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Brief Research Report

The Effects of Long-Term Ketamine Treatment on Cognitive Function in Complex Regional Pain Syndrome: A Preliminary Study

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Abstract

Objective. This preliminary study aimed to investigate the effects of long-term frequent ketamine treatment on cognitive function in [AQ-A] CRPS patients.

Design. A total of 30 CRPS patients were divided into two groups based on both the duration and frequency of ketamine treatment; the long-term frequent ketamine treatment (LF) group (N = 14) and the Non-LF group (N = 16). Participants were asked to complete a questionnaire packet including demographic and clinical characteristics and potential variables affecting cognitive function. Then, they performed the neuropsychological test.

Results. Results indicated that the LF group performed significantly poorer than the Non-LF group on the digit span, digit symbol, Controlled Oral Word Association Test, and Trail Making Test, but not the Stroop task.

Conclusions. Patients with CRPS receiving long-term frequent ketamine treatment showed impairment in cognitive function (specifically executive function) compared with those who do not. These findings may have implications for clinical assessment and rehabilitation of cognitive function in CRPS patients.

Key Words. CRPS; Ketamine; Cognitive Function

Introduction

Complex regional pain syndrome (CRPS) is a neuropathic chronic pain condition usually affecting the extremities after injury or even spontaneously [1]. Characteristics of its symptoms include autonomic (skin temperature and color changes, abnormal sweating), sensory (pain and hyperalgesia) and motor (paresis, tremor, dystonia) disturbances [2]. Many patients with CRPS suffer from severe pain that threatens their quality of life by deteriorating their condition and from disability that has a significant impact on daily functioning [3]. However, specific pathophysiological mechanisms of CRPS remain unclear, and common treatments for them are opioids, antidepressants, antiepileptics, and sympathetic blockade, which have shown only modest therapeutic benefits [4,5].

Recently, the use of ketamine, a non-barbiturate anesthetic medication, as a novel therapeutic intervention has been attempted in pain management [6,7]. Advantages of using ketamine include a rapid onset, brief cardiorespiratory depressant effects, and a benign effect on muscle tone and protective airway reflexes [8]. Numerous studies have reported that the repetitive use of ketamine provides analgesic effects in CRPS [4,9]. However, its frequent or repetitive use for extended time periods may cause impairment in cognitive function [10]. Previous studies have primarily investigated its effects on cognitive function in people who recreationally used or chronically abused ketamine [11]. For example, those who chronically abused ketamine showed impaired cognitive processing speed, verbal learning, and episodic, semantic, and working memory compared with healthy controls [12,13]. In addition, those who frequently used ketamine for recreational purposes showed impaired

verbal fluency and episodic, semantic, and working memory more than those who did not [10,14,15].

Cognitive impairment sometimes becomes problematic in patients with CRPS undergoing chronic ketamine treatment [16]. However, the effects of long-term frequent ketamine treatment for pain management on cognitive functions have been poorly studied and consequently unknown in CRPS. Therefore, this preliminary study aimed to investigate the effects of long-term frequent ketamine treatment (i.e., subanesthetic infusion) on cognitive function in patients with CRPS. We hypothesized that patients with CRPS who were frequently treated with ketamine long term would perform worse on neuropsychological tests than those who were not.

Methods

Subjects

Thirty-two patients with CRPS who were registered in the CRPS Association in Korea were recruited from an advertisement on its website. The inclusion criteria for the present study were having CRPS of a duration of at least six months, being at least 19 years old, being right handed, and having an adequate ability to understand and complete neuropsychological testing. Among the patients, two did not meet the inclusion criteria, resulting in a final sample size of 30 patients. They were divided into two groups based on both duration and frequency of ketamine treatment; the long-term frequent ketamine treatment (LF) group (N = 14) and the Non-LF group (N = 16). Long-term ketamine treatment was defined as treatment that lasted 6 months or more [16] and its frequent use was defined as two times or more per a month [18]. For a group assignment, we calculated the frequency of ketamine treatment over the past six months and considered 12 instances of treatment (two times per a month * six months) or more as 'long-term frequent.' Specifically, the Non-LF group consisted of participants who had never received ketamine, infrequently received ketamine for the long term, or frequently received ketamine treatment for the short term. The LF group and Non-LF group received ketamine treatment, on average, 41.7 times (SD = 13.7) and 2.9 times (SD = 3.3) throughout the past six months, respectively.

Measures

Participants were asked to complete a questionnaire packet including demographic and clinical characteristics and potential variables affecting cognitive function (i.e., sleep quality, fatigue, anxiety, depression). Each potential variable was evaluated using two items by a numerical scale (0: none –10: severe): the degree to which the variable was being experienced in the present and the degree to which it had been experienced in the past week.

Neuropsychological Tests

The *Digit span* is a subtest of the standardized Korean-Wechsler Adult Intelligence-modified version of the revised Wechsler Adult Intelligence Scale (K-WAIS) [19] that assesses attention and concentration, recent memory, and working memory. Digits were read forward or backward. A participant was read sequences of numbers and asked to recall them either forward or backward. The scores were calculated by the number of correct responses.

The *Digit symbol* is a subtest of the K-WAIS that assesses information-processing performance, ability to concentrate, and fine motor coordination. A participant was asked to write the symbol corresponding to its number in a square below each number within 90 seconds as quickly and accurately as possible. The scores were calculated by the number of correct answers obtained.

Stroop Color and Word Test [20] is a test that assesses attention and susceptibility to interference. In the color-naming Stroop task, a participant is asked to say the color of the word and not read the word as quickly and accurately as possible. The word-naming Stroop task, in which the displayed word named a color that was different from that of its ink color. The participant was asked to read 100 words according to what the word says as quickly and accurately as possible. Scoring was calculated by subtracting the response time for word naming from the response time for color naming.

The *Controlled Oral Word Association Test (COWAT)* is a test that assesses sustained attention and semantic memory. A participant was asked to say as many words belonging to a specific category (e.g., fruits, animal) or words that began with a specific letter (e.g., m, p, l, or t) as possible during 90 seconds [21]. The response words were counted. In the present study, we used a Korean language version of the COWAT. The participants were asked to say the words belonging to the animal category and the words that began with a Korean alphabet letter that was pronounced as 'g'.

The Trail-Making Test (TMT) was used to measure speed, psychomotor coordination, response inhibition, and vulnerability to inference [22]. There are two parts of the TMT (A & B). In part A, a participant was instructed to draw lines to connect the numbered circles consecutively, and, in part B, the participant was asked to draw lines to connect the numbered and lettered circles in an alternating fashion. The participant was asked to connect the circles as fast and as accurately as possible. The score was calculated by subtracting the response time for the TMT-A from the response time for the TMT-B.

Procedure

Patients were instructed not to receive ketamine treatment (i.e., subanesthetic infusion) within one day

Table 1 Sample characteristics

	LF	Non-LF	Z or χ^2
N (number of males)	14 (12)	16 (8)	4.29
Age (mean years ± SD)	38.57 ± 8.36	37.5 ± 9.30	−.82
Education (mean years ± SD)	12.9 ± 2.16	13.8 ± 2.37	−.77
Employment (% employed)	20.0	30.0	1.27
Marital status (% married)	10.0	30.0	.20
CRPS duration (mean years ± SD)	5.86 ± 3.57	4.81 ± 2.73	−.06
Pain site (%)			5.31
Upper extremities	7.0	31.0	
Lower extremities	14.0	31.0	
Both extremities	79.0	38.0	
Pain intensity	6.31 ± 1.50	5.17 ± 2.12	−1.45
Ketamine treatment duration (mean years ± SD)	3.82 ± 1.3	1.86 ± 2.2	−1.73
Narcotic analgesic (%)			1.71
No	7.0	25.0	
Yes	93.0	75.0	
Psychiatric medication (%)			.74
No	29.0	44.0	
Yes	71.0	56.0	
Sleep quality	2.59 ± 1.71	2.57 ± 1.50	−.11
Fatigue	6.45 ± 2.11	7.62 ± 1.56	0.93
Anxiety	5.22 ± 2.38	4.67 ± 2.15	−.77
Depression	6.50 ± 2.14	4.53 ± 2.74	−1.76

LF, the long-term frequent ketamine treatment group; CRPS, complex regional pain syndrome.

prior to participation, possibly due to its influence on their performance (the elimination half-life of ketamine: 3–5 hours). Upon their arrival at the pain center, patients were informed about the procedure and completed the questionnaire packet. Then, they performed the neuropsychological test in a quiet room. This procedure was approved by the Institutional Review Board.

Data Analysis

Data analysis was performed using SPSS 17.0 . The non-parametric Mann-Whitney U test and chi-square test were performed to examine the differences in demographics, clinical characteristics, potential variables affecting cognitive function, and neuropsychological test scores between the groups.

Results

Sample Characteristics

There were no significant differences between the groups in demographic and clinical characteristics. Additionally, there were no significant differences in potential variables affecting cognitive function between the groups (Table 1).

Neuropsychological Tests

The means and standard deviations for each neuropsychological test are shown in Table 2. The LF group performed significantly poorer than the Non-LF group on the digit span ($Z = -2.00$; $P < 0.05$), digit symbol ($Z = -2.57$; $P < 0.05$), COWAT ($Z = -2.43$; $P < 0.05$) and TMT ($Z = -2.76$; $P < 0.01$). There were no differences in the Stroop task between the groups ($Z = -1.37$, $P =$ ns).

Discussion

To our knowledge, this is the first study to provide evidence that patients with CRPS receiving long-term frequent ketamine treatment showed impairment in cognitive function (primarily executive function) compared with those who do not. This finding is consistent with prior studies in chronic recreational users of ketamine [10,12–14]. Ketamine is a glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonist, and its repetitive use has been linked to reduced function of the prefrontal dopaminergic system, which plays an important role in executive function [16,23,24]. Given these factors, long-term frequent ketamine treatment may impair the executive function of patients with CRPS by altering dopaminergic function in the prefrontal cortex.

CRPS is often unresponsive to traditional pharmaceutical treatment and is therefore challenging for health

Table 2 Differences in neuropsychological test scores between the groups (mean ± SD)

	LF	Non-LF	Z
Digit span (score)	11.21 ± 3.80	14.25 ± 4.37	−2.00*
Digit symbol (score)	47.57 ± 16.04	63.50 ± 14.24	−2.57*
Stroop interference[a] (sec)	64.90 ± 40.00	45.14 ± 35.85	−1.37
COWAT (score)	22.64 ± 9.05	30.56 ± 7.70	−2.43*
TMT B - TMT A (sec)	103.63 ± 72.75	39.85 ± 21.65	−2.76**

COWAT, Controlled Oral Word Association Test; LF, the long-term frequent ketamine treatment group; [a]Stroop interference = response time for color naming-response time for word naming; TMT, The Trail Making Test.
*P <0 .05,
**P < 0.01.

professionals [25]. Recently, ketamine has been introduced as a novel therapeutic intervention for pain relief [6,7], and prior studies have demonstrated a marked reduction in pain and improved cognitive function after short-term treatment with ketamine in patients with CRPS [4,7,9]. However, given the characteristics of CRPS that involve severe chronic intractable pain [1], its protracted use may be inevitable. Indeed, impairments in cognitive function have been well known to be associated with pain experience [26], and, thus, long-term and frequent ketamine treatment may further exacerbate the impairments in patients with CRPS. Future research needs to clarify whether the mechanism underlying the effects of pain experience and effects of long-term and frequent ketamine treatment on impairments in cognitive function in CRPS are similar.

These preliminary findings may have implications for the clinical assessment and rehabilitation of patients with CRPS. Adjusting to life with CRPS is challenging, and its capacity may depend on the ability to self-regulate thoughts, moods, and behaviors. Such an ability has been well known to be closely associated with executive function of the prefrontal cortex, which is a set of processes related to managing oneself and one's resources (i.e., shifting, updating, and inhibition) to achieve a goal [27]. Given that executive function can be improved [28], routine-based assessment and the consequent rehabilitation of executive function and/or rescheduling of ketamine treatment are necessary for patients with CRPS receiving ketamine treatment.

This study has some potential limitations. First, this study employed a small sample size and a retrospective design, which reduces statistical power and the probability of detecting an effect and restricts causal interpretation. Second, this study relied on a patient's memory of the ketamine treatment (i.e., duration and frequency) and thus may be affected by recall. Third, this study did not consider dose effects and interactions with other medications. Finally, this study measured potential variables affecting cognitive function (i.e., sleep quality, fatigue, anxiety, depression) using a non-validated numerical rating scale. Thus, future research should replicate the findings with a larger sample size, prospective controlled longitudinal design (e.g., serial examination of the same patient over time), objective data, and validated tools. Nevertheless, this preliminary study was worthwhile in that it provided the first empirical evidence for an association between long-term and frequent ketamine treatment and impairments in cognitive function in patients with CRPS. The results suggest the likelihood of adverse effects of long-term and frequent ketamine treatment in CRPS, and, thus, health professionals and patients need to be aware of the potentially adverse effects of ketamine on cognitive function.

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