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# Effects of Alternate Training for Motor Skills on Neurotrophic Factors and Gait in Striatum Stroke-Induced Rats

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## ABSTRACT

**Introduction:** In the brain, haemorrhage causes damage to the patient's brain, and the impairment of neurotrophic factors and cognitive and motor disorders result in restrictions on daily and functional activities.

**Aim and Objective:** In this study, we conducted abutment and familiar exercise in striatal hemorrhagic SD rat to compare neurotrophic factors and functional activities.

**Result:** The manifestation of Brain-derived neurotrophic factor (BDNF) in the brain of the white rat was  $108.34 \pm 4.22$  in the group that conducted the alternate exercise and  $104.56 \pm 3.95$  in the group that performed the familiar exercise, and was statistically significant. The manifestation of Nerve growth factor (NGF) expression in the brain of the white rat was  $106.65 \pm 2.52$  in the group that conducted the alternate exercise and  $102.22 \pm 1.89$  in the group that performed the familiar exercise and was statistically significant. The Beam walking test scores were  $4.53 \pm 0.51$  points for the group that conducted the alternate exercise and  $4.80 \pm 0.41$  points for the group that performed the familiar exercise, and statistically significant. The skilled ladder rung test scores were  $65.55 \pm 8.23$  % for the group that conducted the alternate exercise and  $80.13 \pm 9.54$  % for the group that performed the familiar exercise, and statistically significant.

**Conclusion:** It has been shown that alternating exercise can have a more positive effect on nerve recovery and motor function on striatal stroke.

**Key Words:** Stroke, Neurotrophic factors, Beam walking test, Treadmill, Swimming

## INTRODUCTION

Intracerebral haemorrhage, which accounts for 10% to 15% of stroke cases, occurs due to cerebrovascular diseases, chronic hypertension, and similar conditions.<sup>1</sup> Approximately 40% of patients with intracerebral haemorrhage die within six months after its onset, and only about 20% of these patients recover their abilities to perform activities of daily living (ADLs) independently.

According to a previous study, intracerebral haemorrhage patients can develop cognitive and perceptive disorders as well as long-term motor skills and sensory disorders, which cause limitations in ADLs and functional activity, thus substantially lowering their quality of life.<sup>2</sup> About 65% of intracerebral haemorrhage patients experience loss of their bodies' protective responses and proprioception, and their reduced

muscle tension translates into instability and decreased efficiency of motions.<sup>3</sup> Specifically, the connectivity between the hippocampus and the striatum is responsible for cognitive and motor control, and striatal impairment results in cognitive, motor, and ADL-related disorders.<sup>4</sup>

Stroke patients' exercises have been applied in various ways. A study reported that exercising before stroke onset can prevent brain damage, and wheel running applied in animal models reduces the degrees of cerebral oedema and infarction after the onset of cerebral infarction.<sup>5</sup> Wheel running before the onset of cerebral infarction lowers the blood-brain barrier penetrability and reduces the amount of the neurotransmitter glutamate, thereby decreasing neurotoxicity and impairment immediately after the onset.<sup>6</sup> These findings have led researchers to use running machines and instruments for wheel running or environmental strengthening as

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intervention tools.<sup>7</sup> These tools also improve the connectivity between motor areas during the learning of exercises.<sup>8,9</sup> Also, the application of new exercises in patients with cranial nerve injuries is more effective than the continuance of their familiar exercises.<sup>10</sup>

Proprioception is closely associated with the body's balance ability, and proprioceptive inputs function as important feedback for balance and trunk control. Proprioception creates immediate responses by accepting external stimulations and environmental changes. It also secures the human body's stability and prevents muscle and joint impairments through its adjustment of the locations of muscles and joints. Brain-damaged patients become slow in responding to environmental changes due to proprioceptive disorders, which subsequently causes secondary damage. Therefore, the recovery of proprioception is essential for brain-damaged patients.<sup>7</sup>

Exercises are widely applied for the rehabilitation of intracerebral haemorrhage patients. Most of these exercises are implemented based on clinical research evidence. In particular, the results of studies using animal models are applied with high effectiveness. Notably, a study reported neurological recovery effects via the mechanisms of exercise-induced neuroplasticity.<sup>8</sup> Although many studies have explored pathophysiological aspects or therapeutic values based on the surgery or medical treatment of animal models with intracerebral haemorrhage,<sup>7,8</sup> studies on the effects of exercises on test animals are limited. Nevertheless, they suggest the functional plasticity of aerobic exercises. Exercise can stimulate functions of brain and neurogenesis by increasing several factors. The past studies indicate that dopamine synthesis is improved by serum calcium transported to the brain following exercise. The exercise shows that brain structure for learning and memory is increased to survive.<sup>10</sup>

Treadmill machine exercise is a good way to improve the rhythmical gait of patients with acute stroke and chronic stroke and has been widely used in studying the systematic and neurological changes of laboratory animal models over the past 40 years. Running machine training has the advantage of being easier to calculate the total amount of exercise than other exercises such as wheel running and swimming. The investigator can also control the intensity and duration of the exercise. Another advantage of running machine exercise is that researchers can easily record video cameras while exercising to evaluate the athletic performance of animals.<sup>6,9</sup> Swimming exercises can be used for stroke patients to reduce stress, and on land, they can exert more resistance than exercise. Swimming exercises can be offered to more animals at a time than any other exercise.

The brain's neurotrophic factors include the brain-derived neurotrophic factor (BDNF), the insulin-like factor-1 and nerve growth factors (NGF). These factors are closely linked with the recovery of the central nervous system and can be

activated through a variety of physical exercises and activities.<sup>10</sup> According to previous research, these factors are involved in the survival, differentiation, and formation of nerve cells. Specifically, as a neurotrophic protein, the BDNF also exists in the adult brain; it is isolated from nerve cells, affects learning and memory, and functions as an important signal for the brain's neuroplasticity. Therefore, it is an important factor for brain recovery after brain damage.<sup>11</sup> The purpose of the present study is to compare the effects of steady training and alternate training on the BDNF and hand function in white rats with intracerebral hemorrhage. In the peripheral nervous system, NGF acts as the dominant neurotrophic factor, but in the central nervous system, NGF provides nutritional support to the basal forebrain cholinergic neurons.

## RESEARCH METHODS

### Test animals

In this study, an experiment was conducted using 16 eight-week-old Sprague-Dawley rats without clinical or neurological disorders. During the experiment, these rats were given light and dark cycles at 12-hour intervals at room temperature ( $23^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) and  $60\% \pm 5\%$  humidity. The experimental procedures complied with the Guide for the Care and Use of Laboratory Animals, issued by the Institute of Laboratory Animal Resources (The Guide for the Care and Use of Laboratory Animals issued by the Institute of Laboratory Animal Resources, USA, 1996) and all surgical procedures and experimental protocols followed Daegu University's guidelines and were approved by the Institution of Animal Care and Use Committee (IACUC). The white rats had a five-day acclimation period before the experiment to become accustomed to the breeding environment.

In the control group ( $n=8$ ), the rats were first trained in wheel running for one week, and cerebral haemorrhage was then induced in them. Next, they had to perform wheel running again for two weeks. In the experimental group ( $n=8$ ), the rats were trained in wheel running for one week, and cerebral haemorrhage was then induced. This was followed by a two-week swimming training.

### Exercise methods

Wheel running has widely been used as an effective exercise for patients with nerve injuries to practice rhythmic walking. Its advantage is that the amount of exercise can be easily calculated.<sup>12</sup> In this study, rats were conditioned to perform wheel running for 15 minutes once a day at 55% of the maximum V (Volume) + O<sub>2</sub> (Oxygen) (VO<sub>2</sub>) and speed of 15m per minute.<sup>9</sup> Electrical stimulations were applied at less than 2.0mA to make the rats continue to exercise without breaks.

Swimming can be used to reduce patients' stress levels during training; its advantage is that greater resistance can be applied than that in wheel learning.<sup>13</sup> Moreover, it can train multiple animals at the same time. In this study, the rats performed a swimming exercise under no-load conditions for 15 minutes once a day. The water temperature was maintained at 33°C to 35°C, and the water depth was set at 50 cm to prevent the rats from supporting their tails against the bottom.<sup>14</sup>

### Neurotrophic factors

As a critical factor related to the recovery of the central nervous system, the BDNF controls cerebral development and neurogenesis; it also protects dopamine, cortexes, and motor nerves that prevent the occurrence of neurological disorders on the central nerve system. Thus, the BDNF is frequently expressed in the hippocampus and the cortex and involved in motor learning, memory, and long-term memory.<sup>11, 15</sup>

### Test methods

#### Beam walking test

The beam walking test is used to evaluate the control of motor skills and the sensorimotor system. Repeated toe flexion and extension are highly important. Two weeks after the inducement of striatal haemorrhage, the rats were trained to walk on a wooden beam (2.5 × 2.5 × 80cm), and their gait was then scored from 0 to 6 points. Each rat's performance was measured three times for comparison. The 0 score is the best performance with non-slips and 6 score is unable to maintain the body on the beam for 10 seconds. The 6 is the worst score;

0 point: no foot slips;

- 1 point: able to walk while holding both sides of the beam;
- 2 points: able to walk but with foot slips;
- 3 points: very slow walk due to gait problems;
- 4 points: unable to walk through the beam;
- 5 points: unable to move limbs on the beam; and
- 6 points: unable to maintain the body on the beam for 10 seconds.

#### Skilled ladder rung test

The ladder walking test assesses the loss and recovery of sensory-motor function, which is referred to the Emerick and Kartje's Study (2004).<sup>16</sup> The ladder device consists of a length of 1 m with a distance of 1.5 cm between the cross-bars. The rats practised the test ladder before the operation. The rats passed the rungs of the ladder freely without reinforcement. The test was also carried out three times and the next date was calculated as average. All tests were recorded with a video camera to assess the performance of the rat.

Each group was tested just before the sacrifice. In one test session, the mouse traversed the walkway three times and scored for the number of left front extremity pit defects in

each of the 10 stages. The left limb was analyzed, and the defect in the left forearm is characterized by a complete deviation or slip from the side or a misplaced foot on the side.<sup>16</sup>

### Immunohistochemistry

Immunohistochemistry was employed to compare the levels of BDNF expression. Each rat was given general anaesthesia with a 2mg/kg 1:1 mixture of Zoletil and Rompun. The rat's body was drained of blood through blood perfusion using a 0.9% NaCl solution, and the body was fixed in a 4% paraformaldehyde solution to extract its brain tissue. After 24 hours, the extracted brain tissue was frozen in a cryocooler at -30°C and then severed into 30µm-thick brain slices using a cryostat. After the brain slices were mounted on a slide and the first antibody was applied to them, they were kept at 4°C for 24 hours; each first antibody is mouse anti-NGF (diluted 1:200, Santa Cruz Biotechnology, CA), rabbit anti-BDNF (diluted 1:200, Santa Cruz Biotechnology, Santa Cruz). The slices were then immersed in 0.01M phosphate-buffered saline (PBS) for 10 minutes three times. After the application of the secondary antibody, these slices were preserved at room temperature for two hours. Next, the slices were again immersed in 0.01M PBS for 10 minutes three times and then underwent a dehydration process using ethanol and xylene. Finally, the resulting slices were mounted with a cover glass.

### Data processing

Photos were taken for a comparison of the BDNF expression levels by using an Axiophot light microscope (Carl Zeiss, Göttingen, Germany) with an installed charge-coupled device (software: Optimas 6.5, Cyber Metrics, Scottsdale, Arizona). For each rat, 30 brain slices were used. The staining intensity of NGF and BDNF in all groups was evaluated on basis of a relative optical density (ROD), which was obtained after the transformation of the mean gray level using the formula:  $ROD = \log(256/\text{mean gray level})$ . The photos were calibrated using Adobe Photoshop version 8.0 and analyzed through the program NIH Image 1.59. The data were analyzed using SPSS version 20.0 for Windows. The analysis results were indicated as the mean ± standard deviation, and each group was compared through an independent t-test.

## RESULTS

### Beam walking test

The beam walking test was conducted to evaluate the effects of alternate exercises on sensory function, motor skills, and balance ability. The control and experimental groups recorded  $4.80 \pm 0.41$  and  $4.53 \pm 0.51$  points, respectively. The two groups showed a statistically significant difference as shown in Table 1, Table 2 and Figure 1.

**Table 1: Comparison of beam walking test in the intra-group analysis (Score: 0 to 6 point)**

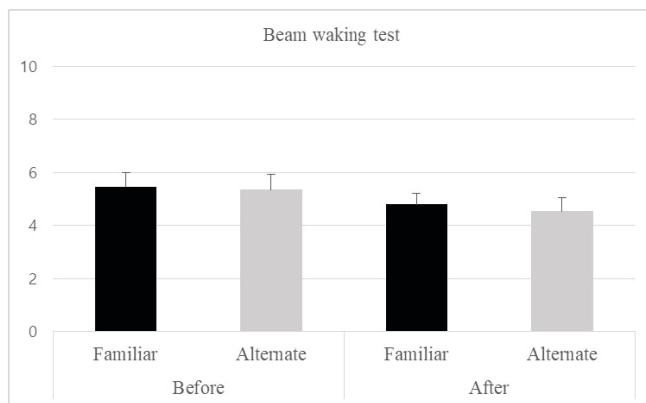
		Mean	SD	t	p
Familiar exercise	Before	5.47	0.52	1.01	0.000
	After	4.80	0.41		
Alternate exercise	Before	5.35	0.56	0.86	0.000*
	After	4.53	0.51		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group

**Table 2: Comparison of beam walking test in each group analysis (Score: 0 to 6 point)**

		Mean	SD	t	p
Before	Familiar	5.47	0.52	1.21	0.756
	Alternate	5.35	0.56		
After	Familiar	4.80	0.41	0.96	0.000*
	Alternate	4.53	0.51		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group



**Figure 1: Beam walking test graph.**

**Skilled ladder rung test**

The skilled ladder rung test was conducted to evaluate the effects of alternate exercises on sensory function, motor skills, and balance ability. The control and experimental groups recorded  $80.13 \pm 9.54$  and  $65.55 \pm 8.23$  points, respectively. The two groups showed a statistically significant difference as shown in Table 3, Table 4 and Figure 2.

**Table 3: Comparison of skilled ladder rung test in the intra-group analysis (%)**

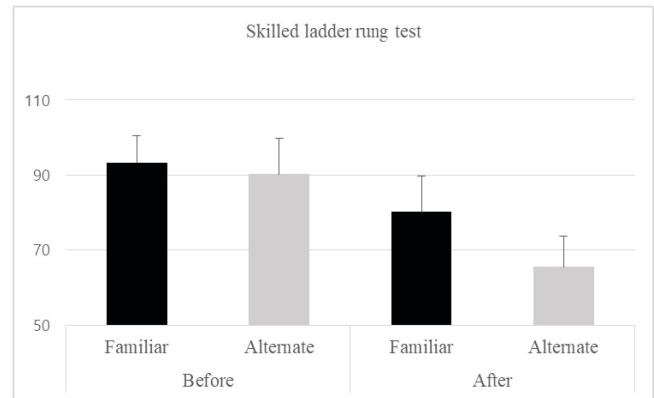
		Mean	SD	t	p
Familiar exercise	Before	93.33	7.24	24.21	0.000
	After	80.13	9.54		
Alternate exercise	Before	90.23	9.56	20.86	0.000*
	After	65.55	8.23		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group

**Table 4: Comparison of skilled ladder rung test in each group analysis (%)**

		Mean	SD	t	p
Before	Familiar	93.33	7.24	32.23	0.699
	Alternate	90.23	9.56		
After	Familiar	80.13	9.54	23.96	0.000*
	Alternate	65.55	8.23		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group



**Figure 2: Skilled ladder rung test graph.**

**Immunohistochemistry**

BDNF immunohistochemistry was conducted to assess the effects of alternate exercises on the expression of neurotrophic factors. The control and experimental groups registered  $104.56 \pm 3.95$  and  $108.34 \pm 4.22$  points, respectively. A statistically significant difference was observed between the two groups shown in Table 5, Table 6 and Figure 3 and Figure 4.

NGF immunohistochemistry was conducted to assess the effects of alternate exercises on the expression of neurotrophic factors. The control and experimental groups registered  $102.22 \pm 1.89$  and  $106.65 \pm 2.52$  points, respectively as shown in Table 7 and Table 8. A statistically significant difference was observed between the two groups as shown in Figure 5 and Figure 6.

**Table 5: Comparison of BDNF expression in the intra-group analysis (point)**

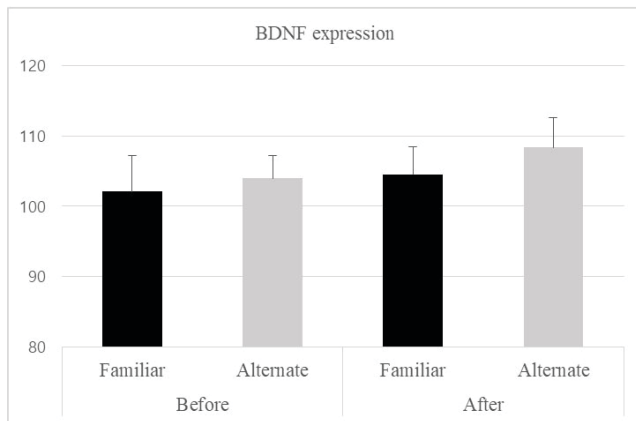
		Mean	SD	t	p
Familiar exercise	Before	102.10	5.13	35.12	0.000
	After	104.56	3.95		
Alternate exercise	Before	103.98	3.23	38.22	0.000
	After	108.34	4.22		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group

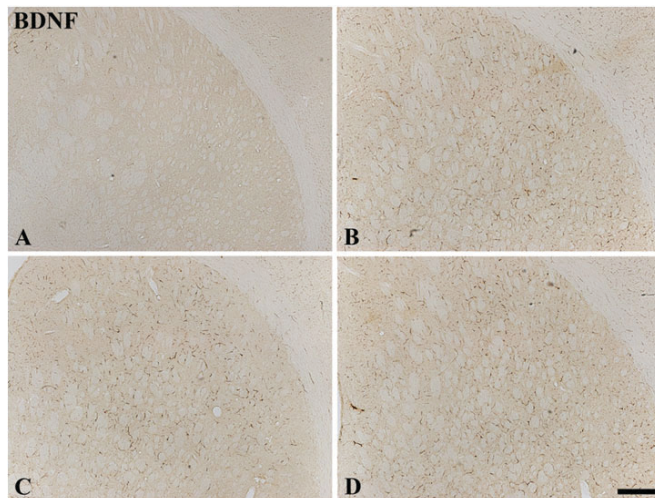
**Table 6: Comparison of BDNF expression in each group analysis (point)**

		Mean	SD	t	p
Before	Familiar	102.10	5.13	36.21	0.153
	Alternate	103.98	3.23		
After	Familiar	104.56	3.95	32.54	.000*
	Alternate	108.34	4.22		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group



**Figure 3: BDNF expression graph.**



**Figure 4: BDNF immunohistochemistry staining for BDNF in the striatum.**

A: familiar exercise before, B: alternate exercise before, C: familiar exercise after, D: alternate exercise after. Bar = 500  $\mu\text{m}$

**Table 7: Comparison of NGF expression in the intra-group analysis (point)**

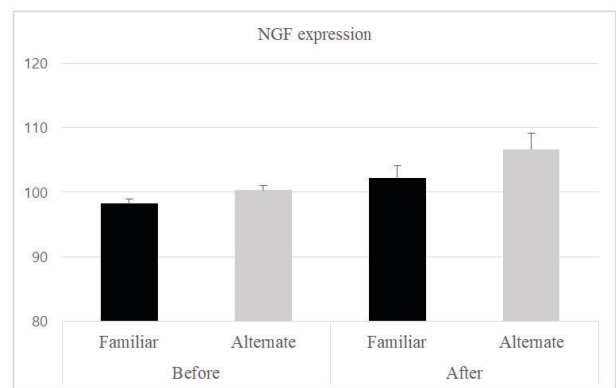
		Mean	SD	t	p
Familiar exercise	Before	98.23	0.68	25.23	0.000
	After	102.22	1.89		
Alternate exercise	Before	100.31	0.79	21.32	0.000
	After	106.65	2.52		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group

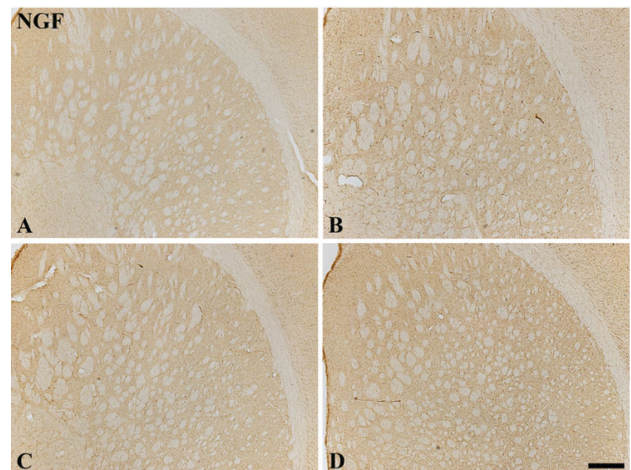
**Table 8: Comparison of NGF expression in each group analysis (point)**

		Mean	SD	t	p
Before	Familiar	98.23	0.68	20.36	0.235
	Alternate	100.31	0.79		
After	Familiar	102.22	1.89	18.96	0.000*
	Alternate	106.65	2.52		

SD: standard deviation,  $p < 0.05$ , Familiar exercise: Control group, Alternate exercise: Experimental group



**Figure 5: NGF expression graph.**



**Figure 6: NGF immunohistochemistry staining for BDNF in the striatum.**

A: familiar exercise before, B: alternate exercise before, C: familiar exercise after, D: alternate exercise after. Bar = 500  $\mu\text{m}$

## DISCUSSION

Brain-damaged patients generally exhibit weakened muscle strength, cognitive imbalance, and proprioceptive dysfunction, which subsequently cause disorders in balance, coordination, and functional movement. This study examined the effects of varied application patterns for exercises on the recovery of motor skills and neurotrophic factors in white rats with intracerebral haemorrhage. The effects of alternate exercises on stroke SD rats were investigated by comparing the group that continued a single exercise and the group that performed a different exercise after the inducement of the disease through an analysis of neurotrophic factors and behaviours.

A dominant portion of studies on cerebrovascular diseases is focused on medical domains, such as medication, surgery, and cell transplantation. Exercise interventions are confined to simple wheel running or swimming. The advantage of physical exercises in patients with cerebrovascular diseases is not only improved motor abilities but also lowered incidences of these diseases and mortality rates<sup>17</sup>. In the present study, the beam walking test was conducted to understand the clinical patterns of stroke-induced white rats and measure their sensory and motor abilities, balance, and control. The beam walking test is a highly effective testing method for evaluating the functions of patients with stroke<sup>6</sup>.

The BDNF is a neurotrophic protein complex that induces neural development and functions. It secretes proteins in locations intended for the survival, differentiation, or growth of neurons.<sup>9,18,20</sup> Neurotrophic substances influence the formation of new blood vessels, the survival and differentiation of neurons, and the formation and plasticity of synapses.<sup>19</sup> The BDNF is a key activator protein that stimulates neurogenesis and post-birth phases with the most dynamic control.<sup>15,20</sup> Because the BDNF is vital for the protection and recovery of nerves against neurotoxins, increased BDNF cells markedly improve motor learning.<sup>19</sup> Neurotrophins are a proteins complex that induces the development and functions of neurons. Neurotrophins are one of the growth factors, secrete proteins which are in a position to survive, differentiate, or grow.<sup>21</sup> Neurotrophins influence angiogenesis, neurogenesis, and synaptogenesis. BDNF is found originally in the brain. BDNF is one of the most active proteins to excite neurogenesis and the most dynamically regulated postnatal stage.<sup>22</sup> If there are plenty of BDNF-immunoreactive cells, several functions such as memory, motor learning are very enhanced because BDNF is important on protection and recovery of neuronal condition against neurotoxins,<sup>23</sup> as BDNF, a factor of neurotrophins, acts on survival, differentiation, synaptogenesis and synaptic plasticity of neurons.<sup>24</sup> NGF is also one of the neurotrophins, the prototypical growth factor. NGF is secreted by a neuron's target cells, and important for survival and maintenance sympathetic, a sensory nerve,

and basal forebrain cholinergic neurons. NGF is important to determine responsiveness and the number of neurons that survive during development and concomitant improvement in memory function.<sup>25-28</sup>

Stroke patients' disorders in functional activity are exhibited in the form of weakened upper and lower limb muscles, poor muscular endurance, and proprioceptive and cognitive disorders, which eventually undermine their motor skills, postural control, and balance ability.<sup>19,29,30</sup> The beam walking test evaluates coordination, motor performance, and balance ability. Improved scores in this test denote enhanced proprioception, cognition, and muscular strength. In this study, haemorrhage was induced in white rats at the bottom of the striatum, and the group with a steady single exercise and the group with alternate exercises were compared. Swimming exercise did not show a statistical significance compared to balance exercise on land, but exercise groups got a significant difference compared with no exercise group. There are many studies comparison about intensity of exercise and exercise form.<sup>30-32</sup>

However, this study had some limitations. First, the swimming exercise might have produced better results than wheel running due to the absence of weight-bearing. Second, because of the prolonged training period, it was unclear whether the recovery of motor skills and neurotrophic substances following cerebral haemorrhage resulted from alternate training only.

## CONCLUSION

The present study investigated the effects of alternate exercises on the recovery of ischemic cerebral infarction-induced white rats. The alternate training group's lowered scores in the beam walking test and increases in the BDNF signified that alternate exercises can have better effects on the recovery of nerves and motor skills than can a single exercise. Therefore, this study proposes this alternate pattern of physical exercises as a useful intervention for patients with intracerebral haemorrhage.

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**Conflict of Interest:** Nil

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## REFERENCES

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *The Lancet*. 2009 May 9;373(9675):1632-44.
2. MacLellan CL, Langdon KD, Churchill KP, Granter-Button S, Corbett D. Assessing cognitive function after intracerebral haemorrhage in rats. *Behavioural brain research*. 2009 Mar 17;198(2):321-8.
3. Mayer SA, Rincon F. Treatment of intracerebral haemorrhage. *The Lancet Neurology*. 2005 Oct 1;4(10):662-72.
4. Eda H, Sato S, Sasaki Y, Adachi A, Ghazizadeh M. Ischemic damage and subsequent proliferation of oligodendrocytes in hippocampal CA1 region following repeated brief cerebral ischemia. *Pathobiology*. 2009;76(4):204-11.
5. Jia J, Hu YS, Wu Y, Liu G, Yu HX, Zheng QP, Zhu DN, Xia CM, Cao ZJ. Pre-ischemic treadmill training affects glutamate and gamma-aminobutyric acid levels in the striatal dialysate of a rat model of cerebral ischemia. *Life sciences*. 2009;84(15-16):505-11.
6. Fox CM, Ramig LO, Ciucci MR, Sapir S, McFarland DH, Farley BG. The science and practice of LSVT/LOUD: a neural plasticity-principled approach to treating individuals with Parkinson disease and other neurological disorders. In *Seminars in speech and language* 2006 Nov (Vol. 27, No. 04, pp. 283-299). Copyright© 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
7. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo A, White SM, Wójcicki TR. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Frontiers in ageing neuroscience*. 2010;2:32.
8. Ma L, Wang B, Narayana S, Hazeltine E, Chen X, Robin DA, Fox PT, Xiong J. Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning. *Brain research*. 2010;1318:64-76.
9. S. Jang. The Effects of Familiar Exercise and Novel Exercise on Brain Recovery after Intracerebral Hemorrhage in Rats. Ph. D. dissertation. Rehabilitation Medicine Department, Daegu University. Gyeongsan-si. Gyeongsangbuk-do. The Republic of Korea. 2012.
10. Cowansage KK, LeDoux JE, Monfils MH. Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. *Current molecular pharmacology*. 2010;3(1):12-29.
11. Nagappan G, Lu B. Activity-dependent modulation of the BDNF receptor TrkB: mechanisms and implications. *Trends in neurosciences*. 2005;28(9):464-71.
12. Brooks GA, White TP. Determination of metabolic and heart rate responses of rats to treadmill exercise. *Journal of applied physiology*. 1978;45(6):1009-15.
13. Chu KS, Eng JJ, Dawson AS, Harris JE, Ozkaplan A, Gylfadóttir S. Water-based exercise for cardiovascular fitness in people with chronic stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation*. 2004;85(6):870-4.
14. Kwon D, Hwang K, Kim Y, Lee K, Kang H, Song Y. Effects of swimming training on immune function of growing rats fed a high-fat diet. *Journal of the Human-Environment System*. 2005;8(1):13-8.
15. Greenberg ME, Xu B, Lu B, Hempstead BL. New insights into the biology of BDNF synthesis and release: implications in CNS function. *Journal of Neuroscience*. 2009;29(41):12764-7.
16. Emerick AJ, Kartje GL. Behavioural recovery and anatomical plasticity in adult rats after cortical lesion and treatment with monoclonal antibody IN-1. *Behavioural brain research*. 2004;152(2):315-25.
17. Wang RY, Yang YR, Yu SM. Protective effects of treadmill training on infarction in rats. *Brain research*. 2001;922(1):140-3.
18. Allen SJ, Dawbarn D. Clinical relevance of the neurotrophins and their receptors. *Clinical Science*. 2006 ;110(2):175-91.
19. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Progress in neurobiology*. 2005;76(2):99-125.
20. Sasaki M, Radtke C, Tan AM, Zhao P, Hamada H, Houkin K, Honmou O, Kocsis JD. BDNF-hypersecreting human mesenchymal stem cells promote functional recovery, axonal sprouting, and protection of corticospinal neurons after spinal cord injury. *Journal of Neuroscience*. 2009 Nov 25;29(47):14932-41.
21. Allen SJ, Dawbarn D. Clinical relevance of the neurotrophins and their receptors. *Clinical Science*. 2006;110(2):175-91.
22. Greenberg ME, Xu B, Lu B, Hempstead BL. New insights into the biology of BDNF synthesis and release: implications in CNS function. *Journal of Neuroscience*. 2009 Oct 14;29(41):12764-7.
23. Han QQ, Jin W, Xiao ZF, Huang JC, Ni HB, Kong J, Wu J, Chen B, Liang WB, Dai JW. The promotion of neurological recovery in an intracerebral haemorrhage model using fibrin-binding brain-derived neurotrophic factor. *Biomaterials*. 2011;32(12):3244-52.
24. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Progress in neurobiology*. 2005;76(2):99-125.
25. Chao MV, Hempstead BL. p75 and Trk: a two-receptor system. *Trends in neurosciences*. 1995;18(7):321-6.
26. Chun Y. A Study of Perceived Parental Faith-nurturing Activities and Children's Psychological Well-being. 2019;3(1):15-20.
27. Jung Hye-Won, Park Soon-Gil, Cho Jeung-Ryeul. A Study on Parenting Styles of Multicultural Mothers. *International Journal of Child Warfare Promotion and Management*. 2018;2(2):31-36.
28. Kim Kyung-Chul, Jung Hye-seung. Changes in Pre-service Early Childhood Teachers' Perceptions of Free Choice Activities. *International Journal of Child Warfare Promotion and Management*. 2018;2(2):101-106.
29. Cho Ho-young, Im Sang-cheol, Kim Kyoung. Effect of Gait in Stroke Patient with Action Observation Using Audiovisual. *Asia-pacific Journal of Psychology and Counseling*. 2018;2(2):141-146.
30. Lee Jung-ho, Choi Yeong-deok, Nam Chan-woo. Extracorporeal Shock Wave Therapy Decreased Spasticity in Stroke. *International Journal of IT-based Public Health Management*. 2017;4(1):41-46.
31. Park Jae-sung. Treadmill Exercise promotes a profitable cellular environment for axonal growth by inducing the macrophages and neurotrophic factors. *International Journal of Beauty Science and Technology*. 2017;1(1):13-18.
32. Lee Dae-hwan, Lee Jung-ho, Sung Yeon-bum. Effects of Alternate Training for Limb Motor Skills on Brain-derived Neurotrophic Factor and Gait in Striatal Hemorrhage-induced Sprague-Dawley Rats. *International Journal of Bio-Science and Bio-Technology*. 2020;12(1):47-54.