J Korean Soc Phys Med, 2015; 10(3): 1-7
http://dx.doi.org/10.13066/kspm.2015.10.3.1

Online ISSN: 2287-7215
Print ISSN: 1975-311X

Research Article

Open Access

The Effects of Exercise Intensity and Initial Timing on Functional Recovery after Sciatic Nerve Crush Injury in Rats

Junyan Cai, PT, PhD · Sang-su Na, PT, PhD[1] · Gak Hwangbo, PT, PhD[1†]

Department of Rehabilitation, Affiliated Hospital of Nantong University
[1]Department of Rehabilitation Science, Daegu University Graduate School

Received: June 25, 2015 / Revised: July 1, 2015 / Accepted: August 1, 2015

| Abstract |

PURPOSE: The aim of this study was to investigate the effects of exercise intensity and initial timing on functional recovery following sciatic nerve injury in rats.
METHODS: Total of 80 Sprague-Dawley rats was used and randomly divided 6 groups. Under deep anesthesia, the sciatic nerve was nipped by adapted hemostatic tweezers for 30 seconds and the injured nerve was transparent under naked eyes. Acute exercise groups was applied treadmill after sciatic nerve crush injury during 5days with three type intensity. Late exercise groups was also applied treadmill during 5 days with three type intensity after 5 days break. Values of sciatic functional index were measured and analyzed in each group after exercise period.
RESULTS: The sciatic functional index values between control groups 1, acute low-intensity group, acute middle-intensity group in acute phase showed statistical significant ($p<.05$). The sciatic functional index values between control groups 2, late low-intensity group, late middle-intensity group and late high-intensity in late phase showed statistical significant ($p<.05$). The comparison in acute and late phase, sciatic functional index values of each low-intensity group and each high-intensity group showed statistical significant ($p<.05$).
CONCLUSION: Whether at acute or late phase, treadmill exercise as a therapy obtained beneficial effects of functional recovery and exercise training at low speed is more beneficial effects on the recovery of motor function in acute phase.

Key Words: Sciatic nerve injury, Treadmill exercise, Intensity and initial timing

Ⅰ. Introduction

Peripheral nerve injury (PNI) results in partial or total motor and sensory autonomic nerve dysfunction in denervated muscle. Denervation or disuse induced by peripheral nerve injury may lead to the advanced atrophy of skeletal muscle, loss of muscle mass, decrease of muscle fiber cross sectional areas, and changes in mechanical and biochemical muscle characteristics (Marqueste et al, 2006). The inactivation and subsequent paralysis of affected skeletal muscles affect the daily activities of patients with peripheral nerve injury, their work or life quality, and

†Corresponding Author: hbgak@daegu.ac.kr

socioeconomic status. Sciatic nerve injury accounts for most peripheral nerve injuries and is mainly caused by femoral fractures, the dislocation of hip joints, total hip replacement, and acetabular fracture. The incidence of acetabular fracture was 10–36% (Small, 2004; Udina et al, 2011).

In general, strategies to improve functional recovery after peripheral nerve injury need to enhance axonal regeneration, target re-innervation, and regulate the abnormal plasticity of neuronal circuits. In clinics, there are two major treatments for peripheral nerve regeneration: non-operative measures and surgical repair. For sciatic nerve crush injury, because of the interruption of the nerve axon while the perineurium and epineurium are preserved, i.e., the continuity of the nerve is preserved, the prognosis is favorable. Therefore, treatment with non-surgical measures, such as electrical stimulation, acupuncture, pharmacotherapy intervention, neurotrophic approaches, aquatics, and exercise (Kuphal et al, 2007; Rochkind et al, 2007), are prioritized to positively influence neuromuscular functional recovery and the promotion of regeneration. Nevertheless, until now, excellent functional recovery is still hard to achieve, so it is crucial to develop a timely, accurate, and standardized physical therapy program for peripheral nerve crush injury.

Treadmill training is a kind of forced motion widely used by human subjects in exercise training programs (Winter et al, 2007), and it differs from voluntary exercise, such as wheel running. The purpose of most forms of physical exercise is to increase muscle strength, range of motion, and cardiovascular endurance. Treadmill exercise can produce those effects by exercising the nervous system for the re-innervation of muscle. Due to the fact that treadmill exercise can be readily utilized both in laboratory animals and in human subjects (Sabatier et al, 2008) and is increasingly recognized as an effective method of task-related training, treadmill running is a recommended and promising method for treatment in clinical studies following peripheral nerve injury.

The selection of an optimum training pattern requires appropriate intensity, frequency, duration, and timing of the intervention, which influences the training outcome. At present, a few studies on the intensity and phase of treadmill exercise after peripheral nerve injury have reported negative effects of exercise on axonal regeneration and functional recovery (Sabatier et al, 2008; Sobral et al, 2008). This may be due to the effect of different training patterns and influences on axon regeneration. Thus, more specific research should be conducted to confirm the effect of treadmill exercise intensity and duration on the treatment of peripheral nerve injury.

This study investigated how to determine physical exercise intensity and duration and how to choose the proper physical treatment opportunity after sciatic nerve crush injury.

Ⅱ. Methods

1. Experimental animals

Eighty male Sprague-Dawley rats (8 weeks old, with body weight 250-300g) were used.

Animals were assigned to 2 control groups and 6 experimental groups randomly according to exercise phase and intensity: namely, the control group 1 (Cont.1, n=10): 5 days after surgery without treadmill exercise; the control group 2 (Cont.2, n=10): 10 days after surgery without treadmill exercise; acute low intensity group (ALI, n=10): the treadmill exercise with low intensity for 5 days after surgery; acute middle intensity group (AMI, n=10): the treadmill exercise with middle intensity for 5 days after surgery; acute high intensity group (AHI, n=10): the treadmill exercise with high intensity for 5 days after surgery; late low intensity group (LLI, n=10): the treadmill exercise with low intensity for 5 days after 5 days break; late middle intensity group (LMI, n=10): the treadmill exercise with middle intensity for 5 days after 5 days break; late high intensity group (LHI, n=10): the treadmill exercise with high intensity for 5 days after 5 days break.

2. Surgery for sciatic nerve crush injury and sciatic functional index (SFI)

Sciatic nerve crush injury surgery was carried out with all animals. Under deep anesthesia, an approximately 1.5cm incision was made to expose the sciatic nerve on the right gluteus region of the animal. The sciatic nerve was nipped by adapted hemostatic tweezers for 30 seconds and the injured nerve was transparent under naked eyes. The muscle and skin incisions were closed with absorbable sutures after nerve reset.

The sciatic functional index (SFI) was used in the present study. Three footprint parameters should be determined, that were print length (PL): the longitudinal distance between the extremity of the third toe and the heel bone of the foot, toe spread (TS): the transverse distance between the first toe and the fifth, intermediary toe spread (ITS): the transverse distance between the second toe and the fourth toe. The parameters of both the normal (N) paws and the experimental (E) paws were necessary to be measured and the data should be with an accuracy of 0.01mm.

The values vary from 0 to -100, with 0 showing normal function and -100 indicating complete dysfunction (Penna et al, 2012).

3. Treadmill exercise

The running speed and duration was determined according to previously exercise protocol with modification (Zhang 등, 2012). The training velocity and duration was gradually increased according to the following schedule: At the first day after surgery, the all acute group ran at a speed of about 5 m/min for 15 min. From 2nd to 5th day, rats of different intensity group separately ran with 8 m/min for 30 min, 15 m/min for 30 min, 20 m/min for 30 min. Starting from the 6 days, LLI group, LMI group, LHI group treadmill exercise intensity and timing were 8 m/min for 30 min, 15 m/min for 30 min, 20 m/min for 30 min, respectively.

4. Statistical analysis

The results were expressed as the means ± standard deviation (SD). Some experiments were analyzed via two-way analysis of variance for comparison of effects of exercise intensity and initial timing between groups, and Fisher's LSD test was used for *post hoc* evaluations. Some experiments were analyzed via t-test. The difference was considered statistically significant when $p < 0.05$.

Ⅲ. Results

1. The statistical analysis of sciatic functional index of each group

The statistical analysis of SFI values of initial timing and exercise intensity of each group was two-way repeated ANOVA and LSD test was used for the post hoc evaluations (Table 1).

The significant probability concerning analysis of different intensities was .001 and had significant difference ($p<.05$). SFI values of different timing showed that there was no statistical significance ($p>.05$) between acute phase and late phase. When the correlation of different intensities and timing was analyzed together, the results showed that statistical significance could be seen ($p<.05$).

2. Comparison of sciatic functional index of each acute group

The measured SFI values between control group 1, ALI group, AMI group in acute phase showed statistically significant difference ($p<.05$) (Fig. 1).

Table 1. The statistical analysis of sciatic functional index of each group (unit: scores)

S	SS	df	MS	F	P
Period	51.73	1	51.73	1.94	.189
Intensity	658.71	2	329.35	12.35	.001*
Period*Intensity	2283.67	2	1141.83	42.84	.000*

*p<.05

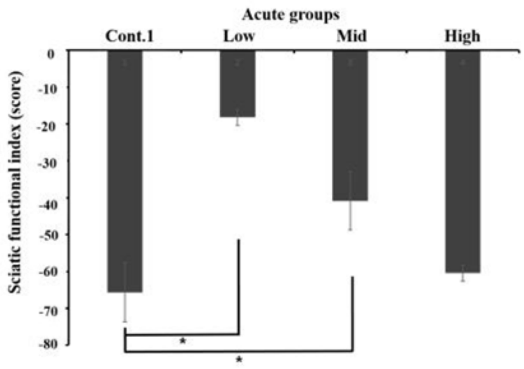

Fig. 1. SFI scores of each acute group

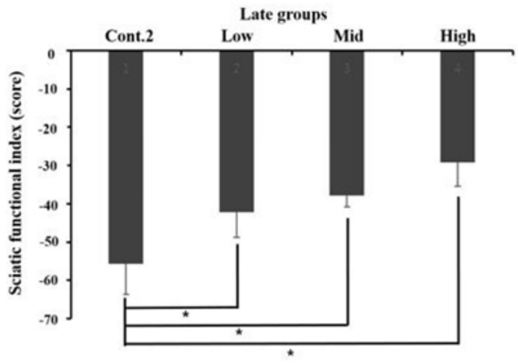

Fig. 2. SFI scores of each late group

Table 2. The statistical analysis of sciatic functional index between each intensity group (unit: scores)

Intensity	group	M± SD	t	p
Control	Cont. 1	-65.67±8.04	-1.36	.628
	Cont. 2	-55.54±9.69		
Low-Intensity	Acute (ALI)	-18.20±2.16	6.03	.004*
	Late (LLI)	-42.20±6.54		
Middle-intensity	Acute (AMI)	-40.89±7.88	-0.61	.569
	Late (LMI)	-37.88±2.93		
High-intensity	Acute (AHI)	-60.45±2.15	-8.36	.001*
	Late (LHI)	-29.28±6.08		

*p<.05

3. Comparison of sciatic functional index of each late group

There was significant difference of SFI values between control group 2, ALI group, AMI group, AHI group in late phase (p<.05) (Fig. 2).

4. Comparison of sciatic functional index between each intensity group

The comparison of statistical analysis of SFI values between each intensity group was t- test (Table 2). In low intensity group, the measured SFI values showed statistically significant difference between acute phase and late phase (p<.05). The measured data showed the difference was significant between acute phase and late phase in high intensity group (p<.05). But the SFI values between acute phase and late phase in middle intensity group was not statistically significant (p>.05).

Ⅳ. Discussion

Peripheral nerve disorders are the most common neurological problems clinicians encounter, yet few therapies and interventions are provided to prevent or reverse related damage (Bobinski et al, 2011). Under clinical observation, functional outcomes after peripheral nerve injury are often poor due to long-term disability. The complicated clinical course and functional recovery after peripheral nerve injury can be a big challenge for clinicians and patients (Intiso et al, 2010).

In the last few years, a variety of techniques have been implemented to promote the regeneration process in damaged nerves. Some research demonstrated the beneficial effects of exercise on axonal regeneration (Ilha et al, 2008; Sobral et al, 2008). Thus, in the present study, the sciatic nerve crush model of rats was adopted to examine the therapeutic effects of treadmill exercise on functional recovery. The protocol was low, middle, and high intensity exercise for different periods of treadmill locomotion. After completing the scheduled exercise training, the data of footprints was measured in all rats of each group.

The sciatic functional index firstly introduced by de Medinaceli (de Medinaceli et al, 1982) and later modified by Bain, is the standard method for assessing regeneration and the analysis of functional recovery (Bain et al, 1989). SFI is one of the most widely used methods for the analysis of gait, which represents the recovery of function, which is the ultimate goal of the repair (Monte-Raso et al, 2010).

SFI scores from the experiment indicate that in both acute and late groups, treadmill training as a treatment had remarkable effects. In the acute groups, a definite advantage was seen in SFI values of low intensity treadmill training compared to middle and high intensity. The data from the ALI group was superior to the other groups. There were statistical significances between the ALI group and the control group and the AMI group and the control group. It is important to note that high intensity exercise may show a worsening instead of spontaneous recovery. This may be attributed to high intensity training causing muscle injury and hampering collateral and terminal axonal sprouting (Tam et al, 2001).

Peripheral nerve crush injury is characterized by axonotmesis, i.e., axonal interruption and preservation of connective sheaths, so nerve regeneration after injury is possible. During the process of regenerating axons, treadmill training enhances the growth in injured peripheral nerves (Sobral et al, 2008). The present study proved that treadmill training, even at low intensity, could improve axon regeneration in the peripheral nervous system. This is consistent with (Sobral et al, 2008). Consequently, early training at low speeds is effective in rat sciatic nerve crush injury treatment.

In the late groups, there were benefits to increasing treadmill training intensity. Three kinds of training intensity were adopted. SFI scores of high intensity training were better than those of low intensity and middle intensity; however, there were no statistical significances between different intensity groups. This suggests that the application of different intensities of treadmill training has a therapeutic effect following sciatic nerve crush injury five days after the injury occurred in rats.

From the comparison of sciatic functional indices between each intensity group, it could be seen that low intensity treadmill exercise of different durations is desirable, and it is an adequate treatment for axon regeneration improvement and muscle re-innervation (Bobinski et al, 2011). In contrast with no physical therapy, the effects of treadmill training were examined on the first day and five days after injury. In addition, treadmill training at the first postoperative day was given a low intensity protocol. Previous studies have shown that exercise done during the acute phase (1-3 days after nerve injury) could accelerate the recovery of motor-sensory function and improve functional recovery in rats (Byun et al, 2005; Seo et al, 2006).

With middle and high intensity protocols, initial application is preferred to late application. For the middle intensity group, although the effects of treadmill training were better in the late phase compared with the acute phase, no statistical significance was shown. If high intensity training were started at the acute stage, therapeutic effects were seen, but damage control is wrong of attention.

The present investigation has demonstrated the importance of the stimulation of denervated muscles. However, there was no statistical significance between the acute phase and the late phase in high intensity exercise groups. It shows that in the initial stage, high intensity treadmill exercise had no significant benefit.

In conclusion, previous studies and the results of the present study are evidence that treadmill training at low speed is an adequate treatment and has beneficial effects on axonal regeneration and motor function improvements (Bobinski et al, 2011). On the whole, there was no statistically significant difference in efficacy between the different exercise periods. The treatment periods were linked to treatment intensity.

In the present study, the SFI scores are evidence that treadmill exercise is an effective and valid strategy to promote functional recovery after sciatic nerve crush injury. In the course of the experiment, we encountered some difficulties, e.g., footprints cannot always be adequately measured due to contractures, autonomy, and smearing in footprint analysis (Weber et al, 1993). Therefore, further studies are necessary to improve experiment measurement techniques and investigate the most appropriate exercise speed and duration for treadmill training to identify better methods to be used following peripheral nerve injury. These studies should also provide recommendations for future clinical investigations.

Ⅴ. Conclusion

In the present study, treadmill exercise was applied to rats with sciatic nerve crush injury in order to investigate the appropriate training intensity and initial timing. Initial timing was manipulated by altering the intervention time of the treadmill training. Intensity was manipulated primarily by altering the speed of treadmill training. It can be seen from the study that phase and intensity modulate the effects of exercise.

According to SFI values measured by footprint analysis, in acute groups, SFI values in both ALI group and AMI group showed significant difference compared with control group. Result of SFI scores of AHI group slightly improved, but it was not significant. In late groups, compared with control group, there were significant differences in LLI group, LMI group and LHI group and the data in LHI was better than other groups.

In conclusion, whether at acute or late phase, treadmill exercise as a therapy obtained beneficial effects and improved functional recovery. Exercise training at low speed is an adequate proposal and showed more beneficial effects on the recovery of motor function.

References

Bain J, Mackinnon S, Hunter D. Functional evaluation of complete sciatic, peroneal, and posterior tibial nerve lesions in the rat. Plastic and reconstructive surgery. 1989;83(1):129-36.

Bobinski F, Martins D, Bratti T, et al. Neuroprotective and neuroregenerative effects of low-intensity aerobic exercise on sciatic nerve crush injury in mice. Neuroscience. 2011;194:337-48.

Byun Y, Lee M, Kim S, et al. Treadmill running promotes functional recovery and decreases brain-derived neurotrophic factor mRNA expression following sciatic crushed nerve injury in rats. Journal of sports medicine and physical fitness. 2005;45(2):222.

de Medinaceli L, Freed WJ, Wyatt RJ. An index of the functional condition of rat sciatic nerve based on measurements made from walking tracks. Experimental neurology. 1982;77(3):634-43.

Ilha J, Araujo RT, Malysz T, et al. Endurance and resistance exercise training programs elicit specific effects on sciatic nerve regeneration after experimental traumatic lesion in rats. Neurorehabilitation and neural repair. 2008;22(4):355-66.

Intiso D, Grimaldi G, Russo M, et al. Functional outcome and health status of injured patients with peripheral nerve lesions. Injury. 2010;41(5):540-3.

Kuphal KE, Fibuch EE,Taylor BK. Extended swimming exercise reduces inflammatory and peripheral neuropathic pain in rodents. The Journal of Pain. 2007;8(12):989-97.

Marqueste T, Decherchi P, Desplanches D, et al. Chronic electrostimulation after nerve repair by self-anastomosis: effects on the size, the mechanical, histochemical and biochemical muscle properties. Acta neuro-pathologica. 2006;111(6):589-600.

Monte-Raso VV, Barbieri G, Mazzer N, et al. A new treadmill-type motorized walking belt machine for video recording of the rat's gait and sciatic functional index measurement. A comparative study with other methods. Journal of neuroscience methods. 2010;189(1):23-9.

Penna V, Wewetzer K, Munder B, et al. The long-term functional recovery of repair of sciatic nerve transection with biogenic conduits. Microsurgery. 2012;32(5):377-82.

Rochkind S, Drory V, Alon M, et al. Laser phototherapy (780 nm), a new modality in treatment of long-term incomplete peripheral nerve injury: a randomized double-blind placebo-controlled study. Photomedicine and laser surgery. 2007;25(5):436-42.

Sabatier MJ, Redmon N, Schwartz G, et al. Treadmill training promotes axon regeneration in injured peripheral nerves. Experimental neurology. 2008;211(2):489-93.

Seo TB, Han IS, Yoon JH, et al. Involvement of Cdc2 in axonal regeneration enhanced by exercise training in rats. Medicine and science in sports and exercise. 2006;38(7):1267-76.

Small SP. Preventing sciatic nerve injury from intramuscular injections: literature review. Journal of advanced nursing. 2004;47(3):287-96.

Sobral L, Oliveira L, Takeda S, et al. Immediate versus later exercises for rat sciatic nerve regeneration after axonotmesis: histomorphometric and functional analyses. Brazilian Journal of Physical Therapy. 2008;12(4):311-6.

Tam SL, Archibald V, Jassar B, et al. Increased neuromuscular activity reduces sprouting in partially denervated muscles. The Journal of Neuroscience. 2001;21(2): 654-67.

Udina E, Cobianchi S, Allodi I, et al. Effects of activity-dependen t strategies on regeneration and plasticity after periphera l nerve injuries. Annals of Anatomy- Anatomischer Anzeiger. 2011;193(4):347-53.

Weber RA, Proctor WH, Warner MR, et al. Autotomy and the sciatic functional index. Microsurgery. 1993;14(5): 323-7.

Winter B, Breitenstein C, Mooren FC, et al. High impact running improves learning. Neurobiology of learning and memory. 2007;87(4):597-609.

Zhang P, Zhang Q, Pu H, et al. Very early-initiated physical rehabilitation protects against ischemic brain injury. Front. Biosci. 2012;4:2476-89.