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Change in C-Reactive Protein Level according to Amounts of Exercise in Chronic Hemiparetic Patients with Cerebral Infarct

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Abstract. [Purpose] We attempted to investigate changes in motor function and C-reactive protein level according to amounts (length of time) of exercise in patients with cerebral infarct. [Method] Forty-six consecutive chronic hemiparetic patients with cerebral infarct were randomly assigned to two groups: Group 1 (exercise time 100 minutes/day) and Group 2 (exercise time 200 minutes/day). Types of exercise included static bicycle, isokinetic exercise, and standing or gait exercise on a treadmill. We also evaluated motor recovery using the Fugl-Meyer Scale (FMS) and the Modified Motor Assessment Scale (MMAS). Assessment of CRP levels and motor recovery were performed 3 times for 12 weeks at pre-treatment, 8 weeks and 12 weeks. [Results] The CRP level was decreased at post-treatment compared with pre-treatment; however, there were no significant differences. The FMS in both groups showed improvement at post-treatment compared with pre-treatment; however, there were no significant differences. The MMAS in both groups showed improvement at post-treatment compared with pre-treatment; however, there were no significant differences. [Conclusion] The exercise program improved the motor function and decreased the elevated CRP levels in chronic patients with cerebral infarct. Also, an increase in the duration of the exercise was correlated with decrease in the CRP level and increase in motor recovery.
Key words: Hemiparesis, C-reactive protein, Motor function

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INTRODUCTION

Measurements of C-reactive protein (CRP), an acute phase protein, act as an index of systemic inflammatory reactions and frequently increases with stroke onset[1)]. A rising CRP value in stroke patients is due primarily to cardiovascular system illness, which is, in turn, caused by changes in the autonomic nervous system[2)]. Thus, an increased CRP level is associated with illness of the cardiovascular system[3)] and the recurrence of stroke. In addition, the CRP level may predict progress and functional recovery in stroke patients[4)]. Therefore, factors that can decrease the CRP level in stroke patients are currently receiving attention.

Along with medical management, exercise programs have been recommended as a modality to decrease the CRP level[5)]. Exercise programs, effective in decreasing CRP concentration, have also been used as significant modalities in physical therapy for functional recovery in stroke patients[2). However, the exercise programs which were adopted to investigate whether the CRP level could be decreased by exercise, in these studies contained general exercises of daily living, not a special exercise program based on physical therapy. In addition, although some studies of patients with cardiovascular disease or normal subjects have been conducted, there have been no studies of exercise programs for stroke patients aiming to control CRP levels[3–5). Therefore, the objective of our study was to identify the changes in the CRP level when a physical therapy exercise program was conducted for inpatients with cerebral infarct. We measured the changes in the CRP level and compared them with the amounts of exercise treatment.

In the current study, we attempted to determine whether the exercise program could improve motor function and decrease the CRP level, and whether the amount of exercise could affect the change of motor function and CRP levels in chronic hemiparetic patients with cerebral infarct.

SUBJECTS AND METHODS

Subjects

A total of 103 stroke patients admitted to a Rusk Rehabilitation Medical Center during an 8-month period were diagnosed with cerebral infarct by a physiatrist via a CT scan or MRI: Sixth-three patients with abnormal CRP levels on the day of hospitalization were involved in an initial cross-sectional study, and 46 patients consented to testing and were chosen to participate in the study.

For this study, all participants were provided with an explanation of the exercise program and physical therapy, and they confirmed in person or through a guardian that they were willing to receive the specified treatment. This protocol was approved by the hospital (local) ethics committee. Inclusion criteria were as follows: 1) first ever stroke, 2) duration of longer than 3 months since stroke onset, 3) CRP level above 0.3 mg/dl, 4) no severe spasticity in the lower extremities (MAS: Modified Ashworth Scale <2), and 5) motor function of the affected upper and lower extremities showing moderated weakness (MMAS < 3, FES < 45). Exclusion criteria included the following: 1) patients who had an abnormal nutritive condition (the nutritive condition of each patient was evaluated by a nutritionist and any patient who consumed below 1,500–2,000 calories a day was considered unsuitable), and 2) patients who showed apraxia, severe sensory problems, and cognitive problems (Glasgow coma scale < 9–12)[6).

The design of this study was two randomly selected single-blind groups (1,2) and exercise was performed 5 times a week for a total of 12 weeks. Based on exercise treatment time during performance of physical therapy for 12 weeks, 46 cerebral infarct patients were divided into group 1 (21 people) and group 2 (25 people). During physical therapy, patient assessments were performed before exercise, 2 months after exercise, and 3 months after exercise, a total of 3 evaluations.

Methods

In order to differentiate length of time, exercise program I (100 minutes) was performed by group 1 and exercise program II (200 minutes) was performed by group 2 (Table 1). However, other physical therapy modalities (hyperthermia treatment and functional electrical treatment) were also given for approximately 40 minutes[7). The program was strictly managed by a professional physical therapist affiliated with the hospital. Also, with the assistance of nurses from the rehabilitation center within the hospital, independent exercise using equipment in the ward outside of the intervention program was restricted.

Range of Motion (ROM) exercises were performed by a physical therapist for maintenance and to promote range of motion in every joint of the limbs (paralyzed and non-paralyzed); these exercises were limited to those in which it did not induce direct pain[7). A static bicycle was used for coordination of lower limbs and for expansion of exercise boundaries for the lower joints[8–10). Isokinetic exercise was performed to promote muscular strength for walking as well as to enhance a range of exercise for joints of the limbs[10–11). Standing or gait exercise was performed on a treadmill to promote a sense of balance for standing or walking, coordination, and muscular strength[7,9–10,12).

The Fugl-Meyer Scale (FMS), published by Duncan (1983) and widely used by Bernardo (2005) was used[13). The FMS measures three areas: motor function, mobility, and sensation. For this study, only the motor function measurement of the lower and upper limbs was used. The FMS motor function assessment maximum score for the upper

Table 1. Exercise Programs I & II

Program class	Program items			
	ROM exercise	Static Bicycle (Lower extremity)	Isokinetic exercise	Standing or Gait exercise
Program I (Group 1) Total time: 100 mim/day	20 min/day	30 min/day	30 min/day	20 min/day
Program II (Group 2) Total time: 200 min/day	20 min/x2/day	30 min/x2/day	30 min/x2/day	20 min/x2/day

Table 2. Subject Demographics

	Group 1 (n=21)	Group 2 (n=25)
Age (years)	64.37 ± 3.23	60.16 ± 4.12
Sex (Male/Female)	9 (43%) / 12 (57%)	11 (44%) / 14 (56%)
Height (cm)	158.22 ± 3.15	162.56 ± 1.27
Weight (kg)	57.23 ± 1.03	61.07 ± 4.34
Months from onset	3.92 ± 2.24	4.37 ± 2.67
Affected side	Right (8) / Left (13)	Right (9) / Left (16)
MAS	0 (7), 1 (5), 1+(9)	0 (9), 1 (5), 1+(11)
FMS	41.11 ± 3.36	39.67 ± 2.29
MMAS	2.81 ± .34	2.41 ± .29
CRP (mg/dl)	4.16 ± 2.08	2.96 ± 4.82

M ± SE, Mean ± Standard Error; MAS, modified Ashworth scale; FMS, Fugl-Meyer scale (upper extremity (57) + lower extremity (36) = maximum score 93); MMAS, modified motor assessment scale (1–6 grade); CRP, c-reactive protein (normal level: below 0.3 mg/dl)

limbs was 57 points, while the lower limb motor function assessment maximum score was 36 points, giving a maximum score for both the upper and lower limbs of 93 points. Also, the Modified Motor Function Assessment (MMAS: Walking) was used for measurement of a stroke patient's motor function[14]. MMAS is made up of a total of 9 categories: 8 categories are associated with motor function, and 1 category is associated with muscle tone. Of these categories, only categories related to walking were used in this study. Scoring levels for walking categories ranged from 0 to 6 points.

A TBA-40FR (Toshiba, Japan) was used for CRP evaluation: The test-kit was purchased from Denka (Japan), and the nephelometric immunoassay with a normal value of 0.000–0.030 (mg/dl) was used. For the test, blood samples were taken after confirmation of a fasting period of over 8 hours, at a designated time, before breakfast (before 7 a.m.). Tests were performed twice, and numerical analyses were interpreted by medical technologists.

For statistical analysis, motor function recovery data and CRP measurements obtained from cerebral infarct patients were processed using SPSS/Windows (version 12.0). For comparison of each test category in group 1 and group 2 based on treatment duration, an analysis using repeated 2-way ANOVA, with within group factors and repeated factors was used: All statistical significance levels were determined to be $p<0.05$.

RESULTS

Table 2 shows subject demographics. There was no significant between group difference in any anthropometric parameter at the start of the study. The age of group 1 was 64.37 years, and that of group 2 was 60.16 years ($p=0.212$). Group 1 was comprised of 9 males and 12 females, and group 2 was comprised of 11 males and 14 females ($p=0.872$). The average height of group 1 was 158.22 cm and 162.56 in group 2 ($p=0.325$). The average weight of group 1 was 57.23 kg and 61.07 kg in group 2 ($p=0.211$). The duration of illness for

Table 3. Comparison of all measures between groups after exercise program

	Group 1				Group 2			
	Pre	8 weeks	12 weeks	p	Pre	8 weeks	12 weeks	p
CRP	4.16 ± 2.08	3.10 ± 1.65	2.83 ± 2.45	0.097	2.96 ± 4.82	2.55 ± 2.54	1.21 ± 3.01	0.050
FMS	41.11 ± 3.36	45.45 ± 4.16	47.75 ± 7.65	0.041†	39.67 ± 2.29	53.61 ± 2.71	54.66 ± 3.99	0.021†
MMAS	2.81 ± 0.34	2.85 ± 2.11	3.14 ± 3.98	0.043†	2.41 ± 0.29	2.90 ± 0.11	3.14 ± 1.24	0.019†

† : statistically significant difference within each group ($p<0.05$), No statistically significant difference between groups.

group 1 was 3.92 months and 4.37 months for group 2 (p=0.301).

Similarly, there were no significant between group differences in the test parameters at the start of the study. The spasticity grades of lower extremity (MAS) in group 1 were grade 0 (7), 1 (5), 1+ (9), and for group 2 were grade 0 (9), 1 (5), 1+ (11) (p=0.551). Lower and upper limb motor function evaluation (FMS) for group 1 was 41.11 points and for group 2 was 39.67 points (p=0.781). The walking ability evaluation (MMAS) of group 1 was 2.81 points and 2.41 points for group 2 (p=0.882). Measurement of CRP, a generalized inflammatory marker, for group 1 was 4.16 and for group 2 was 2.96 (p=0.277).

Table 3 shows the comparison of all measures between groups over time. The within group comparison of CRP based on exercise duration showed that neither Group 1 (p=0.097) nor Group 2 (p=0.050) showed any significant changes with exercise duration. In the comparison of CRP based on exercise duration, within group effect examination showed that group and exercise duration interaction had no statistical significance (p=0.384), and the between-group effect examination also showed no statistical significance (p=0.240).

The significant changes with exercise duration in within group comparison of FMS showed Group 1 (p=0.041) and Group 2 (p=0.021). The within group effect examination showed that the effects of group and exercise duration had statistical significance (p=0.032); however, the between-group effect examination showed no statistical significance (p=0.152).

The within group comparison examination significant changes with exercise duration in Groups MMAS showed that Group 1 (p=0.043) and Group 2 (p=0.019). The comparison of MMAS showed statistical significance for the within group effect and the exercise duration interaction (p=0.020); however, the between-group effect examination showed no statistical significance (p=0.387).

DISCUSSION

In the current study, we found that the exercise program improved motor function and decreased elevated CRP levels in chronic patients with cerebral infarct. In addition, as the amount of exercise performed increased, the motor function improved and the CRP levels decreased.

There have been some studies that have shown that an elevated CRP level could be a risk factor for stroke. Research conducted between 1988 and 1994 with 8,850 Americans as subjects concluded that the CRP level could be used as a predictive factor of stroke and that stroke patients with a continuous increase in CRP levels had a higher likelihood of recurrence of stroke within one year[2]. Another clinical observation of 591 males and 871 female patients over a period of 12–14 years showed that an increased CRP level is an indication of higher probabilities of ischemic stroke and temporary ischemic stroke. These probabilities were two and three times greater for men and women, respectively, compared to patients who did not show an increased CRP level[15]. In this study, a total of 63 (61%) out of 103 ischemic stroke patients showed an increased CRP level at the time of the pre-exercise program.

Studies on exercise and CRP relevance showed that regular exercise has a positive effect on lipid metabolism, body mass index, insulin resistance, blood pressure, and other factors which induce a decrease in CRP, and regular exercise decreases CRP levels in patients with heart disease[16–17]. Also, according to a study of ischemic stroke patients, within one year, patients who worked out regularly had lower CRP levels and had a decreased rate of stroke recurrence in comparison with those who did not[3]. Results from another study conducted over a 3-month period on people with abnormal CRP showed a significant difference in CRP in the group which practiced regular aerobic exercise for more than one hour 5 times a week, compared to the group which did not exercise, which had no significant difference[18]. In contrast, a similar study reported that exercise did not greatly affect the CRP level[19]. Our study showed that CRP levels decreased in both groups after the exercise program, and that different exercise amounts led to different decreases in the CRP level.

Determination of a standard amount of adequate exercise for stroke patient motor recovery and CRP level decrease is difficult. Damage to brain structure and degree of disability due to the damage, as well as response to treatment, is different for each patient[8]. However, selection of a suitable amount of exercise for stroke patients is an important factor in the reorganization of damaged brain structure and recovery of function. Thus, therapists must prepare treatment programs to suit patient characteristics. For this reason, debate about adequate amount of exercise for treatment for functional recovery of stroke patients has been continuous. In response to this debate, research on the time frame for exercise treatment has been a primary interest[20]. Our study did not demonstrate a standard amount of exercise for stroke patients which would lead to a decrease in CRP level and improvement in motor recovery; however, an increase in duration of exercise correlated with a greater decrease in the CRP level and a greater improvement in motor recovery.

In conclusion, we found that an exercise program improved motor function and decreased elevated CRP levels in chronic stroke patients with cerebral infarct. In addition, increment of the amount of exercise may be beneficial in terms of motor function and CRP level. Therefore, appropriate exercise can prevent secondary complications from illnesses of the cardiovascular system, lower the rate of stroke recurrence by decreasing abnormally high CRP levels, and promote motor function. We think further studies are needed on the optimal amount of exercise to decrease CRP levels and improve motor function in stroke patients. In addition, further studies on the relationship between exercise program and other risk factors for stroke would be desirable.

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