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The Result of Combination of Medical and Physical Therapy in Complex Regional Pain Syndrome

Kompleks Bölgesel Ağrı Sendromunda Medikal ve Fizik Tedavi Kombinasyonunun Sonucu

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ABSTRACT Objective: Complex regional pain syndrome (CRPS) is distinguished from other chronic pain conditions with the existence of indications presenting inflammatory and autonomic changes in the painful area. The treatment contains a multidisciplinary approach covering a combination of pharmacological, physical, occupational, and psychological therapies. Therefore, the purpose of the trial is to evaluate the impact of combination of medical and physical therapy on the recovery process in patients with CRPS Type 1. **Material and Methods:** Seventy five patients (40 female, 35 male) with CRPS Type 1 were retrospectively collected. All patients were treated with medical and physical therapy. The state of health (very good, good, moderate, bad, very bad) and visual analog scale (VAS) before the treatments, 1 and 3 months after the treatments were collected from medical records. **Results:** In the study, the average age of patients was 54.47±11.30 years. VAS scores in the baseline, 1 and 3 months after the treatments were 8.59±0.50, 0.49±0.50, and 0.49±0.50, respectively. VAS in 1 and 3 months following the therapies statistically significantly reduced according to baseline ($p<0.001$). There was a statistically significant difference in health status 3 months after treatment compared to baseline ($p<0.001$). **Conclusion:** More targeted therapies should be determined in terms of the pathophysiology behind CRPS. Because of the complex pathological mechanism and often debilitating course and treatment-resistant nature of CRPS, a multidisciplinary approach may provide better results. Moreover, early and appropriate treatment can help resolve the syndrome and prevent prolonged pain, loss of function, and disability.

Keywords: Complex regional pain syndrome; medical treatment; physical therapy

ÖZET Amaç: Kompleks bölgesel ağrı sendromu (KBAS), diğer kronik ağrı durumlarından, ağrılı bölgedeki otonom ve inflamatuar değişiklikleri temsil eden işaretlerin varlığı ile ayrılır. Tedavisinde farmakolojik, fizik tedavi, mesleki ve psikolojik tedavilerin kombinasyonunu içeren multidisipliner bir yaklaşımı gerektirir. Bu nedenle bu çalışmanın amacı, KBAS Tip 1 hastalarında kombine medikal ve fizik tedavinin iyileşme sürecine etkisini değerlendirmektir. **Gereç ve Yöntemler:** KBAS Tip 1'e sahip olan 75 hasta (40 kadın, 35 erkek) retrospektif olarak toplandı. Tüm hastalara medikal ve fizik tedavi verilmişti. Tedavilerden önce ve tedavilerden 1 ve 3 ay sonraki hastaların sağlık durumu (çok iyi, iyi, orta, kötü, çok kötü) ile vizüel analog skala (VAS) değerleri geriye yönelik tıbbi kayıtlardan toplandı. **Bulgular:** Hastaların ortalama yaşı 54,47±11,30 yıl idi. Tedaviden önce ve tedaviden 1 ve 3 ay sonraki VAS skorları sırasıyla 8,59±0,50, 0,49±0,50 ve 0,49±0,50 idi. Tedaviden sonraki 1. ve 3. aydaki VAS skorları, başlangıçtaki VAS düzeyine kıyasla istatistiksel olarak anlamlı derecede azalmıştı ($p<0,001$). Tedaviden önce ve tedaviden sonraki 3 ay içindeki sağlık durumu arasında da istatistiksel olarak anlamlı fark vardı ($p<0,001$). **Sonuç:** KBAS'ın arkasındaki patofizyoloji açısından daha çok hedefe yönelik tedavilerin belirlenmesi gerekmektedir. KBAS'ın karmaşık patolojik mekanizması ve genellikle zayıflatıcı seyri ve tedaviye dirençli yapısı nedeniyle multidisipliner bir yaklaşım daha iyi sonuçlar sağlayabilir. Ayrıca erken ve uygun tedavi, sendromun çözülmesine ve uzun süreli ağrının, fonksiyon kaybının ve sakatlığın önlenmesine yardımcı olabilir.

Anahtar Kelimeler: Kompleks bölgesel ağrı sendromu; medikal tedavi; fizik tedavi

Complex regional pain syndrome (CRPS) is an unusual chronic pain condition that generally affects an arm or leg. CRPS is a complex of clinical symptoms characterized by severe pain, autonomic vasomotor and sudomotor dysfunction (clear alterations to skin coloring, skin temperature, and sweat concerning the uninfluenced part), edema of the skin and subcutaneous tissues, dystrophic changes of the skin

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and bones, disruption of active and passive movements in the affected extremity and psychological changes. There are two types of CRPS: Type 1 CRPS is the most common and develops after a limb injury and Type 2 CRPS, known as causalgia, describes a burning pain related to peripheral nerve injury.[1]

The mean age of CRPS ranges from 37-50 years and women are in the majority. It is reported that the ratio of females to males varies from 2 to 4. The incidence of Type 1 CRPS is 1-2% following fractures, 12% following brain injuries, 5% following myocardial infarction. The mean incidence of Type 2 CRPS is 4% after peripheral nerve injury. The plenty significant triggering condition in Type 1 CRPS is trauma influencing the distal part of the limb (65%), especially fracture in 16-46%, post-surgical status (for example after carpal tunnel surgery, after fasciectomy for Dupuytren contracture) in 3-24%, contusions, immobilization and overload in 8-18%. Asymmetric distal extremity pain and swelling develop without evidence of nerve injury in these patients.[1]

CRPS is separated into three phases of progression depending on the duration of symptoms. Phase I (acute phase: 0-3 months): This is described mainly by pain/sensory abnormalities (such as allodynia and hyperalgesia), indications of vasomotor dysfunction, and marked edema and sudomotor failure. It is well responsive to medical treatment. Phase II (dystrophic phase: 3-9 months): This is defined by more prominent pain/sensory dysfunction, continuous proof of vasomotor dysfunction (such as skin coloring alterations, temperature asymmetry, skin coloring dissymmetry), with the improvement of an important motor/trophic changes (such as reduced range of motion, motor dysfunction such as weakness, tremor, dystonia and trophic changes in hair/nail/skin). In this phase, there is a loss of minerals from bones (periarticular osteopenia) and patchy osteoporosis on X-ray imaging. Phase III (atrophic phase: 9-18 months): This is descriptive of reduced pain/sensory failure, continuous vasomotor disturbance, and remarkably raised motor/trophic changes.[1]

There are a wide variety of treatment options: a) medical treatment (topical analgesics, corticosteroids, tricyclic antidepressants, antiepileptics, calcitonin, bisphosphonates (BPs), calcium channel blockers, sympatholytic drugs, free radical scavengers, N-methyl-D-aspartate (NMDA) receptor antagonists, subcutaneous botulinum toxin injection); b) exercise and physical therapy [range of motion (ROM) and strengthening exercises, whirlpool, contrast baths, transcutaneous electrical nerve stimulation=transcutaneous electrical nerve stimulation (TENS)], and c) interventional treatments (sympathetic nerve-blocking, chemical, and surgical sympathectomy, spinal cord stimulation, spinal pumps, deep brain stimulation, surgery). The primary purposes of treatment are early diagnosis, thrusting and immediate start, relieving pain, functional healing and physiological amelioration.[1]

CRPS is a difficult condition to treat, usually manifested by life-long debilitating sequelae. Because of the complexity of CRPS, a multimodal treatment approach is often used to help improve therapy and functional outcomes. Clinical evidence suggests that every patient should be treated early and aggressively to prevent chronicity. Treatment requires a multidisciplinary approach including a combination of pharmacological, physical, occupational, and psychological therapies.[2-4] It is suggested that a multimodal pharmacologic regimen that combines several different classes (such as oral corticosteroids, anticonvulsants and BPs) may be superior and physical therapies (such as massage, elevation, TENS, contrast baths, gentle range of movement of the affected limb, and strengthening exercises) are important steps in the rehabilitation process in patients with CRPS.[5] Moreover, a multidisciplinary approach including pharmacotherapy, physiotherapy and interventional treatment should be applied properly to improve range of motion, avoid atrophy and contractures and reduce pain intensity. Although the effects of medical treatment or physical therapy were evaluated for CRPS in previous studies, there is no study evaluating the effect of combined treatment.[6] Therefore, the purpose of the trial is to evaluate the impact of combination of medical and physical therapy on the recovery process in patients with CRPS Type 1.

MATERIAL AND METHODS

This retrospective study was based on an analysis of the medical records of the patients with CRPS Type 1 who applied to the Department of Physical Therapy and Rehabilitation, Kocaeli State Hospital, Turkey between January 2019 and December 2019. The study protocol was approved by the Ethics Committee of Kocaeli University (Trial registration: KOU GOKAEK 2017/104). Written informed consent was obtained from all patients. The study was performed by the principles of the Helsinki Declaration.

Seventy five patients (40 female, 35 male) were included in this study. Inclusion criteria were the patients fulfilled the International Association for the Study of Pain clinical diagnostic criteria for CRPS Type 1 at acute and dystrophic phase and age between 18 and 80 years.[7] Exclusion criteria were the patients with CRPS Type 1 at atrophic phase, the presence of nerve damage in the affected area, the patients with diagnosed diabetes mellitus, psychiatric disorders, gastric ulcer and malignancy, a history of kidney and/or severe liver failure, another chronic pain syndrome such as fibromyalgia, phantom pain and rheumatoid arthritis, a relapse of CRPS Type 1, any previous treatment for CRPS, a history of neurological disorder (e.g. stroke, neurodegenerative disease or traumatic brain injury), pregnancy, lactation and other causes for the signs and symptoms such as non-union, osteomyelitis and active infections. The complete blood count, C-reactive protein, erythrocyte sedimentation rate, and serum rheumatoid factor were performed on whole patients for ruling out infections and rheumatologic conditions. The same medical and physical therapy was started immediately after the diagnosis was made in all patients at the outpatient clinic (Figure 1). All patients were treated with prega-

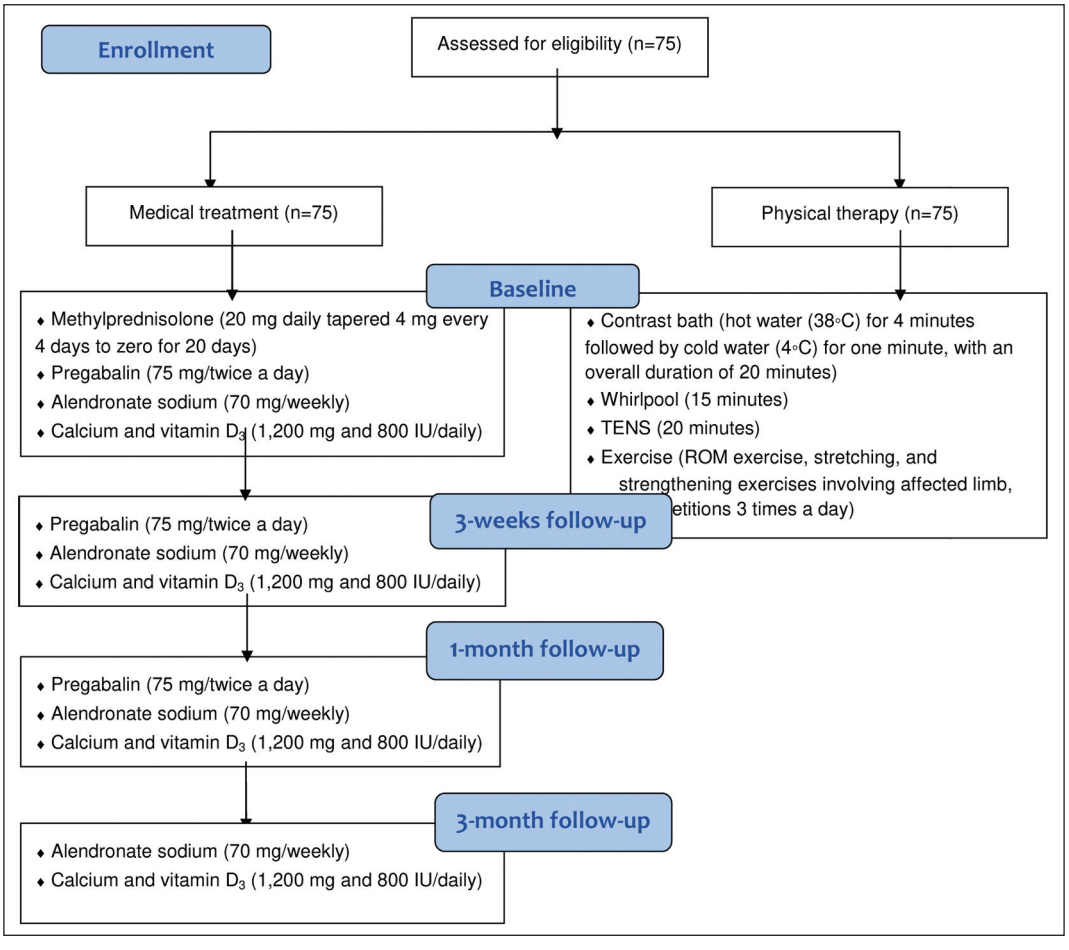

FIGURE 1: Flow diagram for treating patients with complex regional pain syndrome.
ROM: range of motion; TENS: Transcutaneous electrical nerve stimulation.

balin (75 mg/twice a day for 3 months), biphosphonates (BPs) such as alendronate sodium (70 mg/weekly for one year), calcium and vitamin D_3 (1,200 mg and 800 IU/daily for one year), an oral corticosteroid such as methylprednisolone (20 mg daily tapered 4 mg every 4 days to zero for 20 days). The patients were checked in the outpatient clinic for any side effects on the first 10th day, 20th day, 1st and 3rd months of the medical treatment. No side effect was observed with drug treatment. Also, physical therapy including contrast bath (hot water (38 ◦C) for 4 minutes followed by cold water (4 ◦C) for one minute, with an overall duration of 20 minutes), whirlpool (15 minutes), TENS (20 minutes), exercise (ROM exercise, stretching, and strengthening exercises involving affected limb, 10 repetitions 3 times a day) was given to all patients for 3 weeks.[21] All physical therapies were performed by two physiotherapists who are experts in their fields in the department of physical therapy. Applied treatment modalities were presented in Figure 1.

Data including age, sex, symptom duration, affected limb, side and bone, the etiology, the state of health (very good, good, moderate, bad, very bad), and the estimation of the severity of pain by the visual analog scale (VAS) before the treatments, 1 and 3 months after the treatments were collected from medical records. VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10).[8]

The state of health included decreased pain, edema, and hyperalgesia or allodynia and improvement in skin color, ROM, and muscle strength of the limb. The pain was classified as "no longer", "mild pain", "moderate pain" and "severe pain". Remaining or minimal pain, even if insignificant in the patients' daily lives, was grouped as "reduced pain". Edema, temperature asymmetry and skin color changes were determined by a visual comparison between the CRPS-affected and non-CRPS-affected limb without specialized equipment. It was grouped as "present", "some presence" or "not present". Hyperalgesia was evaluated by increased pain response to pinprick and allodynia was determined by painful response to light touch. It was grouped as "present" or "not present". Grip strength for the upper extremity and strength of dorsiflexors and plantar flexors of the ankle for the lower extremity was utilized for muscle strength to measure functioning. Weakness was determined by decreased strength compared to the unaffected side. The muscle strength of limb was stratified into "full muscle strength", "decreased muscle strength" and "no muscle strength". Evaluation of ROM was determined by examining the active and passive ROM of all proximal and distal joints of the affected limb. ROM was classified as "fully restricted", "functionally restricted" and "not restricted". "Fully restricted" ROM meant that patients were able to actively demonstrate the full ROM expected for healthy joints. "Functionally restricted" ROM indicated that patients were capable of using their affected limb for required activities but described or demonstrated residual joint stiffness. "Not restricted" ROM meant that ROM limitations significantly interfered with many of the patient's activities. The state of health was stratified into "very good", "good", "moderate", "bad" and "very bad". It also was presented in Table 1.

TABLE 1: The definition of the state of health.

Variables	Very good	Good	Moderate	Bad	Very bad
Edema	Not present	Not present	Some presence	Some presence	Present
Skin color changes	Not present	Not present	Not present	Some presence	Present
Temperature asymmetry	Not present	Not present	Not present	Some presence	Present
Hyperalgesia/allodynia	Not present	Not present	Not present	Present	Present
Pain	No longer	Mild pain	Moderate pain	Severe pain	Severe pain
ROM	Not restricted ROM	Not restricted ROM	Functionally restricted ROM	Fully restricted ROM	Fully restricted ROM
Muscle strength	Full muscle strength	Full muscle strength	Decreased muscle strength	Decreased muscle strength	No muscle strength

ROM: Range of motion.

STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Kolmogorov-Smirnov test was used to assess the assumption of normality. Continuous variables were presented with mean±standard deviation and median (minimum-maximum). Categorical variables were summarized as counts (percentages). Repeated VAS scores were compared using Friedman two way ANOVA and post hoc test Bonferronni correction was performed for pairwise comparisons. A marginal homogeneity test was used to test the differences between two related groups. All statistical analyses were carried out with 5% significance and a two-sided $p<0.05$ was considered statistically significant.

RESULTS

The demographic characteristics of patients including age, sex, duration of symptoms, affected limb, side and bone fracture, and the etiology were presented in Table 2. The mean age of patients was 54.47±11.30 years. Of all patients, 53.3% (n=40) are female and 46.7% (n=35) are male. The mean duration of symptoms is 2.02±1.00 months. The affected limb was 72% upper (n=54) and 28% lower (n=21). The etiology was 81.3% falling down (n=61), 10.7% traffic accident (n=8) and 8% industrial injury (n=6). The fracture is 40% distal radius (n=30), 12% proximal radius (n=9), 18.7% humerus (n=14), 9.3% talus (n=7), 5.3% calcaneus (n=4), 1.3% cuneiform (n=1) and 1.3% phalanx (n=1). The initial mean level of VAS, VAS in 1 and 3 months after the treatments were 8.59±0.50, 0.49±0.50, and 0.49±0.50, respectively (Table 3). VAS in 1 and 3 months following the therapies statistically significantly reduced according to baseline ($p<0.001$). There was no statistically significant difference between VAS in 1 and 3 months after the treatments ($p=1$). The state of health before treatments is 58.7% very bad and 41.3% bad. The state of health in 3 months after treatments is 50.7% very good and 49.3% good (Table 4). There was a statistically significant difference between the state of health before treatments and in 3 months after treatments ($p<0.001$).

TABLE 2: Patients' characteristics.

Variables	Group (n=75)
Age (years)	53 (36-79)
	54.47±11.30
Sex	
Female	40 (53.3%)
Male	35 (46.7%)
Affected limb	
Upper	54 (72%)
Lower	21 (28%)
Involved extremity	
Right	38 (50.7%)
Left	37 (49.3%)
Symptom duration (months)	2 (1-6)
	2.02±1.00
Etiology	
Falling down	61 (81.3%)
Traffic accident	8 (10.7%)
Industrial injury	6 (8%)
Involved bone fracture	
Distal radius	30 (40%)
Proximal radius	9 (12%)
Humerus	14 (18.7%)
Distal tibia	9 (12%)
Talus	7 (9.3%)
Calcaneus	4 (5.3%)
Cuneiform	1 (1.3%)
Phalanx	1 (1.3%)

All values are expressed as mean±standard deviation, number and percentage.

TABLE 3: Changes in visual analog scale before treatments and 1 and 3 months after the treatments.

Variables	VAS	p value
Before treatments	8.59±0.50	
	*9.00 (8.00-9.00)	
1 month after treatments	0.49±0.50	<0.001[a,b,c]
	*0.00 (0.00-1.00)	
3 months after treatments	0.49±0.50	<0.001[a,b,c]
	*0.00 (0.00-1.00)	

All values are expressed as mean±standard deviation. $p<0.05$, significant difference. *median (25^{th}-75^{th} percentile). [a]there is differences between before treatments and 1 month after treatments; [b]there is differences between before treatments and 3 months after treatments; [c]there is differences between 1 month after treatments and 3 months after treatments; VAS: Visual analog scale.

DISCUSSION

CRPS is distinguished from other chronic pain conditions with the existence of indications presenting

TABLE 4: The state of health before treatments and 3 months after treatments.

The state of health	Very bad	Bad	Good	Very good	p value
Before treatments	44 (58.7%)	31 (41.3%)			
3 months after treatments			37 (49.3%)	38 (%50.7)	<0.001

All values are expressed as mean±standard deviation. p<0.05, significant difference.

inflammatory and autonomic changes in the painful area. CRPS is frequently linked by critical deteriorations in skill to function and daily life activity. It could cause prominent physical and social disablement.[1] Immobilization is a well-known possible cause and/or persistent factor in CRPS.

Addressing the pain cycle resulting from CRPS results in further reduction of mobilization, which contributes to disease progression and worsening of pain.[6] The main principles of treatment in a patient with developing CRPS should be to reduce pain, remove vascular stasis, prevent developing contractures, and improve psychosocial problems in the late period.[2]

When evaluating symptoms and signs of these patients, it is significant for clinicians to notice the underlying pathophysiological mechanisms and use specific therapies to target these mechanisms. Therefore, it should be an alteration from a symptomatic to a more mechanism-based treatment for managing CRPS. The approach in the treatment of CRPS may be a mixture of several drugs and other interventions according to the symptomatology and comorbidities present. Although it has been suggested that there are good experiences with multidisciplinary treatment and these goals are achieved through attentive utilization of chosen medications, physchological and behavioral methods, and physical rehabilitation modalities in recent systematic reviews, there is no study in the literature evaluating the efficacy of combined treatments.[4,6,9] Therefore, in this study, the effect of combined therapy including medical and physical therapy were evaluated for CRPS Type 1, and the favorable outcomes was obtained early intervention with combination of medical and physical therapy.

CRPS occurs in women two or four times than in men. It mostly influences the upper extremities and appears between the age of 30 and 70.[10] This study, having between the ages of 38-78 and the superiority of female and upper limb, was consistent with the literature. The bone fractures seem to be a widespread triggering situation for the progress of CRPS. The informed incidence for CRPS after fractures of the upper and lower extremities is 32.2% for distal radius fracture, 28.1% for Colles' fracture, 7.9% for wrist fracture, 0% for scaphoid fracture, 30% for tibial fracture, 15.2% for ankle fracture and 2.9% for fifth metatarsal fracture.[11] The most common trigger in prevalent cases of CRPS is distal radius fracture as with most patients in this study.

The pathophysiology of CPRS is complicated and not completely understood as yet. The reason for arising failures is linked with aberrant reaction to tissue injury, neurogenic inflammation, disrupted sympathetic-afferent coupling, peripheral and central pain sensitization, endothelial dysfunction, somatosensory cortical reorganization, hyperalgesic priming, genetic predisposition, and autoimmunity.[12]

There are some contradictions about how initiating injury triggers the development of CRPS. The pro-inflammatory and immunological reaction linked by a starting damage is most significantly stimulating. Inflammation should be emerged both enzymatically by the cyclo-oxygenase pathway and non-enzymatically by an oxidative stress pathway. It was demonstrated that the values of pro-inflammatory mediators and neuropeptides (e.g. calcitonin gene-related peptide, substance P, bradykinin) and cytokines [e.g. prostaglandin estradiol, tumor necrosis factor alpha, interleukin (IL)-1β, IL-2 and IL-6] raise in the involved extremities, systemic circulation and cerebrospinal fluid of the patients with CRPS, especially in the acute stage. Moreover, it was noticed that the patients with CRPS have changed innate immune responses (such as broken down neutrophil ac-

tivity) and enhanced mast cells count and B cell activation. An increase in the immunoglobulin M and G antibodies, which cause a pronociceptive impact in the serum of these patients, has also been indicated. The pro-inflammatory and autoimmune processes all together stimulate the sympathetic nervous system and peripheral nerve fibers.[4,9,10,13] While non-steroid anti-inflammatory drugs only inhibit the enzyme of cyclooxygenase, steroids act in various inflammatory pathways.[4] According to this knowledge, it is considered that steroids should be utilized in the treatment of CRPS for both suppressing inflammation which appears to be an initial event and reducing the enhanced sympathetic activity secondary to inflammation. Therefore, steroid treatment was applied to all patients by reducing the dose for a certain period time, and the results of the study positively support the use of steroids in CRPS treatment.

The enhanced sympathetic nervous system outflow causes raised firing in the expression of catecholamine receptors on nociceptive fibers (Aδ and C-type fibers) in the involved region (sympatho-afferent coupling). The release of pro-inflammatory cytokines, inflammatory mediators (e.g. bradykinin), and pronociceptive neuropeptides (e.g. substance P) in conjunction with sympatho-afferent coupling lead to an increased response to painful stimulus and reduced nociceptive firing threshold for mechanical and thermal stimuli (peripheral sensitization). Not only the nerve growth factor (NGF) released by macrophages and mast cells but also the enhancement in the excitability of nociceptive neurons in the spinal cord initiates central sensitization. Glutamate, which is an excitatory amino acid, owns a part in central sensitization via the activation of spinal NMDA receptors. Both peripheral and central sensitization could participate in several typical properties of CRPS such as spontaneous pain, hyperalgesia, and allodynia.[4,10]

The act of steroids in the treatment of CRPS is related to the proposed inflammatory condition and autoimmune mechanisms.[4,10] However, in an in vitro study, while methylprednisolone infusion was influential on edema, spontaneous extravasation, and hind paw warmth by suppression of post-junctional substance P signaling, it had no impact on the periarticular bone loss or allodynia.[14] Moreover, a randomized study has been shown that oral steroids had a limited effect of more than 3 months in the treatment of CRPS.[15] Because both peripheral and central sensitization could participate in the several typical properties of CRPS such as spontaneous pain, hyperalgesia, and allodynia. For this reason, an anticonvulsant drug could be used with oral corticosteroids together. These medications stabilize excitable nerve membranes, alleviate neuronal hyperexcitability, and suppress segmentally and descending excitatory mechanisms. In a randomized controlled study, Van de Vusse et al. evaluated gabapentin and placebo effectiveness in the patients with CRPS Type 1 and observed an important pain reduction in the gabapentin group in the early period and it was expressed that this action disappeared in the long term and the patients returned to the initial values.[16] An animal model using chronic post-ischemic pain in anesthetized rats to simulate CRPS Type 1 pain recommended that standard analgesics are inactive as pregabalin was efficacious.[17] Pregabalin is also efficient for generalized anxiety disorder. It is also thought that pregabalin therapy should be used early because of hyperalgesia and allodynia which are symptoms in the early stage. For this reason, pregabalin was preferred to remove both sensitization and the vicious cycle and the progression from the chronic process since allodynia and hyperalgesia were among the symptoms present at the time of admission in all patients included in the study, and the results of the study were in parallel with this situation.

In the early phase, the typical indication of CRPS is subcortical and subchondral osteopenia in the involved extremity. Osteopenia is associated with the chemical dissolution of hydroxyapatite crystals due to tissue hypoxia, raised anaerobic glycolysis, and low local pH. The acidification of the extracellular environment through osteoclast activation leads to stimulate nociceptive acid-sensing receptors and release pro-inflammatory cytokines. It was demonstrated that there is an increased osteoclastic activity in CRPS Type 1. Not only BPs have a favorable influence on the healing of the disease owing to their antiresorptive features, but also they interact in a complicated behavior with the pathophysiological mechanisms underlying the disease. The effects of BPs except for

osteoclast inhibition are a) to prohibit the dissolution of hydroxyapatite crystals, b) to decrease the level of lactic acid, c) to repress the proliferation and activation of macrophages and monocytes, d) to alleviate the production of NGF and other cytokines and e) to prevent the apoptosis of osteoblasts and osteoclasts.[4,18]

Although other medications utilized in the treatment of CRPS act weak and part impacts in the short-term, BPs are further influential in the long-term on pain decline and functional healing. The possible useful impacts of BPs have been demonstrated in CRPS Type 1 in several clinical studies. Moreover, five randomized controlled trials have been shown that these medications (such as oral or intravenous alendronate and intravenous clodronate, pamidronate, and neridronate) are active in alleviating pain and rehabilitating physical function with a good profile of safety and tolerability. Even though these trials have some limitations such as small sample size, there is adequate proof to promote the utilization of BPs as preferred agents in the treatment of CRPS Type 1.[18] Moreover, osteoporosis is a risk factor for CRPS and was present in most patients in this study.[11] Although the rest of the patients had osteopenia, the T score of some lumbar vertebrae was -2.5 or above. Therefore, it is thought that BPs could be preferred as an additional treatment especially in patients detected osteoporosis via bone mineral densitometry (BMD).

Medical treatment could be initiated with additional physical therapy. The main issue that prohibits the patient from attending the treatment, due to reduced tolerance and motivation, is pain. Efficient physical therapy can be applied to the patients after satisfying pain control with medication. Early active mobilization physical therapy combined with medical treatment must be the primary therapy for CRPS. Additionally, the influential practice of early ROM exercises, before any existence of limb atrophy, contractures, or fibrosis, can improve not only finger ROM and swelling but also grip strength in patients. The treatment advice in the guideline contains pharmacological interventions purposed principally at reducing pain along with physical and/or occupational therapy.[4,19] A narrative review was suggested that physical therapy is taken into account as a first-line treatment in CRPS Type 1.[20] Moreover, physical therapy conduces principally to faster pain reduction, aberrant skin temperature, decreased edema, and mobility. Starting physical therapy at an early stage or immediately after diagnosis will be useful for chronic CRPS Type 1.[4,19] In a randomized controlled study, Bilgili et al. cross-checked TENS and placebo influence in the patients with CRPS Type 1 and indicated that the addition of TENS to the physical therapy program was seen to have an important addition to clinical healing.[21] Devrimsel et al. equated whirlpool bath and TENS in CRPS and demonstrated that both whirlpool bath and TENS are influential in the treatment of CRPS, but the impact of the whirlpool bath treatment was greater.[22] For this reason, the whirlpool bath and TENS were used as physical therapy and positive results were obtained in patients with the applied physical therapy methods.

As stated by the findings of the study, it has seemed that the combination of physical therapy and medical treatment rapidly alleviates the signs and symptoms of CRPS subsequent traumatic damages of the upper or lower limb, ensures sufficient pain control, reforms the functional talents and quality of life and turns back to the patient's daily activities.

Some limitations of this study include being retrospective, not only the medical treatment group, not only the physical therapy group, and no long-term consequences. Further studies comparing both medical therapy, physical therapy, and a combination of these treatments are needed.

CONCLUSION

Although no single treatment has been found to be universally effective, an inter-disciplinary approach to early diagnosis and treatment appears to be key to treat CRPS. Rather than addressing each of the pathophysiological factors that occur in CRPS independently of each other, it would be more logical to accept them to be in complex and interacting each other leading to the general manifestations of CRPS. The treatment modalities to be chosen should provide not only the relief of pain, but also the reversal of trophic changes, improvement of functionality and mood. Combining treatment options that target pathophysi-

ological factors that contribute to the onset of CRPS may conduce to good outcome. More randomized controlled trials are needed to test treatment combinations to determine the best treatment options for this potentially debilitating disorder.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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