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Prognostic Value of Pain Sensitization During Early Recovery After Distal Radius Fracture in Complex Regional Pain Syndrome

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Abstract

Objective. To evaluate the influence of pain sensitization in the early recovery of distal radius fractures (DRFs) on the occurrence and prognosis of complex regional pain syndrome (CRPS) type I. **Methods**. We enrolled 58 patients who were diagnosed with CRPS I based on Budapest criteria within six months after sustaining DRF; they were age- and gender-matched with 58 patients with DRF who did not have CRPS I. We commonly measured patients' pressure pain thresholds (PPTs) in the forearm and administered a Pain Sensitivity Questionnaire (PSQ) when patients complained of pain with numeric rating scale $\geq$4 at three-month follow-up. Participants were followed up three, six, and 12 months after injury, and the symptoms and sign of CRPS were evaluated at each follow-up. **Results**. Patients with CRPS I were more likely to have sustained high-energy injuries, had severe fractures, and had significantly higher PSQ scores and lower PPTs than the age- and gender-matched controls. At 12 months after injury, CRPS symptoms improved in 52% (30/58) of patients who had been diagnosed with CRPS I at three months after injury. The initial degree of pain sensitization and high-energy injury were associated with persistence of CRPS symptoms up to 12 months after initial injury. **Conclusions**. Patients with CRPS I after DRF exhibited significantly higher pain sensitization in the early post-trauma period, and the degree of initial pain sensitization and high-energy injuries were associated with prolonged CRPS I signs and symptoms up to one year after initial injury.

Key Words: Pain Sensitization; Distal Radius Fracture; Early Recovery; Complex Regional Pain Syndrome; Prognosis

Introduction

Patients with upper extremity fractures are at high risk for developing complex regional pain syndrome type I (CRPS I) [1,2], with reported incidence rates after a distal radius fracture ranging from 1% to 37% [2–8]. Differentiated by the presence of a demonstrated nerve lesion, CRPS can be classified into type I and type II, of which type I, without a nerve lesion, is more common [9]. CRPS has serious impacts on patient quality of life and daily function because it causes severe pain with adverse psychosocial and socioeconomic effects [9,10]. However, the pathophysiology of CRPS has not been determined, and its treatment remains largely empirical and symptom based [11]. Although a substantial number of cases resolve with limited or no specific intervention early in the course of the condition, functional outcomes in patients with CRPS are often inadequate even with aggressive pain intervention [12]. In contrast to acute CRPS, the limited data on the natural course of well-established chronic CRPS (defined as CRPS of more than one year's duration) suggest much lower resolution rates even with specialty pain care [13].

In a prospective study in a large sample of postfracture patients, CRPS was commonly diagnosed three months after cast removal, and diagnosis rates decreased after three months [2]. The onset of CRPS symptoms after this three- to four-month window can be related to pain sensitization during early recovery after distal radius fracture. Peripheral pain sensitization refers to the normal increase in responsiveness of peripheral nociceptors caused by inflammatory mediators and neuropeptides released locally within the painful area, acting to lower the neuronal activation threshold, thereby leading to local enhanced pain sensitivity [14]. Central sensitization includes wind-up mechanisms in the spinal cord, maladaptive neuroplasticity with changes in endogenous pain modulation, and reorganization of the somatosensory cortex [13]. Clarifying the role of sensitization in predicting CRPS I occurrence and prognosis after distal radius fracture could help clinicians understand the extent to which a therapeutic approach aimed at reducing sensitization may be needed in the postoperative management of distal radius fracture to prevent the occurrence of CRPS I.

Therefore, we asked: (1) Does increased pain sensitization in the early recovery after distal radius fractures predict development of long-term CRPS? (2) What demographic, clinical, or pain sensitization factors are associated with development of chronic CRPS after distal radius fractures?

Methods

Between June 2011 and May 2016, we identified 63 patients who were diagnosed with CRPS I within six months of sustaining distal radius fractures. This study was approved by our institutional review board, and all patients provided informed consent. Patients were eligible if their diagnoses of CRPS I were based on Budapest diagnostic criteria for research, which are modified from the International Association for the Study of Pain guidelines [15,16], and if they completed the 12-month follow-up. Patients were not eligible if they had 1) systemic, multi-organ, or head injuries, 2) concomitant upper extremity or bilateral fractures, or 3) if they had been treated more than two weeks after initial injuries; based on these criteria, we approached 58 patients for study, and we age- and gender-matched them with 58 patients with distal radius fracture who did not have CRPS I during the study period. We selected the controls by cumulative sampling before the three-month follow-up visit according to matching variables in a stepwise fashion, first attempting to match on age and then on gender. The energy of injury was classified as low (a simple fall from a standing position) or high (any other injury including open fractures, combined muscle/tendon injuries, and car accident or industrial crushing/abrasion wounds).

CRPS I was diagnosed when at least one symptom in all four symptom categories and at least two signs from different categories were present with disproportionate pain (numeric rating scale [NRS] $\geq$4 at three-month follow-up) in the wrist, including the area distal to the wrist (hand and fingers). These four symptom categories were 1) hyperalgesia or allodynia (sensory), 2) skin color asymmetry and temperature (vasomotor), 3) edema or sweating asymmetry (sudomotor/edema), and 4) a decreased range of motion, motor dysfunction, or a trophic change (motor/trophic). The four sign categories were 1) evidence of hyperalgesia (pinprick) and allodynia (light touch), 2) evidence of temperature asymmetry or a skin color change, 3) evidence of edema or a sweating change, and 4) evidence of a decreased range of motion, motor dysfunction, or trophic changes. When a patient was diagnosed with symptoms related to CRPS I by one hand specialist, the patient was referred to a pain physician for the diagnosis of CRPS I at each session; the patient was diagnosed with CRPS I when the two physicians agreed on the diagnosis. Patients were followed up three, six, and 12 months after injury by the same orthopedic hand specialist, and the symptoms and signs of CRPS I were re-evaluated at each follow-up visit.

We commonly measured pain sensitization by assessing pressure pain thresholds (PPTs) [14,17] and administering a Pain Sensitivity Questionnaire (PSQ) [18,19] if patients with distal radius fracture complained of moderate to severe pain (defined as NRS $\geq$ 4) at three-month follow-up, which was considered disproportionate pain considering the usual recovery pattern after distal radius fractures. The PPT is defined as the cutoff point when a sense of pressure changes to pain [20], and we performed this test to document deep tissue hyperalgesia [21]. We assessed PPTs in the mid-dorsal forearms of the affected side using a digital algometer (Somedic, Hörby, Sweden) that consisted of a 1-cm^2 rubber-tipped plunger mounted on a force transducer. We applied the pressure at a rate of 30 KPa/second and instructed the participants to press a switch when the sensation changed from pressure to pain. We performed the pressure algometry three times, and between each reading, we altered the position of the algometer on the skin very slightly to avoid sensitizing the test area. The primary exposure was a standardized average of the three PPT values. The reliability of pressure algometry has been found to be high (intraclass correlation coefficient = 0.91, 95% confidence interval = 0.82–0.97) [22]. The self-reported PSQ comprises 17 items, each describing a daily life situation and asking respondents to rate how painful this situation would be for individuals on an 11-point numeric rating scale ranging from 0 (not painful at all) to 10 (worst pain imaginable) [23]. Fourteen of the 17 items are simulated situations that a majority of healthy subjects rate as painful, and they cover a range of pain intensities; a variety of different types of pain such as hot, cold, sharp, and blunt; and different body sites including the head and the upper and lower extremities. Conversely, the remaining three items describe situations that healthy subjects do not

normally rate as painful (we did not include these items in the final score) [23]. Two PSQ subscales, the PSQ-moderate and PSQ-minor, each contain seven items that patients rate on average as moderately painful (mean rating = 4–6 for PSQ-moderate) or as causing minor pain (mean rating < 4 for PSQ-minor) [18].

The patients who had been diagnosed with CRPS I at each occasion were given combination oral medication and physical therapy, tailored to each individual person. Physical therapy interventions for CRPS I included specific modalities such as transcutaneous electrical nerve stimulation, tactile desensitization, massage, and contrast bath therapy, and oral medication included anti-inflammatory drugs such as corticosteroids and nonsteroidal anti-inflammatory drugs, antidepressants, and GABA analogs such as gabapentin and pregabalin.

Statistical Analysis

A power analysis indicated that a sample consisting of 58 patients in each group (CRPS and control group) would provide 91% statistical power to detect a large effect size (Cohen's d = 0.8) in pain sensitization measures between the two groups, with an alpha level of 0.05 using the *t* test.

We used descriptive statistics to represent the demographics and clinical characteristics of the patients, the Kolmogorov-Smirnov test to identify the normality of the variable distributions, and a *t* test to determine any significant differences between the two groups in terms of continuous variables. We also used the chi-square and Fisher exact tests to determine any significant differences in the categorical variables. We considered $P < 0.05$ to indicate statistical significance.

Results

The ages and genders of the CRPS group were similar to those of the control group, and there were no significant differences between the two groups in fracture side, body mass index, or the duration of immobilization. Patients with CRPS I were more likely to have sustained high-energy injuries ($P = 0.03$) and severe fractures ($P = 0.04$) and had significantly higher PSQ scores ($P < 0.01$) and lower PPTs ($P < 0.01$) than did the age- and gender-matched controls without CRPS I (Table 1).

At 12-month follow-up, CRPS I signs and symptoms had improved in 30 patients (52%) (signs and symptoms did not meet Budapest diagnostic criteria), but in 28 patients (48%), the signs and symptoms had persisted. Patients who had persistent CRPS I symptoms up to 12 months after initial injury were more likely to have had an initial high PSQ score ($P = 0.01$) and lower PPTs ($P < 0.01$) or to have sustained a high-energy injury ($P = 0.01$) (Table 2).

Table 1. Demographic and clinical characteristics of participants in the study

Variable	CRPS (+)	CRPS (–)	*P*
Number	58	58	
Age, y*	56.1 ± 16.9	57.4 ± 17.2	0.68
Female/male	41/17	41/17	–
Side of fractures			
Dominant	37	35	0.79
Nondominant	21	23	
BMI, kg/m^2*	23.4 ± 6.2	24.0 ± 7.0	0.63
Fracture type (AO)			
A (extra-articular)	14	26	**0.04**
B (partial articular)	9	12	
C (complete articular)	35	20	
Energy of injury†			
Low	37	51	**0.03**
High	21	7	
Immobilization			
≤6 wk	34	42	0.27
>6 wk	24	16	
Pain sensitization measures*			
PPT, KPa	134 ± 68	252 ± 81	**<0.01**
PSQ	85 ± 21	53 ± 19	**<0.01**

AO = Arbeitsgemeinschaft für Osteosynthesefragen; BMI = body mass index; CRPS = chronic regional pain syndrome; PSQ = Pain Sensitivity Questionnaire; PST = pain pressure threshold.

*Values are expressed as mean ± standard deviation; the remaining values are expressed as number of patients. Significant *p*-value is shown in bold font.

†The energy of injury was classified as low (a simple fall from a standing position) or high (any other injury including open fractures, combined muscle/tendon injuries, and car accident or industrial crushing/abrasion wounds).

Discussion

The present study data shows that patients diagnosed with CRPS I within six months of injury had significantly higher pain sensitization measures (increased PSQ score and lower PPTs) than age- and gender-matched controls at three months after injury. Importantly, the 48% (28/58) of patients with long-term (refractory) CRPS at 12 months correlated with high-energy injury or higher PSQ scores and lower PPTs measured at three months.

Both peripheral and central sensitization have been proposed as pathophysiological mechanisms of CRPS [13,14]. This study exhibited increased pressure pain sensitivity, which could be considered a type of peripheral sensitization, in a population diagnosed with CRPS within six months of injury. These results are consistent with previous findings that patients with CRPS-I have more sensory gain (heat and pressure pain) and less sensory loss (thermal and mechanical detection, hypoalgesia to heat or pinprick) compared with those with other peripheral nerve injuries [24]. In addition, previous studies in patients with unilateral CRPS demonstrated evidence of bilateral facilitated neurogenic inflammation [25], bone demineralization [26], impaired sympathetic nervous system function [27], brain changes [28], and systemically circulating autoantibodies against autonomic structures [29]. These contralateral changes in unilateral CRPS may imply a form of central mediated injury

Table 2. Demographic and clinical differences between refractory and resolved CRPS Groups

Variable	Refractory Group	Resolved Group	*P*
No.	28	30	
Age, y*	54.1 ± 14.1	58.2 ± 17.2	0.32
Female/male	19 / 9	23 / 10	0.45
Side of fractures			
Dominant	18	19	0.94
Nondominant	10	11	
BMI, kg/m^2*	22.8 ± 6.2	24.0 ± 6.4	0.47
Fracture type (AO)			
A (extra-articular)	8	14	0.12
B (partial articular)	4	5	
C (complete articular)	16	11	
Energy of injury†			
Low	15	24	**0.03**
High	13	6	
Immobilization			
≤6 wk	15	19	0.45
>6 wk	13	11	
Pain sensitization measures			
PPT, KPa	96 ± 54	169 ± 62	**<0.01**
PSQ	94 ± 22	77 ± 20	**0.01**

AO = Arbeitsgemeinschaft für Osteosynthesefragen; BMI = body mass index; CRPS = chronic regional pain syndrome; PSQ = Pain Sensitivity Questionnaire; PST = pain pressure threshold.

*Values are expressed as mean ± standard deviation; the remaining values are expressed as number of patients. Significant *p*-value is shown in bold font.

†The energy of injury was classified as low (a simple fall from a standing position) or high (any other injury including open fractures, combined muscle/tendon injuries, and car accident or industrial crushing/abrasion wounds).

response and can be associated with high PSQ scores in patients diagnosed with CRPS within six months of injury. The provoking factor for peripheral sensitization could be the continuous nociceptive input in the early phase of distal radius fractures, leading to central sensitization that might result in generalized nociceptive facilitation [13,14,30]. In this study, the increased mechanical pain sensitivity of the affected extremity and patient-reported central sensitization symptoms at three months after injury were statistically significant predictors of chronic CRPS I after distal radius fractures.

This study found that 52% of patients with CRPS-I after distal radius fractures showed considerable improvement of symptoms and function at 12 months, whereas high-energy injuries and higher pain sensitization at three months after distal radius fractures were associated with refractory CRPS I up to 12 months. Although functional outcomes in patients with CRPS in tertiary pain care settings are often inadequate even with aggressive pain intervention, high rates of resolution have been reported [31]. A substantial number of cases resolve with limited or no specific intervention early in the course of the condition, with a smaller subset of more persistent cases being seen in tertiary care pain clinics [12]. Fracture type and energy of injury were already found to be predictive of CRPS development in previous studies [2,8]. Previous studies have also shown that vasomotor and sudomotor symptoms of CRPS tended to be the most common in the early stages of the disease and were the most likely to resolve in later stages [12]. Vasomotor and sudomotor symptoms of CRPS appear to be caused by acute inflammatory processes leading to increased plasma extravasation and vasodilatation, and these inflammatory factors contribute to CRPS in the acute phase but play a lesser role in later phases of the disease [11]. In contrast, sensory and motor symptoms with pain play a major role in later, persistent CRPS I [30]. Thus, pain sensitization appears play a more important role in chronic CRPS I after distal radius fractures. The results of this study are consistent with previous findings that the mechanical pain sensitivity on the affected extremity (peripheral sensitization) correlated with the mean pain intensity or ongoing pain and was further associated with a higher CRPS severity score at follow-up examination [30]. In this regard, future research is warranted to show whether early identification and treatment of pain sensitization, such as pharmacological therapies, cognitive behavioral therapy, or exercise therapy, will improve the CRPS I prognosis.

This study has several limitations. First, there is no gold standard for diagnosing CRPS I, and its diagnosis after a distal radius fracture is obviously affected by the diagnostic criteria considered. In addition, the presence and severity of specific symptoms and signs are likely to show substantial variability, and physicians' experience can influence the diagnosis of CRPS I. Second, our sample size was small, which limited its statistical power; even though the statistics in this study revealed significant differences in pain sensitization scores and in the ratio of high-energy injuries between refractory and resolved CRPS patients at the final follow-up, our analyses of other risk factors might have been underpowered. Nevertheless, the clinical relevance of the observed significantly high pain sensitization in patients with refractory CRPS I is obvious. Third, identifying pain sensitization for CRPS clinically is challenging due to the absence of a reference standard, although PPT has been shown to be a reliable and sensitive measure of pain sensitization. Pressure pain sensitivity over the joints was reported to be more sensitive than over muscles in discriminating CRPS from other pain diseases [32]. Fourth, the associations between higher pain sensitization scores and the occurrence of CRPS I after distal radius fracture were mainly based on a cross-sectional design at three-month follow-up visits, which prevented our investigating the causal relationship between the degree of pain sensitization and the occurrence of CRPS I. However, additional longitudinal follow-up in the present study confirmed the prognostic value of pain sensitization in patients with complex regional pain syndrome. Finally, this study's subjects were limited to one ethnic population drawn from an urban area, which means that their characteristics and the results may not be representative of other populations.

In conclusion, patients with CRPS I after distal radius fracture exhibited significantly higher pain sensitization

in the early post-trauma period, and the degree of initial pain sensitization and high-energy injuries were associated with prolonged CRPS signs and symptoms up to one year after initial injury. More research is needed to show whether early identification and treatment of pain sensitization, such as pharmacological therapies, cognitive behavioral therapy, or exercise therapy, will improve CRPS I prognosis after distal radius fractures.

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