Effect of Early Orthopedic Rehabilitation on Development of Complex Regional Pain Syndrome Type I

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ABSTRACT

Objective: Complex regional pain syndrome (CRPS) is a syndrome usually occurs in one extremity and characterized by pain, tenderness with palpation, and symptoms of autonomic nervous system dysfunction. An essential factor in the etiology of CRPS is immobilization of the extremity as a result of a fracture. Delaying the start of physical medicine and rehabilitation program after removal of the plaster or splint may increase the rates of CRPS development in patients with fractures. This study aims to determine a direct relationship between delay time in rehabilitation and CRPS development.

Materials and Methods: Patients admitted to our physical therapy and rehabilitation outpatient clinic within the last 3 years (January 2016 to January 2018) for orthopedic rehabilitation following fractures were retrospectively analyzed. CRPS development status, the delay time for the rehabilitation program was determined in 38 CRPS patients of 91 patients with fractures. Probit regression was used to reveal the relationship between delay time for rehabilitation and CRPS development.

Results: CRPS development rates were decreased by years (48.71% in 2016, 43.47% in 2017, and 31.03% in 2018). When cases in 2016 were taken as a reference, it was seen that cases in 2017 and 2018 were exposed to CRPS approximately 0.03% and 16.00% lower than the reference year, 2016. A delay of one day exposes the patient to approximately 0.35% more CRPS.

Conclusion: As the delay time for rehabilitation in our clinic decreased, the incidence of CRPS decreased. The awareness of physicians and patients about the importance of early rehabilitation should be improved.

Keywords: Complex regional pain syndrome, fracture, physical and rehabilitation medicine.
mainly based on clinical signs and symptoms (2003 Budapest diagnostic criteria), as well as diagnostic methods such as X-ray, bone scintigraphy, magnetic resonance imaging (MRI), and thermography [10, 11].

Early diagnosis and treatment of CRPS-1 is of great importance in the prognosis of the disease, particularly for providing functionality. Early orthopedic rehabilitation can prevent serious complications such as chronic pain, contractures, and extremity atrophy, even permanent disability [10].

The goal of the treatment is to reduce pain and to provide a functional repair of the extremity with CRPS. The main treatment applications in CRPS are medical treatment for pain, physical therapy and rehabilitation (PTR), psychotherapy, and interventional pain treatments. PTR applications are the basis of the treatment in CRPS [10, 12].

The study aimed to investigate the relationship between the delay time of rehabilitation and CRPS-1 development. To the best of our literature search, this is the first study determining CRPS development percentages by years among these patients. The study was conducted by retrospective analysis of patients admitted to our PTR outpatient clinic within the last 3 years (January 2016 to January 2018) for orthopedic rehabilitation following fractures. Patients who had CRPS-1 on more than one extremity were excluded. The fracture site, the immobilization time (duration of plaster or splint), the number of days from the end of immobilization to the start of rehabilitation, and the total number of days from fracture to rehabilitation were determined. CRPS-1 was developed in 38 of 91 patients who had fractures. The study design and patient selection criteria are shown in a flowchart (Figure 1).

**Statistical Analysis**

The data were analyzed using the current version (3.6.1) of the R program. The relationship between delay time and CRPS-1 occurrence was determined by the probit regression model. We investigated whether there was a relationship between the operative status and the development of CRPS-1. Patients who have fractures for more than 1 year and who have been reoperated because the fracture did not merge were excluded.

Probit regression, one of the binary choice models, was used to reveal such a relationship. Probit regression is derived from the inverse normal distribution and is widely used as an alternative to the logit regression model in binary selection models. The presence or prevalence of CRPS is associated with the risk factors mentioned above, and the probit regression was used to achieve such aim. Therefore, it is coded as 1, otherwise 0 as numerical values for characterizing the presence of CRPS. Since the factors affecting the probability of CRPS are not linear in the model, their impact on the probability should be measured separately with their corresponding standard errors. We have measured these unitary (marginal) effects along with their standard errors. Before discussing such marginal impacts on the likelihood of CRPS, the Wald test was conducted to determine whether the factors used as explanatory variables in the regression could adequately explain the variation in the probability of CRPS.

**Results**

A total of 91 patients (51 male, 40 female) with fracture history were included in the study. Number of patients by years were as follows: 39 (22 male, 17 female) patients in the year 2016, 23 (12 male, 11 female) patients in the year 2017, and 29 (17 male, 12 female) patients in the year 2018. CRPS-1 development percentages by years among these patients are shown in Figure 2. Demographic (age, sex) and some clinical properties (mean delay time of rehabilitation, time after frac-

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**Figure 1. Study design**

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### Patients and Methods

#### Study Design and Ethical Approval

The study was designed as retrospective analysis and approved by the local ethics committee.

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Table 1. Characteristics of CRPS-1 patients

| Characteristics                  | Years          |
|----------------------------------|----------------|
|                                  | 2016-2018      | 2016 | 2017 | 2018 |
| Number of patients, n (male/female) | 38 (16/22)     | 19 (9/10) | 10 (3/7) | 9 (4/5) |
| Age, years (mean±SD)             | 44.87±16.88    | 43.16±11.44 | 44.80±24.59 | 48.56±17.91 |
| Delay time of rehabilitation, days (mean±SD) | 37.32±50.39    | 51.32±66.05 | 10.50±14.23 | 37.56±18.27 |
| Time after fracture, days (mean±SD) | 88.42±61.61    | 99.32±78.19 | 60.30±27.86 | 96.67±39.76 |
| Immobilization time, days (mean±SD) | 52.82±31.08    | 45.26±30.12 | 55.80±26.11 | 59.11±39.44 |
| Operation status, if yes, n (%) | 15 (39.5%)     | 7 (36.8%) | 5 (50%) | 3 (33.3%) |

SD: standard deviation; CRPS: complex regional pain syndrome

Table 2. Estimates of a probit model and their corresponding marginal effects

| Variable  | Probit model | Marginal effects |
|-----------|--------------|------------------|
|           | Estimate     | Standard error   | p value | Estimate     | Standard error   | p     |
| Constant  | -2.6778      | 0.7595           | 0.0006  | -78.3810    | 19.2010          | 0.0000 |
| Sex       | 0.6464       | 0.3564           | 0.0728  | 20.0350     | 9.4690           | 0.0370 |
| Age       | 0.0226       | 0.0080           | 0.0057  | 0.6620      | 0.2150           | 0.0030 |
| Region 1  | 0.3629       | 0.6527           | 0.5795  | 10.5420     | 16.6350          | 0.5280 |
| Region 2  | 1.1586       | 0.6136           | 0.0620  | 31.9980     | 14.2630          | 0.0270 |
| Region 4  | 1.3024       | 0.6385           | 0.0441  | 35.8770     | 15.0560          | 0.0190 |
| Delayed time | 0.0118     | 0.0047           | 0.0143  | 0.3460      | 0.1060           | 0.0010 |
| Operation | 0.6655       | 0.3510           | 0.0609  | 19.4660     | 9.4650           | 0.0420 |
| Year 2017 | -0.0009      | 0.3811           | 0.9981  | -0.0260     | 9.8080           | 0.9980 |
| Year 2018 | -0.5421      | 0.3893           | 0.1668  | -15.6830    | 9.7240           | 0.1100 |

Figure 2. CRPS-1 development percentages by years

Figure 3. CRPS regions of patients with CRPS-1

Figure 4. CRPS incidence distribution

Discussion

In this study, we determined the relationship between the delay time of rehabilitation and CRPS-1 development by using the probit regression model. Additionally, we determined that CRPS incidence increases with age, women’s gender and has been operated.

Geographical Factors

Our region is located in Eastern Anatolia where winter season is long and winter conditions are severe. Therefore, fractures, especially caused by falls, are very common in our region. Considering that fracture and immobilization is one of the important causes of CRPS development, our study brings an additional contribution to the awareness of physicians about early diagnosis and treatment of CRPS.

Sex

As evaluating the probit regression results, marginal effects of the explanatory variables used in the regression on the CRPS probability show that women are exposed to about 20% points more risk than men. This result is consistent with the literature findings. Studies reporting higher CRPS incidences in women than in men suggest that this difference may be attributed to the hormonal differences in men and women [4, 13]. A population-based study conducted in the Netherlands has reported that the incidence of CRPS in women was more than three-fold higher than in men [4]. Authors have reported that the majority of CRPS cases have developed after the menopausal period (in the age category of 61-70 years) [4] among women.
Our study has a limitation being retrospective, and we had not questioned the menopausal status of patients. However, because the mean age of women with CRPS-1 in our study was 51.14±16.22 years, we can speculate that most of the women were in the post-menopausal period, thereby explaining the high incidence of CRPS in women.

Age Factor
Another factor that may affect CRPS development is age. In our study, there is a positive correlation between the patient’s age and the likelihood of CRPS. The probability of CRPS increases by approximately 0.66% point as a result of aging of the patient for an additional year. Similar to our study, a study [4] has reported that CRPS incidence increases with age, being highest in the age group of 61-70 years. Such results are expected in the elderly because of the difficulties inherent in the age, for example, due to joint and cartilage deterioration, bone resorption intensity, and increased oxidative stress.

CRPS Region
Situations in the second and fourth regions are about 11% and 32% more likely to have CRPS than the referenced region (third region). The most important finding of this study was the positive correlation between CRPS and the duration of the arm or leg stay in the cast and the delay in the starting of physical therapy after the cast, that is, an additional delay of one day exposes the patient to approximately 0.35% more likelihood of having CRPS. A study aimed to provide an overview of CRPS has remarked that late diagnosis and, thus, late rehabilitation
In our study, cases in 2016 were taken as a reference to reveal the difference between the probability of CRPS and years. Cases in 2017 and 2018 were, respectively, exposed to CRPS approximately 0.03% and 16% lower than those in the reference year, 2016. As long as patients are reminded of the importance of starting physical therapy as soon as they are cast or after the removal of the cast, the likelihood of exposure to CRPS decreases. In conclusion, we recommend starting a PTR program immediately after from the end-up immobilization.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ataturk University School of Medicine (26.09.2019/426).

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - FB; Design - FB; Supervision - FB; Resources - FB, A.K.; Materials - FB, A.K.; Data Collection and/or Processing - FB, A.K.; Analysis and/or Interpretation - FB, A.K.; Literature Search - FB, A.K.; Writing Manuscript- FB; Critical Review - FB, A.K.

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