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The Effects of Task-Oriented Training on Motor and Cognitive Function in Focal Ischemic Brain Injury Model of Rat

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Abstract

The purpose of this study was to investigate the effects of the task-oriented training according to the application time with the change of motor and cognition function. Focal ischemic brain injury was produced in Sprague-Dawley rats (20 rats, 250±50 g) through middle cerebral artery occlusion (MCAo). Before MCAo induction, all rats were trained in treadmill training and Morris water maze training for 1 week. Then they were randomly divided into groups; Group Ⅰ: MCAo induction (n_1=5), Group Ⅱ: the application for simple treadmill task training after MCAo induction (n_2=5), Group Ⅲ: the application for Morris water maze cognitive task training after MCAo induction (n_3=5), Group Ⅳ: the application for progressive treadmill task training and Morris water maze cognitive task training after MCAo induction (n_4=5). Modified limb placing tests (MLPTs) and motor tests (MTs) were performed to test motor function and then Morris water maze acquisition test (MWMAT) and Morris water maze retention test (MWMRT) were performed to test cognitive function. For MTs, there were significant interactions among the groups with the time ($p<.001$). Group Ⅳ showed the steeper increasing pattern than those in other Groups on the 7th and 14th day. For MLPTs, there were significant interactions among the groups with the time ($p<.001$). The scores in Group Ⅲ, Ⅳ had showed the more decreasing pattern than those in Group Ⅰ, Ⅱ since the 7th day and 14th day. For MWMAT, there were significant interactions among the groups with the time ($p<.001$). Group Ⅱ found the quadrant circular platform showed the steeper decreasing pattern than that in Group Ⅰ on the 9th, 10th, 11th and 12th day. Group Ⅲ, Ⅳ found the quadrant circular platform showed the slower decreasing pattern than that in Group Ⅰ, Ⅱ. For MWMRT, there were significant differences among the four groups ($p<.001$). The time to dwell on quadrant circular platform in Group Ⅳ on the 13th day was the longest compared with other groups. These results suggested that the combined task training was very effective to improve the motor and cognition function for the rats affected on their focal ischemic brain injury.

Key Words: Cognition function; Motor function; Task-oriented training.

Introduction

Cerebral ischemia is caused by reduced brain perfusion due to temporal or permanent occlusion of cerebral arteries (Leker and Shohami, 2002) and brings about multiple problems such as motor, sensory, perception, and cognition impairment due to the apoptosis of cells in the blood-supplied region (Pedersen et al, 1996; Sims and Anderson, 2002). Among others cognitive impairment is one of the

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most common deficits in people after ischemic or hemorrhagic stroke. The rats of incidence of post-stroke cognitive deficit have been reported to be 20% to 37.1% (Tang et al, 2004; Tang et al, 2007; Zhou et al, 2005). It is also one of factors which make successful rehabilitation difficult and is important in deciding a functional prognosis after stroke (Paolucci et al, 1996). Thus, early intervention approach is necessary to treat impaired cognitive function.

For patients to participate in rehabilitation with success, their intelligent state which is learning and order execution ability must be identified in the process of intervention (Claesson et al, 2005). Since patients with cognitive impairment may not easily understand interventional introductions or education by the therapist, they may not carry out the demands of motor performance (Rao et al, 1988). They also may not focus on motor learning because of attention problems (Karatekin et al, 2003) and not perform motor tasks repeatedly because they cannot remember what to do. These factors all may contribute to their passive participation in physical training process (Zafonte et al, 1997). To enhance the effect of physical therapy, it is necessary to conduct task training to promote physical functions and at the same time task training of cognitive intervention to induce their active participation in exercise.

Neurologic rehabilitation models for stroke patients largely include the muscle reeducation approach, the neurotherapeutic facilitation approach, and the contemporary task-oriented approach (Shumway-Cook and Woollacott, 2007). The contemporary task-oriented approach is mainly influenced by motor learning theory and has given great change in the physical therapy approach for patients with impaired central nervous system. However, this approach does not aim to recover motor ability in patients with cognitive impairment, and focus only on the motor system which is a physical function. As a result, the integrated intervention for perception and cognition has been ignored or not been executed (Trombly, 1983).

Recently many researches have reported the effect of exercise in rats with ischemic brain injury. The results suggest that treadmill training improved significantly neurological outcomes in middle cerebral artery occlusion (MCAo) rats (Yang et al, 2003) and increased cell formation in dentate gyrus of hippocampus (Trejo et al, 2001), and Morris water maze training increased nerve cells in the hippocampal formation in rats (Hairston et al, 2005; Leuner et al, 2004).

Accordingly, this study intended to examine the effects of task training on motor and cognitive function and understand difference among task training in focal ischemic brain injury-induced rats. Task training used for this study included simple treadmill task training for physical training, Morris water maze cognitive training for cognitive training, and combined task training of these two methods.

Methods

Subjects

Experimental Animals

Twenty adult male Sprague-Dawley rats[1)] weighting 250±50 g were used for the experiment. For individual selection, neurological evaluation developed by Menzies et al (1992) was conducted. Rats that had palsy of affected side and spontaneous contralateral circling when pulled by the tail in the air were only tested.

The motor function test was conducted on the 1st, 7th, and 14th day after MCAo induction and the Morris water maze test was conducted 9th, 10th, 11th, 12th and 13th day for the cognitive function test. One-week adaption period was given for task training to reduce stress caused by task training. All rats were randomly divided into four groups; Group Ⅰ: MCAo induction (n_1=5), Group Ⅱ: the application for simple treadmill task training after MCAo induction (n_2=5), Group Ⅲ: the application for Morris

1) Daehan Bio Link Co., Korea.

water maze cognitive task training after MCAo induction (n_3=5), Group Ⅳ: the application for progressive treadmill task training and Morris water maze cognitive task training after MCAo induction (n_4=5). The temperature was 25±1℃, humidity was 55±10%, and light and darkness was given every 12 hours in the laboratory.

Induction of MCAo

Middle cerebral artery occlusion (MCAo) was executed according to Nagasawa and Kogure (1989)'s method. After general inhalation anesthesia, the body was kept at a uniform temperature using a heating pad and a rectal thermometer. The right common carotid artery was separated from the vagus nerve and then the external and internal carotid arteries were separated from the right common carotid artery. The common and external carotid arteries were ligated loosely with a pre-hung thread and a microvascular clip was used for the branch of internal carotid artery. After the origin of the branch of internal carotid artery was incised, the probe made of 4-0 nylon surgical suture[2] of 1.5 ㎝ long coated with silicone was put into the internal carotid artery and fixed by tying the thread hung in the internal carotid artery and the microvascular clip was removed. Reperfusion was achieved by removing the suture except silicon two hours after MCAo.

Task Training Designs

Treadmill Task Training

Treadmill task training used the methods which became universal in previous researches (Carro et al, 2000) after modification and complement using a small rodent animal treadmill at mild intensity to minimize stress in animals. The training was conducted for two weeks with intensity fixed at 0° incline 24 hours after MCAo. The Group Ⅱ rats were put on the treadmill to run at 10 m/min for 20 min once a day, 6 days a week for 2 weeks.

On the other hand, the Group Ⅳ rats were put on the treadmill to run at 10 m/min for the first 10 min and at 5 m/min for the second 10 min for the 6 days of the 1st week, and then, at 7 m/min for the first 10 min and at 10 m/min for the second 10 min for 6 days of the second week.

Morris Water Maze Cognitive Task Training

Modified Fukunaga et al's method (1999) was used for the Morris water maze cognitive task training. The rats were trained to find a circular platform entering water invisibly in 120 seconds for each time. It was conducted ten times. If the rat failed to locate the platform within 30 seconds, it was guided by hand to the circular platform. When they could not find the circular platform until the 5th time, then they were given a 10-minute break to minimize their stress.

Motor Function Test

Motor Tests (MTs)

Motor tests (MTs) comprised the inclined plane test, the balance beam test, and the prehensile test, which were used for integrated sensory motor and modified by Tominaga and Ohnishi (1989). The inclined plane test used a 60×40 ㎝ board with a groove 3 ㎜ deep at 1 ㎝ interval and measured the time when rats stayed on the board at 60° angle. The balance beam test measured the time when rats stayed on the square wood beam 70 ㎝ long and 40 ㎝ high (3 ㎝ long in ones side) placed in the center. The prehensile test measured the time when rats hung onto the nylon rope 70 ㎝ long and 4 ㎜ in diameter stretching 40 ㎝ above. The score was 0 for <1 second, 1 for 1~10 seconds, 2 for 11~20 seconds, 3 for 21~30 seconds, and 4 for >30 seconds. The total motor score ranged from 0 to 12 points. The motor score was quantified by summing up all three tests. After two trials, the better score was recorded.

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2) Xantopren, Bayer Dental, Germany.

Modified Limb Placing Tests (MLPTs)

This test consisted of three tasks according to the methods described by De Ryck et al (1989). First, the forward visual limb placing test observed the stretch of the forelimbs towards the table when the tester held the middle body of the rat and suspended it 10 ㎝ over the table. The normal stretch of both forelimbs was scored as 0 point and the abnormal flexion of one forelimb was scored as 1 point. Second, the proprioceptive limb placing test observed the retrieval and placement of each forelimb of the rat. The tester positioned the forelimbs of the rat on the edge of a table and turned its head at 45° angle to remove visual perception and tactile stimulation by whiskers and then gently pulled the forelimbs down and released to stimulate the joints and muscle of forelimbs. Finally, the lateral pushing limb placing test observed the lateral placement of the forelimb and the hindlimb of the rat. The tester placed the rat along the table edge and pushed its lateral body gently toward the table edge. When the rat positioned its left and right forelimbs and forelimbs and hindlimbs normally, it was scored as 0 point, when the rat reacted with a delay or incompletely, it was 1, and when the rate had no reaction, it was 2. Each point was added.

Cognitive Function Test

Morris Water Maze Acquisition Test (MWMAT)

The Morris water maze tests were conducted using modified and complemented Fukunaga et al's method (1999). The water tank used as the Morris water maze was a circular pool 160 ㎝ in diameter and 50 ㎝ high. The depth of water in the water tank was 30 ㎝ and the temperature of water was 22±2℃. The circular platform was made of a circular transparent acrylic 12 ㎝ in diameter wrapped in the gauze for convenient lifting and was located 4 ㎝ below the water surface for rats not to see with the naked eye. The test table, chairs, and tester in the outside of the water maze needed to be always at the same place to be used as a cue. Because the water was made opaque by black ink, the circular platform was not seen and could not be used as a visual cue. The video tracking system was used to record the rats moving in the water maze. The circular escape platform was placed in the center of the southeast quadrant and one of the last quadrant was used as the starting point. The rats entered water at the spot 5 ㎝ away from the edge of the Morris water maze, facing the wall of the Morris water maze. The rats were given four trials a day for five days and the time of latency to acquire the submerged escape platform was measured using S-MART[3] program. When the rats could not arrive at the circular escape platform after 90 seconds, then they were guided to the escape platform, stayed for 20 seconds, and tried again. The direction of putting rats in the Morris water maze varied every time using Table of Random Numbers.

Morris Water Maze Retention Test (MWMRT)

In the 13th day at the end of test, the circular escape platform was removed and the rats were released between west and north where the circular platform was located previously in the same way as the acquisition test. The trials lasted 90 seconds, and their dwelling time around the quadrant where the circular escape platform was located previously.

Statistical Analysis

All statistical tests were run using SPSS version 12.0 software, and the results were expressed as the mean and standard deviation. MTs, MLPTs, and MWMAT were analyzed using repeated measures ANOVA. MWMRT was analyzed using one-way ANOVA followed by Tukey post hoc analysis. Value of less than .05 was considered to be statistically significant.

3) Pab Lab, Spain.

Results

Motor Function Test

Motor Tests (MTs)

The results of MTs using repeated measures ANOVA shows that there were significant interactions between groups and time and the MTs pattern varied with time (F (6, 32)=15.123, p<.001). Group Ⅰ was changed from 7.80±.45 to 9.40±.55; Group Ⅱ, from 9.40±.55 to 11.40±.55; Group Ⅲ, from 9.20±.45 to 11.20±.45, and Group Ⅳ, from 10.20±.45 to 11.80±.45 on the 7th and 14th days, suggesting a increasing pattern with time. Of them, Group Ⅳ had the highest increasing pattern from the 7th day (Figure 1).

Modified Limb Placing Tests (MLPTs)

The results of MLPTs using repeated measures ANOVA shows that there were significant interactions between groups and time and the MLPTs pattern varied with time (F (6, 32)=17.083, p<.001). While Group Ⅰ was changed from 5.00±.71 to 3.80±.84 and Group Ⅱ, from 4.00±.71 to 2.40±.55 on the 7th and 14th days, suggesting a slowly decreasing pattern, Group Ⅲ was changed from 2.80±.84 to 1.80±.45 and Group Ⅳ, from 2.00±.71 to 1.00±.71, suggesting a rapid decreasing after the 7th day until the second week (Figure 2).

Cognitive Test

Morris Water Maze Acquisition Test (MWMAT)

The results of MWMAT using repeated measures ANOVA shows that there were significant interactions between groups and time, and the MLPTs pattern varied with time (F (9, 48)=13.562, p<.001). While Group Ⅰ was changed from 90.00±.00 to 38.23±10.38 and Group Ⅱ, from 89.09±2.03 to 19.01±7.12, suggesting a decreasing pattern from the 9th day to the 12th day, Group Ⅲ was changed from 25.39±6.59 to 7.62±2.46 and Group Ⅳ, from 29.14±11.35 to 4.81±1.22, suggesting a slowly decreasing pattern at the low state. Group Ⅰ slowly decreased with time, whereas Group Ⅱ more rapidly decreased from the 10th day than Group Ⅰ (Figure 3) (Figure 5).

Morris Water Maze Retention Test (MWMRT)

For MWMRT, the dwelling time around the quadrant was examined using one-way ANOVA shows that there were significant difference among groups (F (3, 16)=70.914, p<.001). The post hoc analysis showed the dwelling time was 15.52±2.61 for Group Ⅰ, 27.82±3.90 for Group Ⅱ, 36.37±2.71 for Group Ⅲ, and 40.11±2.05 for Group Ⅳ, suggesting a significant difference in Group Ⅰ, Ⅱ, Ⅲ, and Ⅳ. Also, there was a significant difference between Group Ⅱ and Ⅲ, and between Group Ⅱ and Ⅳ. The dwelling time of Group Ⅳ was found to be longer than other groups (Figure 4).

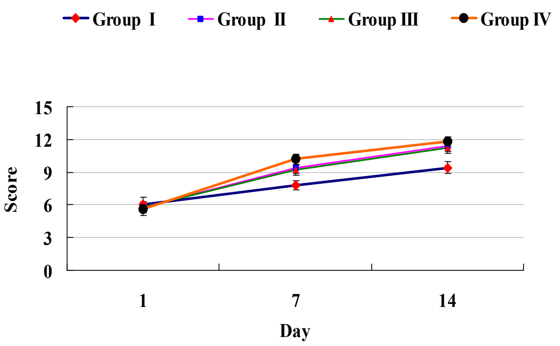

Figure 1. Comparison of motor test scores on task-oriented training among the four groups of MCAo in rats.

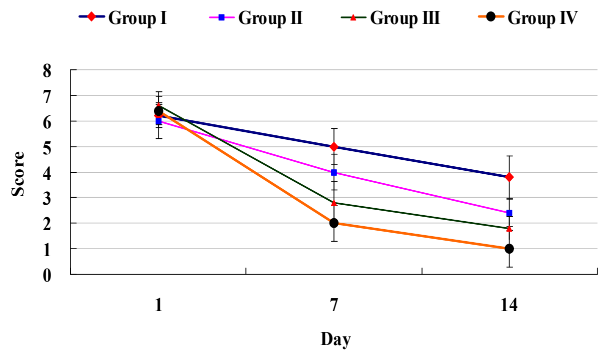

Figure 2. Comparison of modified limb placing test scores on task-oriented training among the four groups of MCAo in rats.

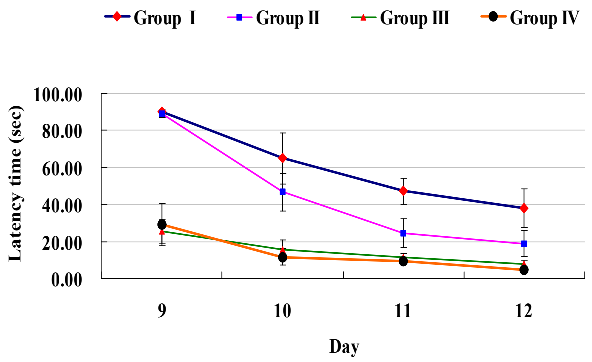

Figure 3. Comparison of acquisition performances on task-oriented training among the four groups of MCAo in rats.

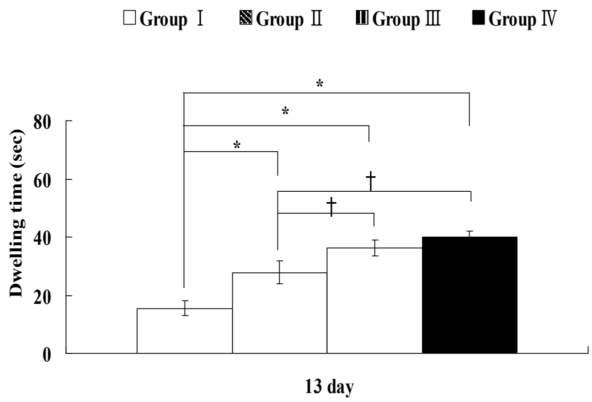

Figure 4. Comparison of dwelling times in target quadrant of retention test on task-oriented training among the four groups of MCAo in rats (*: significant difference in Group Ⅰ, Ⅱ, Ⅲ, and Ⅳ, †: significant difference between Group Ⅱ and Ⅲ, and between Group Ⅱ and Ⅳ).

Discussion

This study intended to examine the effects of task training on motor and cognitive functions in rats with focal ischemic brain injury using simple tread-mill for physical training, Morris water maze for cognitive training, and combined task training. This study conducted MLPTs to assess sight, proprio-ceptive sensation, and tactile sensory motor of fore-limbs and hindlimbs of rats. As a result, while Group Ⅱ slowly decreased from the 7th day, Group Ⅲ and Ⅳ rapidly decreased, compared with Group Ⅰ. This results are consistent with the report that when swimming and treadmill training was given to MCAo rats, the group having both training showed more significant effect than the groups having only one training (Lee, 2006). It is suggested that MLPTs score was decreased because in the process of finding the circular escape platform, spatial learning ability and the sensation and perception ability of forelimbs were improved through visual-spatial training. Also, buoyancy may have a positive effect on proprioceptor or sensory motor in water (Danneskiold-Samsoe et al, 1987; Wilder and Brennan, 1993).

Motor tests (MTs) consisted of the inclined plane test, the balance beam test, and the prehensile test to assess the motor weakness in MCAo rats (Combs and D'Alecy, 1987). The reduce of neural system ac-tivity caused by cerebral ischemia and the lack of motor activity and exercise may hinder the develop-ment of muscle, causing muscle weakness (Dennis, 2000) and Burke (1988) reported that the loss of

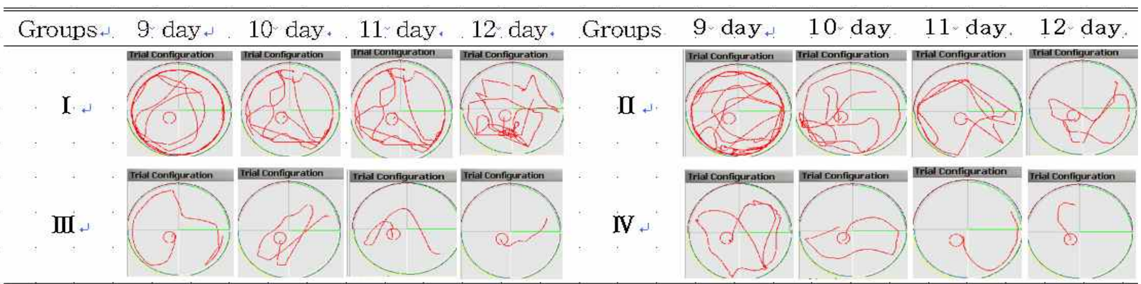

Figure 5. Comparison of acquisition performance on task-oriented training among the four groups of MCAo in rats. Note thigmotaxis behaviour in MCAo rats.

muscle strength disturbed function recovery after brain injury. In this study, Group Ⅱ, Ⅲ, and Ⅳ which were given task training had more significant increase than Group Ⅰ, and Group Ⅳ showed the highest score in the 7th day. It is consistent with the reports by An et al (2000) that 7-day treadmill training for endurance immediately after stroke increased muscle weight and then reduced muscle weakness and by Lee et al (2004) that 30-min swimming inhibited cerebral ischemia and further improved muscle weakness of tibialis anterior muscle in MCAo rats. It is considered that the training groups had higher score than the Group Ⅰ because they could reinforce the muscle strength of hindlimbs and recover their motor function through task training. It is consistent with previous research result that the training group of combining swimming and treadmill training after MCAo had significant higher MTs score at the early stage (Lee, 2006) and that the group Ⅳ having combined training had a positive effect on motor function (Lee et al, 2005).

The Morris water maze is frequently used to assess a cognitive function in rats (Jolkkonen et al, 2003) out of many methods to assess learning and memory in animals. The Morris water maze task training conducted acquisition training to reinforce external visual cues and spatial location and retention training to improve the recollection of stored spatial memory. Rats with hippocampal damage caused by focal cerebral ischemia have the deficit of spatial learning ability as Morris water maze (Squire and Zola, 1996). The experiment of this study showed that in the MWMAT, group Ⅰ had problem to find the circular escape platform on the 9th day after the induction of focal cerebral ischemia, but Group Ⅱ reduced its time to find the circular platform over time. It is consistent with the report that wheel running improved spatial learning ability (van Praag et al, 1999). On the other hand, Group Ⅲ and Ⅳ training in the similar situation in the early stage showed better performance, reducing the time to find the circular platform on the first 9th day. This study set up the height of circular platform 4 ㎝ below the water surface in MWMAT. It is considered that Group Ⅲ and Ⅳ improved their sensation and perception of forelimbs of rats through repeated learning, leading to the reduction of time to find the circular platform. In the 13th day, the MWMRT was used to assess spatial learning ability and memory. It measured the dwelling time to stay around the quadrant where the circular platform was located previously. The time was increased most in Group Ⅳ, followed by Group Ⅲ and Ⅱ compared with Group Ⅰ. It is considered that training groups could increase dwelling time because their spatial learning ability and memory was improved through appropriate feedback and intentional repetition in similar training as Morris water maze test. It is consistent with the report that based on the principle of similarity, tasks could be transferred successfully through intentional task practice in the similar situation and it resulted in the promotion of the motor learning of individual skill (Lederman, 2005).

Accordingly, in therapeutic exercise approach of stroke with impaired cognitive function, when physical task training was combined on the basis of cognitive task training, it will be a great effect on motor function recovery as well as cognitive function. Further clinical research on the intervention of cognitive approach is necessary in the physical therapy area.

Conclusion

These results suggested that the combined task training in rats with focal ischemic brain injury has a more significant impact on restoring motor function and cognitive function.

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