KOMPLEKSNI REGIONALNI BOLNI SINDROM: PREGLED LITERATURE KAO PUTOKAZ ZA SVAKODNEVNU KLINIČKU PRAKSU

PREGLEDNI RAD

REVIEW ARTICLE

COMPLEX REGIONAL PAIN SYNDROME: LITERATURE REVIEW AS A GUIDE FOR THE PRACTICING CLINICIAN

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SAŽETAK

Kompleksni regionalni bolni sindrom (KRBS) je hronični kompleksni poremećaj koji značajno utiče na kvalitet života osoba koji od njega pate. Ovaj sindrom zahvata ekstremitete nakon traume ili povrede nerava. Hiperalgezija i alodinija ekstremiteta često prate ovo stanje. Postavljanje dijagnoze i lečenje ovog oboljenja je veoma kompleksno. Budimpeštanski kriterijumi su trenutno najšire prihvaćeni dijagnostički kriterijumi. Rana dijagnoza i rano započinjanje lečenja su od suštinskog značaja za povoljan ishod KRBS-a. Terapijski modaliteti dostupni za lečenje KRBS-a obuhvataju fizikalnu terapiju, farmakoterapiju i interventne tehnike. Dodatne visokokvalitetne studije su potrebne za određivanje najbolje terapijske opcije.

Ključne reči: kompleksni regionalni bolni sindrom, bol, hronični bol

ABSTRACT

Complex regional pain syndrome (CRPS) is a chronic complex disorder that significantly affects the quality of life of the people suffering from it. This syndrome affects the extremities after trauma or nerve injury. Hyperalgesia and allodynia of the extremities often accompany this condition. Diagnosing and treating this disease is very complex. The Budapest criteria are currently the most widely accepted diagnostic criteria. Early diagnosis and treatment are essential for a favorable outcome in CRPS. Therapeutic modalities available for the treatment of CRPS include physical therapy, pharmacotherapy, and interventional techniques. Additional high-quality studies are needed to determine the best therapeutic option.

Key words: complex regional pain syndrome, pain, chronic pain

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UVOD

Kompleksni regionalni bolni sindrom (KRBS) je hronično neurološko oboljenje sa prevalencijom od 5,4 – 26,2% na 100.000 osoba. Može se podeliti na dva podtipa u zavisnosti od odsustva (KRBS I, ranije poznat kao refleksna simpatička distrofija) ili prisustva (KRBS II, ranije poznat kao kauzalgija) lezije nerva. Razlikuje se od drugih bolnih sindroma zbog prisustva poremećaja autonomne funkcije, regionalnih zapaljenskih promena, te gubitka dermatomalne distribucije. Često ga karakterišu alodinija, hiperalgezija, promena temperature kože i otok. Epidemiološke analize ukazuju da su ženski pol, povreda gornjeg ekstremiteta, kao i povreda koja nastaje kao posledica dejstva sile visokog intenziteta, faktori rizika za nastanak ovog poremećaja [1].

Ovo oboljenje karakterišu varijabilna klinička slika i tok, te otežana dijagnostika i lečenje. Patohistološki mehanizam ovog oboljenja takođe nije jasno definisan [1]. Mnogi pacijenti imaju značajno pogoršanje kvaliteta života i lošu prognozu, uprkos terapiji. Pravovremena dijagnostika i rano započinjanje terapije su od ključnog značaja za ograničavanje progresije oboljenja i poboljšanje kvaliteta života.

Cilj ovog rada je da prikaže najnovija saznanja iz postojeće literature koja se odnose na epidemiologiju, patofiziologiju i savremenu terapiju KRBS-a.

ISTORIJAT

U vreme Američkog građanskog rata, 1864. godine, američki lekar, Sajlas Vir Mičel, prvi je opisao jedan od najranijih slučajeva KRBS-a. On je tada opisao specifičan tip bola koji se javio kao komplikacija povreda nanetih vatrenim oružjem. Njegovi pacijenti žalili su se na pekući bol praćen sjajnom crvenom kožom [2]. Mičel je ovo stanje nazvao kauzalgija. Sudek, 1900. godine, opisuje radiografski vidljivu mrljastu osteopeniju, dok Evans, pedesetih godina prošlog veka, uvodi pojam „refleksna simpatička distrofija" (RSD), verujući da je simpatička hiperaktivnost odgovorna za nastanak ovog poremećaja. Internacionalna asocijacija za izučavanje bola, 1994. godine, uvodi pojam „kompleksni regionalni sindrom bola". KRBS I, ranije poznat kao refleksna simpatička distrofija, posledica je traume bez prisustva povrede nerava, i odgovoran je za većinu slučajeva ovog sindroma. KRBS II, ranije poznat kao kauzalgija, podrazumeva prepoznatljivu leziju nerva, kao posledicu traume ili hirurške intervencije [1].

PATOFIZIOLOGIJA

Prva teorija o patofiziologiji KRBS-a se odnosi na poremećaj simpatičke aktivnosti. Zbog toga je KRBS ranije i nazivan refleksna simpatička distrofija. Vremenom su

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic neurological disease with a prevalence of 5.4 – 26.2% per 100,000 people. It can be categorized into two subtypes, depending on the absence (CRPS I, previously known as reflex sympathetic dystrophy) or presence (CRPS II, previously known as causalgia) of nerve lesions. It differs from other pain syndromes due to the presence of autoimmune function disorder, regional inflammatory lesions, as well as the loss of dermatomal distribution. It is often characterized by allodynia, hyperalgesia, change in skin temperature, and swelling. Epidemiological analyses indicate that the female gender, injury to the upper extremity, as well as injury resulting from high-intensity force, represent risk factors for the development of this disorder [1].

This disease is characterized by varying clinical presentation and development, as well as by difficult diagnostics and treatment. The pathohistological mechanism of this disease is also not clearly defined [1]. Many patients experience a significant decrease in the quality of life and a poor prognosis, despite treatment. Timely diagnosis and early start of treatment are of key importance for limiting the progression of the disease and improving the quality of life.

The aim of this paper is to present the latest discoveries from existing literature related to the epidemiology, pathophysiology, and contemporary treatment of CRPS.

BACKGROUND

During the Civil War in the United States of America, in the year 1864, an American doctor, Silas Weir Mitchell was the first to describe one of the earliest cases of CRPS. At the time, he described a particular type of pain, which developed as a complication of injuries caused by firearms. His patients complained of burning pain accompanied by glowing red skin [2]. Mitchell named this condition causalgia. In 1900, Sudeck described radiographically visible patchy osteopenia, while in the 1950s, Evans introduced the term *reflex sympathetic dystrophy* (RSD), believing that sympathetic hyperactivity was responsible for the development of this disorder. In 1994, the International Association for the Study of Pain introduced the term *complex regional pain syndrome* (CRPS). CRPS I, previously known as reflex sympathetic dystrophy, results from trauma without nerve damage and it is responsible for a majority of cases of this syndrome. CRPS II, previously known as causalgia, involves recognizable nerve lesions, resulting from trauma or surgical procedure [1].

PATHOPHYSIOLOGY

The first theory on the pathophysiology of CRPS relates to disturbance in sympathetic activity. This is why CRPS was previously referred to as reflex sympathetic

utvrđeni i drugi potencijalni mehanizmi koji utiču na nastanak ovog sindroma, zbog čega je preimenovan u kompleksni regionalni bolni sindrom [3]. Patofiziologija KRBS-a je veoma komplikovana i teško ju je objasniti. U nastanku ovog stanja, veoma verovatno ima ulogu zapaljenje, naročito u njegovim ranim fazama. To se može prepoznati po prisutnim znacima akutnog zapaljenskog procesa, kao što su crvenilo, otok, povišena temperatura i bol. Uz to, prisutno je povećanje proinflamatornih citokina (TNF α i MIP-1β), kao i smanjenje antiinflamatornih proteina (IL-1Ra) [4]. Istraživanja takođe govore u prilog autoimunog procesa koji učestvuje u razvoju i progresiji KRBS-a [5]. Periferna senzitizacija, kao posledica inicijalnih zapaljenskih i imunoloških odgovora, dovodi do centralne senzitizacije i verovatno učestvuje u patofiziologiji oboljenja [4].

Postoje izvesni dokazi koji ukazuju na to da psihološki stres može učiniti pacijenta podložnim nastanku oboljenja. Pacijenti sa posttraumatskim stresnim poremećajem (PTSP) imaju veći rizik za nastanak KRBS-a [6]. Kod mnogih takvih pacijenata, PTSP je bio prisutan pre nastanka KRBS-a, što ukazuje na predispoziciju nastalu usled ovog stanja [7]. Ono što je izvesnije jeste da psihološki stres utiče na progresiju oboljenja. Pacijenti koji imaju veći stepen anksioznosti, izraženiji osećaj onesposobljenosti i strah od bola imaju lošiji ishod. Ovo je verovatno posledica povećanog oslobađanja kateholamina usled povećanog stepena anksioznosti, što dovodi do povećanja nociceptivne senzitizacije. Trenutno se istražuje genetski uticaj na nastanak KRBS-a [1].

Umesto da se pojedinačno razmatraju svi gore navedeni patofiziološki faktori u nastanku KRBS-a, nezavisno jedni od drugih, smislenije je posmatrati ih u kompleksnim, mada još uvek nerazjašnjenim interakcijama, koje dovode do opštih manifestacija KRBS-a.

EPIDEMIOLOGIJA

Zbog činjenice da je dijagnoza KRBS-a klinička, incidencija nastanka ove komplikacije varira u različitim studijama. Epidemiološki podaci iz dve velike studije pokazuju incidenciju od između 5,5/100.000 godišnje [8] i 26,2/100.000 godišnje [9]. Na osnovu najveće populacione studije koja se bavila KRBS-om, utvrđeno je da su ženski pol, bela rasa, viši socioekonomski status, anamneza depresije i glavobolje, kao i pozitivna anamneza zloupotrebe lekova, bili u vezi sa nastankom KRBS-a [10].

DIJAGNOSTIČKI KRITERIJUMI

Ne postoji definitivni test kojim se potvrđuje dijagnoza KRBS-a. Trenutno prihvaćeni dijagnostički kriterijumi za dijagnozu KRBS-a su Budimpeštanski kriterijumi, koji su definisani 2003. godine.

dystrophy. With time, other potential mechanisms influencing the development of this syndrome were also identified, which is why it was renamed, and is now referred to as complex regional pain syndrome [3]. The pathophysiology of CRPS is very complicated and very hard to explain. It is highly probable that inflammation plays a part in its development, especially in its early stages. This can be recognized by the signs of acute inflammatory process, such as redness, swelling, elevated temperature, and pain. Additionally, the elevation of pro-inflammatory cytokines (TNF α and MIP-1β) is also present, as well as the decrease of anti-inflammatory proteins (IL-1Ra) [4]. Studies also indicate an autoimmune process, which is involved in the development and progression of CRPS [5]. Peripheral sensitization, as the result of initial inflammatory and immunological responses, leads to central sensitization and is probably involved in the pathophysiology of the disease [4].

There is certain evidence indicating that psychological stress may make the patient more susceptible to the development of the disease. Patients with posttraumatic stress disorder (PTSD) are at higher risk of developing CRPS [6]. In many such patients, PTSD was present before the development of CRPS, which indicates a predisposition stemming from this disorder [7]. What is more definite is that psychological stress affects the progression of the disease. Patients who have a higher level of anxiety, a more marked sense of disability, and a greater fear of pain, have a less favorable outcome. This is probably the result of an increased release of catecholamines due to an elevated level of anxiety, which leads to the increase in nociceptive sensitization. Currently, the impact of genetics on the development of CRPS is being researched [1].

Instead of individually investigating all the above-mentioned pathophysiological factors in the development of CRPS, independently of one another, it makes more sense to observe them in complex, albeit as yet unelucidated interactions, which lead to the general manifestations of CRPS.

EPIDEMIOLOGY

Due to the fact that the diagnosis of CRPS is a clinical one, the incidence of the development of this complication varies in different studies. Epidemiological data from two large studies show an incidence of between 5.5/100,000 per year [8] and 26.2/100,000 per year [9]. Based on the largest population study dealing with CRPS, it has been established that the female sex, being Caucasian, a higher socioeconomic status, an anamnesis of depression and headache, as well as a history of substance abuse, were linked to the development of CRPS [10].

Budimpeštanski kriterijumi podrazumevaju: 1) kontinuirani bol koji nije proporcionalan inicijalom uzročnom događaju; 2) najmanje jedan simptom u tri od četiri kategorije (senzorni, vazomotorni, sudomotorni/otok i/ili motorni/trofički); 3) prilikom pregleda, mora da postoji najmanje jedan znak u dve ili više od četiri prethodno navedene kategorije; 4) ne postoji druga dijagnoza koja bolje opisuje simptome i znakove koje pacijent ima [10].

Senzorni simptomi podrazumevaju prijavu ili prisustvo hiperestezije i/ili alodinije. Vazomotorni simptomi podrazumevaju prijavu ili prisustvo asimetrije temperature i/ili promene boje kože i/ili asimetriju boje kože. Sudomotorni/otok simptomi obuhvataju prijavu ili prisustvo otoka i/ili promene znojenja i/ili asimetriju znojenja. Motorni/trofički simptomi podrazumevaju prijavu ili prisustvo ograničenja obima pokreta i/ili poremećaj motorne funkcije (slabost, tremor, distonija) i/ili trofičke promene (koža, nokti, kosa) [10].

Budimpeštanski kriterijumi dodatno kategorizuju KRBS kao Tip I i Tip II. Pacijent ispunjava kliničke kriterijume za KRBS nakon relevantne povrede nerva (KRBS II) ili bez relevantne povrede nerva (KRBS I). Povreda nerva se može dijagnostifikovati ili elektromiografijom ili neurološkim pregledom.

Da bi se dodatno kvantifikovala težina oboljenja, Harden i autori su, 2010. godine, razvili skor kojim se procenjuje težina oboljenja – *CRPS severity score (CSS)*. Na osnovu skora se procenjuje 17 različitih simptoma, pri čemu se svakom simptomu dodeljuje jedan bod [1].

Pored kliničkih dijagnostičkih kriterijuma, pojedini autori definisali su „tople" i „hladne" podtipove, koji diferenciraju inicijalne simptome povećane temperature kože i otoka kod jednih i hladniji ekstremitet kod drugih. Razumevanje potencijalno različitih podtipova podržava ranije opise pacijenata koji ne prolaze kroz tri tipične sekvencijalne kliničke faze – od inicijalne faze (Faza 1), preko faze otoka (Faza 2), do konačne trofičke faze (Faza 3). Umesto toga, oni mogu imati simptome iz bilo koje faze [1].

Iako je klinička dijagnoza na osnovu anamneze i kliničkog pregleda najšire prihvaćena, za potvrđivanje dijagnoze ispitivani su pojedini dijagnostički testovi. Termografija je najčešće korišćena i osnovna pomoćna dijagnostička metoda koja se koristi kod pacijenata sa KRBS-om. Promene temperature za ≥1 °C se smatraju značajnim. Međutim, veće temperaturne razlike nisu u korelaciji sa percepcijom bola [4]. Međutim, ova metoda nema dobru specifičnost i senzitivnost i ne može se savetovati kod ovih bolesnika. Scintigrafija kostiju je trenutno najsenzitivnija i najspecifičnija dijagnostička metoda za pacijente sa KRBS-om. Sistematski pregled literature pokazuje da se scintigrafija kostiju ne može

DIAGNOSTIC CRITERIA

There is no definitive test for confirming the diagnosis of CRPS. The currently accepted diagnostic criteria for the CRPS diagnosis are the Budapest Criteria, defined in 2003.

The Budapest Criteria include: 1) continuing pain, which is disproportionate to any inciting event; 2) at least one symptom in three of the four categories (sensory, vasomotor, sudomotor/edema, and/or motor/trophic); 3) at time of evaluation, there must be at least one sign in two or more of the previously stated categories; 4) there is no other diagnosis that better explains the signs and symptoms [10].

Sensory symptoms involve reports or presence of hyperesthesia and/or allodynia. Vasomotor symptoms refer to reports or presence of temperature asymmetry and/or skin color changes and/or skin color asymmetry. Sudomotor/edema symptoms involve reports or presence of edema and/or sweating changes and/or sweating asymmetry. Motor/trophic symptoms involve reports or presence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) [10].

The Budapest Criteria additionally categorize CRPS as Type I and Type II. A patient fulfills the clinical criteria for CRPS after relevant nerve injury (CRPS II) or without relevant nerve injury (CRPS I). Nerve injury may be diagnosed either with electromyography or with a neurological examination.

In order to additionally quantify the severity of the disease, in 2010, Harden et al. developed a score assessing the severity of the disease – *CRPS severity score (CSS)*. Based on this score, 17 different symptoms are assessed, whereby each symptom is given one point [1].

In addition to clinical diagnostic criteria, some authors have defined 'warm' and 'cold' subtypes, which differentiate initial symptoms of increased skin temperature and edema, in one category of patients, and a colder extremity, in the other. The understanding of potentially different subtypes supports earlier reports given by patients who did not go through the three typical sequential clinical stages – from the initial stage (Stage 1), the edema stage (Stage 2), to the final trophic stage (Stage 3). Instead, patients may experience symptoms pertaining to any of the stages [1].

Although clinical diagnosis based on anamnesis and clinical examination is the most widely accepted one, certain diagnostic tests have also been investigated for the purpose of diagnosis confirmation. Thermography is the most frequently used and basic adjunct diagnostic method applied in patients with CRPS. Temperature changes of ≥1 °C are considered significant. Yet, greater temperature differences do not correlate with the perception of pain [4]. However, this method does not

koristiti za isključivanje dijagnoze, ali se može koristiti za njeno potvrđivanje [11]. Radiografija ima nisku senzitivnost, ali ukoliko je pozitivna, može se koristiti kao još jedan argument u prilog dijagnozi [11].

TERAPIJA

Lečenje KRBS-a podrazumeva multimodalni pristup, koji se zasniva na nefarmakološkim i farmakološkim merama. Uspeh lečenja zavisi u velikoj meri od pravovremenog započinjanja lečenja. Već na početku lečenja, važno je u najvećoj mogućoj meri obezboliti pacijenta i inicirati aktivne pokrete u granicama njegovih mogućnosti. Pasivni pokreti, naspram volje i bez kontrole pacijenta, su kontraindikovani. Analgetska terapija je najvažnija karika u ovoj fazi lečenja. Sa smanjenjem bolova, postepena aktivacija postaje sve važnija.

Farmakoterapija

Antiinflamatorni lekovi

Lekovi koji se tradicionalno koriste za lečenje KRBS-a su nesteroidni antiinflamatorni lekovi (NSAIL) i kortikosteroidi. Antiinflamatorna terapija ima opravdano mesto u lečenju KRBS-a, naročito u ranim mesecima ovog sindroma, usled toga što inflamacija ima ulogu u KRBS-u, naročito u početnim fazama.

Nesteroidni antiinflamatorni lekovi se mogu koristiti kao inicijalna terapija u lečenju KRBS-a. Međutim, studije koje su ispitivale primenu nesteroidnih antiinflamatornih lekova kod KRBS-a su bile male, a rezultati nekonzistentni [12,13]. Nesteroidni antiinflamatorni lekovi deluju inhibicijom ciklooksigenaze 1 i 2, tako što smanjuju prostaglandine koji izazivaju inflamaciju.

Nasuprot njima, kortikosteroidi mogu da smanje inflamaciju različitim mehanizmima. Objavljene studije podržavaju kratkotrajnu upotrebu kortikosteroida u lečenju pacijenata u ranim fazama KRBS-a sa izraženom zapaljenskom komponentom [14,15]. U svojim smernicama za lečenje KRBS-a, iz 2018 godine, Nemačko udruženje neurologa savetuje lečenje ekvivalentom prednizolona u dozi > 30 – 40 mg/dan, kod akutnog KRBS-a, u trajanju od preko četiri nedelje (do šest meseci). Navodi se da sami autori vodiča imaju bolja iskustva sa inicijalno značajno višim dozama (ekvivalent prednizolona >/= 100 mg, oralno), koje se postepeno smanjuju tokom 2,5 nedelje. Takođe se napominje da je često neophodno individualno prilagođavanje doze, kao i ponavljanje lečenja kod pogoršanja tegoba [18]. Kortikosteroidi se, međutim, ne savetuju kod hroničnog KRBS-a, kod kojeg simptomi traju duže od tri meseca. Takođe, pažljiv izbor pacijenata i dužina primene kortikosteroida je od velikog značaja zbog dobro dokumentovanih neželjenih dejstava.

have good specificity and sensitivity and cannot be advised for these patients. Bone scintigraphy is currently the diagnostic method with the greatest sensitivity and specificity for patients with CRPS. A systematic literature review shows that bone scintigraphy cannot be used for excluding the diagnosis, but it can be used for confirming it [11]. Radiography has low sensitivity, however, if it is positive, it can be used to support the diagnosis [11].

TREATMENT

The treatment of CRPS involves a multimodal approach based on nonpharmacological and pharmacological measures. The success of treatment largely depends on the timely start of treatment. At the very beginning of treatment, it is important to alleviate the pain in the patent, as much as possible, and to initiate active movements within the scope of the patient's abilities. Passive movements, against the will or outside the control of the patient, are contraindicated. Analgesic therapy is the most important component in this stage of the treatment. With pain reduction, gradual activation becomes more and more important.

Pharmacotherapy

Anti-inflammatory drugs

Drugs that are traditionally used to treat CRPS are nonsteroid anti-inflammatory drugs (NSAID) and corticosteroids. Anti-inflammatory therapy is rightly used in CRPS treatment, especially in the early months of this syndrome, due to the fact that inflammation plays a part in CRPS, especially in its initial stages.

Nonsteroid anti-inflammatory drugs can be used as initial therapy in the treatment of CRPS. However, studies investigating the use of nonsteroid anti-inflammatory drugs in CRPS were small, and the results were inconsistent [12,13]. Nonsteroid anti-inflammatory drugs act through the inhibition of cyclooxygenase 1 and 2 by reducing prostaglandins that cause the inflammation.

Conversely, corticosteroids can reduce inflammation through different mechanisms. Published studies support the short-term use of corticosteroids in the treatment of patients in the early stages of CRPS, if there is a marked inflammatory component [14,15]. In its guidelines for treating CRPS, from 2018, the German Neurological Society advises treatment with prednisolone equivalent at a dose of > 30 – 40 mg/day, in acute CRPS, over a period of more than four weeks (up to six months). The guidelines state that the authors themselves have had better experience with initially significantly higher doses (prednisolone equivalent >/= 100 mg, orally), which should then gradually be reduced over a period of 2.5 weeks. It is also noted that it is often necessary to adjust the dose individually, as

Lekovi za neuropatski bol

Lekovi za neuropatski bol nisu podrobno ispitani u lečenju KRBS-a. Korišćenje lekova za neuropatski bol se zasniva na utemeljenosti ove grupe lekova u lečenju drugih neuropatskih stanja. U ograničenom broju studija, gabapentin se pokazao kao efikasan za smanjenje bola kod pacijenata sa KRBS-om [18]. Braun i saradnici su upoređivali efikasnost amitriptilina naspram gabapentina u randomizovanoj kontrolisanoj studiji, i pokazali značajno smanjenje bola, koje se nije razlikovalo između grupa [19].

Bisfosfonati

Bisfosfonati se često koriste u lečenju KRBS-a. Iako tačan mehanizam dejstva nije jasan, aktuelna istraživanja ukazuju na to da bi bisfosfonati mogli da deluju tako što moduliraju zapaljenske medijatore, kao i proliferaciju i migraciju ćelija koštane srži [20]. Kohranov pregled literature, iz 2013. godine, ukazuje na nizak nivo dokaza o efikasnosti bisfosfonata u smanjenju bola kod pacijenata sa KRBS-om [21]. Novija meta-analiza, međutim, pokazuje efikasnost ove grupe lekova u lečenju bola kod pacijenata koji imaju KRBS I [22]. Prema preporukama Nemačkog udruženja neurologa, alendronat se daje ili *per os* u visokim dozama od 40 mg/24 h ili intravenozno (7,5 mg), tri uzastopna dana [18].

Antioksidansi

Lečenje KRBS-a antioksidansima se zasniva na pretpostavci da lokalna inflamacija kod KRBS-a proizvodi slobodne radikale kiseonika [20]. Vitamin C je jedini antioksidans za koji postoje dokazi da može da deluje preventivno na nastanak KRBS-a, ukoliko se daje preventivno kod operativnog lečenja ekstremiteta. Najnovija meta-analiza pokazuje značajno smanjenje rizika kod dnevnog unosa vitamina C, u dozi od 500 mg, tokom 50 dana [23].

Ketamin

Ketamin je antagonista NMDA receptora u perifernom i centralnom nervnom sistemu [4,20,24]. U svom pregledu literature, Žao i saradnici su zaključili da postojeće studije podržavaju kliničku efikasnost ketaminskih infuzija, ali i da su neophodne dodatne randomizovane kontrolisane studije koje dodatno potvrđuju njihovu efikasnost [24].

Ostalo

U poslednje vreme, zahvaljujući unapređenom razumevanju molekularnih i ćelijskih mehanizama koji su u osnovi razvoja KRBS-a, ispituju se različiti novi farmakoterapijski pristupi, sa ciljem poboljšanja uspeha lečenja. U novije lekove ubraja se naltrekson, antagonista opioida, koji u malim dozama inhibira aktivaciju mikroglija i na taj način smanjuje zapaljenski odgovor. Kao

well as to repeat treatment in case of the exacerbation of symptoms [18]. Corticosteroids, however, are not recommended in chronic CRPS, wherein symptoms last longer than three months. Also, a careful selection of patients and the duration of corticosteroid application are of great importance, due to well documented adverse effects.

Drugs for neuropathic pain

Drugs for neuropathic pain have not been thoroughly investigated in the treatment of CRPS. The use of drugs for neuropathic pain is based on the established use of this group of drugs in the treatment of other neuropathic conditions. In a limited number of studies, gabapentin has proven to be efficient in reducing pain in patients with CRPS [18]. Brown et al. compared the efficiency of amitriptyline against gabapentin in a randomized controlled study, and they demonstrated significant reduction of pain, which did not vary amongst the groups [19].

Bisphosphonates

Bisphosphonates are frequently used in CRPS treatment. Although the precise mechanism of their action is not clear, current research indicates that bisphosphonates may act by modulating inflammatory mediators, as well as the proliferation and migration of bone marrow cells [20]. Cochrane's literature review, from 2013, indicates a low level of evidence on the efficiency of bisphosphonates in reducing pain in patients with CRPS [21]. A recent meta-analysis, however, demonstrates the efficiency of this group of drugs in the treatment of pain in patients with CRPS I [22]. According to the recommendations of the German Neurological Society, alendronate is either administered orally in high doses of 40 mg/24 h or intravenously (7.5 mg), for three consecutive days [18].

Antioxidants

Treatment of CRPS with antioxidants is based on the premise that local inflammation in CRPS produces oxygen free radicals [20]. Vitamin C is the only antioxidant for which proof exists that it can act preventively on the development of CRPS, if it is administered preventively in surgical treatment of the extremities. The most recent meta-analysis shows a significant reduction of risk when 500 mg of vitamin C are taken daily over a period of 50 days [23].

Ketamine

Ketamine is an antagonist of the NMDA receptor in the peripheral and central nervous system [4,20,24]. In their literature overview, Zhao et al. concluded that existing studies support the clinical efficiency of ketamine infusions, but also that additional randomized controlled studies are necessary in order to additionally confirm their efficiency [24].

nove alternative u lečenju KRPS-a mogu se razmatrati i ketamin, botulinum toksin A i kanabinoidi, ali su potrebne nove studije koje će dokazati efikasnost i bezbednost ove grupe lekova [20].

Procedure

Simpatički nervni blokovi

Uprkos niskom nivou dokaza u korist opravdanosti simpatičkih nervnih blokova, oni se često primenjuju od strane lekara koji se bave interventnom terapijom bola. Simpatički nervni blokovi daju se zbog pretpostavke da je patofiziologija KRBS-a delimično u vezi sa poremećajem autonomne funkcije zahvaćenog ekstremiteta i naglašenim odgovorom na kateholamine [1].

Stimulacija kičmene moždine i gangliona dorzalnih rogova

Stimulacija kičmene moždine je neuromodulaciona tehnika koja redukuje bol električnom stimulacijom dorzalnih rogova kičmene moždine. Implantirane elektrode odašilju impulse, koji složenim mehanizmima moduliraju osećaj bola. Rezultati istraživanja sprovedenih na temu opravdanosti ove metode kod pacijenata sa KRBS-om nisu konzistentni [25]. Dodatna istraživanja su neophodna za procenu efikasnosti i bezbednosti ove metode.

Stimulacija gangliona dorzalnih rogova je novija tehnika, koja je u razvoju, i gde se električna stimulacija primenjuje na dorzalne rogove. Ovaj vid stimulacije je specifičniji u odnosu na stimulaciju kičmene moždine, zato što može da specifično cilja bolne regije ekstremiteta. Neophodna su dodatna istraživanja na ovu temu [1].

Jedna od novijih metoda lečenja, koja bi mogla imati efekta, jeste transkranijalna magnetna stimulacija (TMS). Ovo je bezbedna i neinvazivna tehnika koja proizvodi kratkotrajni magnetni impuls u mozgu i može indukovati kortikalnu ekscitabilnost. Neophodno je dodatno istraživanje radi donošenja definitivnog zaključka [20].

Nefarmakološko lečenje

Nefarmakološko lečenje podrazumeva multidisciplinarni pristup, koji uključuje fizikalnu, okupacionu i psihološku terapiju. Zbog bola koji prati ovo stanje, pacijenti izbegavaju korišćenje zahvaćenog ekstremiteta. Kod pacijenata sa KRBS-om, cilj fizikalne i okupacione terapije je poboljšanje funkcionalnosti i pokretljivosti ekstremiteta, kao i smanjenje bola. Ovakva terapija sprečava i kasnije komplikacije kao što su kontrakture, koje se formiraju zbog izbegavanja bolnih pokreta. Korišćenje ovih terapija se savetuje rano u procesu rehabilitacije i smatraju se terapijama prvog reda [1].

Kontrola bola je veoma važna tokom rehabilitacije. Čim bol dozvoli aktivaciju ekstremiteta može se

Other

Lately, thanks to the advanced understanding of molecular and cellular mechanisms that are at the heart of the development of CRPS, different new pharmacotherapeutic approaches have been investigated, for the purpose of improving the success of treatment. Amongst the newest drugs is naltrexone, an opioid antagonist, which, in small doses, inhibits the activation of microglia, thus reducing the inflammatory response. As new alternatives in CRPS treatment, ketamine, botulinum toxin A, and cannabinoids can also be considered. However, new studies, which would prove the efficiency and safety of this group of drugs, are necessary [20].

Procedures

Sympathetic nerve blocks

Despite the small body of evidence justifying the use of sympathetic nerve blocks, they are often used by doctors who are involved in interventional pain management. Sympathetic nerve blocks are administered due to the premise that the pathophysiology of CRPS is partially linked to a disturbance in the autonomous function of the affected limb and the excess response to catecholamines [1].

Stimulation of the spinal cord and the ganglia of the dorsal horns

Spinal cord stimulation is a neuromodulation technique which reduces pain through electrical stimulation of the spinal cord dorsal horns. Implanted electrodes emit impulses, which modulate the sensation of pain through a complex mechanism. The results of studies investigating the validity of the application of this method in CRPS patients are inconsistent [25]. Further studies are necessary in order to assess the efficiency and safety of this method.

Stimulation of the ganglia of the dorsal horns is a new developing technique, whereby electrical stimulation is applied to the dorsal horns. This form of stimulation is more specific, as compared to spinal cord stimulation, as it can specifically target painful regions of the extremities. Further research to this effect is necessary [1].

One of the recently developed methods of treatment, which may have the desired effect, is transcranial magnetic stimulation (TMS). This is a safe and noninvasive technique, which produces a short-lasting magnetic impulse in the brain and may induce cortical excitability. Further research is necessary for the purpose of reaching a definitive conclusion [20].

Nonpharmacological treatment

Nonpharmacological treatment entails a multidisciplinary approach, which includes physical, occupational, and psychological therapy. Due to the pain that accom-

započeti sa mobilizacijom zahvaćenih zglobova. Kasnije se uvode i vežbe sa opterećenjem, a kod zahvaćenosti donjih ekstremiteta i vežbe hoda. Pacijente treba ohrabriti da aktivno koriste oboleli ekstremitet u svakoj fazi oboljenja.

Kohranov pregled, iz 2016. i 2022. godine, koji je analizirao različite fizioterapijske intervencije, izdvojio je dve terapije sa najvećim rehabiltiacionim potencijalnom, koje mogu da smanje bol i poboljšaju funkcionalnost i kvalitet života kod pacijenata koji imaju KRBS I. To su terapija ogledalom i graduisana motorna imaginacija [26,27]. Ove dve terapijske metode nametnule su se kao važne komponente lečenja pacijenta sa KRBS-om.

Terapija ogledalom, kao izolovana terapijska procedura, naročito je efikasna kod akutnih oblika KRBS-a, naročito nakon moždanog udara [28]. Kod hroničnog KRBS-a je efikasna graduisana motorna imaginacija, koja se sastoji od prepoznavanja leve i desne strane, zamišljanja pokreta i terapije ogledalom [29]. Dve studije pokazale su poboljšanje bola i smanjenje funkcionalne onesposobljenosti kod pacijenata sa KRBS-om, u šest meseci, prilikom primene ove dve metode [26,29].

Ove dve terapije se, nakon instrukcije od strane terapeuta, sprovode samostalno od strane pacijenta, u trajanju od deset minuta svakog budnog sata tokom šest nedelja [18].

Psihoterapijske intervencije

Psihoterapijske intervencije su važna komponenta lečenja kod pacijenata sa KRBS-om, naročito kada postoje udružena psihička oboljenja ili kada se simptomatologija tokom dužeg vremenskog perioda, uprkos adekvatnog terapiji, ne menja [30].

Postoje dve studije sa malim brojem pacijenata koje potvrđuju efikasnost psihoterapijskih intervencija kod KRBS-a, u poređenju sa izolovanom fizikalnom terapijom [31,32]. Međutim, rezultati velikog broja istraživanja na pacijentima sa hroničnim bolnim sindromima mogu se preneti sa velikom verovatnoćom na pacijente sa KRBS-om [33].

ZAKLJUČAK

KRBS je kompleksno i multifaktorijalno oboljenje. Iako je naše razumevanje ovog stanja daleko odmaklo od njegove najranije definicije, još uvek nije u potpunosti razjašnjeno. Veće visokokvalitetne studije su neophodne za bolje razumevanje mehanizama koji leže u osnovi ovog oboljenja, a koje će pomoći razvoj precizno usmerenih terapija. Upravo zbog toga, neophodni su stalni istraživački napori usmereni na kombinacije terapijskih metoda za buduće lečenje KRBS-a.

Sukob interesa: Nije prijavljen.

panies this condition, patients avoid using the affected limb. In patients with CRPS, the goal of physical and occupational therapy is to improve the functionality and mobility of the extremities, as well as to reduce pain. Such therapy also prevents later complications, such as contractures, which form due to the avoidance of painful movements. It is advised that these forms of treatment should be applied early on in the rehabilitation process, as they are considered first-line therapies [1].

Pain management is very important during rehabilitation. As soon as pain allows the activation of the extremities, the affected joints can be mobilized. Later, resistance exercises are introduced, and if the lower extremities are affected, walking exercises are also included. Patients should be encouraged to actively use the affected limb in each stage of the disease.

Cochrane's review, from 2012 and 2016, which analyzed different physiotherapeutic interventions, singled out two forms of therapy with the highest rehabilitation potential, which can reduce pain and improve functionality and the quality of life in patients with CRPS I. These are mirror therapy and graded motor imagery [26,27]. These two methods of therapy have become important components in the treatment of CRPS patients.

Mirror therapy, as an isolated therapeutic procedure, is especially efficient in acute forms of CRPS, especially after stroke [28]. In chronic CRPS, graded motor imagery is efficient. It consists of recognizing the left and right side in the mirror, imagining movement, and mirror therapy [29]. Two studies have shown improvement in pain and a decrease in functional disability in patients with CRPS, within six months, when this method was applied [26,29].

Following instructions from the therapist, patients carry out these two forms of therapy independently, for ten minutes every waking hour, over a period of six weeks [18].

Psychotherapeutic interventions

Psychotherapeutic interventions are an important component of treatment in patients suffering from CRPS, especially when there is an accompanying mental illness or when the symptomatology, despite appropriate therapy, does not change over a longer period of time [30].

There are two studies, with a small number of patients, confirming the efficiency of psychotherapeutic interventions in CRPS, as compared to isolated physical therapy [31,32]. However, the results of a great number of studies on patients with chronic pain syndrome may be applied with a high degree of probability to patients suffering from CRPS [33].

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CONCLUSION

CRPS is a complex multifactorial disease. Although our understanding of this disease has advanced greatly since it was described and defined for the first time, it has as yet not been fully clarified. Larger high-quality studies are necessary to facilitate a better understanding of the underlying mechanisms of this syndrome, which would enable the development of precisely targeted treatments. This is why constant research efforts, directed towards devising combinations of therapeutic methods for future treatment of CRPS, are necessary.

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