의학석사 학위논문

Clinical factors influencing the outcomes of inpatient rehabilitation in patients with complex regional pain syndrome

복합부위통증증후군 환자의 입원재활치료 결과에 영향을 미치는 요인

2022년 2월

서울대학교 대학원

의학과 재활의학전공

김세훈

Clinical factors influencing the outcomes of inpatient rehabilitation in patients with complex regional pain syndrome

지도 교수 임재영

이 논문을 의학석사 학위논문으로 제출함

2021년 10월

서울대학교 대학원

의학과 재활의학전공

김세훈

김세훈의 의학석사 학위논문을 인준함

2021년 12월

위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

Abstract

Clinical factors influencing the outcomes of inpatient rehabilitation in patients with complex regional pain syndrome

Introduction: Patients with complex regional pain syndrome (CRPS) suffer from chronic refractory pain and a reduced quality of life. Providing timely and proper rehabilitation treatments can alleviate the pain, improve the quality of life, and reduce the burden of medical expenses. This study investigated factors influencing the effectiveness of inpatient rehabilitation in CRPS patients and identifies indications for such treatment.

Methods: We retrospectively reviewed medical records from January 2017 to June 2020. Patients over 18 years of age who were diagnosed with CRPS according to the Budapest criteria and received inpatient rehabilitation during that period were included. The rehabilitation program included medication, interventions, and physiotherapy. The primary outcome of the present study was the pain intensity at discharge minus the pain intensity at admission according to a numeric rating scale (NRS). To analyze the effect of inpatient rehabilitation on pain improvement, the following factors were analyzed: demographic factors, duration of disease, using an intravenous opioid as a rescue medicine, having a spinal cord stimulator, receiving scrambler treatment, CRPS severity score, CRPS type, region affected by CRPS, three-phase bone scan (TPBS) result, electromyography result, thermography result, and NRS score at admission. The Mann-Whitney test, simple linear regression test, and multiple regression analysis were performed to identify variables associated with pain improvement.

Results: A total of 51 patients (19 male and 32 female) were included. Patients without abnormalities in their TPBS had better pain relief than those with abnormalities (mean difference = 0.82, P = 0.041). However, patients without abnormalities in the

thermography test had worse outcomes than those with abnormalities (mean difference = 1.89, P = 0.032). Patients who had pain intensity ≥ 5 at initial admission had better results from inpatient rehabilitation than those who had pain intensity < 5 (mean difference = 1.49, P = 0.001). A simple linear regression test also revealed that the initial pain intensity significantly influences the effect of inpatient rehabilitation therapy, with the effect increasing with the initial pain intensity (R2 = 0.263, β = −0.486, P < 0.001). In the multiple regression analysis, only the initial pain intensity showed statistically significant results (adjusted R2 = 0.256, β = −0.584, P = 0.002).

Conclusions: Our results suggest that some clinical factors can affect the pain relief effect of inpatient rehabilitation. Severe initial pain intensity, abnormalities in a thermography test, and a lack of abnormalities in a TPBS gave better outcomes from inpatient rehabilitation. We suggest that these are indicators for inpatient rehabilitation therapy for patients with CRPS.

Key words: complex regional pain syndrome, inpatient rehabilitation

목 차

표 목차

그림 목차

1. Introduction

Complex regional pain syndrome (CRPS) is a deteriorating neurological condition with a prevalence of 5.4–26.2 per 100,000 person-years.[1] CRPS has a clinical diagnosis based on the patient's history and physical findings and can be classified into two types based on the absence (type I) or presence (type II) of identifiable major nerve injury.[2] CRPS is distinct from other pain syndromes in that it is characterized by the presence of autonomic dysfunction, persistent focal inflammatory changes, trophic impairment, and irrelevance of dermatomal distribution.[3] CRPS has a diverse course, ranging from a mild self-limiting condition to a chronic devastating disease that impairs the patient's normal daily activities and worsens their quality of life, thus exerting a significant economic burden on the healthcare system.[2,4] Some studies have suggested that a significant proportion of patients with CRPS remain disabled even after a long time.[5,6]

The treatment for CRPS is a combination of neuropathic pain medication, anti-inflammatory intervention techniques,[7,8] psychological therapy, and physical and occupational therapies.[9,10] The latter is a key component of the CRPS rehabilitation process and thus is recommended as the first-line treatment.[11] Physical therapy helps patients to overcome their kinesiophobia on affected limbs using multiple modalities, and occupational therapy encourages patient to use the affected limbs in their daily lives.[12,13,14] One systemic review analyzed 18 randomized controlled trials and found that multimodal physiotherapy programs may provide a small, long-term improvement in impairment, and graded motor imagery (GMI) may provide clinically meaningful medium- and long-term improvements in both disability and pain.[15] Another study suggested that a multidisciplinary rehabilitation program can significantly reduce pain and body perception disturbance.[16]

However, there are still many difficulties in diagnosis and

treatment due to a lack of understanding of the pathogenesis and nature of CRPS.[1,17] Also, rehabilitation is challenging for these patients due to the long-lasting pain and the fear of activity.[18,19] Appropriate and timely intervention for CRPS patients might reduce their impairment and prevent disability, and ultimately can improve quality of life and reduce the burden of medical expenses.[15] Therefore, finding factors related to effective treatment in CRPS patients is imperative for their proper management.

Recently, we developed a multidisciplinary rehabilitation program for CRPS patients. The program provides intensive inpatient rehabilitation treatment based on the timing and condition of the patients, followed by ongoing care through outpatient therapies. Some studies have suggested the effectiveness of multidisciplinary rehabilitation programs; however, the real-life effect is inconsistent.[1] Clinically, it is crucial to find relevant factors that can give a good prognosis after multidisciplinary rehabilitation. Therefore, this study aimed to investigate factors influencing the effectiveness of inpatient rehabilitation in CRPS patients and identify indicators for inpatient rehabilitation.

2. Materials and Methods

2.1. Study design and participants

In this study, we retrospectively reviewed the medical records of patients diagnosed with CRPS and who received inpatient rehabilitation treatment from January 2017 to June 2020. The inclusion criteria were clinically diagnosed CRPS according to the Budapest criteria,20 inpatient rehabilitation treatment at the department of rehabilitation medicine at Seoul National University Bundang Hospital, South Korea, and age > 18 years. The exclusion criteria were patients with infectious diseases or medical diseases being treated that impede proper rehabilitation treatment, pregnant patients or patients with obstetric problems, and insufficient medical records such as the pain intensity score or Budapest criteria. The study protocol was approved by our institutional review board (IRB no. B 2009/634 114).

2.2. Assessment and evaluation

A rehabilitation physician performed the examination for diagnosis of CRPS and functional evaluation for impairment and disability including the modified Barthel index (MBI), 10 meter walk test (10MWT), and Berg balance scale (BBS). Further examinations were determined considering the patient's current status and medical history of examinations and treatments prior to admission.[21,22] Three-phase bone scan (TPBS), nerve conduction study and needle electromyography (NCS/EMG), and thermography tests were sometimes performed, mainly to identify any objective findings of CRPS. TPBS is a commonly used imaging technique used to support a diagnosis of CRPS. A digital infrared thermography test was performed to evaluate the degree of temperature asymmetry. Electromyography was performed to differentiate CRPS types when peripheral nerve damage was suspected. Psychiatric evaluation included the Minnesota

Multiphasic Personality Inventory profiles and the Beck Depression Inventory (BDI II).

To investigate the effect of multimodal rehabilitation on pain improvement, the following patient details were analyzed: age, sex, body mass index (BMI), duration of disease, whether intravenous (IV) opioid was used as a rescue medicine during the admission period, whether the patient had a spinal cord stimulator (SCS), whether the patient received scrambler therapy, CRPS severity score (0–17) using the Budapest criteria,[23] the type of CRPS (I or II), the area affected by CRPS, TPBS result, NCS/EMG result, thermography result, and numeric rating scale (NRS) of pain intensity at initial admission. The areas affected by CRPS varied, including upper limbs, lower limbs, trunk, and whole body; we divided these areas into two groups: involving only one limb, and involving two or more limbs or areas beyond them. If TPBS, NCS/EMG, or thermography tests were performed during the admission period, those results were used to confirm the diagnosis of CRPS. However, if they were not, the results of any of these tests performed before admission were used regardless of whether they were performed in our hospital or another one. TPBS images were reviewed by radiologists who determined whether the test findings were in favor of CRPS based on the increase or decrease of the uptake in the blood flow, pool, and delayed phases.[22] Thermography was considered positive if the temperature difference between the CRPS-affected area and the unaffected area on the opposite side was >1℃.[24] NCS/EMG were performed and interpreted by a rehabilitation physician, and the test result was considered positive if there was a peripheral nerve lesion that was thought to be the cause of CRPS.

2.3. Inpatient management program for CRPS

CRPS, as its name suggests, has very complex and complicated characteristics, so a comprehensive and multidisciplinary approach is critical for the treatment of CRPS patients. To foster the

multidisciplinary approach, we have formed a pain consultation team consisting of anesthesiology, psychiatry, and rehabilitation medicine personnel (Fig. 1). When CRPS patients are admitted to our rehabilitation department, rehabilitation physicians take the role of primary doctor and consult a pain specialist and a psychiatrist for evaluation of the patient and to provide appropriate treatments. Psychiatrists evaluate a patient's mental state, such as the presence of depression or anxiety, prescribe medicines accordingly, and provide counseling services or biofeedback. This process of psychiatric diagnosis and treatment is essential for the proper treatment of CRPS patients.[25,26] Bean et al. suggested that a higher level of depression was associated with more significant disability in patients with CRPS.[27] As a pain relief strategy, pain specialists provide adequate interventional pain management, including minimally invasive pain treatments such as sympathetic nerve block, IV ketamine infusion, or epidural steroid injection.

The rehabilitation physician adapts the medications for pain control and establishes an appropriate rehabilitation plan based on a restorative or adaptive approach.[28] Pain medications include non-steroidal anti-inflammatory drugs, oral steroid pulse therapy, oral or IV opioids, benzodiazepine, and neuropathic pain medication such as pregabalin. The main goal of medication management during hospitalization is to minimize opioid analgesics and, especially, to reduce their IV dosing.

Our multimodal rehabilitation program consists of three treatment modalities: mechanism-based (GMI, desensitization, scrambler therapy), impairment-based, and cognitive behavioral therapy. GMI is widely used as a rehabilitation treatment method for CRPS.[29] The GMI proceeds in three stages: left and right discrimination, explicit motor imagery, and mirror therapy. If symptoms worsen, patients return to the previous stage of treatment.[30] Desensitization therapy is a gentle, controlled stimulation using massage, vibration, and movement to restore sensory processing.[31] Depending on the degree of hyperalgesia, allodynia, and localization, self-administered tactile stimulation and

desensitization techniques are implemented. If the desensitization therapy is performed too early, errors in pain memory may occur; therefore, it is performed after left and right discrimination indicates that it is possible. In recent years, scrambler therapy has been used to improve chronic pain, and it has been reported that it could be an effective option for CRPS in one case series.[32] We apply this therapy to patients unless the pain becomes so severe that it cannot not be tolerated. The frequency, intensity, and duration of stimulation are 43–52 Hz, 5 mA, and approximately 20 minutes, respectively. When the patient's pain is tolerable while moving the affected body part, we begin the impairment-based physical and occupational therapy for movement. This impairment-based and functional program is designed to be individualized for the conditions of each patient. In addition, it is provided step-by-step in a gradual manner that does not worsen CRPS symptoms (pain and swelling). The steps are pain-free active range of motion (ROM), isometric exercise, pain-tolerable active ROM, passive ROM and stretching, isotonic exercise, and functional training. Education on pain mechanism, coping strategies, and awareness of less painful motion are included as a cognitive behavioral treatment. Patients receive routine rehabilitation therapy, including GMI, desensitization, impairment-based physical therapy, and cognitive behavioral treatment twice per day for 30 minutes to 1 hour at each session. If applied, scrambler therapy is performed once or twice per week. The treatment steps for CRPS patients are summarized in Figure 2.

2.4. Outcome measures

The primary outcome for the present study was pain improvement during the admission period. For patients with CRPS, pain relief is a top priority for recovery.[33] To evaluate the degree of pain improvement, two variables were considered: the NRS at discharge minus the NRS at admission (NRSd), and the NRS at discharge divided by the NRS at admission (NRSr). There can be ceiling and

floor effects with NRSd; if it is used alone as the primary outcome, a similar degree of pain improvement may be exaggerated in patients with a higher initial pain level. For example, even if the pain improvement is the same extent of 50%, NRSd is 5 in patients with an initial pain score of 10, but 2 in those with an initial score of 4. Therefore, we adopted NRSr jointly as a primary outcome measure. Patients were asked to fill out a pain diary during the admission period and record their NRS pain score every hour. The NRS values at admission and discharge were calculated as the average of the pain diary values on the first and last days of hospitalization, respectively. If the patient did not complete the pain diary correctly or the diary data was missing, the first and last day values of NRS assessed by their rehabilitation therapists were used.

The secondary outcome was pain improvement at 6 months after discharge. NRS pain scores 6 months after discharge were obtained for patients who received outpatient rehabilitation treatment after discharge or whose pain intensity was evaluated in an outpatient clinic. The NRS at 6 months after discharge was calculated as the average of the scores at 5–7 months after discharge. To identify the long-term pain relief effect of inpatient treatment for patients with CRPS, the difference between the NRS at hospitalization and the NRS at 6 months after discharge was analyzed for two variables: the NRS at 6 months after discharge minus the NRS at admission (NRSd6), and the NRS at 6 months after discharge divided by the NRS at admission (NRSr6).

2.5. Statistical analysis

The Shapiro–Wilk test was used to determine whether the values followed a normal distribution. The Mann–Whitney test was performed for univariable analysis to identify the effect of the following variables: sex, duration of disease as two groups ($\leq$ 6 months vs > 6 months), whether IV opioid was used, whether the patient had an SCS, whether the patient received scrambler therapy, CRPS severity score as two groups ($\leq$ 11 vs > 11), type of CRPS,

affected region of CRPS (only one limb involved vs any other regions), TPBS result, NCS/EMG result, thermography result, and NRS at initial admission as two groups (≤ 5 vs > 5). A simple linear regression test was used when the independent variable was a continuous variable (age, BMI, duration of disease, CRPS severity score, or NRS at initial admission). In multivariable analysis, we used a stepwise method to identify the effect of the independent variables above on NRSd and NRSr; the selection method of the stepwise method was set to an entry value of 0.05 and a removal value of 0.1. In multivariable analysis, we included the following variables: age, BMI, duration of disease, CRPS severity score, and NRS at admission as continuous variables and sex, use of IV opioid, having an SCS, receiving scrambler treatment, CRPS type, region of CRPS, TPBS, and thermography result were converted into dummy variables. Because the CRPS type was determined by the NCS/EMG result, we assumed that the correlation between the two variables was high and therefore excluded the latter from multivariable analysis. Finally, the Mann–Whitney test and a simple linear regression test were used to identify the effects of NRS at initial admission on NRSd6 and NRSr6. Statistical analysis was performed using the SPSS program (version 19; SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Data are presented as mean ± standard deviation.

3. Results

3.1. Participant's demographics and clinical variables

A total of 51 patients who met the criteria were included in this study. Among them, 19 (37.3%) were male and 32 (62.7%) were female. The mean age was 35.3 ± 11.2 years, and the mean duration of disease was 3.26 ± 3.71 years. The mean CRPS severity score was 11.2 ± 2.90, and 28 (54.9%) patients had a severity score > 11. The mean NRS at admission was 5.83 ± 1.96. The patients' demographic and clinical variables are summarized in Table 1. Seventeen patients (33.3%) used an IV opioid during the admission period to manage acute pain. Fifteen patients (29.4%) had an SCS implanted before hospitalization and used it for pain control during hospitalization. Twenty-seven (52.9%) received scrambler therapy as an additional treatment. The areas affected by CRPS were diverse, with 19.6% involving the upper extremities, 62.7% involving the lower extremities, 5.9% involving both upper and lower extremities, and 11.8% involving the trunk or whole body. Among diagnostic studies, 35 patients had a bone scan, 28 patients had NCS/EMG, and 43 patients had thermography, with positive test results in 51.4%, 32.1%, and 88.4% of these patients, respectively. Only nine patients (17.6%) were diagnosed with CRPS type II. The mean NRS at admission was 6.01 in CRPS type I patients and 4.97 in type II patients. After multimodal rehabilitation, pain improved by 0.67 points in patients with CRPS type I; however, it worsened by 0.96 points in patients with CRPS type II, although this result was not statistically significant. Functional assessment at admission was performed via BBS in 50 patients, 10MWT in 47 patients, and MBI in 42 patients, with mean scores of 43.38 ± 14.96, 22.10 ± 19.83 s, and 84.76 ± 13.10, respectively. BDI II results were obtained before admission and 1 year after the date of admission in 32 patients, with a mean score of 33.50 ± 12.82. Of the 32 patients, 23 had severe depression, four had moderate depression, two had mild depression,

and three did not have depression.

The mean admission period of patients was 16.29 ± 4.53 days, and the mean number of treatment sessions during the admission period was 28.06 ± 15.96. The treatment sessions included all types of rehabilitation therapy and functional evaluation. The duration of the treatment sessions varied from a minimum of 30 minutes to a maximum of 1 hour, depending on the patient's condition.

3.2. Primary outcome

The mean NRS at discharge of all 51 patients was 5.30 ± 1.89, and the mean NRSd was −0.53 ± 1.86. For NRSd, patients without abnormalities in the TPBS test had significantly better pain relief than those with abnormalities (mean difference = 0.82, P = 0.041). However, this result was not statistically significant for NRSr (P = 0.057). For both NRSd and NRSr, patients with abnormalities in the thermography test had better outcomes than those without abnormalities (NRSd: mean difference = 1.89, P = 0.032; NRSr: P = 0.021). Patients who had a pain intensity NRS > 5 at initial admission had better results from inpatient rehabilitation than those who had a pain intensity NRS ≤ 5 (NRSd: mean difference = 1.41, P = 0.002; NRSr: P = 0.001). Detailed results of the univariable analyses of the binary variables are listed in Table 2.

A simple linear regression test revealed that the initial pain intensity significantly influenced the effect of inpatient rehabilitation therapy, with the effect increasing with initial pain intensity (NRSd: R2 = 0.263, β = −0.486, P < 0.001; NRSr: R2 = 0.357, β = −0.106, P < 0.001; Table 3, Fig. 3.1). There were no statistically significant results in the simple linear regression test for age, BMI, duration, or CRPS severity score. In the multiple regression analysis, only initial pain intensity showed statistically significant results (NRSd: adjusted R2 = 0.256, β = −0.584, P = 0.002; NRSr: adjusted R2 = 0.258, β = −0.099, P = 0.002).

3.3. Secondary outcome

NRS at 6 months after discharge was only available in 18 patients, who had NRS evaluation data at least once between 5 and 7 months after discharge. Of the 18 patients, seven had an NSR at admission score $\leq$ 5, and 11 had this > 5. The mean NRSd6 was 0.26 $\pm$ 1.71, which means that the pain at 6 months after discharge was slightly worse than the pain at the time of admission. Patients who had a pain intensity > 5 at initial admission showed much better pain improvement at 6 months after discharge than those with a pain intensity $\leq$ 5 (NRSd6: mean difference = 2.14, P = 0.008; NRSr6: P = 0.011; Table 2). Figure 4 shows the NRS at admission, discharge, and 6 months after discharge in these two groups. In both groups, the pain was worse at 6 months after discharge than at discharge.

Finally, simple linear regression tests to identify the effects of NRS at initial admission on NRSd6 and NRSr6 showed that the initial pain intensity also significantly influenced the long-term effect of inpatient rehabilitation therapy (NRSd6: R2 = 0.528, β = −0.540, P = 0.001; NRSr6: R2 = 0.508, β = −0.275, P = 0.001; Table 3, Fig. 3.2).

4. Discussion

In this study, we investigated factors that affect the pain improvement of inpatient rehabilitation in CRPS patients. This study is meaningful in that it investigated factors that could predict feasibility, responsiveness, and effectiveness in inpatient rehabilitation by systematically designing an interdisciplinary multimodal rehabilitation program. The main finding of our study is that such treatment caused better pain relief in patients with more severe pain at the initial assessment. This finding was statistically significant in both the two-group analysis based on an NRS value of 5 and the simple linear regression analyses for both NRSd and NRSr.

Various methods, including GMI, desensitization, scrambler therapy, impairment-based physical and occupational therapy, and cognitive behavioral treatment, have been proposed for the rehabilitation of CRPS patients.[4,11,12] However, in most of the previous studies, each treatment was analyzed separately. In our study, we designed a multimodal inpatient rehabilitation program tailored to each individual patient's condition and focused on a step-by-step approach for rehabilitating CRPS patients. Each step consists of specific rehabilitation programs optimized for pain tolerance and the CRPS status. In addition to rehabilitation treatment, a multidisciplinary team approach that included anesthesiology and psychiatry was implemented in this program. Raque et al. also investigated the effectiveness of interdisciplinary multimodal inpatient pain therapy in patients with CRPS.[34] In that study, the average length of stay was 37.5 days, and 265 patients were included, of whom 99 received a peripheral nerve block with local anesthetics. The authors found that after their inpatient rehabilitation program, pain was significantly improved. However, there were no results to suggest that the initial pain intensity affected the degree of improvement in inpatient rehabilitation.

Park et al. suggested that the depression of CRPS patients is different from patients with major depressive disorder.[35] CRPS

patients had better emotional regulation and were more psychologically adaptable. However, CRPS patients should be evaluated and treated for distress. In the present study, 29 of 32 patients had depression, of whom 23 were severely depressive. However, this result is likely to be an adaptive response to pain rather than a true emotional dysregulation in CRPS patients. In the present study, patients received 28.06 sessions of rehabilitation during the 16.29 days of the admission period. This number of rehabilitation treatments during hospitalization was less than expected, with treatments not being performed on holidays or weekends, and in cases in which the patient complained of sudden catastrophic pain and refused a session.

In patients with severe initial pain scores, pain improvement following inpatient rehabilitation was greater than that in patients with less severe pain. Also, considering the regression equation in the simple linear regression test (Fig. 3), the NRSd had a negative value, which means pain improvement after admission, if the NRS at admission of patients was > 4.737. In our multivariate analyses, statistical significance was found only for NRS at admission. Lee et al. suggested that a moderate or severe initial pain score (NRS = 5–10) was an independent predictor of a better treatment outcome.[36] However, the study differed from the present one in that it was an analysis of outpatient–based treatment and the proportion of men to women was much higher. Also, they did not suggest any possible mechanism for this result. Rehabilitation treatment programs, including GMI, desensitization, scrambler therapy, and impairment–based treatment, may exacerbate pain in CRPS patients, especially with mild pain. In fact, many patients complained of more severe pain immediately after rehabilitation. However, for patients with severe initial pain, the improvement of pain due to the rehabilitation treatment may outweigh any extra pain that the treatment itself caused. Also, patients with a low pain intensity may have had less willingness to comply with treatment. The degree to which the rehabilitation physician prescribed pain medications may also affect this result. If the pain is not severe, the

rehabilitation physician may have tried to reduce the use of pain medications as much as possible, whereas they may have prescribed pain medications such as opioids more aggressively in patients complaining of severe pain. Finally, there can be ceiling and floor effects with NRSd. For example, if the patient's NRS at admission was 1, then the maximum score for pain improvement is only 1.

When we analyzed the NRS at 6 months after discharge in 18 patients, the correlation between the initial NRS and NRSd6 was significant. In simple linear regression tests, the R2 was 0.528 and the β was −0.540 for NRSd6, and the R2 was 0.263 and the β was −0.486 for NRSd. However, in the long−term follow−up result, although the effect was small (0.26), the average pain score had worsened. In patients with an initial NRS score ≤ 5, the NRSd6 was 1.57. Although the number of patients evaluated at 6 months was small (18), the R2 was 0.528 in the 6 month follow−up study. Thus, it can be postulated that inpatient rehabilitation treatment results in pain improvement in patients with moderate to severe pain intensity, and this tendency is more pronounced in the long term.

The CRPS severity score is an index of CRPS severity, like the NRS pain score; however, there was no statistically significant result with this variable. Harden et al.[23] found that a higher CRPS severity score was significantly associated with a higher pain intensity. However, in this study, we did not find a significant association between the CRPS severity score and the NRS at admission under Pearson correlation analysis (P = 0.236). Since the components of the CRPS severity score are mainly objective findings, they may not reflect the patient's symptoms and level of impairment well. Previous studies mainly focused on the diagnostic value of TPBS and thermography. However, we found no previous studies on how the results of these tests affect the treatment of CRPS patients. Under univariate analysis, the thermography test results showed significant associations with both NRSd and NRSr. However, this significance was not confirmed by the multivariate

analysis, and only five of the 43 patients who had undergone a thermography test received negative results. Also, TPBS was significant only for NRSd. However, this significance was not confirmed in the NRSr and there was no statistical significance under the multivariate analysis. Therefore, although the results of univariate analysis of thermography and TPBS were statistically significant, this seems to have limited clinical meaning. Therefore, we can deduce that the effects of the various indicators and objective tests for diagnosing and tracking CRPS, other than the initial pain intensity, on inpatient rehabilitation are not significant.

This study has some limitations. The number of patients we reviewed was small. It is difficult to recruit many subjects due to the low incidence of CRPS and the requirement that they receive intensive inpatient rehabilitation treatment. Also, we used two-group, univariable, nonparametric statistical analysis, although the consistent results of NRS at admission for all outcomes (NRSd, NRd6, NRSr, and NRSr6) suggest that these results are significant despite this statistical limitation. There was also a lack of uniformity in the treatment method and evaluation. The therapist assigned to each patient, the rehabilitation doctors who performed and read the NCS/EMG, and the radiologists who read the TPBS results varied. For patients with pain diary data, these NRS values were used for the evaluation, but for the patients who lacked this, we used the value assigned by the therapist in the rehabilitation unit. Despite these limitations, we believe that this study has clinical significance, in that it is based on real-world data.

Our results suggest that some clinical factors can affect the pain relief effect of inpatient rehabilitation, with severe initial pain intensity giving better outcomes. From these results, we can suggest one indication for inpatient rehabilitation therapy for patients with CRPS, in that we recommend this for patients with moderate to severe pain intensity. Further studies are necessary to confirm the effect of clinical factors on inpatient rehabilitation and to identify further indications for this treatment.

Reference

1. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. *Br J Anaesth.* 2019;123(2):e424-e433.
2. Goh EL, Chidambaram S, Ma D. Complex regional pain syndrome: a recent update. *Burns Trauma.* 2017;5:2.
3. Petersen PB, Mikkelsen KL, Lauritzen JB, Krogsgaard MR. Risk Factors for Post-treatment Complex Regional Pain Syndrome (CRPS): An Analysis of 647 Cases of CRPS from the Danish Patient Compensation Association. *Pain Pract.* 2018;18(3):341-349.
4. Galve Villa M, Rittig-Rasmussen B, Moeller Schear Mikkelsen L, Groendahl Poulsen A. Complex regional pain syndrome. *Man Ther.* 2016;26:223-230.
5. Savas S, Baloglu HH, Ay G, Cerci SS. The effect of sequel symptoms and signs of Complex Regional Pain Syndrome type 1 on upper extremity disability and quality of life. *Rheumatol Int.* 2009;29(5):545-550.
6. Subbarao J, Stillwell GK. Reflex sympathetic dystrophy syndrome of the upper extremity: analysis of total outcome of management of 125 cases. *Arch Phys Med Rehabil.* 1981;62(11):549-554.
7. Hayashi K, Nishiwaki K, Kako M, et al. Combination of Continuous Epidural Block and Rehabilitation in a Case of Complex Regional Pain Syndrome. *J Nippon Med Sch.* 2016;83(6):262-267.
8. Goff BJ, Naber JW, McCallin JP, et al. Immediate Return to Ambulation and Improved Functional Capacity for Rehabilitation in Complex Regional Pain Syndrome following Early Implantation of a Spinal Cord Stimulation System. *Case Rep Anesthesiol.* 2014;2014:784021.
9. Urits I, Shen AH, Jones MR, Viswanath O, Kaye AD. Complex Regional Pain Syndrome, Current Concepts and Treatment Options. *Curr Pain Headache Rep.* 2018;22(2):10.
10. Zecevic Lukovic T, Ristic B, Jovanovic Z, Rancic N, Ignjatovic Ristic D, Cukovic S. Complex regional pain syndrome type I in the upper extremity - how efficient physical therapy and rehabilitation are. *Med Glas (Zenica).* 2012;9(2):334-340.
11. Ghai B, Dureja GP. Complex regional pain syndrome: a review. *J Postgrad Med.* 2004;50(4):300-307.

12. Karmarkar A, Lieberman I. Mirror box therapy for complex regional pain syndrome. *Anaesthesia.* 2006;61(4):412-413.
13. Kotsougiani-Fischer D, Choi JS, Oh-Fischer JS, et al. ICF-based multidisciplinary rehabilitation program for complex regional pain syndrome of the hand: efficacy, long-term outcomes, and impact of therapy duration. *BMC Surg.* 2020;20(1):306.
14. Rome L. The place of occupational therapy in rehabilitation strategies of complex regional pain syndrome: Comparative study of 60 cases. *Hand Surg Rehabil.* 2016;35(5):355-362.
15. Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev.* 2016;2:CD010853.
16. Lewis JS, Kellett S, McCullough R, et al. Body Perception Disturbance and Pain Reduction in Longstanding Complex Regional Pain Syndrome Following a Multidisciplinary Rehabilitation Program. *Pain Med.* 2019;20(11):2213-2219.
17. Miller C, Williams M, Heine P, Williamson E, O'Connell N. Current practice in the rehabilitation of complex regional pain syndrome: a survey of practitioners. *Disabil Rehabil.* 2019;41(7):847-853.
18. Nedeljkovic UD. How to treat complex regional pain syndrome in rehabilitation settings? *Acta Chir Iugosl.* 2013;60(1):69-75.
19. Veizi IE, Chelimsky TC, Janata JW. Complex [corrected] regional pain syndrome: what specialized rehabilitation services do patients require? *Curr Pain Headache Rep.* 2012;16(2):139-146.
20. Harden NR, Bruehl S, Perez R, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain.* 2010;150(2):268-274.
21. Melis M, Zawawi K, al-Badawi E, Lobo Lobo S, Mehta N. Complex regional pain syndrome in the head and neck: a review of the literature. *J Orofac Pain.* 2002;16(2):93-104.
22. Kwon HW, Paeng JC, Nahm FS, et al. Diagnostic performance of three-phase bone scan for complex regional pain syndrome type 1 with optimally modified image criteria. *Nucl Med Mol Imaging.* 2011;45(4):261-267.
23. Harden NR, Bruehl S, Perez R, et al. Development of a severity score for CRPS. *Pain.* 2010;151(3):870-876.

24. Park SH LP, Lim YH, Lee SY, Choi IY, Lee SJ. The usefulness of three-phase bone scan and thermography for making the diagnosis of CRPS-I. *Korean J Pain.* 2006;19:81-86.
25. Brinkers M, Rumpelt P, Lux A, Kretzschmar M, Pfau G. Psychiatric Disorders in Complex Regional Pain Syndrome (CRPS): The Role of the Consultation-Liaison Psychiatrist. *Pain Res Manag.* 2018;2018:2894360.
26. Cruz N, O'Reilly J, Slomine BS, Salorio CF. Emotional and neuropsychological profiles of children with complex regional pain syndrome type-I in an inpatient rehabilitation setting. *Clin J Pain.* 2011;27(1):27-34.
27. Bean DJ, Johnson MH, Heiss-Dunlop W, Kydd RR. Factors Associated With Disability and Sick Leave in Early Complex Regional Pain Syndrome Type-1. *Clin J Pain.* 2016;32(2):130-138.
28. Harden RN, Swan M, King A, Costa B, Barthel J. Treatment of complex regional pain syndrome: functional restoration. *Clin J Pain.* 2006;22(5):420-424.
29. Mendez-Rebolledo G, Gatica-Rojas V, Torres-Cueco R, Albornoz-Verdugo M, Guzman-Munoz E. Update on the effects of graded motor imagery and mirror therapy on complex regional pain syndrome type 1: A systematic review. *J Back Musculoskelet Rehabil.* 2016.
30. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain.* 2004;108(1-2):192-198.
31. Stanton-Hicks M, Baron R, Boas R, et al. Complex Regional Pain Syndromes: guidelines for therapy. *Clin J Pain.* 1998;14(2):155-166.
32. Raucci U, Tomasello C, Marri M, Salzano M, Gasparini A, Conicella E. Scrambler Therapy((R)) MC-5A for Complex Regional Pain Syndrome: Case Reports. *Pain Pract.* 2016;16(7):E103-109.
33. Llewellyn A, McCabe CS, Hibberd Y, et al. Are you better? A multi-centre study of patient-defined recovery from Complex Regional Pain Syndrome. *Eur J Pain.* 2018;22(3):551-564.
34. Raque J, Chung BY, Benrath J. [Effectiveness of inpatient interdisciplinary multimodal pain therapy (IMPT) in patients with complex regional pain syndrome (CRPS) : A retrospective study]. *Schmerz.* 2021.
35. Park HY, Jang YE, Oh S, Lee PB. Psychological Characteristics in Patients with Chronic Complex Regional Pain Syndrome: Comparisons with

Patients with Major Depressive Disorder and Other Types of Chronic Pain. *J Pain Res.* 2020;13:389-398.

36. Lee HJ, Lee CS, Yoo Y, et al. Complex regional pain syndrome in the young male population: a retrospective study of 200 Korean young male patients. *Korean J Pain.* 2019;32(4):292-300.

국문 초록

복합부위통증증후군 환자의 입원재활치료 결과에 영향을 미치는 요인

서울대학교 대학원
의학과 재활의학전공
김세훈

주요어 : 입원재활치료, 복합부위통증증후군
학 번 : 2020-20285

복합부위통증증후군(CRPS)환자는 만성 통증과 삶의 질 저하로 고통받는다. 이 환자들에게 시기 적절하고 적합한 재활 치료를 제공하면 통증을 완화하고 삶의 질을 향상시키며 의료비 부담을 줄일 수 있다. 이 연구는 CRPS 환자에서 입원환자 재활의 효과에 영향을 미치는 요인을 조사하고 입원환자 재활의 적응증을 확인하는 것을 목적으로 한다.

환자의 의무기록을 2017년 1월부터 2020년 6월까지 후향적으로 분석하였다. 부다페스트 기준에 따라 CRPS로 진단되어 해당 기간 동안 입원 재활치료를 받은 18세 이상의 환자를 본 연구의 대상으로 하였다. 입원재활치료로는 약물 치료, 통증에 대한 중재 시술 및 물리 치료가 포함되었다. 주요 결과는 숫자 등급 척도(NRS)로 표기된 통증 점수의 입원시점과 비교하여 퇴원 시점에서의 호전 정도이다. 퇴원 시 통증 강도 값에서 입원 시 통증 강도 값을 뺀 값이다. 입원재활이 통증 개선에 미치는 영향을 분석하기 위해 인구통계학적 요인, 유병 기간, 정맥 아편계 약물 사용 여부, 척수 자극기 보유 여부, 스크램블러 치료를 받았는지 여부, CRPS 중증도 점수, CRPS 유형, CRPS 이환 부위, 3상 골스캔 검사 결과, 근전도 결과, 열화상 검사 결과 및 입원 시점에서의 NRS 점수를 요인으로 분석하였다. 통계방법으로는 Mann-Whitney 테스트와 단순 선형 회귀 분석 및 다중 회귀 분석을 하였다.

총 51명(남 19/여 32)의 환자가 포함되었다. 3상 골스캔 검사 검사에서 이상이 없는 환자는 검사에서 이상이 있는 환자보다 통증 완화 정도가 더 좋았다. (평균 차이: 0.82; P=0.041) 그러나 열화상 검사에서 이상이 없는 환자는 검사에서 이상이 있는 환자보다 치료에 대한 반응이

더 안 좋았다. (평균차: 1.89; P=0.032) 초기 입원 시 통증 강도가 5점 이상이었던 환자는 입원 당시 통증 강도가 5 미만이었던 환자보다 입원 재활의 결과가 더 좋았다. (평균 차이: 1.49; P=0.001) 단순선형회귀검사에서도 초기 통증 강도가 입원환자 재활치료의 효과에 유의한 영향을 미치는 것으로 나타났으며, 초기 통증 강도가 높을수록 입원환자 재활치료의 효과가 높은 것으로 나타났다. ($R2=0.263$, $\beta = -0.486$; $P<0.001$) 다중회귀분석에서는 초기 통증 강도만 통계적으로 유의한 결과를 보였다. (adjusted $R2=0.256$, $\beta = -0.584$, $P=0.002$)

이번 연구 결과는 일부 임상 요인이 입원 환자 재활의 통증 완화 효과에 영향을 미칠 수 있음을 시사한다. 심한 초기 통증 강도, 열화상 검사에서 이상이 있는 경우, 3상 골스캔 검사에서 이상이 없는 경우 입원 재활에서 더 나은 결과를 보였다. 이러한 결과로부터 CRPS 환자의 입원환자 재활치료 적응증을 제시할 수 있을 것이다.

Table1. Participant's demographics and clinical variables

	Mean ± Standard deviation
Age (yrs)	35.30 ± 11.18
Duration (yrs)	3.26 ± 3.71
CRPS Severity score	11.16 ± 2.90
NRS at admission	5.83 ± 1.96
BMI	24.89 ± 5.00
	No. (%)
Sex	
Male	19 (37.3%)
Female	32 (62.7%)
IV opioid	
Used	17 (33.3%)
Not used	34 (66.7%)
SCS	
Used	15 (29.4%)
Not used	36 (70.6%)
Scrambler treatment	
Received	27 (52.9%)
Not received	24 (47.1%)

CRPS type	
Type1	42 (82.4%)
Type2	9 (17.6%)
Limb involvement	
Upper extremity	10: (19.6%)
Lower extremity	32: (62.7%)
Both	3: (5.9%)
Others	6: (11.8%)
One limb	34 (66.7%)
More than one limb	17 (33.3%)
TPBS (35)	
Positive	18 (51.4%)
Negative	17 (48.6%)
NCS/EMG (28)	
Positive	9 (32.1%)
Negative	19 (67.9%)
Thermography (43)	
Positive	38 (88.4%)
Negative	5 (11.6%)
Duration group	
6M or less	12 (23.5%)
more than 6M	39 (76.5%)
Severity group	

11 or less	23 (45.1%)
more than 11	28 (54.9%)
NRS at admission group	
5 or less	19 (37.3%)
more than 5	32 (62.7%)

Table2. Mann-Whitney results for the primary and secondary

Variables	NRSd				NRSr		
	Group1 Mean	Group2 Mean	Mean difference	P value	Group1 Mean	Group2 Mean	P value
Sex	−0.30	−0.67	0.37	0.609	1.0037	0.9615	0.651
IV opioid	−0.48	−0.56	0.08	0.936	0.9609	0.9854	0.825
SCS	−0.63	−0.49	0.14	0.867	0.9415	0.9921	0.983
Scrambler treatment	−0.30	−0.80	0.50	0.065	1.0157	0.8078	0.083
CRPS type	−0.67	0.96	1.63	0.818	0.9352	1.1733	0.818
Limb involvement	−0.44	−0.71	0.27	0.250	1.0132	0.9053	0.259
TPBS	−0.39	−1.21	0.82	0.041*	0.9805	0.8720	0.057
NCS/EMG	0.99	−0.29	1.28	0.595	1.1788	0.9993	0.735
Thermography	−0.69	1.20	1.89	0.032*	0.9467	1.3666	0.021*
Duration group	−0.95	−0.41	0.54	0.929	0.9630	0.9816	0.911
Severity group	−0.63	−0.45	0.18	0.492	0.9947	0.9629	0.593
NRS at admission	0.35	−1.06	1.41	0.002**	1.1710	0.8622	0.001**
Variables	NRSd6				NRSr6		

	Group1 Mean	Group2 Mean	Mean difference	P value	Group1 Mean	Group2 Mean	P value
NRS at admission	1.57	−0.57	2.14	0.008**	1.8305	0.9279	0.011*

Group 1: sex, male; IV opioid, used; SCS, used; scrambler treatment, received; CRPS type, I; limb involvement, one limb; TPBS, positive; NCS/EMG, positive; thermography, positive; duration group, ≤ 6 months; severity group, ≤ 11; NRS at admission, ≤ 5.

Group 2: sex, female; IV opioid, not used; SCS, not used; scrambler treatment, not received; CRPS type, II; limb involvement, more than one limb; TPBS, negative; NCS/EMG, negative; thermography, negative; duration group, > 6 months; severity group, > 11; NRS at admission, > 5.

*P < 0.05, **P < 0.01.

CRPS, complex regional pain syndrome; IV, intravenous; NCS/EMG, nerve conduction study and needle electromyography; NRS, numeric rating scale; NRSd, NRS at discharge minus NRS at admission; NRSd6, NRS at 6 months after discharge minus NRS at admission; NRSr6, NRS at 6 months after discharge divided by NRS at admission; SCS, spinal cord stimulator; TPBS, three−phase bone scan.

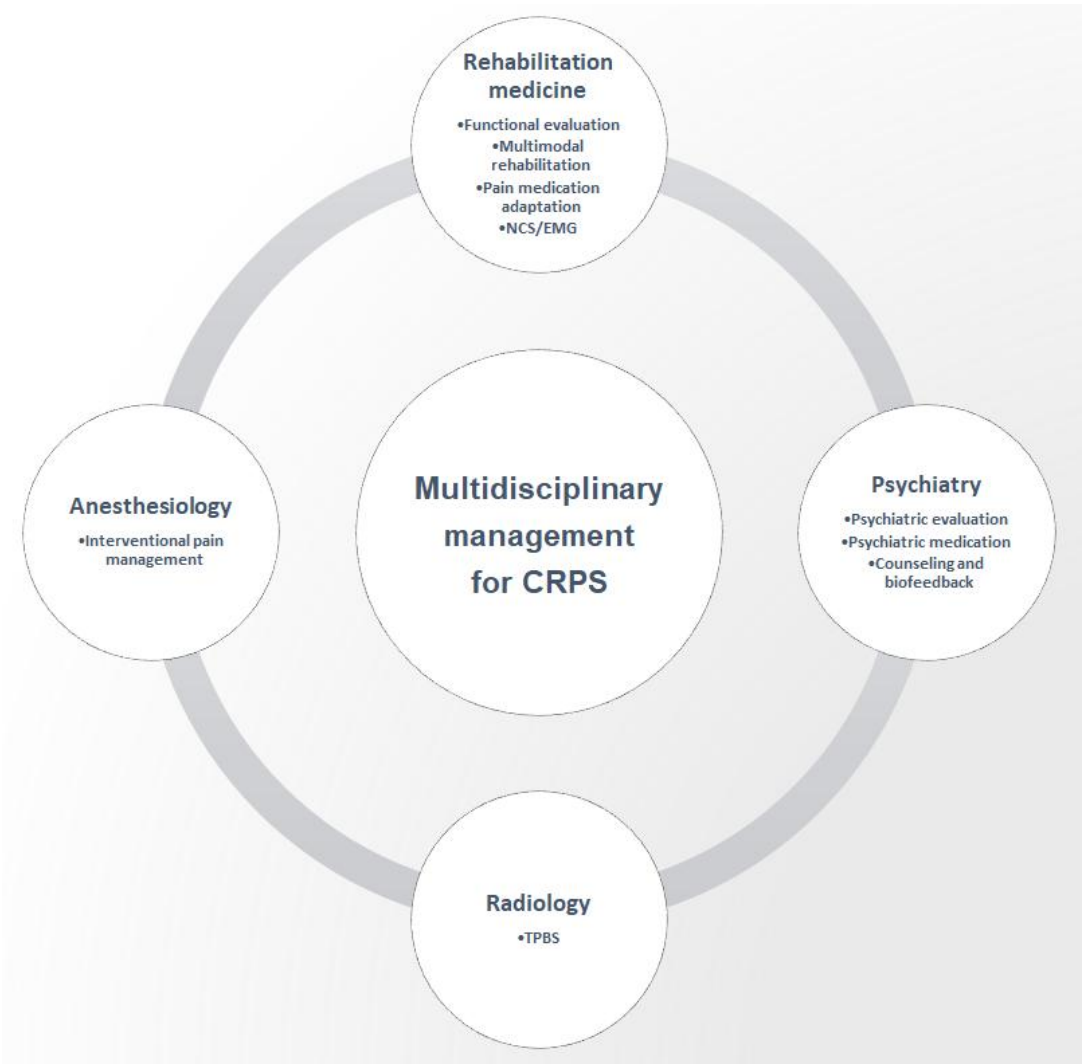
Table3. Simple linear regression results for the primary and secondary outcomes

Variables	NRSd			NRSr		
	R^2	β	P value	R^2	β	P value
Age	0.003	0.010	0.680	0.008	0.003	0.531
BMI	0.004	0.022	0.676	0.001	0.003	0.793
Duration	0.010	0.050	0.484	0.003	0.005	0.716
Severity score	0.021	−0.094	0.306	0.034	−0.022	0.198
NRS at admission	0.263	−0.486	<0.001**	0.357	−0.106	<0.001**
Variables	**NRSd6**			**NRSr6**		
	R^2	β	P value	R^2	β	P value
NRS at admission	0.528	−0.540	0.001**	0.508	−0.275	0.001

*P value<0.05, **P value<0.01

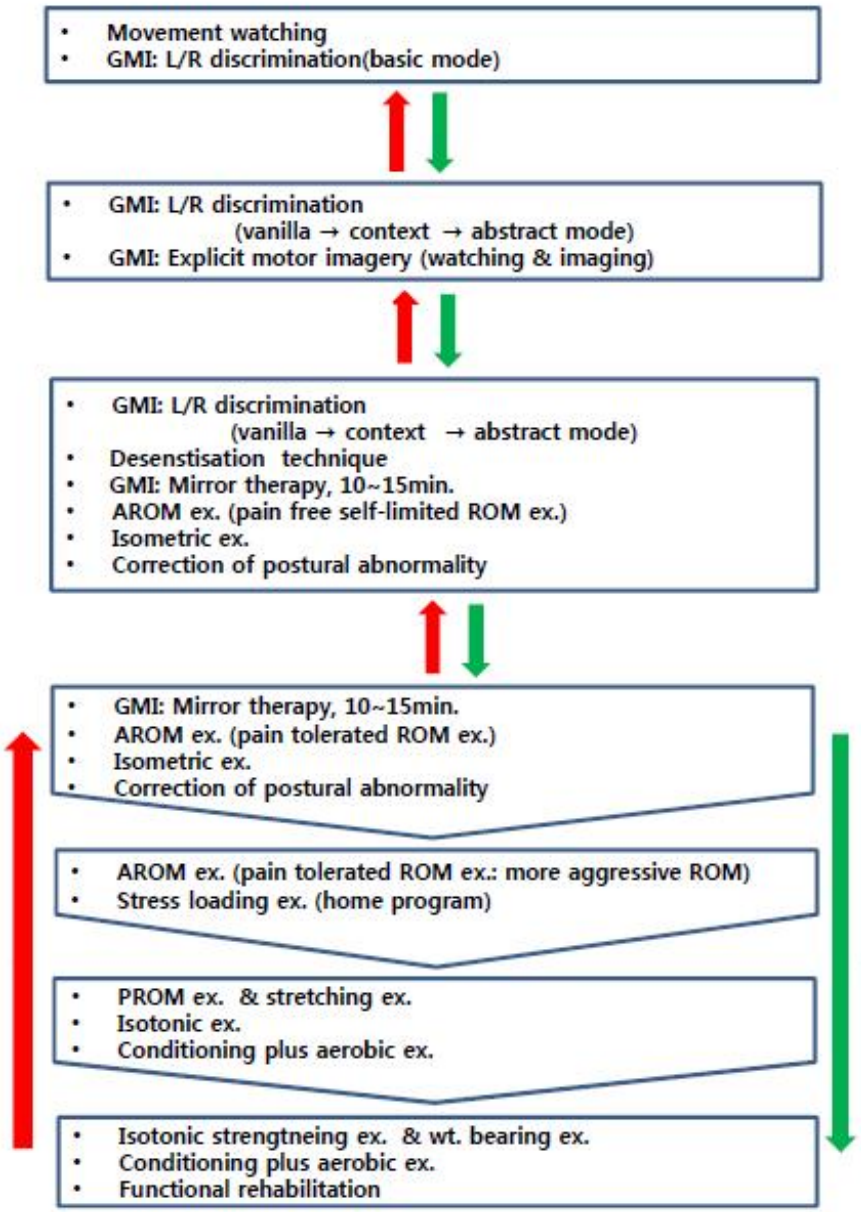
NRS, numeric rating scale; NRSd, NRS at discharge minus NRS at admission; NRSd6, NRS at 6 months after discharge minus NRS at admission; NRSr6, NRS at 6 months after discharge divided by NRS at admission.

Figure 1. Multidisciplinary pain consultation team



CRPS, complex regional pain syndrome; NCS/EMG, nerve conduction study and needle electromyography; TPBS, three-phase bone scan.

Figure 2. Steps of treatment for CRPS patients



The patients proceeded with treatment step-by-step, as shown. If symptoms improved after a treatment stage, the patient received the next stage of treatment. However, patients returned to the previous stage if symptoms worsened. GMI, graded motor imagery; ROM, range of motion.

Figure 3.

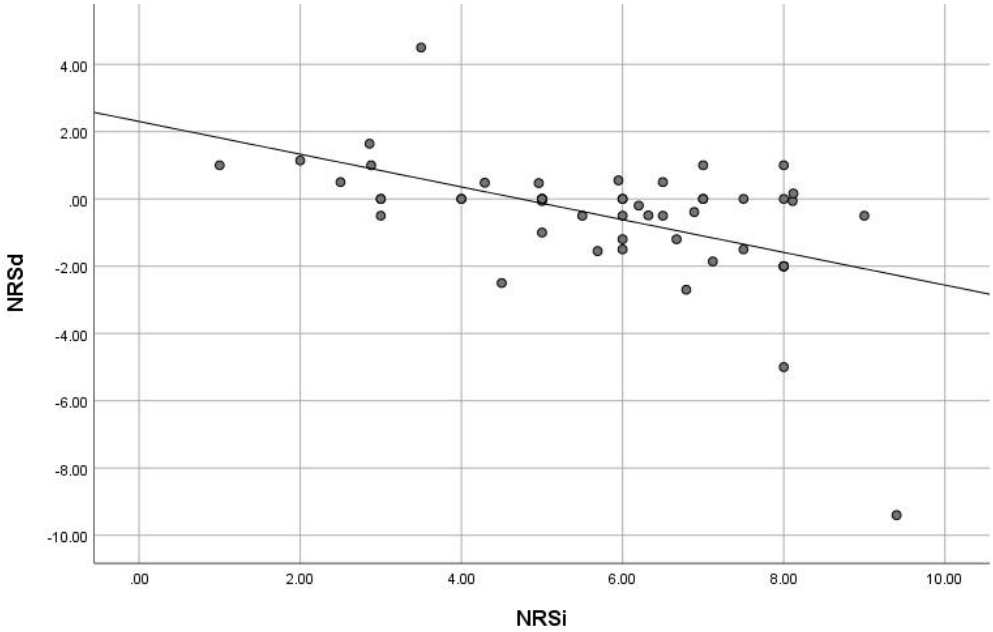


Figure 3.1. Scatterplot and linear regression line to predict numeric rating scale (NRS) at discharge minus NRS at admission (NRSd) based on NRS at initial admission (NRSi). A significant regression equation was found: NRSd = −0.486 × NRSi + 2.302.

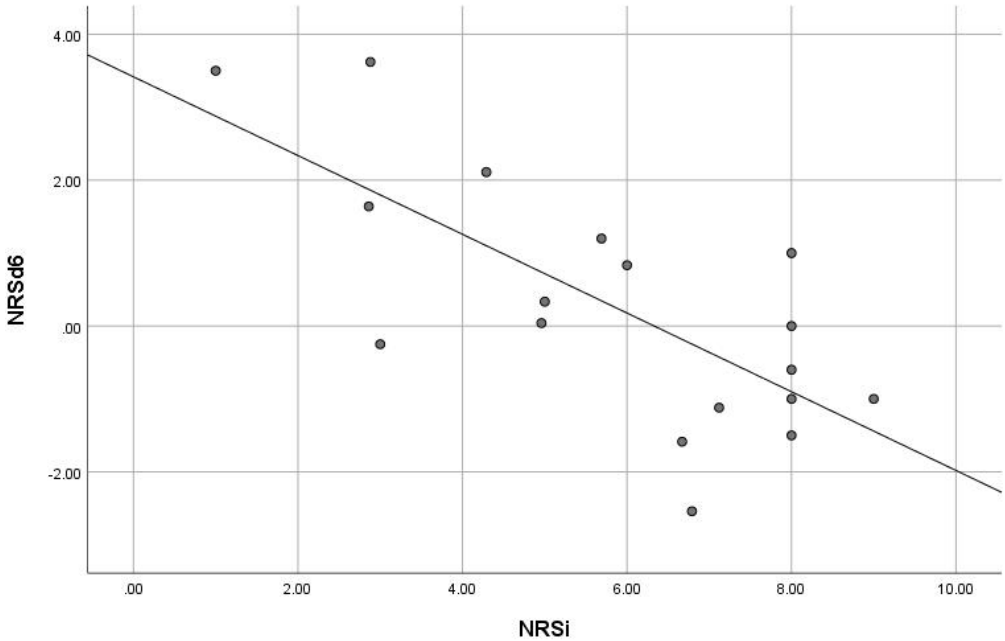
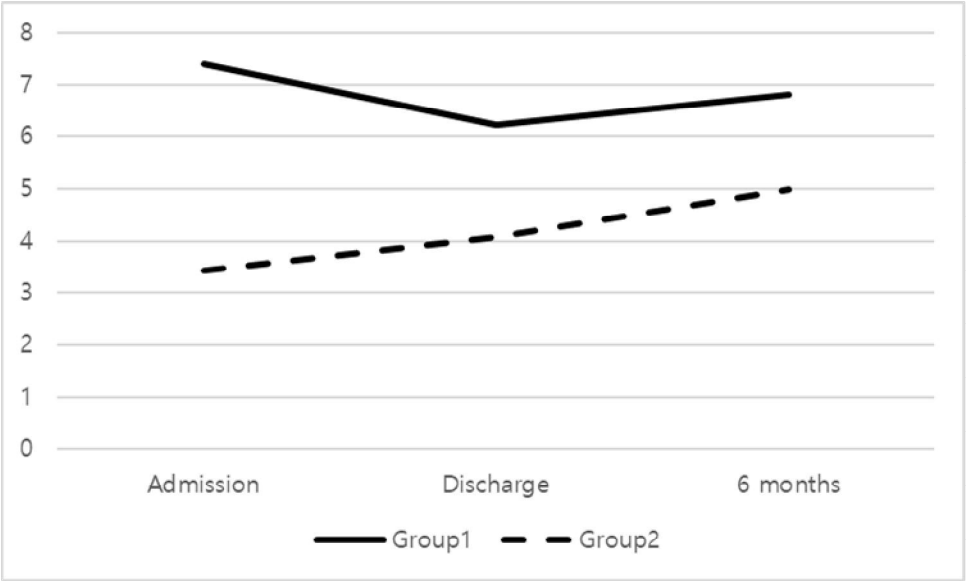


Figure 3.2. Scatterplot and linear regression line to predict NRS at 6 months after discharge minus NRS at admission (NRSd6) based on NRS at initial admission (NRSi). A significant regression equation was found: NRSd6 = −0.540 × NRSi + 3.416.

Figure 4.



Group 1: numeric rating scale at admission > 5

Group 2: numeric rating scale at admission ≤ 5