anksioznost, depresiju ili druge probleme mentalnog zdravlja, lečenje bola bez lečenja ovih poteškoća neće rešiti problem. Ovi pacijenti imaju tendenciju da budu česti posetoci klinika za bol, povećavaju troškove zdravstvene zaštite i češće koriste bolovanja.

Rano otkrivanje ovih komorbiditeta i obučavanje lekara koji se bave terapijom bola da koriste integrativniji pristup terapije bola mogli bi biti od pomoći onda kada nema dovoljno dostupnih resursa za mentalno zdravlje.

Ključne reči: hronični bol, anksioznost, depresija, mentalno zdravlje, integrativni pristup

INTEGRATIVE THERAPY IN RHEUMATIC PATIENTS

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Most rheumatic diseases are chronic conditions and they are often the cause of significant disability. Therefore, it is very important to strive for early diagnosis and timely initiation of treatment. Rheumatic patients suffer from deficiency of body functions and structures, which manifests through musculoskeletal pain, fatigue, stiffness and swelling of the joints, reduced range of motion, muscle weakness and damage to the joints. The link between damage, reduced physical activity and participating in social activities is mostly affected by the disease itself, but the factors such as social support and/or working conditions also have an important role. There is a need for a multidisciplinary approach in the treatment of rheumatic patients because of frequent neuropsychological manifestations (disorders of sleep, cognitive function and emotional manifestations). The knowledge of the psychology of pain in rheumatology has enabled the advancement of new and different treatments that are not focused solely on the sensory pain qualities. As opposed to acute pain in rheumatology, where the main focus is on the assessment and treatment, in chronic pain self-management, possession of certain skills and a treatment plan, formed by healthcare professionals, that is adjusted to the needs of the individual patient, is important. The optimal use of scientific knowledge and skills requires teamwork that involves different types of healthcare professionals, such as rheumatologists, physical medicine and rehabilitation specialists, physical and occupational therapists, psychologists, nurses, with patients being in the focus of their activities. Integrative approach includes different strategies of treatments that involve traditional and complementary medicine, or the combination of both.

Key words: *pain, rheumatology, integrative therapy*

INTEGRATIVNI PRISTUP PACIJENTIMA U REUMATOLOGIJI

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Većina reumatskih bolesti ima hroničan tok i može uzrokovati značajnu nesposobnost, pa je veoma važno težiti ranom postavljanju dijagnoze i pravovremenom započinjanju lečenja. Kod reumatskih bolesnika javljaju se oštećenja u telesnim funkcijama i strukturama, što najčešće obuhvata mišićno-skeletni bol, umor, ukočenost i otok zglobova, smanjenje obima pokreta u zglobovima, mišićnu slabost i oštećenje zgloba. Na vezu između oštećenja, ograničenja aktivnosti i učešća u društvu najviše utiče sama bolest, mada važnu ulogu imaju i faktori sredine (npr. socijalna podrška i/ili zahtevi posla). Potreba za multidisciplinarnim pristupom kod reumatskih bolesnika postoji zbog učestalih neuropsiholoških manifestacija (poremećaji spavanja, kognitivnih funkcija i emocionalnih manifestacija). Poznavanje psihologije bola u reumatologiji omogućilo je razvoj novih i drugačijih terapijskih pristupa, koji nisu isključivo orijentisani na senzorni kvalitet bola. Za razliku od akutnog bola u reumatologiji, sa fokusom na proceni i tretmanu, kod hroničnog bola bitno je samoupravljanje i posedovanje određenih veština, te osmišljavanje tretmana od strane zdravstvenih profesionalaca u skladu sa individualnim potrebama obolelih. Optimalna primena stručnih i naučnih saznanja podrazumeva timski rad koji uključuje različite vrste zdravstvenih profesionalaca – reumatologe, fizijatre, fizioterapeute i radne terapeute, psihologe, medicinske sestre – ali i bolesnika, koji je u fokusu navedenog tima. Integrativni pristup uključuje različite strategije tretmana koji obuhvataju tradicionalnu i komplementarnu medicinu ili njihovu kombinaciju.

Ključne reči: *bol, reumatologija, integrativni pristup*

ACUTE POSTOPERATIVE PAIN IN THE LIGHT OF INTEGRATIVE CARE

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Acute postoperative pain is associated with acute tissue damage due to operative trauma. It occurs in over 80% of patients, and more than 50% of them experience moderate to severe pain in the first 24 hours after surgery. In most cases, within a few postoperative days, the pain subsides and tissue healing stops. The experience of pain is individual and depends on the biological response, psychological and social status. Inadequately treated acute pain and prolonged duration increase the likelihood of progression to chronic postoperative pain. Prevention and relief of acute pain after surgery is a fundamental human right, a moral imperative and a great responsibility of health professionals.

The International Association for the Study of Pain (IASP) identified priorities and promoted 2017 as the Global Year against Post-Surgical Pain, and the Global Year 2023 was dedicated to Integrative Pain Care. There is no ideal analgesic in the treatment of pain, as evidenced by the low NNT (number needed to treat). An integrative approach to treating acute pain involves the integration of multiple evidence-based pharmacological and non-pharmacological treatments, personalized and focused (person-centered) with the use of opioid sparing techniques and regional analgesia techniques, which, with their additive and synergistic interactions, aim to optimize analgesia and minimize side effects. Today, multimodal postoperative analgesia is an essential component of the ERAS (Enhanced Recovery After Surgery) program. Its implementation significantly contributes to early recovery, early discharge from hospital, and a better outcome after surgery.

Key words: *acute postoperative pain, integrative pain care, multimodal analgesia, enhanced recovery after surgery*

AKUTNI POSTOPERATIVNI BOL U SVETLU INTEGRATIVNOG ZBRINJAVANJA

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Akutni postoperativni bol povezan je sa akutnim oštećenjem tkiva zbog operativne traume. Javlja se kod više od 80% bolesnika, a preko 50% njih doživljava bol umereno jakog i jakog intenziteta u prvih 24 sata posle operacije. Tokom nekoliko postoperativnih dana kod većine bol slabi i prestaje sa ozdravljenjem tkiva. Doživljaj bola je individualan i zavisi od biološkog odgovora, psihološkog i socijalnog statusa. Neadekvatno lečen akutni bol i prolongirano trajanje povećavaju verovatnoću progresije u hronični postoperativni bol. Prevencija i otklanjanje akutnog bola posle operacije fundamentalna su ljudska prava, moralni imperativ i velika odgovornost zdravstvenih profesionalaca.

Međunarodna asocijacija za izučavanje bola (IASP) identifikovala je prioritete i 2017. godinu promovisala kao Svetsku godinu protiv posthirurškog bola, a Svetsku 2023. godinu posvetila je integrativnom zbrinjavanju bola. Idealnog analgetika u tretmanu bola nema, što dokazuje i nizak NNT (engl. *number needed to treat*). Integrativni pristup zbrinjavanja akutnog bola podrazumeva integrisanje *evidence-based* farmakoloških i nefarmakoloških tretmana, personalizovanih i fokusiranih (engl. *person-centered*) sa upotrebom *opioid sparing* tehnika i tehnika regionalne analgezije, koje svojim aditivnim i sinergističkim interakcijama teže ka optimizaciji analgezije i minimizaciji neželjenih efekata. Multimodalna postoperativna analgezija danas je suštinska komponenta ERAS (engl. *Enhanced Recovery After Surgery*) programa, čija implementacija značajno doprinosi ranom oporavku, ranom otpuštanju iz bolnice i boljem ishodu posle operacije.

Ključne reči: *akutni postoperativni bol, integrativno zbrinjavanje, multimodalna analgezija, multimodalno perioperativno zbrinjavanje*

ERECTOR SPINAE PLANE BLOK

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Erector spinae plane block (ESP) is one of the newer interfascial techniques with multiple applications and effects. The ESP block is an interfascial block that can be performed with a superficial or deep needle approach. In the superficial needle approach technique, the local anesthetic is injected between the rhomboid major muscle and the erector spinae muscle, while with the deep needle approach, the local anesthetic is injected under the erector spinae muscle. It is recommended to use a deep needle approach because the anesthetic is deposited closer to the costotransverse openings and the dorsal and ventral rami. When the anesthetic is injected into the interfascial plane deep to the erector spinae muscles bilaterally, craniocaudally, the spread of the infiltrate goes from C7 to T8 on the right side, as well as T1 to T8 on the left side. It is diagnosed in the paraspinous space with lateral expansion to the transverse processes at all levels. Local anesthetic has been also observed just posterior to the costotransverse junctions at the levels T3 to T6 on the right side and T4 to T8 on the left side. Cadaveric studies have shown that blockade at the level of T5 is sufficient for unilateral multidermatome sensory block ranging from T1 to L3. This block allows a paravertebral block without the risk of pleural injury.

The first application of this block was related to the treatment of chronic pain. Later, it found its place in the treatment of acute pain in rib fractures and in the perioperative pain treatment of cardiothoracic and abdominal surgery as well as hip and femoral surgery. ESPB causes multidermatomal sensory block without motor block. Studies have shown that it reduces the amount of perioperatively administered opioids and the intensity of postoperative pain. In patients with coagulation disorders, ESPB is safer than epidural and paravertebral blocks and carries a lower risk of neurological damage and pneumothorax. It can be used in all patients, from premature babies to elderly people with comorbidities. ESPB is a simple and safe block that provides good analgesia for acute postoperative and post-traumatic pain and for chronic pain conditions.

Key words: *acute and chronic pain therapy, interfascial block, erector spinae plane block*

INTERFASCIJALNI BLOKOVI

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Blok *Erector spinae plane* (ESP) jedna je od novijih interfascijalnih tehnika sa višestrukom primenom i efektom. ESP blok je interfascijalni blok koji se može izvesti površnim ili dubokim pristupom iglom. U tehnici površinskog pristupa iglom, lokalni anestetik ubrizgava se između romboidnog velikog mišića i mišića erektora kičme, dok se u pristupu dubokom iglom lokalni anestetik ubrizgava ispod mišića erektora kičme. Preporučeno je da se koristi pristup dubokom iglom jer se anestetik deponuje bliže kostotransverzalnim otvorima i dorzalnim i ventralnim ramijama. Kada je anestetik ubrizgan u interfascijalnu ravan duboko do mišića erektora kičmenog stuba bilateralno, kraniokaudalno, širenje infiltrata ide od C7 do T8 na desnoj strani, kao i od T1 do T8 na levoj strani. Dijagnostikuje se u paraspinoznom prostoru sa bočnim širenjem do poprečnih nastavaka na svim nivoima. Lokalni anestetik je takođe primećen malo iza kostotransverzalnih spojeva na nivoima od T3 do T6 na desnoj strani i od T4 do T8 na levoj strani. Kadaverične studije su pokazale da je blokada na nivou T5 dovoljna za unilateralni multidermatomni senzorni blok u rasponu od T1 do L3. Ovaj blok omogućava paravertebralni blok bez rizika od povrede pleure.

Prva primena ovog bloka bila je vezana za terapiju hroničnog bola. Kasnije je našao svoje mesto u terapiji akutnog bola kod preloma rebra i u perioperativnoj terapiji bola u kardiorakalnoj, abdominalnoj hirurgiji, kao i u hirurgiji kuka i femura. ESPB izaziva multidermatomalni senzorni blok bez motornog bloka. Studije su pokazale da smanjuje količinu perioperativno primenjenih opioida i intenzitet postoperativnog bola. Kod pacijenata sa poremećajima koagulacije, ESPB je bezbedniji od epiduralnog i paravertebralnog bloka i nosi manji rizik za nastanak neuroloških oštećenja i pneumotoraksa. Može se primeniti kod svih pacijenata, od prematurusa do starijih osoba sa komorbiditetima. ESPB je jednostavan i bezbedan blok koji obezbeđuje dobru analgeziju za akutni postoperativni i posttraumatski bol i za hronična bolna stanja.

Ključne reči: *terapija akutnog i hroničnog blok, interfascijalni blok; Erector spinae plane blok*

THE APPLICATION OF MONOCLONAL ANTIBODIES IN MIGRAINE THERAPY

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Migraine is a chronic neurological disease with episodic headache attacks whose characteristics are described in the International Classification of Headache Disorders.

Migraine therapy depends on the clinical course, severity and duration of individual attacks, their frequency and the disability they cause. Epidemiological studies show that in about 38% of cases there is an indication for the introduction of prophylactic therapy.

Prophylactic therapy aims to reduce the frequency and duration of headache attacks, intensity of pain and severity of migraine attacks, as well as to improve the effectiveness of acute therapy, reduce disability and improve the quality of life in patients suffering from migraine. For a long time, medications that were primarily produced for another indication were used in migraine prophylaxis. Their prophylactic effectiveness in migraine was first observed empirically, and then confirmed through studies. Until recently, guidelines for migraine prophylaxis were based on the use of beta blockers, calcium channel inhibitors, antiepileptics, and antidepressants.

The modern approach to prophylactic migraine therapy involves etiological therapy and is based on the use of drugs that act on the calcitonin gene-related peptide (CGRP) or CGRP receptor. Calcitonin gene-related peptide plays a significant role in the pathophysiology of migraine both peripherally and centrally.

Clinical studies involving a large number of patients confirmed the short-term and long-term efficacy and safety of monoclonal antibodies (mAbs) in patients with episodic and chronic migraine.

For the purpose of migraine prevention, four monoclonal antibodies were tested: Fremanezumab, Eptinezumab and Galcanezumab, which bind to CGRP, and Erenumab, which exerts its effect by binding to the CGRP receptor. In 2019, the European Headache Federation (EHF) issued a guideline for the use of CGRP mAbs in the prevention of migraine in adults. The guidelines were updated in 2022 and indicate that CGRP mAbs can be the drug of first choice in adults with migraine.

Innovative biological therapy based on the pathophysiological mechanisms of migraine allows better control of the disease, which contributes to a better quality of life of the patient and reduction of disability, and in addition to medical, it also has large socioeconomic importance.

Keywords: *migraine, monoclonal antibodies, calcitonin gene-related peptide*

PRIMENA MONOKLONSKIH ANTITELA U TERAPIJI MIGRENE

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Migrena je hronična neurološka bolest sa epizodičnim atacima glavobolje, čije su karakteristike opisane u Međunarodnoj klasifikaciji glavobolja.

Terapija migrene uslovljena je kliničkim tokom, težinom i trajanjem pojedinačnih ataka, njihovom učestalošću i onesposobljenošću koju uzrokuju. Epidemiološke studije pokazuju da kod oko 38% obolelih od migrene ima indikacija za uvođenje profilaktičke terapije.

Profilaktička terapija ima za cilj da smanji učestalost, dužinu trajanja ataka glavobolje, jačinu bola i težinu napada migrene, kao i da poboljša efikasnost akutne terapije, smanji onesposobljenost i poboljša kvalitet života obolelih od migrene. Dugo su u profilaksi migrene korišćeni medikamenti koji su primarno proizvedeni za drugu namenu. Njihova efikasnost u profilaksi migrene najpre je empirijski zapažena, a potom kroz studije potvrđena. Daskora su vodiči za profilaksu migrene bili bazirani na primeni beta-blokatora, inhibitora kalcijumovih kanala, antiepileptika i antidepresiva.

Savremeni pristup profilaktičkoj terapiji migrene podrazumeva etiološku terapiju i bazira se na primeni medikamenata koji deluju na peptid povezan sa kalcitoninskim genom (CGRP) ili CGRP receptor. Peptid povezan sa kalcitoninskim genom ima značajnu ulogu u patofiziologiji migrene i na perifernom i na centralnom nivou.

Kliničkim studijama, na velikom broju pacijenta potvrđene su kratkoročna i dugoročna efikasnost i bezbednost monoklonskih antitela (mAbs) kod obolelih od epizodične i hronične migrene. U svrhu prevencije migrene ispitivana su četiri monoklonska antitela: Fremanezumab, Eptinezumab i Galkanezumab, koji se vezuju za CGRP, i Erenumab, koji svoje dejstvo ostvaruje vezivanjem za CGRP receptor. Evropsko udruženje za glavobolje (EHF) 2019. godine izdalo je smernice za upotrebu CGRP mAbs za prevenciju migrene kod odraslih; smernice su 2022. godine ažurirane i sada ukazuju na to da CGRP mAbs može biti lek prvog izbora kod odraslih osoba obolelih od migrene.

Inovativna biološka terapija, zasnovana na patofiziološkim mehanizmima migrene, omogućava bolju kontrolu bolesti, što doprinosi boljem kvalitetu života obolelog i smanjenju onesposobljenosti, te pored medicinskog ima i veliki socio-ekonomski značaj.

Ključne reči: migrena, monoklonska antitela, peptid povezan sa kalcitoninskim genom

ACUPUNCTURE TREATMENT FOR HEADACHE

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In the concept of traditional Chinese medicine (TCM), acupuncture has developed as a philosophical approach to the human body and spirit. It can be said that it is basically a method of treatment without drugs, an external treatment of internal diseases. The therapy technique consists of inserting acupuncture needles into the certain points on the body, so that is where the Latin name was derived from (*acus* = needle, *pungere* = puncture). TCM explains its diagnostic approach, therapeutic treatment and pathophysiological changes, with theories based on the idea of simple materialism and naive dialectics. They are increasingly viewed from a historical point of view, but their importance is not diminished when choosing the type and method of treatment, especially in situations where comparison with modern diagnostic findings provides an appropriate combination of acupuncture point selection.

Headaches are one of the first painful syndromes to be treated with the acupuncture method. Based on the favorable effect on the dynamics of occurrence, intensity of pain, and improvement of the quality of life, it was considered as one of the alternative procedures in their prophylaxis and treatment. The mechanism of action of acupuncture is multiple, including the endogenous opiate system, serotonergic projections, and noradrenergic projections that synergistically participate in the descending inhibitory control of pain (diffuse noxious inhibitory controls - DNICs).

A special internal mechanism of supraspinal "return force", which is located in the mesolimbic part of the brain in the form of an "analgesic ring", is capable of descending pain control. It consists of periaqueductal gray matter, nucleus habenula, nucleus amygdala, nucleus accumbens and nucleus raphe magnus. Serotonergic, noradrenergic and dopaminergic neurons are also involved. Neurotransmitters in the gelatinous substance of the spinal cord perform the descending inhibition of pain. Acupuncture activation of this system is done by selecting distant acupuncture points.

Key words: *acupuncture, headache, migraine, pain*

AKUPUNKTURA U TERAPIJI GLAVOBOLJA

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U konceptu tradicionalne kineske medicine (TKM) akupunktura se izgradila kao filozofski pristup ljudskom telu i duhu. Predstavlja način lečenja koji se razvijao tokom nekoliko milenijuma. Može se reći da je ona u osnovi način lečenja bez lekova, spoljno lečenje unutrašnjih bolesti. Tehnika terapije sastoji se u ubadanju akupunkturnih igala u određene tačke na telu, tako da je odatle i izveden latinski naziv (*acus* = igla; *pungere* = zabadanje, bodenje). TKM svoj dijagnostički pristup, terapijski tretman i patofiziološke promene objašnjava teorijama koje u osnovi imaju ideju jednostavnog materijalizma i naivne dijalektike. Sve se više posmatraju sa istorijskog stanovišta, ali njihov značaj nije umanjen prilikom odabira vrste i načina tretmana, pogotovo u situacijama kada se upoređivanjem sa savremenim dijagnostičkim nalazima obezbeđuje odgovarajuća kombinacija izbora akupunkturnih tačaka.

Glavobolje su jedan od prvih bolnih sindroma koji je tretiran akupunkturnim metodom. Na osnovu povoljnog efekta na dinamiku javljanja, intenzitet bolova i poboljšanje kvaliteta života, uzeta je u razmatranje kao jedan od alternativnih postupaka u njihovoj profilaksi i lečenju. Mehanizam delovanja akupunkture je višestruk. Uključeni su endogeni opijadni sistem, serotonergičke projekcije i noradrenergičke projekcije, koji sinergistički učestvuju u descendentnoj inhibitornoj kontroli bola.

Za descendentnu kontrolu bola osposobljen je jedan poseban unutrašnji mehanizam supraspinalne „povratne snage”, koji se u vidu „analgetičnog prstena” nalazi u mezolimbicnom delu mozga. Njega sačinjavaju: periakveduktalna siva supstanca, nukleus habenule, nukleus amigdale, nukleus akumbeus i nukleus rafe magnus. Tu se nalaze serotonergični, noradrenergični i dopaminergični neuroni. Njihovi neurotransmiteri u supstanci gelatinozi kičmene moždine vrše descendentnu inhibiciju bola. Akupunkturna aktivacija ovog sistema vrši se izborom udaljenih akupunkturnih tačaka.

Ključne reči: akupunktura, glavobolja, migrena, bol

THE ROLE OF PSYCHOLOGISTS IN CHRONIC PAIN MANAGEMENT

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Pain is a biopsychosocial phenomenon and therefore requires a multidimensional approach in treatment. It is a complex problem that is often associated with a number of psychological comorbid conditions. About 44% of people with chronic pain face certain psychological difficulties such as depression and anxiety, which inevitably negatively affect the success of therapeutic treatments. Therefore, the role of the psychologist in the treatment of chronic pain has become an indispensable part of modern diagnostic and therapeutic protocols. Psychological assessment allows to establish to what degree cognitive, emotional, psychological and social factors contribute to the occurrence, persistence or intensification of chronic pain, after which a proposal is made for the application of a certain psychological therapeutic modality. When choosing a therapeutic treatment, psychologists are primarily guided by evidence-based recommendations. In this sense, three types of therapy were distinguished: cognitive-behavioral therapy, behavioral therapy, as well as acceptance and commitment therapy. The goal of each given modality is to change pain-related behavior and re-establish the functional patterns of behavior through the identification and modification of dysfunctional cognitive and behavioral patterns. In this sense, different therapeutic strategies can be used, such as: exposure, hypnotherapy, mindfulness, psychoeducation, strategies for managing anxiety and PTSD symptoms, improving the quality of sleep and healthy lifestyle, applied relaxation. Evaluation of psychological treatment – both process and outcome – is a vital part of treatment, which should be evidence-based and present throughout the intervention.

Keywords: *pain, psychologist, treatment*

ULOGA PSIHOLOGA U ZBRINJAVANJU HRONIČNOG BOLA

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Budući da bol predstavlja biopsihosocijalni fenomen, zahteva multidimenzionalni pristup u tretmanu. Reč je o kompleksnom problemu koji je često povezan sa nizom psiholoških komorbidnih stanja. Oko 44% osoba sa hroničnim bolom suočava se sa određenim psihološkim poteškoćama poput depresivnosti i anksioznosti, koje neizbežno negativno utiču na uspešnost terapijskih tretmana. Stoga, uloga psihologa u tretmanu hroničnog bola postala je nezaobilazan deo savremenih i dijagnostičkih i terapijskih protokola. Psihološka procena omogućava da se ustanovi u kom stepenu kognitivni, emocionalni, psihološki i socijalni činioci doprinose nastanku, perzistenciji ili intenziviranju hroničnog bola, nakon čega se daje predlog za primenu određenog psihološkog terapijskog modaliteta. U odabiru terapijskog tretmana psiholozi se prvenstveno rukovode preporukama zasnovanim na dokazima. U tom smislu izdvojila su se tri tipa terapije: kognitivno-bihevioralna terapija, bihevioralna terapija i terapija prihvatanjem i posvećenošću. Cilj svakog od datih modaliteta jeste promena ponašanja u vezi sa bolom i ponovno uspostavljanje funkcionalnih obrazaca ponašanja kroz identifikaciju i modifikaciju disfunkcionalnih i kognitivnih i ponašajnih obrazaca. U tom pogledu mogu se koristiti i različite terapijske strategije – izlaganje, hipnoterapija, majndfulness, psihoedukacija, strategije za upravljanje anksioznošću i PTSD simptomima, unapređenje kvaliteta sna i zdravog životnog stila, primenjena relaksacija. Evaluacija psihološkog tretmana, samog procesa i ishoda, vitalni je deo tretmana, koji treba biti zasnovan na dokazima i prisutan tokom čitave intervencije.

Ključne reči: bol, psiholog, tretman

TREATMENT OF CHRONIC CANCER PAIN IN CLINICAL PRACTICE - CASE REPORTS

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Effective treatment of pain is a very important part of the management of cancer patients. From the point of view of pathophysiology, pain may induce several disturbances in the function of the respiratory, circulatory, and nervous systems. Pain limits patients' activities, with a negative effect on physical and psychological functioning. The fact that pain continuously reminds patients about the disease may lead to the development of depression and profound hopelessness. It should be kept in mind that unrelieved pain induces the suffering not only of patients but of families and careers as well.

The paper will present three cases of chronic cancer pain treatment. The first is the case of a 62-year-old female with metastatic colon cancer, in which an example of proper rotation of opioid analgesics will be presented, knowing that more than 20% of patients discontinue traditional therapy due to side effects (nausea, vomiting and constipation). The second case presents a 54-year-old patient with locoregionally advanced lung cancer, treated in the wrong way regarding planning, titration, and conversion of pain therapy; we will also show how to overcome these mistakes. The third case, the case of a patient with prostate cancer and bone metastases, illustrates the correct therapy for neuropathic cancer pain originating from bone metastases.

Chronic cancer pain remains prevalent and severe for many oncology patients, especially those with advanced disease. The goal of pain management is to relieve pain to a level that provides an acceptable quality of life.

Key words: chronic cancer pain, quality of life, opioid analgesics

TERAPIJA HRONIČNOG KANCERSKOG BOLA U KLINIČKOJ PRAKSI – PRIKAZI SLUČAJEVA

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Efikasno lečenje bola predstavlja veoma važan deo lečenja onkoloških pacijenata. Sa stanovišta patofiziologije, bol može izazvati poremećaj funkcije respiratornog, cirkulatornog i nervnog sistema. Bol ograničava aktivnosti pacijenata i ima negativan uticaj na njihovo fizičko i psihičko funkcionisanje. Činjenica da bol neprestano podseća pacijente na bolest može dovesti do razvoja depresije i produbljivanja beznađa. Neublaženi bol izaziva patnju ne samo pacijenata nego i porodice i bliskog okruženja.

U okviru rada biće prikazana tri slučaja primene terapije hroničnog kancerskog bola. Prvi je slučaj pacijentkinje stare 62 godine sa metastatskim karcinomom debelog creva i prikazuje primer pravilne rotacije opioidnih analgetika; poznato je da više od 20% pacijenata prekida tradicionalnu terapiju zbog neželjenih efekata (mučnina, povraćanje i opstipacija). Drugi je slučaj pacijenta starog 54 godine sa lokoregionalno odmaklim karcinomom pluća; u vezi sa njim ukazaćemo na greške u planiranju, titraciji i konverziji terapije bola i pokazaćemo kako ih prevazići. Treći slučaj, slučaj pacijenta sa karcinomom prostate i metastazama u kostima, poslužio je za predstavljanje pravilne terapije neuropatskog kancerskog bola porekla koštanih metastaza.

Hronični kancerski bol ostaje preovlađujući i jak za mnoge pacijente, posebno one sa uznapređovalom bolešću. Cilj upravljanja bolom jeste ublažavanje bola do nivoa koji omogućava prihvatljiv kvalitet života.

Ključne reči: hroničan kancerski bol, kvalitet života, opioidni analgetici

REGENERATIVE REHABILITATION OF THE MUSCULOSKELETAL SYSTEM: A STEP FORWARD

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The science of regenerative medicine fits naturally into the field of rehabilitation as a medical specialty. Neither is defined by any particular organ system into which traditional medicine is divided. Both have functional restoration as their primary outcome. As with any emerging field, definitions pose a challenge: overly inclusive definitions lack clarity and overly restrictive definitions limit the scope. The key concepts that are central to the field are that innate regenerative processes can be enhanced by biophysical, electrical, and thermal stimuli; that cell transplantation can be optimized by subjecting cells to stimuli *ex vivo* and *in vivo*, such as tensile loading or compression, which enhance their regenerative potential, and that building upon the synergies of physical stimuli and regenerative responses is likely to improve functional outcomes. Regenerative rehabilitation is the synergistic integration of principles and approaches from the regenerative medicine and rehabilitation fields, with the goal of optimizing form and function as well as patient independence. Regenerative medicine approaches for repairing or replacing damaged tissue or whole organs vary from utilizing cells (e.g., stem cells), to biologics (e.g., growth factors), to approaches using biomaterials and scaffolds, to any combination of these. Regenerative rehabilitation offers the opportunity to positively influence regenerative medicine by inclusion of principles from rehabilitation sciences. Regenerative rehabilitative strategies can include activity-mediated plasticity, exercise dosing, electrical stimulation, and nutritional enhancers. As science advances and technology matures, researchers need to consider the integrative approach of regenerative rehabilitation to maximize the outcome to fully restore the function of patients.

Key words: *regenerative rehabilitation, regenerative medicine, rehabilitation*

REGENERATIVNA REHABILITACIJA MIŠIĆNO-SKELETNOG SISTEMA – KORAK NAPRED

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Regenerativna medicina kao nauka prirodno se uklapa u oblast rehabilitacije kao medicinske specijalnosti. Ni jedna ni druga nauka nisu definisane nekim određenim organskim sistemom, na koje je tradicionalna medicina inače podeljena. Obe discipline imaju funkcionalnu restauraciju kao primarni ishod. Kao i kod svake nove oblasti, definicije predstavljaju izazov – previše inkluzivnim definicijama nedostaje jasnoća, a previše restriktivne definicije ograničavaju obim. Ključni koncepti koji su centralni za ovu oblast zasnivaju se na tome da urođeni regenerativni procesi mogu biti poboljšani biofizičkim, električnim i termalnim stimulusima.

Regenerativna rehabilitacija predstavlja sinergističku integraciju principa i pristupa iz oblasti regenerativne medicine i polja rehabilitacije, sa ciljem optimizacije forme i funkcije, kao i nezavisnosti pacijenata. Princip obnavljanja oštećenog tkiva ili organa regenerativna medicina bazira na korišćenju ćelija (npr. matičnih ćelija), bioloških faktora (npr. faktora rasta), biomaterijala i na kombinaciji ovih faktora.

Fokus regenerativne medicine je na oporavku ili zameni tkiva izgubljenog usled povrede, bolesti ili starosti, prvenstveno putem poboljšanja funkcije endogenih matičnih ćelija ili transplantacije egzogenih matičnih ćelija. Fokus nauke o rehabilitaciji je na upotrebi mehaničkih i drugih stimulansa za promovisanje funkcionalnog oporavka. Oblast regenerativne rehabilitacije integriše ova dva pristupa, sa krajnjim ciljem optimizacije ishoda. Regenerativna rehabilitacija uključivanjem principa iz rehabilitacionih nauka potencira i ima pozitivan uticaj na efekte regenerativne medicine. Strategija regenerativne rehabilitacije može uključiti plastičnost posredovanu aktivnošću, dozirano vežbanje, električnu stimulaciju i izbalansiranu, obogaćenu ishranu.

Napredak nauke i tehnologije potencira integrativni pristup regenerativne rehabilitacije u cilju potpunog obnavljanja funkcije pacijenata.

Ključne reči: regenerativna rehabilitacija, regenerativna medicina, rehabilitacija

MECHANISMS OF ANALGESIC ACTION OF ACUPUNCTURE, ELECTROACUPUNCTURE AND MOXIBUSTION

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The effects of applying acupuncture, electroacupuncture and moxibustion on certain reflexogenic (acupuncture) points on the surface of the body are the result of turning physical stimulation into biological activation, with the release of biologically active substances in localized regions and their spread throughout our body. This activation leads to different cascade reactions to acupuncture, electroacupuncture and moxibustion, which affect the overall regulation of homeokinesis, including the reduction or elimination of pain of various origins.

Depending on the location of the analgesic effect of acupuncture, electroacupuncture and moxibustion on pain, their mechanisms can be divided into peripheral and central analgesic mechanisms, in which the immune system and nervous system with their mediators play a key role.

The mechanisms of analgesic action of acupuncture, electroacupuncture and moxibustion are relatively similar, with certain specificities related to mechanical, electrical, thermal and chemical stimuli. In general, they all involve a release of biologically active substances and mediators from the irritated layers of the skin, subcutaneous tissue and muscles, such as: adenosine, adenosine triphosphate (ATP), serotonin [5-hydroxytryptamine (5-HT)], nitric oxide (NO), calcium ions (Ca²⁺), corticotropin-releasing hormone (CRH), various neurotransmitters and cytokines, including endogenous opiates, which, by binding to their receptors, lead to reduction and elimination of pain.

The effects of acupuncture, electroacupuncture and moxibustion were found to be mediated by suppression of oxidative stress and apoptosis, regulation of metabolism, direct and indirect modulation of inflammation, which forms the basis of all the mechanisms of their analgesic action.

Key words: *acupuncture, electroacupuncture, moxibustion, mechanisms, analgesia*

MEHANIZMI ANALGETIČKOG DELOVANJA AKUPUNKTURE, ELEKTROAKUPUNKTURE I MOKSIBUSTIJE

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Efekti primene akupunkture, elektroakupunkture i moksibustije na određene refleksogene (akupunkturne) tačke na površini tela nastaju kao rezultat pretvaranja fizičke stimulacije u biološku aktivaciju, sa oslobađanjem biološki aktivnih supstanci u lokalizovanim regionima i njihovim širenjem po celom našem telu. Ova aktivacija dovodi do raznih kaskadnih reakcija na akupunkturu, elektroakupunkturu i moksibustiju, koje utiču na celokupnu regulaciju homeokineze, uključujući smanjenje ili eliminisanje bola različitog porekla.

U zavisnosti od lokalizacije analgetičkog dejstva akupunkture, elektroakupunkture i moksibustije, njihovi mehanizmi mogu se podeliti na periferne i centralne analgetičke mehanizme, u kojima ključnu ulogu imaju imunski sistem i nervni sistem sa svojim posrednicima.

Mehanizmi analgetičkog delovanja akupunkture, elektroakupunkture i moksibustije relativno su slični, sa određenim specifičnostima vezanim za mehanički, električni, toplotni i hemijski podražaj. Uopšteno, svi oni uključuju oslobađanje biološki aktivnih supstanci i medijatora iz podraženih slojeva kože, potkožnog tkiva i mišića, kao što su: adenzin, adenzin-trifosfat (ATP), serotonin [*5-hydroxytryptamine* (5-HT)], azot-monoksid [*nitric oxide* (NO)], joni kalcijuma (Ca²⁺), kortikotropin-oslobađajući hormon [*corticotropin-releasing hormone* (CRH)], razni neurotransmiteri i citokini, uključujući i endogene opijate, koji vezivanjem za svoje receptore dovode do smanjenja i otklanjanja bola.

Utvrđeno je da su efekti akupunkture, elektroakupunkture i moksibustije posredovani supresijom oksidativnog stresa i apoptoze, regulacijom metabolizma, direktnom i indirektnom modulacijom zapaljenja, što čini osnovu svih mehanizama njihovog analgetičkog delovanja.

Ključne reči: akupunktura, elektroakupunktura, moksibustija, mehanizmi, analgezija

POSSIBILITIES OF TREATING PAIN IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES

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Pain is the leading symptom of inflammatory rheumatic diseases, which is directly related to function and quality of life. The mechanism of pain in these diseases has not been clarified to the same extent as the mechanism of inflammation and autoimmunity. Control of inflammation and regulation of autoimmunity are therapeutically defined in contrast to optimal pain management. This is partly why there is an increase in the abuse of opioids and narcotics. Recent research in animals and molecular biology has led to significant advances in the understanding of pain in inflammatory rheumatic diseases. The evaluation of molecular mediators and translational studies can help define therapeutic targets for the treatment of arthritic pain. Acute pain in rheumatic diseases is most often treated with disease-modifying DMARDs, anti-inflammatory drugs and analgesics. Chronic pain, however, is much more difficult to treat and often requires a multidisciplinary approach to the disease. Treatment usually begins with medications (classic disease-modifying drugs csDMARDs, biological disease-modifying drugs bDMARDs, target disease-modifying drugs tsDMARDs, anti-inflammatory drugs, analgesics with different mechanisms of action). If drug therapy is not effective enough, we apply more invasive methods, such as central and peripheral nerve blocks, blockades of the so-called trigger points, etc. Therapeutic goals for patients with pain in inflammatory rheumatic diseases are multidimensional, involving primarily the rehabilitation of the inflammatory process that leads to it, eliminating pain, improving functionality, returning to work activities, as well as reducing the need for medicines and the use of the health system. The use of drugs in the treatment of pain in inflammatory rheumatic patients is long-term and can cause a problem in the control of chronic pain due to uncritical and long-term use of drugs with numerous adverse reactions. The importance of physical agents (laser therapy, magnetotherapy, transcutaneous electrostimulation, diadynamic currents, interference currents, galvanic current, electrophoresis, ultrasound, sonophoresis) in the therapy of chronic pain is great because it reduces the need for medication, 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. Emotional skills building can help overcome stress, which is associated with health conditions and pain intensity. A holistic approach to treatment is necessary, including, in addition to pharmacological therapy, education in the direction of an adequate way of life, healthy nutrition, and the application of adequate adapted physical activity.

Key words: *pain, rheumatology, inflammatory diseases*

MOGUĆNOSTI LEČENJA BOLA KOD PACIJENATA SA ZAPALJENJSKIM REUMATSKIM BOLESTIMA

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Bol je vodeći simptom zapaljenjskih reumatskih bolesti i direktno je povezan sa funkcijom I kvalitetom života. Mehanizam nastanka bola u ovim bolestima nije razjašnjen onoliko koliko je razjašnjen mehanizam nastanka inflamacije i autoimunosti. Kontrola inflamacije i regulacija autoimunosti terapijski su definisane, za razliku od optimalnog upravljanja bolom; zbog toga je delimično prisutan porast zloupotrebe opioida i narkotika. Novija istraživanja na životinjama i u molekularnoj biologiji dovela su do značajnog napretka u razumevanju bola u zapaljenjskim reumatskim bolestima. Procena molekularnih medijatora i translacione studije mogu pomoći da se definišu terapijski ciljevi za lečenje artritisanog bola. Akutni bol u reumatskim bolestima najčešće se leči lekovima koji modifikuju bolest DMARDs, antiinflamatornim lekovima i analgeticima. Hronični bol je, međutim, mnogo teži za lečenje i često zahteva multidisciplinarni pristup bolesti. Lečenje se obično započinje medikamentima (klasičnim lekovima koji modifikuju bolest csDMARDs, biološkim lekovima koji modifikuju bolest bDMARDs, target lekovima koji modifikuju bolest tsDMARDs, antiinflamatornim lekovima, analgeticima različitog mehanizma dejstva). Ukoliko medikamentna terapija nije dovoljno efikasna, pristupa se invazivnijim metodama, kao što su centralni i periferni nervni blokovi, blokade tzv. trigger tačaka itd. Terapijski ciljevi za bolesnike sa bolom u zapaljenjskim reumatskim bolestima su multidimenzionalni – prvenstveno podrazumevaju saniranje inflamatornog procesa, što vodi ka otklanjanju bola, poboljšanju funkcionalnosti, povratku radnim aktivnostima, kao i smanjenju potrebe za lekovima i korišćenjem zdravstvenog sistema. Primena lekova u terapiji bola zapaljenjskih reumatskih bolesnika je dugotrajna, te se može javiti problem u kontroli hroničnog bola zbog nekritične i dugotrajne upotrebe lekova sa brojnim neželjenim reakcijama. Značaj fizikalnih agenasa (laseroterapija, magnetoterapija, transkutana elektrostimulacija, dijadinamičke struje, interferentne struje, galvanska struja, elektroforeza, ultrazvuk, sonoforeza) u terapiji hroničnog bola je velik jer smanjuje potrebu za lekovima, a nema nikakvih nuspojava. Na raspolaganju su i različite alternative metode, koje takođe mogu biti od pomoći: tai či vežbanje, joga, akupunktura, terapija muzikom i umetnošću, terapija kućnim ljubimcima, psihoterapija, masaža, meditacija. Izgradnja emocionalnih veština može pomoći da se prevaziđe stres, koji je povezan sa zdravstvenim stanjem i intenzitetom bola. Neophodan je holistički pristup lečenju, koji pored farmakološke terapije, uključuje edukaciju u vezi sa adekvatnim načinom življenja, zdravom ishranom, primenom adekvatne adaptirane fizičke aktivnosti.

Ključne reči: *bol, reumatologija, zapaljenjske bolesti*

ADRESSING LOW BACK PAIN: THE BENEFITS OF INTEGRATING PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENT

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Low back pain (LBP) is a global health concern that affect millions, putting a strain on the healthcare systems.

This work aims to distill the key recommendations from the most influential guidelines. The method involved an analysis of the LBP management, recommended by clinical guidelines from the following authorities: the National Institute for Health and Care Excellence (NICE), the American College of Physicians (ACP), the Dutch Society for Physical Therapy, and the International Association for the Study of Pain (IASP).

Guidelines converge on the pivotal role of non-pharmacological interventions (exercise therapy, physical therapy, and psychological interventions, etc.) as the primary strategy for LBP management. Regarding pharmacological treatment, consensus exists, however, with nuances. Acetaminophen (paracetamol) is generally discouraged as a standalone treatment option for LBP. Non-steroidal anti-inflammatory drugs (NSAIDs) receive endorsement, albeit cautiously, primarily for short-term use in cases of acute exacerbations or moderate to severe pain. Emphasis is placed on employing the lowest effective NSAID dose for the shortest duration. Opioids are unanimously discouraged as a first-line treatment for LBP, particularly for the chronic form, due to addiction risks and side effects. Their consideration is reserved for exceptional cases where alternative treatments have proven ineffective. Muscle relaxants are an option for short-term relief of acute LBP linked to muscle spasms, though the majority of guidelines advise against their routine or prolonged use due to concerns about dependence and side effects.

In conclusion, healthcare professionals must remain aware of the evolving nature of medical knowledge and the latest information in LBP management. A consensus among leading guidelines advocates non-pharmacological interventions as a first-line approach, fostering effective, patient-centered care, cost reduction, and enhanced patient well-being. Adherence to evidence-based guidelines represents a collective effort to alleviate the LBP burden on patients and society, ultimately enhancing healthcare outcomes and quality of life.

Key words: *low back pain, guidelines, non-pharmacological approach, multidisciplinary, evidence-based medicine*

BOLU DONJEMDELULEĐA: INTEGRACIJAFARMAKOLOŠKOG INEFARMAKOLOŠKOGPRISTUPA

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Bol u donjem delu leđa (LBP) predstavlja veliki zdravstveni problem, pogađa milione ljudi i opterećuje zdravstveni sistem.

Ovaj rad ima za cilj izdavanje ključnih preporuka iz najuticajnijih smernica za lečenje bola u donjem delu leđa. Rad je zasnovan na analizi tretmana LBP-a, preporučenih u kliničkim smernicama sledećih udruženja: Nacionalni institut za zdravlje i brigu o kvalitetu (NICE), Američki koledž lekara (ACP), Holandsko društvo za fizikalnu terapiju, Međunarodno udruženje za proučavanje bola (IASP).

Smernice su saglasne po pitanju ključne uloge nefarmakoloških intervencija (terapeutske vežbe, fizikalna terapija, psihološke intervencije itd.) kao primarnih strategija za tretman LBP-a. Što se tiče farmakološkog tretmana, postoji saglasnost, ali uz manje razlike. Acetaminofen (paracetamol) se generalno ne preporučuje kao samostalna opcija za lečenje LBP-a. Nesteroidni antiinflamatorni lekovi (NSAIL) preporučuju se, uz oprez, pre svega za kratkotrajnu upotrebu u slučajevima akutnih pogoršanja ili umerenih do jakih bolova. Naglasak je na primeni minimalne efikasne doze NSAIL-a tokom najkraćeg mogućeg perioda. Opioidi se ne preporučuju kao prva linija tretmana za LBP, posebno za hronični oblik, zbog rizika od zavisnosti i neželjenih efekata. Njihova primena je rezervisana za izuzetne slučajeve gde su se ostali tretmani pokazali kao neefikasni. Miorelaksansi mogu biti upotrebljeni za smanjenje tegoba akutnog LBP-a povezanog sa mišićnim spazmom. Ipak, većina smernica ne savetuje njihovu rutinsku ili dugotrajnu upotrebu zbog potencijalnog razvoja zavisnosti i drugih neželjenih efekata.

Zdravstveni radnici moraju biti svesni da naše znanje o tretmanu LBP-a konstantno evoluira. Vodeće smernice su saglasne i promovišu nefarmakološke intervencije kao prvu terapijsku liniju, naglašavajući efikasnu, ka pacijentima usmerenu negu, smanjenje troškova i unapređenje dobrobiti pacijenata. Smernice zasnovane na dokazima predstavljaju najefikasnije oruđe za smanjenje tereta koji LBP donosi kako pacijentima, tako i društvu.

Ključne reči: bol u donjem delu leđa, smernice, nefarmakološki pristup, multidisciplinarno, medicina zasnovana na dokazima

HOW TO "MEASURE" PAIN DURING INTEGRATIVE PAIN CARE?

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The key condition for the successful control of all pain conditions is a comprehensive, thorough pain assessment. The goals of pain measurement are determining the presence of pain, defining the localization of all painful places, measuring the intensity and other characteristics of pain, as well as evaluating the effectiveness of therapy. Screening for the presence of pain begins with determining the relevant factors of the patient's general condition, taking a detailed history and obtaining information about the previously applied diagnostic and therapeutic procedures. Through a conversation with the patient, the doctor learns all the necessary information about the pain quality, etiology, duration, localization, distribution, intensity, and also the quality, frequency of pain onset, and factors that increase or decrease the intensity of pain. All of the above can help in establishing the diagnosis of painful conditions, however, for the establishment of the final diagnosis, communication between the doctor and the patient is very important, where the doctor helps the patient describe in more detail the quality and intensity of his painful experience. Pain scales in medicine are used to make it easier for patients to describe the different types of pain they feel. That is why pain scales are considered a special kind of "tool" for describing the pain experienced by the patient. Pain scales can be designed to measure only pain intensity, and then they are one-dimensional scales such as: numerical, visual analog, and verbal scales. For research purposes, more complex, multidimensional scales are generally used, which, in addition to measuring the intensity of pain, serve to assess other characteristics of pain, such as: different qualities of pain (for example, piercing, sharp, dull, etc.), possible propagation, the effect of pain on the function of the organism as a whole, the effect of previous and current analgesic therapy, etc. The condition of the patient and the stage of the disease also significantly influence the choice of pain scale. Each medical institution is obliged to have its own pain measurement scales, which must first be standardized and validated for the appropriate population.

Key words: *pain, physical examination, assessment, one-dimensional scales, multidimensional scales*

KAKO „IZMERITI“ BOL TOKOM INTEGRATIVNOG ZBRINJAVANJA BOLA?

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Dobra procena bola jeste ključan uslov za uspešnu kontrolu svih bolnih stanja. Merenje bola sprovodi se sa ciljem utvrđivanja prisustva bola, definisanja lokalizacija svih bolnih mesta, merenja intenziteta i drugih karakteristika bola, kao i procene efikasnosti terapije. Provera prisustva bola počinje utvrđivanjem relevantnih faktora opšteg stanja pacijenta, uzimanjem detaljne anamneze i informacija o prethodno primenjenim dijagnostičkim i terapijskim procedurama. U razgovoru sa pacijentom lekar saznaje sve neophodne informacije o kvalitetu bola, etiologiji, trajanju, lokalizaciji, distribuciji, intenzitetu, kvalitetu, učestalosti prodora bola i faktorima koji pojačavaju ili smanjuju intenzitet bola. Sve prethodno navedeno može pomoći u postavljanju dijagnoze bolnih stanja. Međutim, za postavljanje konačne dijagnoze veoma je važna komunikacija između lekara i pacijenta; lekar pritom pomaže pacijentu da detaljnije opiše kvalitet i intenzitet svog bolnog iskustva. Skale bola se u medicini koriste kako bi pacijenti što lakše opisali različite vrste bola koji osećaju. Stoga, skale bola smatraju se posebnom vrstom „alata“ za opis bola koji pacijent doživljava. Skale bola mogu biti dizajnirane za merenje samo intenziteta bola – u tom slučaju radi se o jednodimenzionalnim skalama, kakve su numeričke, vizuelno-analogne i verbalne skale. U istraživačke svrhe uglavnom se koriste složenije, multidimenzionalne skale, koje osim za merenje jačine bola služe i za procenu drugih karakteristika bola, kao što su različiti kvaliteti bola (npr. probadajući, oštar, tup itd.), eventualna propagacija, efekat bola na funkciju organizma u celini, efekat prethodne i sadašnje analgetske terapije i slično. Stanje pacijenta i stadijum bolesti takođe značajno utiču na izbor skale bola. Svaka medicinska ustanova u obavezi je da ima svoje skale za merenje bola, koje prethodno moraju biti standardizovane i validirane za odgovarajuću populaciju.

Ključne reči: bol, fizikalni pregled, procena, jednodimenzionalne skale, multidimenzionalne skale

PHANTOM LIMB PAIN – A CASE REPORT

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Phantom limb pain (PLP) is a common problem that occurs after limb amputation. It is described as severe pain in the missing limb. Pathogenetic mechanisms are still not clearly defined, although research results increasingly shift the paradigm of proposed mechanisms towards the theory of neuropathic pain. The treatment of PLP is complex and involves a multidisciplinary approach. The purpose of the case presentation is to point out the complexity of the therapeutic approach to patients with PLP. The case of a 74-year-old male patient with the symptoms of phantom pain, occurring ten years after traumatic amputation of the right arm, is presented. The patient stepped on a mine in a minefield, losing his left leg above the knee and his entire right arm up to the shoulder joint. Immediately after the surgical intervention, phantom limb syndrome and PLP in the area of the non-existent right hand arose. Despite a series of therapeutic options in the postoperative course, which included high doses of morphine, the pain persisted. During the next ten years, the patient complained of constant "unbearable" pain in the form of a combination of burning and sharp pain in the non-existent distal part of the right arm. The intensity of the maximum pain was indicated by a score of 9 on the numerical pain rating scale. In the mentioned period, various therapeutic options were applied, which did not give results (non-steroidal anti-rheumatic drugs, tricyclic antidepressants, carbamazepine, fentanyl patch, physical procedures, acupuncture). The introduction of Pregabalin into the therapy with a gradual titration to a dose of 375 mg led to an almost complete reduction of pain. After one year, with a maintenance dose of 150 mg per day, satisfactory pain control was achieved. To conclude, PLP therapy is a challenge for both patients and doctors and requires an individual approach to each individual patient in order to find the most effective therapeutic option.

Key words: *phantom pain, neuropathic pain, numeric pain rating scale*

FANTOMSKI BOL – PRIKAZ SLIČAJA

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Sindrom fantomskog bola (FB) čest je problem koji nastaje nakon amputacije ekstremiteta. Opisuje se kao jak bol u delu ekstremiteta koji nedostaje. Patogenetski mehanizmi još uvek nisu jasno definisani, mada rezultati istraživanja tokom proteklih decenija sve više pomeraju paradigmu predloženih mehanizama ka teoriji neuropatskog bola. Lečenje FB-a je kompleksno i podrazumeva multidisciplinarni pristup sa farmakološkim i nefarmakološkim terapijskim modalitetima. Prikaz slučaja upravo ima za cilj da ukaže na kompleksnost i zahtevnost terapijskog pristupa pacijentima sa fantomskim bolom, kao i na probleme sa kojima se u svakodnevnoj kliničkoj praksi susreću kako pacijenti, tako i njihovi lekari. Prikazan je slučaj pacijenta muškog pola, starog 74 godine, sa simptomima fantomskog bola deset godina nakon traumatske amputacije desne ruke. Pacijent je nagazio na minu u minskom polju, pri čemu je izgubio levu nogu do iznad kolena i celu desnu ruku do ramenog zgloba. Neposredno nakon hirurške intervencije nastaje sindrom fantomskog uda i fantomskog bola u predelu nepostojeće desne ruke. Uprkos nizu terapijskih opcija u postoperativnom toku, koje su podrazumevale i visoke doze morfina, bol se održavao. Tokom narednih deset godina, pacijent se žalio na konstantan „nepodnošljiv” bol u vidu kombinacije žarećeg i oštrog bola u nepostojećem distalnom delu desne ruke. Intenzitet maksimalnog bola označavao je ocenom 9 na Numeričkoj skali bola. U navedenom periodu primenjivane su različite terapijske opcije (nesteroidni antireumatici, triciklični antidepresivi, karbamazepin, fentanilski flaster, fizikalne procedure, akupunktura), ali one nisu dale rezultate. Uvođenje pregabalina u terapiju, sa postepenim titriranjem do doze od 375 mg, dovelo je do gotovo potpune redukcije bola. Nakon godinu dana, sa dozom održavanja od 150mg dnevno, postignuta je zadovoljavajuća kontrola bola, sa prosečnom ocenom 3 na Numeričkoj skali bola. Može se zaključiti da terapija FB-a predstavlja izazov i za pacijente i za lekare i da zahteva individualni pristup svakom pojedinačnom pacijentu kako bi se pronalažla najefikasnija terapijska opcija.

Ključne reči: *fantomski bol, neuropatski bol, Numerička skala bola*

PERCUTANEOUS LASER DISC DECOMPRESSION

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Lumbar radicular pain is defined as the pain in the lumbar spine with spread to the lower extremities. In modern society, it represents a major public health, social and economic problem, and it is one of the most common reasons why patients visit a doctor. A modern, sedentary lifestyle, excess body weight and lack of physical activity lead to an increase in the incidence of lumbar radicular pain. It is estimated that around 70–85% of the world's population experiences pain in the lumbar spine at least once during their lifetime. The most common cause of lumbar radicular pain is intervertebral disc herniation. Rheumatic and degenerative diseases are more common in older patients, while in younger people, the most common cause is overloading of the spine, incorrect posture and genetic predisposition. All of the above causes lead to the weakening of the connective intervertebral disc, which results in disc herniation.

In order to avoid systemic and unwanted effects of analgesics, anesthesia and surgical procedures, minimally invasive procedures are increasingly used in the treatment of lumbar radicular pain. Epidural administration of steroids and local anesthetic (ESI) and percutaneous laser disc decompression (PLDD) are some of these methods.

PLDD is performed under local anesthesia under the control of a fluoroscope to confirm the placement of the needle in the intervertebral disc. The laser energy leads to the heating of the tissue of the nucleus pulposus, which leads to the evaporation of a small volume of water inside the disc. Viewing the disc as a closed hydraulic system, a small decrease in the water content within the disc leads to a disproportionate decrease in intradiscal pressure, resulting in retraction of the herniated disc. Thermal energy also leads to protein denaturation, which causes structural changes and thus prevents further retention of water in the disc, and a stable scar is created at the point of laser action. Indications for PLDD are radicular pain in the lower extremities, disc protrusion confirmed by imaging studies without disc extrusion, failed non-invasive treatment methods, and preservation of 75% of the disc height. Rare but possible complications are septic and aseptic discitis, spondylodiscitis and pain caused by a free fragment.

Percutaneous laser disc decompression is a minimally invasive procedure with a low complication rate, high success rate and quick recovery. Proper selection of patients gives good results and can delay and in some cases be an alternative to surgery.

Key words: *herniated disc, laser, percutaneous discectomy, radiculopathy*

PERKUTANA LASERSKA DEKOMPRESIJADISKA

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Lumbalna radikularna bol definira se kao bol u lumbalnom dijelu kralježnice sa širenjem u donjeekstremitete. U modernom društvu predstavlja veliki javnozdravstveni, socijalni i ekonomski problem, te je jedan od najčešćih razloga zbog kojih se pacijenti javljaju liječniku. Moderan, sjedilački način života, te prekomjerna tjelesna težina i manjak tjelesne aktivnosti dovode do porasta incidencije lumbalne radikularne boli. Procjenjuje se da oko 70% do 85% svjetske populacije barem jednom tijekom svog života doživi bol u lumbalnom dijelu kralježnice. Najčešći uzrok lumbalne radikularne boli jeste hernija intervertebralnog diska. Reumatske i degenerativne bolesti češće su kod starijih bolesnika, dok je kod mlađih osoba uzrok najčešće preopterećenje kralježnice, nepravilno držanje ili genetska predispozicija. Svi navedeni uzroci dovode do slabljenja vezivnog intervertebralnog diska, što rezultira hernijom diska.

Kako bi se izbjegli sustavni i neželjeni učinci analgetika, podvrgavanje anesteziji i operativni zahvati, u liječenju lumbalne radikularne boli sve se više primjenjuju minimalno invazivni postupci. Epiduralna primjena steroida i lokalnog anestetika (ESI) i perkutana laserska dekompresija diska (PLDD) neke su od tih metoda.

PLDD se izvodi u lokalnoj anesteziji pod kontrolom fluoroskopa zbog potvrde plasiranja igle u intervertebralni disk. Laserska energija dovodi do zagrijavanja tkiva nukleusa pulposusa, što dovodi do evaporacije malog volumena vode unutar diska. Ako se disk promatra kao zatvoreni hidraulički sustav, zapaža se da malo smanjenje sadržaja vode unutar diska dovodi do disproporcionalnog smanjenja intradiskalnog tlaka, što rezultira retrakcijom hernije diska. Toplinska energija dovodi i do denaturacije proteina, što uzrokuje strukturne promjene, te na taj način sprječava daljnje zadržavanje vode u disku, a na mjestu djelovanja lasera stvara se stabilni ožiljak. Indikacije za PLDD su radikularna bol u donjim ekstremitetima, protruzija diska potvrđena slikovnim pretragama bez ekstruzije diska, neuspjele neinvazivne metode liječenja, te očuvanost 75% visine diska. Rijetke ali moguće komplikacije jesu septički i aseptički discitis, spondilodiscitis i bol prouzročena slobodnim fragmentom.

Perkutana laserska dekompresija diska je minimalno invazivni zahvat s niskom stopom komplikacija, visokom stopom uspješnosti i brzim oporavkom. Pravilan odabir pacijenata daje dobre rezultate i može odgoditi operaciju, a u nekim slučajevima biti i njena alternativa.

Ključne reči: *hernija diska, laser, perkutana diskektomija, radikulopatija*

EFFECT OF MAGNESIUM ON PAIN AND NEUROINFLAMMATION

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Magnesium is a mineral that is important for many physiological processes in the body. It is used in the treatment of preeclampsia, certain heart rhythm disorders. Recent research shows that magnesium plays a significant role in the treatment of pain, inflammation, depression, anxiety, etc. Magnesium has numerous mechanisms of action that may be important for the development of neuroinflammation. It is a blocker of N-methyl-D aspartate (NMDA) receptors and a modulator of the activities of various ion channels and neurotransmitters. Magnesium is a blocker of calcium channels; it also modulates the activity of various ion channels, such as of vanilloid (V1 and V4) and ankyrin (A1) channels for transient receptor potentials. The aforementioned mechanisms, especially the activation and sensitization of NMDA receptors, have a significant role in the occurrence of pain. By the modulation of nitric oxide (NO) signaling pathway, magnesium affects pain and inflammatory edema. It prevents mast cell degranulation. Research shows that magnesium potentiates the analgesic effect of opioids. Although the results of clinical studies of the effect of magnesium on pain are somewhat inconsistent, the analgesic effect of magnesium depends on the type of pain and protocol of use.

Key words: *magnesium, adjuvant analgesics, anti-inflammatory effect*

DEJSTVO MAGNEZIJUMA NA BOL I NEUROINFLAMACIJU

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Magnezijum je mineral značajan za mnoge fiziološke procese u organizmu. Koristi se u terapiji preklampsije, određenih poremećaja srčanog ritma. Novija istraživanja pokazuju da magnezijum ima značajnu ulogu u bolu, inflamaciji, depresiji, anksioznosti itd. Magnezijum ima brojne mehanizme dejstva koji mogu biti značajni za razvoj neuroinflamacije. Magnezijum je blokator N-metil-D-aspartatnih (NMDA) receptora, modulator aktivnosti različitih jonskih kanala i neurotransmitera. Blokator jekalcijumskih kanala, a moduliše i aktivnost različitih jonskih kanala, npr. vaniloidnih (V1 i V4) i ankirinskih (A1) kanala za prolazne receptorske potencijale. Pomenuti mehanizmi, a posebno aktivacija i senzitivizacija NMDA receptora, imaju značajnu ulogu u razvoju bola. Magnezijum modulacijom azot-oksida (NO) signalnog puta utiče na bol i inflamatorni edem. Ovaj mineral takođe sprečava degranulaciju mastocita. Istraživanja pokazuju da magnezijum u kombinaciji sa opioidima ostvaruje sinergističku interakciju, potencirajući njihov analgetski efekat. Iako su rezultati kliničkih studija o dejstvu magnezijuma na bol donekle neusaglašeni, analgetski efekat magnezijuma zavisi od vrste bola i protokola primene.

Ključne reči: magnezijum, adjuvantni analgetici, antiinflamatorno dejstvo

NEURAL PROLOTHERAPY IN THE TREATMENT OF PERINEAL PAIN

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Compressive neuropathies are serious medical conditions caused by compression, stretching or irritation of the peripheral nerves. Neuroinflammation, defined as the production of inflammatory cytokines, is not only a key aspect of neuropathic pain but also a feature of chronic nerve compression. The most common causes of perineal pain are pudendal and obturator neuropathy.

Pudendal neuropathy represents the neuropathic pain component of the syndrome caused by damage to the pudendal nerve. It is usually a bilateral process with characteristic perineal pain that worsens when sitting. It can occur as sciatic pain, pain in the medial part of the thigh, pain after ejaculation and sexual intercourse. Other symptoms may include: erectile dysfunction, urinary incontinence, dyspareunia, etc.

Pudendal neuralgia affects 4% of all pain patients. The incidence of pudendal neuropathy is thought to be higher because it often goes unrecognized or misdiagnosed.

The most common causes can be: prolonged sitting, injuries during childbirth, repetitive hip flexion, pelvic trauma and surgery, malignant and benign pelvic changes, etc.

Obturator neuropathy represents the neuropathic pain component of the syndrome caused by damage to the obturator nerve. It is even less often recognized and explained in the literature because it most often remains unrecognized. The incidence is 0.6-2%.

The clinical picture includes inguinal pain that radiates to the front and inner side of the thigh to the inner side of the knee. Other symptoms may be tingling and allodynia in the region of innervation. In over 90% of patients, the pain intensifies during walking and sports activities. Weakness, atrophy, and denervation of the hip adductor muscles may occur.

The diagnosis of pudendal and obturator neuropathy is clinical as there are no specific tests. Nantes criteria for pudendal neuropathy, obturator sign, skin-rolling test, and pudendal and obturator nerve infiltration are used to confirm the diagnosis.

Neural prolotherapy in the treatment of pudendal and obturator neuropathy leads to hyperpolarization of C fibers via the Na/K pump, increase in K⁺ conductivity, decrease in excitability, and inhibition of TrpV1 receptors, which modulates neural activity and inflammatory reaction and helps in restoring the normal nerve function.

Key words: *perineal pain, pudendal neuropathy, obturator neuropathy*

NEURALNA PROLOTERAPIJA U TRETMANU PERINEALNOG BOLA

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Kompresivne neuropatije predstavljaju ozbiljna zdravstvena stanja izazvana kompresijom, istezanjem ili iritacijom perifernih nerava. Neuroinflamacija, definisana kao proizvodnja inflamatornih citokina, nije samo ključni aspekt neuropatskog bola već i karakteristika hronične kompresije nerva.

Najčešći uzroci perinealnog bola su pudendalna i opturatorna neuropatija.

Pudendalna neuropatija predstavlja neuropatsku bolnu komponentu sindroma uzrokovanog oštećenjem pudendalnog nerva. Obično je to bilateralni proces sa karakterističnim perinealnim bolom, koji se pogoršava pri sedenju. Može se javiti kao išijadični bol, bol u medijalnom delu butine, bol nakon ejakulacije i seksualnog odnosa. Ostali simptomi mogu uključiti erektilnu disfunkciju, urinarnu inkontinenciju, dispareuniju i dr.

Pudendalna neuralgija pogađa 4% svih pacijenata sa bolom. Smatra se da je incidencija pudendalne neuropatije veća, jer često ostaje neprepoznata ili pogrešno dijagnostikovana.

Najčešći uzroci mogu biti dugotrajno sedenje, povrede pri porođaju, ponavljajuća fleksija kuka, traume i operacije karlice, maligne i benigne promene karlice i dr.

Opturatorna neuropatija predstavlja neuropatsku bolnu komponentu sindroma uzrokovanog oštećenjem opturatornog nerva; još je ređe prepoznata i u literaturi objašnjena, jer najčešće ostaje neprepoznata. Incidenca je od 0,6% do 2%.

Klinička slika podrazumeva ingvinalni bol koji iridira u prednju i unutrašnju stranu butine do unutrašnje strane kolena. Ostali simptomi mogu biti peckanje i alodinija u regiji inervacije. Kod više od 90% pacijenata bol se pojačava u toku hodanja i sportskih aktivnosti. Mogu se javiti slabost, atrofija i denervacija mišića aduktora kuka.

Budući da ne postoje specifični testovi, dijagnoza pudendalne i opturatorne neuropatije je klinička.

Nantovi kriterijumi za pudendalnu neuropatiju, opturatorni znak, *skin-rolling* test i infiltracija pudendalnog i opturatornog nerva koriste se za potvrdu dijagnoze.

Neuralna proloterapija u tretmanu pudendalne i opturatorne neuropatije dovodi do hiperpolarizacije C vlakana preko Na/K pumpe, povećanja K⁺ provodljivosti i smanjenja ekscitabilnosti, inhibicije TrpV1 receptora, što modulira neuralnu aktivnost i inflamatornu reakciju i pomaže u obnavljanju normalne nervne funkcije.

Ključne reči: *perinealna bol, pudendalna neuropatija, obturatorna neuropatija*

CASE REPORTS OF PHARMACOTHERAPY OF CANCER PAIN FROM ONCOLOGY PRACTICE

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In our daily work with oncology patients, we often encounter the previously prescribed and initiated pharmacotherapy of cancer pain by general medicine doctors, which is often inadequate and does not represent an adequate pharmacotherapeutic and individual approach to the solution of this pharmacotherapeutic problem. The lecture shows the case reports of three oncology patients with inadequate pharmacotherapy previously prescribed by general medicine doctors to relieve their cancer pain, and it is a presentation of the most common mistakes we encounter in everyday oncology practice. The aim of the lecture was to present an adequate pharmacotherapeutic solution for the relief of pain in these patients and to monitor their pain through several control examinations after the correction of the original pharmacotherapy.

The first case report is the presentation of an inadequate choice of pharmaceutical opioid formulation (transdermal) against the patient's general condition, after which he was switched to an adequate oral formulation and followed through subsequent control examinations. The second case report presents an inadequate prescription of opioids due to the non-prescription of pharmacotherapy for pain relief, and as a result, there was a higher dose of long-acting opioids, which resulted in the appearance of side effects, so this patient received pain relief therapy, the basal long-acting analgesia was corrected, side effects were resolved, and the patient was monitored through subsequent control examinations. The third case report presents a patient who had only the nociceptive component of the pain treated, while the neuropathic component of pain was not considered and adequate pharmacotherapy for his mixed cancer pain was not prescribed. The patient was prescribed adequate co-analgesic pharmacotherapy for the neuropathic component of pain and was followed through subsequent control examinations.

It is necessary to adapt pharmacotherapy to each patient individually within the framework of a personalized pharmacotherapeutic approach to the patient and in accordance with their general condition, to adequately relieve all components of their cancer pain, to predict possible side effects and prevent them, and to inform the patient about the whole procedure in order to have adequate compliance, adequate relief of cancer pain, and the absence of pharmacotherapy side effects.

Key words: *pharmacotherapy, cancer pain, compliance, side effects*

PRIKAZI SLUČAJEVA FARMAKOTERAPIJE KANCERSKOG BOLA IZ ONKOLOŠKE PRAKSE

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U svakodnevnom radu sa onkološkim pacijentima često se srećemo sa farmakoterapijom kancerskog bola koju su prethodno propisali i započeli lekari opšte medicine, ali to neretko nije adekvatan farmakoterapijski i individualni pristup rešenju ovog farmakoterapijskog problema. Predstavljaju se slučajevi tri onkološka pacijenta sa prethodno propisanom neadekvatnom farmakoterapijom za kupiranje kancerskog bola od strane lekara opšte medicine kao prikaz najčešćih grešaka sa kojima se srećemo u svakodnevnoj onkološkoj praksi. Cilj predavanja jeste da prikaže adekvatno farmakoterapijsko rešenje za kupiranje bola ovih pacijenata i proprati njihov bol kroz nekoliko prikazanih kontrola nakon korekcije prvobitne farmakoterapije.

Prvi prikaz slučaja jeste izbor neadekvatne farmaceutske formulacije opioida (transdermalna) naspram opšteg stanja pacijenta, te je on preveden na adekvatnu peroralnu formulaciju i praćen kroz naredne kontrole. Drugi prikaz slučaja predstavlja neadekvatno propisavanje opioida usled nepropisivanja farmakoterapije za proboj bola, pa je posledično bila veća doza dugodelujućeg opioida usled koje je došlo do pojave neželjenih efekata; ovom pacijentu je uvedena terapija za proboj bola, korigovana je bazalna dugodelujuća analgezija, rešeni su neželjeni efekti i praćen je kroz naredne kontrole. Treći prikaz slučaja predstavlja pacijenta koji ima kupiranu samo nociceptivnu komponentu bola, dok neuropatska komponenta bola nije sagledana i nije propisana adekvatna farmakoterapija njegovog mešovitog bola; njemu je propisana adekvatna koanalgetska farmakoterapija za neuropatsku komponentu bola i praćen je kroz naredne kontrole.

Neophodno je prilagoditi farmakoterapiju svakom pacijentu ponaosob u okviru personalizovanog farmakoterapijskog pristupa pacijentu i u skladu sa njegovim opštim stanjem, adekvatno kupirati sve komponente njegovog kancerskog bola, predvideti moguće neželjene efekte i prevenirati ih i sve to objasniti pacijentima kako bi se postigla adekvatna komplijansa, adekvatno kupirao njihov kancerski bol, a neželjeni efekti farmakoterapije izostali.

Ključne reči: farmakoterapija, kancerski bol, komplijansa, neželjeni efekti

A PATH THAT LEADS TO MORE SUCCESSFUL CONTROL OF MALIGNANT PAIN

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Pain in malignant disease is a reality, however, it is not an inevitability that needs to be reconciled with. It is important to change the attitude towards cancer pain, eliminate the fear of medication, make medicaments accessible, warn about their proper use, and solve regulatory problems, costs, and compensation for effective treatment.

The pain is still in the sphere of decreased optimal control. Some patients are treated inappropriately (due to the doctors' ignorance and their negative approach to pain control, and the barriers they make themselves). On the other hand, a certain number of patients will not respond satisfactorily to the existing analgesic modalities, due to the complex mechanisms underlying the pain syndrome, and other individual factors.

Significant progress in pain control can be divided into two categories: 1) The development of non-opioid drugs with various mechanisms of activity that can further reduce pain and improve the analgesic reaction when added to opioids; 2) The use of the existing opioids through the development of new drugs, new administration systems and new combinations. Both of these categories aim to solve complex clinical situations, more successful analgesia by various mechanisms, and reduce side effects by limiting large doses of opioids.

A therapeutic approach based on the mechanism of pain genesis presents the key to successful prevention and control of malignancy-induced chronic pain. Recognizing, comprehending, and focusing on multiple mechanisms that are involved in chronic pain syndrome aims to expand rather than replace the traditional treatment. Such a method primarily considers diagnosing and mitigating potential damage with the empirical use of analgesics. This approach involves a combination of specific pharmacotherapy, psychotherapy, physical rehabilitation, and integrative medicine methods (acupuncture, massage, meditation, and behavior modification), in accordance with the guidelines (SIO and ASCO) that emphasize a multidisciplinary approach to the treatment plan of chronic pain conditions, aimed at each patient individually (personalization of therapy).

The correct approach to the treatment of pain is a complex problem that involves careful assessment of the qualitative and quantitative properties of pain, their constant evaluation during the treatment and adaptation of the therapy to the stage of the disease.

Key words: *cancer pain, multimodal therapy, integrative approach to treatment*

PUT KOJI VODI KA USPEŠNIJOJ KONTROLI MALIGNOG BOLA

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Bol kod maligne bolesti jeste realnost, ali ne i neotklonjiva neminovnost s kojom se treba pomiriti. Važno je promeniti stav prema kancerskom bolu i ukloniti strah od medikacije; takođe, lekove treba učiniti pristupačnim i upozoravati na njihovu pravilnu upotrebu. Potrebno je i rešiti probleme u vezi sa regulativom i troškovima, kao i nadoknade za efektivno lečenje.

Bol je još uvek u sferi umanjene optimalne kontrole. Pojedini pacijenti se, zbog neznanja lekara i negativnog pristupa kontroli bola, ali i barijera koje postavljaju oni sami, neodgovarajuće leče; s druge strane, određen broj pacijenata neće zadovoljavajuće reagovati na postojeće analgetske modalitete, što zbog složenih mehanizama koji su u osnovi bolnog sindroma, što zbog drugih individualnih faktora.

Značajan napredak u kontroli bola može se podeliti u dve kategorije: 1) razvoj neopioidnih lekova sa različitim mehanizmima delovanja koji mogu dodatno smanjiti bol i poboljšati analgetsku reakciju kada se dodaju opioidima; 2) upotreba postojećih opioida kroz razvoj novih lekova, novih sistema davanja i novih kombinacija. Obe ove kategorije usmerene su na rešavanja složenih kliničkih situacija, na uspešnije analgezije različitim mehanizmima i na smanjenje pojava neželjenih efekata limitiranjem velikih doza opioida.

Terapijski pristup zasnovan na mehanizmu nastanka bola predstavlja ključ uspešne prevencije i kontrole malignitetom izazvanog hroničnog bola. Prepoznavanje, razumevanje i fokusiranje na višestruke mehanizme uključene u hronični bolni sindrom ima za cilj da proširi, a ne da zameni tradicionalni način lečenja, koji prvenstveno uzima u obzir dijagnozu i ublažavanje potencijalnih oštećenja uz empirijsku primenu analgetika. Ovakav pristup podrazumeva kombinaciju specifične farmakoterapije, psihoterapije, fizičke rehabilitacije, metode integrativne medicine (akupunktura, masaža, reflexoterapija, meditacija, modifikacija ponašanja), u skladu sa smernicama (SIO i ASCO) koje naglašavaju multidisciplinarni pristup planu lečenja hroničnih bolnih stanja, usmeren ka svakom pacijentu ponaosob (personalizacija terapije).

Pravilan pristup lečenju bola je kompleksan problem, koji podrazumeva pažljivu procenu kvalitativnih i kvantitativnih osobina bola, njihovu stalnu evaluaciju u toku lečenja i prilagođavanje terapije fazi bolesti.

Ključne reči: kancerski bol, multimodalna terapija, integrativni pristup lečenju

CASE REPORTS OF PATIENTS WITH TRIGEMINAL NEURALGIA - DIAGNOSIS, EVALUATION AND THERAPY

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Trigeminal neuralgia (TN) is a common cause of intense, unbearable facial pain. It belongs to the most common neuropathic pains and can be primary (classic) and secondary TN. In the differential diagnosis, a larger number of trigeminal autonomic headaches (TAGs), which are characterized by longer duration of pain and presence of autonomic symptoms, should be considered. Also, diseases of all facial structures can be the cause of pain that partially resembles TN. The goal of this series of case reports is to point out the elements of each of these syndromes, the way they differ from TN and, based on all of the above, to choose the correct therapy.

A 48-year-old male patient, M. N., reported sharp, recurrent, short-lasting pain in the region of innervation of the maxillary branch of the trigeminal nerve. The mentioned pain can be caused by sensory stimuli (brushing teeth, shaving, etc.). Complementary diagnostics (magnetic resonance (MR) of the brain) was normal, and the diagnosis of classic TN was established. A 33-year-old female patient, V. A., described pain with similar characteristics as in the previous case. The MR of the brain showed demyelinating lesions of supra- and infratentorial localization, some of which were localized in the pons, and based on all of the above, the diagnosis of symptomatic TG was made. A therapeutic response to the application of co-analgetics was inadequate, and it was only after taking a closer history that information was obtained about the autonomic symptoms during pain existence, as well as the fact that the pain was sometimes of longer duration. Based on all of the above, therapy with indomethacin was started because a type of TAG was suspected - paroxysmal hemicrania, and the pain was significantly reduced by the use of this drug.

Correct diagnosis is the key to an adequate therapeutic response. In addition to a well-taken medical history and clinical examination, it is necessary to correctly choose auxiliary diagnostic methods. TN is treated with co-analgetics, and in case of refractory pain, there is a large number of surgical methods as a possibility.

Key words: *trigeminal neuralgia, trigeminal autonomic headaches, neuropathic pain*

PRIKAZI PACIJENATA SA TRIGEMINALNOM NEURALGIJOM – DIJAGNOZA, EVALUACIJA I TERAPIJA

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Trigeminalna neuralgija (TN) je čest uzrok intenzivnog, neizdrživog bola lica. Spada u najčešće neuropatske bolove i može biti primarna (klasična) i sekundarna. U toku diferencijalne dijagnoze treba misliti na veći broj trigemino-autonomnih glavobolja (TAG), koje se odlikuju dužim trajanjem bola i prisustvom autonomnih simptoma. Bolesti svih struktura lica mogu biti uzrok bola koji delimično, po lokalizaciji ili intenzitetu, nalikuje na TN. Cilj ove serije prikaza jeste da ukaže na elemente svakog od ovih sindroma, na način na koji se razlikuju od TN-a i, na osnovu svega navedenog, na pravilan odabir terapije.

Četrdesetogodišnji bolesnik M. N. prijavljuje oštar ponavljajući kratkotrajni bol u predelu inervacije maksilarne grane trigeminalnog nerva. Navedeni bol može se izazvati senzornim stimulusima poput pranja zuba, brijanja i sl. Dopunska dijagnostika – magnetna rezonanca (MR) glave – bila je uredna, te je postavljena dijagnoza klasične TN. Tridesetogodišnja bolesnica V. A. opisuje bol karakteristika sličnih onima navedenim u prethodnom slučaju. Nalaz MR mozga opisuje demijelinizacione lezije supra i infratentorijalne lokalizacije, od kojih su pojedine lokalizovane u ponsu, te je na osnovu svega navedenog postavljena dijagnoza simptomatske TG. Terapijski odgovor na primenu koanalgetika bio je neodgovarajući; tek je bliže uzetom anamnezom dobijen podatak i o autonomnim simptomima za vreme trajanja bola, kao i informacija da bol povremeno duže traje. Na osnovu svega navedenog započeta je terapija indometacinom jer je postavljena sumnja na jednu vrstu TAG – tzv. paroksizmalnu hemikraniju. Upotrebom ovog analgetika bol je značajno redukovan.

Pravilno postavljanje dijagnoze jeste ključ za adekvatan terapijski odgovor. Pored dobro uzete istorije bolesti i kliničkog pregleda, potrebno je pravilno odabrati pomoćne dijagnostičke metode. TN se leči koanalgeticima; kod refraktornog bola pak moguća je i primena većeg broja hirurških metoda.

Ključne reči: trigeminalna neuralgija, trigemino-autonomne glavobolje, neuropatski bol

PAIN TREATMENT AS AN INDICATOR OF THE QUALITY OF HEALTH CARE

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Quality health care is defined as "the extent to which health services for individuals and populations increase the likelihood of desired health outcomes consistent with current professional knowledge." Pain is the most common reason for contacting the health service and therefore has a central role in the evaluation of the quality of health care. Inadequate treatment of pain has a detrimental effect on the possibility of healing. The degree of patient satisfaction with the provided health care is directly related to the degree of pain reduction. Despite the remarkable progress in recognizing the importance of adequate pain treatment and improving treatment options, research still indicates that pain treatment is not adequate and that a significant number of patients in the health care system still report dissatisfaction with pain treatment. Patient's expectations, requirements of the regulatory bodies, and quality standards of health care provision recognize the treatment of pain as one of the most significant indicators of the treatment outcomes. Therefore, for years, efforts have been directed to develop the adequate quality indicators that would give an exact insight into the effectiveness of certain treatment procedures. When we consider patient satisfaction, as an indicator of the outcome of the health service provided, we are addressing a very complex indicator that is influenced by a number of aspects unrelated to the effectiveness of the applied therapeutic procedure. In order to evaluate the quality of pain treatment, it would be necessary to develop indicators that will enable an objective evaluation of the patient's satisfaction with pain treatment. In order to achieve this goal, it is necessary to improve the management of documentation related to the evaluation, reevaluation and treatment of pain, apply valid instruments in the assessment of pain, select adequate and reliable indicators of the quality of health care and integrate into them the indicators related to the evaluation and treatment of pain and develop patient-oriented outcome indicators that would objectify whether the current practice in prescribing analgesic regimens affects patients and the quality of health care provided.

Key words: *pain treatment, health care quality, health care quality indicators*

TRETMAN BOLA KAO POKAZATELJ KVALITETA ZDRAVSTVENE ZAŠTITE

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Kvalitetna zdravstvena zaštita se definiše kao „stepen do kojeg zdravstvene usluge za pojedince i stanovništvo povećavaju verovatnoću željenih zdravstvenih ishoda u skladu sa trenutnim profesionalnim znanjem”. Bol je najčešći razlog obraćanja zdravstvenoj službi i zato ima centralno mesto u evaluaciji kvaliteta zdravstvene zaštite. Neadekvatan tretman bola ima štetan efekat na mogućnost izlječenja. Stepem zadovoljstva pacijenta pruženom zdravstvenom zaštitom direktno je povezan sa stepenom smanjenja bola. Uprkos izuzetnom napretku u prepoznavanju značaja adekvatnog tretmana bola i unapređenju mogućnosti lečenja, istraživanja ipak ukazuju na to da tretman bola nije adekvatan i da još uvek značajan broj pacijenata u sistemu zdravstvene zaštite prijavljuje nezadovoljstvo u vezi sa tretmanom bola. Očekivanja pacijenta, zahtevi regulatornih tela i standardi kvaliteta pružanja zdravstvene zaštite prepoznaju tretman bola kao jedan od najznačajnijih pokazatelja ishoda lečenja. Stoga, godinama se ulažu napor da se razviju adekvatni pokazatelji kvaliteta koji bi dali egzaktnu uvid u efikasnost određenih postupaka. Kada se govori o zadovoljstvu pacijenta kao pokazatelju ishoda pružene zdravstvene usluge, govori se o vrlo složenom pokazatelju na koji utiče niz aspekata nevezanih za efikasnost primenjenog terapijskog postupka. Zato bi, u cilju evaluacije kvaliteta tretmana bola, trebalo razviti pokazatelje koji će omogućiti objektivnu evaluaciju zadovoljstva pacijenta tretmanom bola. U ostvarenju ovog cilja neophodno je unaprediti vođenje dokumentacije u vezi sa evaluacijom, reevaluacijom i tretmanom bola, primenjivati validne instrumente u proceni bola, odabrati adekvatne i pouzdane pokazatelje kvaliteta zdravstvene zaštite i u njih integrisati pokazatelje vezane za evaluaciju i tretman bola, te razviti indikatore ishoda orijentisane na pacijenta koji bi objektivizirali kako trenutna praksa u propisivanju analgetskih režima utiče na pacijente i kvalitet pružene zdravstvene usluge.

Ključne reči: tretman bola, kvalitet zdravstvene zaštite, pokazatelji kvaliteta zdravstvene zaštite

ANALGESIC EFFECT OF PHYSICAL AGENTS – DOGMAS AND PROOFS

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In the analysis of the analgesic effect and overall effectiveness of most physical agents, placebo testing is not applicable, which further complicates the conclusion.

In published meta-analyses that examined different forms of electrotherapy, a placebo trial was mentioned. It is essential to point out that in such placebo groups the "fake devices" were covered with a towel, or only their lights were on; the stimulator electrodes were placed appropriately, but the stimulator was not tuned, or the intensity was not increased at all. Such a design cannot be considered a placebo group, and the results significantly reduce the effectiveness of the investigated agents. Too many objective factors increase the heterogeneity of groups. The inclusion of such designed "placebo" controlled studies in meta-analyses and Cochrane reviews has questioned the analgesic effect of transcutaneous electrical nerve stimulation (TENS), for which there is ample evidence of analgesic efficacy. Similar studies have concluded that interferential current therapy alone or added to other interventions is not more effective than comparative treatments in reducing musculoskeletal pain. Pulsed electromagnetic field (PEMF) therapy showed more significant pain alleviation than placebo or other therapy alone in patients with chronic low back pain despite having no advantage in improving physical function. No significant difference was observed in patients with acute low back pain. It is interesting that PEMF therapy significantly reduces the intensity of pain in the first days after mammoplasty. An analysis of the use of the low-level laser therapy (LLLT) concluded that LLLT has short-term effects on pain relief, range of motion, and reduction in morning stiffness. On the other hand, it should be emphasized that the analgesic effect of ultrasound is mediated only through the muscle relaxant effect. There is no evidence of an analgesic effect for diadynamic (DD) currents, although all textbooks claim the opposite. Extracorporeal shockwave therapy (ESWT) has an analgesic effect on fasciitis and tendinitis, the goal of which is not the destruction of calcifications.

A major effort is underway to re-prove the importance of using physical agents for analgesic purposes.

Key words: *analgesic effect of interferential current, analgesic effect of TENS, analgesic effect of PEMF, analgesic effect of LLLT, analgesic effect of ESWT*

ANALGETSKI EFEKAT FIZIKALNIH AGENASA – DOGME I DOKAZI

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U ispitivanju analgetskog efekta i ukupne efikasnosti većine fizičkih agenasa placebo ispitivanje nije primenljivo, što dodatno otežava zaključak. U publikovanim metaanalizama, koje su ispitivale različite oblike elektroterapije, pomenuto je placebo ispitivanje. Od suštinskog je značaja istaći da su dizajni ovakvih studija podrazumevali placebo grupu u kojoj su „lažni uređaji” bili pokriveni peškirom ili su im samo svetla bila upaljena; elektrode stimulatora bile su postavljene na odgovarajući način, ali stimulator nije bio podešen ili intenzitet uopšte nije bio povećan. Ovakav dizajn ne može se smatrati placebo grupom, a rezultati značajno umanjuju efikasnost ispitivanih agenasa. Pored mnogih realnih faktora koji povećavaju heterogenost grupa, klasifikacija ovako dizajniranih „placebo” kontrolisanih studija u metaanalize i Cochrane recenzije dovela je u pitanje čak i analgetski efekat TENS-a (engl. *transcutaneous electrical nerve stimulation* – TENS), za koji postoje mnogobrojni dokazi analgetske efikasnosti. U sličnim studijama zaključeno je da interferentna struja, sama ili dodata drugim intervencijama, nije efikasnija od uporednih tretmana u smanjenju muskulo-skeletnog bola. Impulsna elektromagnetna terapija (engl. *pulsed electromagnetic therapy* – PEMF) značajnije je ublažavala bol nego placebo ili druga terapija data kao monoterapija kod pacijenata sa hroničnim bolom u donjem delu leđa, uprkos tome što nije imala prednost u poboljšanju fizičke funkcije. Nije primećena značajna razlika kod pacijenata sa akutnim bolom u donjem delu leđa. Interesantno je da PEMF značajno smanjuje intenzitet bola u prvim danima nakon mamoplastike. Analizom primene niskog nivoa (netermalne) laserske terapije zaključeno je da LLLT (engl. *low-level laser therapy* – LLLT) ima kratkoročne efekte na ublažavanje bola, obim pokreta i smanjenje jutarnje ukočenosti. S druge strane, treba istaći da je analgetski efekat UZ posredovan samo kroz miorelaksantno dejstvo. Za DD (engl. *diadynamic* – DD) struje ne postoje dokazi analgetskog dejstva, iako se u svim udžbenicima tvrdi suprotno. Terapija udarnim talasima (engl. *extracorporeal shockwave therapy* – ESWT) ima analgetski efekat u fascitisima i tendinitisima, čiji cilj nije destrukcija kalcifikata.

Predstoji veliki napor da se ponovo dokaže značaj primene fizikalnih agenasa u analgetske svrhe.

Ključne reči: *analgetski efekat interferentne struje, analgetski efekat TENS-a, analgetski efekat PEMF-a, analgetski efekat LLLT-a, analgetski efekat ESWT-a*

COMBINED CHONDROPROTECTIVE THERAPY, REGENERATIVE THERAPY OR RADIOFREQUENCY ABLATION - A TRILEMMA IN THE TREATMENT OF KNEE OSTEOARTHRITIS

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Osteoarthritis (OA) is the most common form of arthritis. OA is a condition that represents an imbalance between degenerative and reparative processes in the entire joint and its components, with secondary inflammatory changes, especially in the synovium but also in the joint cartilage.

Treatment of OA requires a multidisciplinary approach.

Platelet-rich plasma (PRP) is defined as a volume of plasma with a higher than average concentration of platelets in the peripheral blood. The results of available randomized clinical trials favor the use of PRP over other intra-articular treatments when it comes to pain reduction.

There is a small number of controlled studies on the efficacy of mesenchymal stem cells (MSC) in OA therapy that reported superior efficacy with superior radiological results favoring stem cell therapy. A review of PubMed, MEDLINE and Cochrane databases found 3,867 publications, of which 28 studies met the inclusion criteria in this review. All studies reported improvement. Review of these studies provides strong evidence that autologous intra-articular MSC therapy is safe, with generally positive clinical outcomes.

The application of combined chondroprotective therapy using collagen injections, hyaluronic acid and corticosteroids gives good effects in reducing pain and increasing the range of motion of the knee joint in patients with a severe degree of damage as well as in patients in the third stage of osteoarthritis of the knee followed by synovial effusion, and it is applied as a therapy that precedes regenerative procedures.

Surgical treatment is indicated when conservative treatment fails and in patients with more severe structural changes. Knee endoprosthesis is recommended for patients with end-stage knee OA. Valgus and varus osteotomies are also important for knee deformities.

Radiofrequency ablation is a new, modern method in the treatment of pain that detects and destroys the sensitive branches of the genicular nerves by means of a thermoactive probe, which blocks the transmission of painful stimuli from pain receptors to the central nervous system. RFA is one of the methods of choice in the treatment of patients with severe structural changes in the knee joint, but also in patients who refuse surgical intervention and installation of an artificial joint or have contraindications for surgery due to other comorbidities.

Key words: *chondroprotection, hyaluronic acid, collagen, stem cells, radiofrequency ablation*

KOMBINOVANA HONDROPROTEKTIVNA TERAPIJA, REGENERATIVNA TERAPIJA ILI RADIOFREKVENTNA ABLACIJA – TRILEMA U LEČENJU OSTEOARTRITISA KOLENA

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Osteoarthritis (OA) je najčešća forma artritisa. OA je stanje koje predstavlja neuravnoteženost degenerativnih i reparativnih procesa u celom zglobu i njegovim sastavnim delovima, sa sekundarnim inflamatornim promenama, naročito u sinoviji, ali i u samoj zgloboj hrskavici. Lečenje OA zahteva multidisciplinarni pristup.

Plazma bogata trombocitima (PRP) se definiše kao zapremina plazme čija je koncentracija trombocita veća od prosečne u perifernoj krvi. Rezultati dostupnih randomizovanih kliničkih istraživanja favorizuju upotrebu PRP-a u odnosu na druge intraartikularne tretmane kada je u pitanju redukcija bola.

O efikasnosti matičnih ćelija (MSC) u terapiji OA postoji mali broj kontrolisanih studija koje su prijavile superiornu efikasnost, uz vrhunske radiološke rezultate koji favorizuju terapiju matičnim ćelijama. Pregledom baza podataka *PubMed*, *MEDLINE* i *Cochrane* pronađeno je 3867 publikacija, a 28 studija je ispunilo kriterijume za uključenje u ovaj pregled. Sve studije su prijavile poboljšanje. Pregled ovih studija pruža snažan dokaz da je autologna intraartikularna MSC terapija bezbedna, sa generalno pozitivnim kliničkim ishodima.

Primena kombinovane hondroprotektivne terapije korišćenjem kolagenskih injekcija, hijaluronske kiseline i kortikosteroida daje dobre efekte u smanjenju bola i povećanju obima pokretljivosti zgloba kolena kod pacijenata sa težim stepenom oštećenja, kao i kod pacijenata u trećem stadijumu osteoartroze kolena praćenom sinovijalnim izlivom, i to kao terapija koja prethodi regenerativnim procedurama.

Hiruško lečenje je indikovano kod neuspeha konzervativnog lečenja i kod bolesnika sa težim strukturnim promenama. Endoproteza kolena je preporuka za pacijente sa OA kolena u završnoj fazi. Značajne su i valgizacije ili varizacije osteotomije kod deformiteta kolena.

Radiofrekventna ablacija je nova, savremena metoda u lečenju bola; putem termoaktivne sonde detektuje i uništava senzitivne grane genikularnih nerava, što blokira transmisiju bolne draži od receptora bola ka centralnom nervnom sistemu. RFA je jedna od metoda izbora pri lečenju pacijenata sa težim strukturnim promenama zgloba kolena, kao i kod pacijenata koji odbijaju hiruršku intervenciju i ugradnju veštačkog zgloba ili imaju kontraindikacije za operaciju zbog drugih komorbiditeta.

Ključne reči: hondroprotekcija, hijaluronska kiselina, kolagen, matične ćelije, radiofrekventna ablacija