Issue Rehabil. Orthop. Neurophysiol. Sport Promot. 2019; 28: 29–38. ISSN 2300-0767
DOI: 10.19271/IRONS-000102-2019-29

REVIEW ARTICLE

NON-INVASIVE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME (CRPS) – AN UPDATED REVIEW

NIEINWAZYJNE LECZENIE ZŁOŻONEGO ZESPOŁU BÓLU MIEJSCOWEGO (CRPS)- PRZEGLĄD AKTUALNYCH BADAŃ

Aleksandra Wadas-Żołna
Clinic for Rehabilitation, University of Medical Science, Poznań, Poland

ABSTRACT

Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition involving the limbs that is characterized by severe pain along with sensory, autonomic, motor and trophic impairment, which can no longer be explained by the initial trauma. Due to the complexity and wide spectrum of symptoms, patients with CRPS require input from various clinical specialties including orthopaedic surgeons, anesthesiologists, rheumatologists, rehabilitation physicians, physiotherapists. Effective management of the syndrome is often challenging. This review aims to provide an update on the recent trials on conservative treatment of CRSP.

Aim

The aim of the article is to present methods of treatment of local pain syndrome, the effectiveness of which has been confirmed in clinical trials.

Material and methods

Cochrane, Pubmed and MEDLINE databases were searched with key words: complex regional pain syndrome, CRPS, non-invasive treatment.

The search period was restricted to from April 1997 to October 2019.

Results

Reviews of available trials suggest that new kinesiotherapy techniques as graded motor imagery and pain exposure physiotherapy, bisphosphonates, corticosteroids and few physical techniques may be the effective ways of treatments.

Conclusions

Modern kinesitherapy as well as corticosteroids and gabapentin are proven to be effective treatment for CRPS, while the use of vitamin C reduces the risk of developing the syndrome.

Keywords: Complex regional pain syndrome, CRPS, non-invasive treatment.

Author responsible for correspondence:
Aleksandra Wadas-Żołna
Rehabilitation Clinic
University of Medical Science
28 Czerwca 1956 No 135/147
61-545 Poznań, Poland
aleksandra.wadas-zolna@mail.com

Authors reported no source of funding
Authors declared no conflict of interest

Date received: 28th October 2019
Date accepted: 3rd December 2019

STRESZCZENIE

Wstęp

Złożony zespól bólu miejscowego (CRPS) to schorzenie charakteryzujące się neuropatycznym bólem kończyny współistniejącym z zaburzeniami czuciowymi, naczynioruchowymi, motorycznymi i zmianami troficznymi, którego nie da się uzasadnić pierwotnym urazem. Ze względu na szerokie spektrum objawów, leczenie chorych na CRPS ma charakter wielodyscyplinarny i wymaga zaangażowania wielu specjalistów: ortopedów, reumatologów, anestezjologów, lekarzy rehabilitacji i fizjoterapeutów. Skuteczne leczenie pacjenta z CRPS jest często wyzwaniem. Przegląd ma na celu przedstawienie najnowszych badań dotyczących zachowawczego leczenia CRSP.

Cel

Celem artykułu jest przedstawienie metod leczenia zespołu bólu miejscowego, których skuteczność została potwierdzona w badaniach klinicznych.

Materiał i metody

Dokonano przeglądu bazy Cochrane, Pubmed i MEDLINE z wykorzystaniem słów kluczowych: złożony zespół bólu miejscowego, CRPS, leczenie nieinwazyjne. Okres wyszukiwania obejmował przedział od kwietnia 1997 do października 2019.

Wyniki

Przegląd dostępnych badań sugeruje, że nowe techniki kinezyterapeutyczne, takie jak trening lateralizacji i wyobrażania ruchów oraz terapia z eksponowaniem na ból, farmakoterapia obejmująca bisfosfoniany i kortykosteroidy oraz nieliczne techniki fizykoterapeutyczne są skutecznymi metodami leczenia. Efektywne jest również zapobieganie rozwojowi CRPS u pacjentów z grup ryzyka przez podawanie witaminy C.

Wnioski

Nowe techniki kinezyterapeutyczne oraz kortykosteroidy i gabapentyna są skutecznymi metodami leczenia CRPS, natomiast stosowanie witaminy C zmniejsza ryzyko zachorowania.

Słowa kluczowe: złożony zespól bólu miejscowego, CRSP, leczenia nieinwazyjne.

Introduction

Complex regional pain syndrome (the term introduced by International Association for the Study of Pain – IASP in 1994) is a chronic neurological condition involving the limbs that is characterized by severe neuropathic pain with sensory, autonomic, motor and trophic impairment (Merskey *et al.* 1994). The upper extremity is affected more frequently (60%) than the lower extremity (de Mos *et al.* 2006).

The main symptoms of CRPS are severe continuing pain, allodynia (sensitization following normally non-painful stimulation), hyperalgesia (abnormally increased sensitivity to pain), motor dysfunctions, temperature asymmetry or skin color changes, edema and/or sweating changes, trophic changes of skin and its appendages (Harden *et al.* 2006).

The diagnosis of CRPS is made on the basis of the Budapest criteria or "the new IASP criteria" – Table 1 (Goabel *et al.* 2018). It should be emphasized that the diagnosis of CRPS is made primarily on clinical basis and no specific test is known to confirm or exclude CRPS diagnosis (Lee *et al.* 2018).

The most common cause of CRPS is a fracture (> 40% of CRPS cases), followed by limb

Table 1. Budapest Criteria of CRPS

continuing pain, which is disproportionate to any inciting event must report at least one symptom in three of the four following categories must display at least one sign at time of evaluation in two or more of the following categories there is no other diagnosis that better explains the signs and symptoms	
Category	**Symptoms**
Sensory	hyperesthesia and/or allodynia
vasomotor	temperature asymmetry and/or skin color changes and/or skin color asymmetry
sudomotor/edema	edema and/or sweating changes and/or sweating asymmet
motor/trophic	decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

surgery and other injuries like a sprain, contusion or burn (de Mos *et al.* 2006). In more than ten percent of the cases no precipitating event was reported (de Mos *et al.* 2006).

The prevalence is higher among women (63.6%) and the median age is 52.8 (Beerthuizen A *et al.* 2012). Data on incidence vary considerably – from 5.46/100.000(de Mos *et al.* 2006) to 26.2/100.000 (Sandroni *et al.* 2003). The introduction of new diagnostic criteria as an international standard resulted in a reduction of CRPS recognition by approximately 50% (De Boer *et al.*2011).

It is accepted that there are multiple mechanisms involved in pathophysiology of CRPS including central (Eisenberg *et al.* 2005, Sieweke *et al.* 1999) and peripheral sensitisation (Vaneker *et al.* 2005), autonomic dysfunction and inflammatory changes (Russo *et al.* 2018; Uçceyler *et al.* 2007; Parkitny *et al.* 2013), reduced representation of the CRPS-affected limb in somatosensory cortex (Maihöfner *et al.* 2003; Maihöfner *et al.* 2004; Pleger *et al.* 2006). The existence of genetic factors of susceptibility to CRPS is also postulated (Van Rooijen *et al.* 2012).

Aim

The aim of this study is to present the conservative methods of treatment of CRPS, the effectiveness of which has been confirmed in clinical trials.

Material and methods

Cochrane, Pubmed and MEDLINE databases were searched. The search period was from April 1997 to October 2019. The keywords used were "complex regional pain syndrome," in combination with "trial" or "randomized trial".

Results

Eleven studies were found concerning the use of various forms of kinesiotherapy in CRPS, the characteristics of which are presented in Table 2.

Four studies were found assessing the effectiveness of physical therapy methods (Table 3).

Seventeen papers concerned pharmacotherapy (Table 4), including four reports regarding CRPS prophylactic use of vitamin C in risk groups. Four studies evaluated the effectiveness of topically administered drugs in patients with CRPS (Table 5).

Discussion

The multifactorial etiology of the CRPS, the large diversity of patients (in terms of severity and variability of symptoms, response to treatment) makes the management of a patient with CRPS a challenge for both doctors and physiotherapists. Physiotherapy is widely recognized as a first choice treatment of CRPS (Goebel *et al. 2018*). Clinical studies published in recent years concern new kinesiotherapy techniques based on the pathophysiological concepts that highlight changes in the cortical representation of the affected limb. Mirror therapy and a method that combines this technique with motor imagery, called graded motor imagery (GMI), have proven to be very effective in reducing pain (Moseley 2004, 2005, 2006). The success of this method was the basis for further research, the results of which, unfortunately,

Table 2. Summary of works on kinesiotherapy used in CRPS

Author	Year	Sample size	Type of therapy	Assessment methods	Control group	Outcome
de Jong	2005	8	graded exposure in vivo + education program	Radboud Skills Questionnaire (RASQ), Walking Stairs Questionnaire (WSQ), questionnaires of pain related fear, pain disability, and self-reported signs and symptoms	no	decreasing levels of self-reported pain-related fear, pain intensity, and disability
McCabe	2003	8	mirror visual feedback (MVF)	pain severity and vasomotor changes	placebo	MVF in early CRPS ((8 weeks) had an immediate analgesic effect, no change was found in chronic CRPS
Moseley	2004	13	motor imagery program (MIP)	neuropathic pain scale (NPS), edema (circumferences)	ongoing management	significant effect in treatment group
Moseley	2005	20	motor imagery program (MIP)	neuropathic pain scale (NPS)	three groups with (MIP) – in different order of components	significant reduction in pain and disability in one of the group
Moseley	2006	51	motor imagery program (MIP)	McGill Pain Questionnaire (MPQ), VAS, neuropathic pain, scale (NPS)	physical therapy and ongoing medical care	significant reduction in pain and disability
Moseley	2009	10	30-min tactile discrimination training session	two-point discrimination threshold (TPD), VAS	no	significant improvement TPD and VAS
Johnson	2012	32	graded motor imagery (GMI) treatment in conjunction with 'best practice' interventions	Brief Pain Inventory	no	average pain intensities did not improve with treatment

Table 3. Summary of trials on physical modalities for the treatment of CRPS

Author	Year	Sample size	Type of therapy	Assessment methods	Control group	Outcome
Dimitrijevic	2014	45	interferential current + kinesiotherapy	VAS, edema (eight circumferences) ROM	low-level laser therapy and kinesiotherapy	significant differences in both groups, the greater difference in laser group
Duman	2009	34	manual lymphatic drainage (MLD) + NAIDs, physical therapy and therapeutic exercise program for 3 weeks	VAS, functional measurements	NAIDs, physical therapy and therapeutic exercise program for 3 weeks	not significant differences in both of the groups
Uher	2000	35	exercise in combination with manual lymphatic drainage (MLD)	VAS, edema, temperature, ROM	only exercise	not significant differences after 6 months
Sezgin	2019	30	3 week conventional rehabilitation program + 15 sessions additional fluidotherapy application to the affected upper extremity (40°C, 20 minutes in continuous mode)	VAS, edema with a volumeter, painDETECT questionnaire for presence, Brunnstrom recovery stages	3 week conventional rehabilitation program plus placebo	only the decrease in edema volume and the painDETECT scores were greater in fluidotherapy group

Table 4. Summary of works on systemic pharmacotherapy used in CRPS

Author	Year	Sample size	Type of therapy	Type of therapy	Control group	Outcome
Adami	1997	20	alendronate 7.5mg intravenous for 3 days	VAS, ROM, oedema, tenderness	placebo intravenous for 3 days	improvement in motion, spontaneous pain, tenderness, and swelling
Varenna	2000	32	clodronate 300 mg intravenous for 10 days	VAS, clinical global assessment (CGA)	placebo intravenous for 10 days	significant decreases of VAS and CGA
Robinson	2004	27	pamidronate 60 mg intravenous single time	VAS, global assessment of disease severity score, and SF-36	placebo intravenous single time	improvement in pa-mindronate group
Varenna	2013	82	neridronate100 mg intravenous four times	VAS	placebo intravenous four times	VAS score decreased significantly more in the neridronate group
Manicourt	2004	40	alendronate 40 mg oral for 56 days	joint mobility, edema, tolerance to pressure, levels of type I collagen N-telopeptide (NTX)	placebo oral for 56 days	improvement in levels of spontaneous pain, pressure tolerance, and jointmobility, as well as significant reduction in urinary levels of NTX
Bianchi	2006	31	prednisolon (maximum dose of 60 mg for four days and tapered)	clinical severity scale	no	significant improvement in one year follow-up
Nilgun	2014	45	prednisolon (maximum dose of 30 mg for four days and tapered)	VAS, grip strength (GS) (kg), lateral pinch (LP) (pound), tip-to-tip pinch (TP) (pound), chuck pinch (CP) (pound) ROM using third finger tip-distal crease distance (FT-DC) (cm); Q-DASH, SF-36	no	significant improvement in post-treatment results
Kalita	2016	58	prednisolone (40 mg for 14 days and then tapered)	CRPS, VAS, mRS, and BI scores, ROM	no prednisolone group	improvement in CRPS and VAS score but not in mRS and BI scores
Barbalinardo	2016	31	prednisolone 100 mg daily tapered	average pain intensity	no	no significant reduction in the average pain intensity
Kumowski	2019	12	prednisolone (180–36 mg)	remote ischemic conditioning (RIC), ROM, VAS	no	pain level and finger-palm distance were decreased significantly

are not as promising as expected. The application of the modified GMI technique in practice resulted in a slight reduction in pain intensity and a slight improvement in limb function (Johnson *et al.* 2012) and in quite numerous cases even an increase in pain (Lagueux *et al.* 2012). Further studies are needed to identify groups of patients for whom GMI is inadvisable, as well as clear recommendations on the details of using the method.

Another examined method of conducting kinesiotherapy is the technique known as PEPT – pain exposure physiotherapy. It is based on the theory that the fear of pain lead to a vicious cycle of pain, fear, and disability. Two studies have proven the superiority of this method over standard physiotherapy (Barnhoorn *et al.* 2015; den Hollander *et al.* 2016). Individual studies have demonstrated the effect of 30 minutes touch discrimination training for in reducing pain (Moseley *et al.* 2009) and mirror therapy (Cacchio *et al.* 2009).

In clinical practice, the exercise program is often supplemented by physical modalities of unproven effectiveness. The analyzed studies evaluated a very diverse group of

Table 4. cont. Summary of works on systemic pharmacotherapy used in CRPS

Author	Year	Sample size	Type of therapy	Type of therapy	Control group	Outcome
Eun Young	2016	21	prednisolone (1 mg/kg, tapered) or pamidronate (60 mg infusion intravenously)	VAS, edema (circumference of the middle finger-CMF, and the wrist-CW)	prednisolone group, pamidronate group	both groups showed significant improvement in VAS, significant change in CW in the pamidronate group
van den Vusse	2004	58	gabapentin (GBP) in slowly increased doses (600 mg, 1200 mg, 1800 mg)	global perceived effect (GPE) on pain, neuropathic pain scale (NPS), sensibility through Von Frey monofilament, allodynia test, edema, discoloration, and changed skin temperature	placebo	significant pain relief only in the first period, this sensory deficit significantly reversed
Tan	2007	22	gabapentin (GBP) in slowly increased doses (600 mg, 1200 mg, 1800 mg)	provoked and static pain scores, dynamometric measurement, third finger palmar crease distance circumferential measurement, ROM	no	significant pain relief, no statistically significant difference in functional parameters
Zollinger	1999	123	500 mg vitamin C daily for 50 days	CRPS was diagnosed when four of six symptoms were present	placebo	lower risk of CRPS in vitamin C group
Zollinger	2007	416	200, 500, or 1500 mg of vitamin C daily for 50 days	CRPS was diagnosed when four of six symptoms were present	placebo	lower risk of CRPS in 500 mg vitamin C group
Ekrol	2014	336	500 mg vitamin C daily for 50 days	DASH score, wrist and finger motion, grip and pinch strength, pain, and a CRPS score	placebo	no difference in the CRPS rate
Laumonerie	2019	542	500 mg vitamin C daily for 50 days	IASP diagnostic criteria for CRPS	placebo	lower risk for CRPS-I in vitamin group

Table 5. Summary of trials on topical drugs for the treatment of CRPS

Author	Year	Sample size	Type of therapy	Assessment methods	Control group	Outcome
Perez	2003	146	DMSO (dimethyl-sulfoxide 50%) five times daily	impairment level sumscore (ISS) , Radboud skills questionnaire, Short Form-36, walking stairs questionnaire (WSQ), questionnaire rising and sitting down (QRSD	N-acetylcysteine (600 mg effervescent tablets three times daily)	no differences in effects
van Dieten	2003	131	DMSO (dimethyl-sulfoxide 50%) five times daily	impairment level sumscore (ISS)	N-acetylcysteine (600 mg effervescent tablets three times daily)	total direct costs significantly lower in the DMSO group
Rob-bins	1998	13	capsaicin at doses of 5%-10%	VAS	no	The mean verbal analog scale (VAS) scores decreased from 8.0 to 3.0

ISS – validated score for assessing the severity of CRPS symptoms, based on the assessment of pain, difference in temperature and volume between limbs and loss of function

procedures (fluidotherapy, laserotherapy, lymphatic drainage), showing only a small effectiveness of fluidotherapy (Sezgin *et al.* 2019) and laserotherapy (Dimitrijevic *et al.* 2014).

Pharmacotherapy plays an important role in the treatment of CRPS consequently the efficacy of many drugs have been tested. The drugs whose use is currently most hopeful are bisphosphonates. They affect the increased bone metabolism observed in CRPS, which may be responsible for the pain formation, because osteoclasts resorb the bone by acidifying the extracellular matrix, which activates the nociceptive channels. All of the analyzed trials showed that bisphosphonates are effective. The effectiveness of several substances was studied, including alendronate (Adami *et al.*1997; Manicourt *et al.* 2004), clodronate (Varenna *et al.* 2000), pamidronate (Robinson *et al.* 2004) and neridronate (Varenna *et al.* 2013). Corticosteroids are another group of drugs already well established in the treatment of CRPS (Kozin *et al.* 1976; Christensen *et al.* 1982). They are the only anti-inflammatory drugs that have also been proven in recent studies. All the cited studies showed that the use of prednisolone reduces pain, swelling and increases the range of motion of the limb (Bianchi *et al.* 2006, Nilgun *et al.* 2014; Kalita *et al.* 2016; Barbalinardo *et al.* 2016; Kumowski *et al.* 2019). Gabapentin, the first choice drug in other neuropathic pain syndromes, is also an effective in CRPS (van den Vusse *et al.* 2004, Tan *et al.* 2007).

Due to the ease of use, safety and lack of systemic side effects, topical drugs are also used in the treatment of CRPS. Studies comparing the effectiveness of dimethyl sulfoxide with another N-acetylcysteine (NAC) administered orally, did not show a significant difference between the use of these two drugs, but it should be noted that a significant improvement was observed in both groups of patients (Perez *et al.* 2004; van Dieten *et al.* 2003). One study was conducted to evaluate the effectiveness of capsaicin at high concentrations, which confirmed its effectiveness (Robbins *et al.*1998). However, such high doses can be used only after local anesthesia, which significantly limits this method of treatment. Even lower concentrations of capsaicin (0.075%) are often poorly tolerated by patients due to transient burning or stinging sensations, and erythema after application (Peikert *et al.* 1991).

An interesting issue is preventing the development of CRPS by oral administration of vitamin C in patients at risk. The results of four studies are contradictory (Zollinger *et al.* 1999; Zollinger *et al.* 2007; Ekrol *et al.* 2014; Laumonerie *et al.* 2019) and the meta-analysis of research on this issue has not proved the existence of benefits from the use of this method of prevention (Evaniew *et al.*2015).

Conclusions

Few CRPS treatments conventionally used, or even recommended in the guidelines, are the subject of clinical trials. The limitations of their conduct are certainly controversies regarding diagnosis criteria (adoption of different criteria in individual studies) and high variability of symptoms in patients with CRPS. Further high-quality randomized, multicenter clinical trials are extremely needed.

REFERENCES

Adami S., Fossaluzza V., Gatti D., Fracassi E., Braga V. (1997) *'Bisphoshonate therapy of reflex sympathetic dystrophy syndrome.'* Ann Rheum Dis., 56(3): pp. 201–204.

Barbalinardo S., Loer S.A., Goebel A., Perez R.S. (2016) *'The Treatment of longstanding Complex Regional Pain Syndrome with Oral Steroids.'* Pain Med,17(2): pp. 337–343.

Barnhoorn K.J.,van de Meent H.,van Dongen R.T.M. (2015) *'Pain exposure physical therapy-(PEPT)compared to conventional treatment in complex regional pain syndrometype1: a randomised controlled trial.'* BMJ, 5(12).

Beerthuizen A., Stronks D.L., Van't Spijker A. (2012) *'Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture.'* Pain 153(6): pp. 1187–1192.

Bianchi C., Rossi S., Turi S., Brambilla A., Felisari G., Mascheri D. (2006) *'Long-term functional outcome measures in corticosteroids-trated*

complex regional pain syndrome.' Eura Medicophys 42: pp. 103–111.

Cacchio A., De Blasis E., Necozione S., di Orio F., Santilli V. (2009) *'Mirror therapy for chronic complex regional pain syndrome type 1 and stroke.'* New England Journal of Medicine; 361(6), pp. 634–636.

Christensen K., Jensen E.M., Noer I. (1982) *'The reflex dystrophy syndrome response to treatment with systemic corticosteroids.'* Acta Chir Scand.148, pp. 653–655.

De Boer R.D., Marinus J., van Hilten J.J. (2011) *'Distribution of signs and symptoms of complex regional pain syndrome type I in patients meeting the diagnostic criteria of the International Association for the Study of Pain.'* Eur J Pain15(8);830, pp. 1–8.

de Mos M., de Bruijn A.G., Huygen F.J., Dieleman J.P., Stricker B.G., Sturkenboom M.C. (2006) *'The incidence of complex regional pain syndrome.'* Pain;129; pp. 12–20.

den Hollander M., Goossens M., de Jong J., Ruijgrok J., Oosterhof J., Onghena P., Smeets R., Vlaeyen J. (2016) *'Expose or protect? A randomized controlled trial of exposure in vivo versus pain-contingent treatment as usual in patients with Complex Regional Pain Syndrome Type 1.'* Pain;157(10), pp. 2318–2329.

Dimitrijevic I.M., Lazovic M.P., Kocic M.N., Dimitrijevic L.R., Mancic D.D., Stankovic A.M. (2014) *'Effects of low-level laser therapy and interferential current therapy in the treatment of complex regional pain syndrome'* Turkish Journal of Physical Medicine and Rehabilitation, 60(2), pp. 98–105.

Duman I., Ozdemir A. Tan A.K., Dincer K. (2009) 'The efficacy of manual lymphatic drainage therapy in the management of limb edema secondary to reflex sympathetic dystrophy.' Rhemuatol. Int., 29(7), pp. 759–763.

Eisenberg E. , Chistyakov A.V., Yudashkin M., Kaplan B., Hafner H., Feinsod M. (2005) *'Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: A psychophysical and transcranial magnetic stimulation study.'* Pain, 115, pp. 219–220.

Ekrol I., Duckworth A.D., Ralston S.H. ,Court-Brown C.M., McQueen M.M. (2014) *'The influence of vitamin C on the outcome of distal radial fractures: a double-blind, randomized controlled trial.'* J Bone Join Surg Am; 96(17), pp. 1451–1459.

Evaniew N., Kleinlugtenbelt Y.V., McCarthy C., Gheret M., Bhandari M. (2015) *'Vitamin C to Prevent Complex Regional Pain Syndrome in Patients With Distal Radius Fractures: A Meta-Analysis of Randomized Controlled Trials.'* J Orthop Trauma, 29(8), pp. 235–241.

Goebel A., Barker C.H., Turner-Stokes L. *et al.* (2018) *'Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care.'* London: RCP.

Harden R.N., Bruehl S. (2006) *'Diagnosis of Complex Regional Pain Syndrome: Signs, symptoms and new empircally deriverd diagnostic criteria.'* Clinical Journal of Pain, 22(5), pp. 415–419.

Johnson S., Hall J., Barnett S. (2012) *'Using graded motor imagery for complex regional pain syndrome in clinical practice: Failure to improve pain.'* European Journal of Pain,; pp. 550–561.

Kalita J., Misura U., Kkumar A., Bho S.K.' (2016) *'Long-term Prednisolone in Post-stroke Complex Regional Pain Syndrome.'* Pain Physician, Nov-Dec; 19(8); pp. 565–574.

Kozin F., McCarty D.J., Sims J. *et al.* (1979) *'The reflex sympathetic dystrophy syndrome. I. Clinical and histologic studies: evidence for bilaterality, response to corticosteroids and articular involvement.'* Am J Med, 60, pp. 321–331.

Nyn *'Term Glucocorticoid Treatment Normalizes the Microcirculatory Response to Remote Ischemic Conditioning in Early Complex Regional Pain Syndrome.'* Pain Pract.,19(2), pp. 168–175.

Lagueux E., Charest J., Lefrançois-Caron E. (2012) *'Modified graded motor imagery for complex regional pain syndrome type 1 of the upper extremity in the acute phase: a patient series.'* International Journal of Rehabilitation Research, 35(2), pp. 138–145.

Laumonerie P., Martel M., Tibbo M.E., Azoulay V., Mansat P., Bonnevialle N. (2019) *'Influence*

of vitamin C on the incidence of CRPS-I after subacromial shoulder surgery.'

Lee J.W., Lee S.K., Chov W.S. (2018) *'Complex Regional Pain Syndrome Type 1: Diagnosis and Management.'* J Hand Surg Asian Pac Vol., Mar;23(1): pp. 1–10.

Maihöfner C., Handwerker H.O., Neundörfer B., Birklein F. (2003) *'Patterns of cortical reorganization in complex regional pain syndrome.'* Neurology, 61(12); pp. 1707–1715.

Maihöfner C., Handwerker H.O., Neundörfer B., Birklein F. (2004) *'Cortical reorganization during recovery from complex regional pain syndrome.'* Neurology, pp. 693–701 88.

Manicourt D.H., Brasseur J.P., Boutsen Y. (2004) *'Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity.'* Artritis Rheum.,Nov; 50 (11), pp. 3690–3697.

Merskey H., Bodguk N. (1994) *'Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms.'* In: Classificaion of chronic pain. vol. 2. Seattle: IASP Press.

Moseley G. L. (2004) *'Graded motor imagery is effective for long standing Complex Regional Pain Syndrome: A randomised controlled trial.'* Pain, 108; pp. 192–198.

Moseley G. L. (2005) *'Is successful rehabilitation of Complex Regional Pain Syndrome due to sustained attention to the affected limb? A randomised clinical trial.'* Pain,114: pp. 54–61.

Moseley G. L. (2006) *'Graded motor imagery for pathologic pain: A randomised controlled trial.'* Neurology;67, pp. 2129–2134.

Moseley GL, Wiech K. (2009) *'The effect of tactile discrimination training is enhanced when patients watch the reflected image of their unaffected limb during training'*, 144(3), pp. 314–319.

Nilgun Simsir Atalay, Ozlem Ercidogan, Nuray Akkaya, Fusun Sahin (2014) *'Prednisolone in Complex Regional Pain Syndrome.'* Pain Physician, 17:179–185.

Parkitny L., McAuley J.H., Di Pietro F. (2013) *'Inflammation in complex regional pain syndrome: a systematic review and meta-analysis.'* Neurology, 80(1), pp. 106–117.

Peikert A., Hentrich A., Echs G. (1991) *'Topical 0.0025% capsaicin in chronic post-herpetic neuralgia: Efficacy, predictors of response and long-term course.'* J Neurol., 238, pp. 452–456.

Perez R.S., Zuurmond W.W., Bezemer.PD., Kuik D.J., van Loenen A.C., de Lange J.J., Zuidhof A.J. (2003) *'The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study.'* Pain,102, pp. 297–307.

Pleger B., Ragert P., Schwenkreis P., Fo¨rster A.F., Wilimzig C., Dinse H., Nicolas V., Maier C., Tegenthoff M. (2006) *'Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome.'* Neuroimage, 32, pp. 503–510.

Pollard C., (2013) *'Physiotherapy management of complex regional pain syndrome'*, New Zealand Journal of Physiotherapy, 41 (2), pp. 65–72.

Robbins W.R., Staats P.S., Levine H.L., Allen R.W., Campbell J.N., Pappagallo P. (1987) *'Treatment of intactable pain with topical large dose of capsaicin: preliminary report.'* Anest Analg.,86, pp. 579–583.

Robinson J.N., Sandom J., Chapman P.T. (2004) *'Efficacy of pamidronate in complex regional pain syndrome type I.'* Pain Med, pp. 5: 276–280.

Russo M., Georgius P., Santarelli D.M. (2018) *'A new hypothesis for the pathophysiology of complex regional pain syndrome.'* Med Hypotheses., 119, pp. 41–53.

Sandroni P., Benrud-Larson L.M., McClelland R.L. (2003) *'Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study.'* Pain, pp. 103(1–2).

Sezgin Ozcan D., Tatli H.U., Polat C.S., Oken O., Koseoglu B.F. (2019) *'The Effectiveness of Fluidotherapy in Poststroke Complex Regional Pain Syndrome: A Randomized Controlled Study.'* J Stroke Cerebrovasc Dis.;28(6); pp. 1578–1585.

Sieweke N., Birklein F., Riedl B., Neunörfer B., Handwerker H.O. (1999) *'Patterns of hyperalgesia in complex regional pain syndrome.'* Pain, 80; pp. 171–177.

Tan A.K., Duman I., Taskaynatan M.A., Hazeneci B., Kalyon T.A. (2007) *'The effects of gabapentin in earlier stage of reflex sypathethic dystrophy.'* Clin Rheumatol.;26(4); pp. 561–565.

Uçceyler N., Eberle T., Rolke R., Birklein F., Sommer C. (2007) *'Differential expression patterns of cytokines in complex regional pain syndrome.'* Pain,132; pp. 14–15.

Uher E.M., Vacariu G., Schneider B., Fialka V. (2000) 'Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome, type I. A comparative randomized controlled therapy study.' Wien Klin Wochenschr.; 112(3), pp. 133–137.

Vaneker M., Wilder-Smith O.H., Schrombges P., de Man-Hermsen I., Oerlemans H.M. (2005) *'Patients initially diagnosed as "warm" or "cold" CRPS 1 show differences in central sensory processing some eight years after diagnosis: A quantitative sensory testing study.'* Pain,115; pp. 204–211.

van den Vusse A.C., Stomp-van den Berg S.G., Kessels S.H., Weber W.E. (2004) *'Randomised controlled trial of gabapentin in coplex regional pain syndrome.'* BMC Neurol.;4:13.

van Dieten H.E., Perez R.S., van Tulder M.W., de Lange J.J., Zuurmond WW, Ader HJ, Vondeling H, Boers M. (2003) *'Cost effectiveness and cost utility of acetylcysteine versus dimethyl sulfoxide for reflex sympathetic dystrophy.'* Pharmacoeconomics ;21:139–148.

Van Rooijen D.E., Roelen D.L., Verduijn W. (2012) *'Genetic HLA associations in complex regional pain syndrome with and without dystonia.'* J Pain, 13; pp. 784–789.

Varenna M., Zucchi F., Ghiringhelli D. (2000) *'Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study.'* J Rheumatol;27; pp. 1477–1483.

Varenna M., Adami S., Rossini M. *et al.* (2013) *'Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study.'* Rheumatology;52, pp. 534–542.

Zollinger P.E., Tuinebreijer W.E., Kreis R.W., Breederveld R.S. (1999) *'Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fracures: a randomise trial.'* Lancet; 354(9195), pp. 2025–2028.

Zollinger P.E., Tuinebreijer W.E., Kreis R.W., Breederveld R.S. (2007) *'Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study.'* J Bone Join Surg Am, 89; pp. 1424–1431.