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Reversible Spasticity Suppression and Locomotion Change After Pulsed Radiofrequency on the Dorsal Root Ganglia of Rats With Spinal Cord Injury

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Objectives: Radiofrequency has been used to suppress spasticity affecting motion in patients with cerebral palsy and spinal cord injury. This study tested spasticity suppression and locomotion change after pulsed radiofrequency (PRF) at the dorsal root ganglion of rats with spasticity.

Materials and Methods: Twenty-four rats that survived for 28 days after thoracic spinal cord injury and showed spasticity in the right hind limb were separated randomly to a PRF group or Sham operation group. PRF consisted of 2 Hz biphasic 25 msec trains of PRF (500 kHz, 5 V intensity) applied on the right L5 dorsal root ganglion for 300 sec. Muscle tension of the right triceps surae was measured at 450 deg/sec of passive ankle dorsiflexion on the day before and 3, 7, and 14 days after PRF or sham operation. Locomotive function was evaluated by obtaining Basso, Beattie, and Bresnahan (BBB) scores.

Results: Muscle tension of the triceps surae decreased significantly three days after PRF, and gradually returned to baseline 14 days later. In the sham operation group, muscle tension increased significantly more than 14 days. The BBB scores declined from 10 to 8 after PRF and returned to pre-PRF levels 14 days later, while scores remained constant after sham operation.

Conclusions: PRF produced significant and reversible suppression in spasticity, but this was accompanied by deterioration in locomotive function. Thus, caution should be exercised in considering the benefits and costs in suppressing spasticity *in ambulatory patients*, and implanted devices that apply titratable doses of PRF may be best to optimize patients' needs.

Keywords: Dorsal root ganglion, locomotive function, muscle tension, pulsed radiofrequency, rats, spasticity, spinal cord injury

Conflict of Interest: The authors have no competing interests that might be perceived to influence the results and/or discussion reported in this article.

INTRODUCTION

Spasticity is a common pathological symptom in patients with stroke, spinal cord injury, and cerebral palsy characterized by heightened neural activity in lower motor neurons (1). Hyperactivity of lower motor neurons in spasticity is triggered by afferent impulses from muscle spindles and can lead to aberrant muscle contractions, joint stiffness, and chronic pain (2–4). The comorbidities and sequelae of spasticity result in an increased burden on family and medical care providers (5,6).

Several treatment modalities, including oral medications (7,8), physical therapy (9), botulinum toxin injections (10–12), selective dorsal rhizotomy (13–15), and intrathecal baclofen pumps (16,17), have been used to reduce spasticity. However, each of these treatment modalities has limitations and drawbacks. Oral medications and intrathecal baclofen pumps cause nonselective suppression of neuronal activity, and the cost of intrathecal baclofen therapy is high (6). Botulinum toxin induces short-term suppression at the target neuromuscular junction, but the effects decline with repeated injections. Selective dorsal rhizotomy offers permanent reduction of afferent impulses, but involves major surgery, is irreversible, and cannot be adjusted to meet individual needs.

Radiofrequency is a form of electromagnetic energy that can alter tissue characteristics due to electrothermal effects when intense electric fields are concentrated on a focal area. Although the

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mechanism by which radiofrequency affects the surrounding tissue has not been completely clarified (18–21), radiofrequency has been used clinically on the dorsal root ganglia to suppress pain from neuropathy or radioculopathy (22–24), as well as the afferent tensile impulse from muscle spindles (25–27). Kasdon et al. (25) reported that rhizotomy by percutaneous radiofrequency decreased spasticity in the lower extremities. Vles et al. (26,27) used radiofrequency to produce thermal lesions adjacent to the dorsal root ganglia and alleviate spasticity in patients with severe cerebral palsy.

Pulsed radiofrequency (PRF) is a technique that produces intense electric fields within a very short duration. PRF affects the transmembrane potentials of neurons and the release of neurotransmitters without thermal ablation of surrounding tissue (18,28–30). In previous studies, in which we applied PRF on the dorsal root ganglion in rats with neuropathic pain, the evoked field-potentials in the spinal cord dorsal horn cells were altered and the neuronal stress markers were only minimally increased in the dorsal root ganglion (31). Since PRF reduces afferent neuronal potentials, it can be administrated in a targeted fashion to the dorsal root ganglion to produce selective suppression of spasticity. However, suppression of spasticity may reduce muscle tone and power, and whether suppression of spasticity can result in improvement of motor function is unknown. Here, we report the results of a preliminary study using a rat model of spinal cord injury to assess the treatment effects from PRF on spasticity suppression and locomotive function. The purposes of the study were to test the hypothesis that PRF on the dorsal root ganglion can produce greater suppression effects on spasticity and improve locomotive function vs. a sham operation.

METHODS

The experimental protocols followed the Animal Protection Law and the Guide of the Care and Use of Laboratory Animals by the Council of Agriculture, Executive Yuan, Republic of China, and were approved by the Institutional Animal Care and Use Committee of Chang Gung University (CGU12–067). The study protocol included two operations. The first operation produced spinal cord injury (SCI) via right hemisection of the thoracic spinal cord (32), and the second operation applied treatment to the right L5 dorsal root ganglion 28 days later. Treatment was either PRF or a sham operation that used a posterior approach to the lumbar spine. Five assessments of muscle tension in the right triceps surae were performed: before SCI, 28 days after SCI, and 3, 7, and 14 days after treatment (Fig. 1).

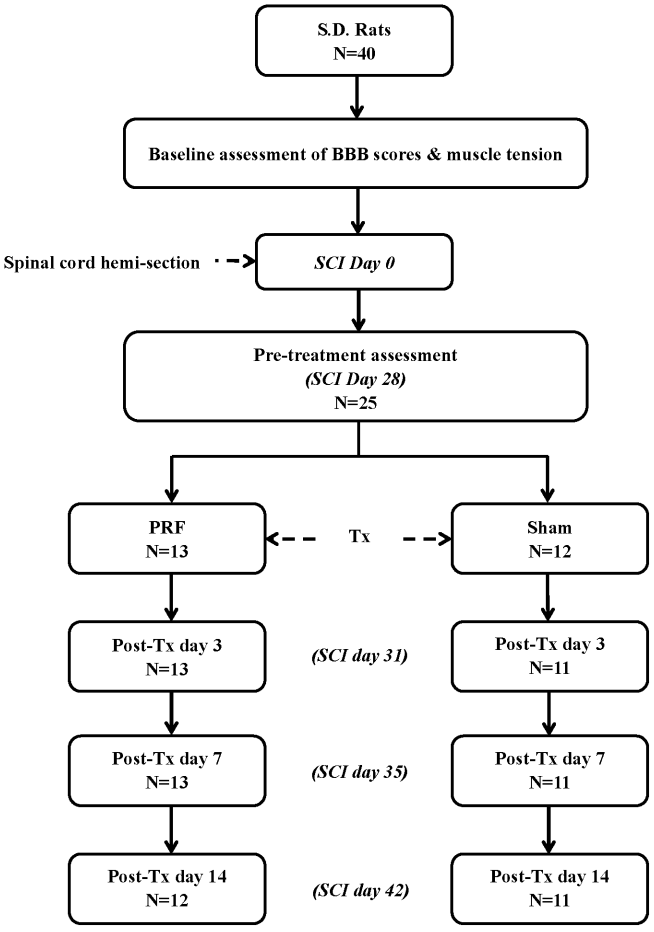

Figure 1. Study protocol.

Rat Model for Hind Limb Spasticity

Sprague–Dawley rats (250–300 g) were anesthetized with 2–3% isoflurane using a mask. A posterior midline incision was made over the thoracic spine to expose the T6 spinal lamina. After removing the lamina using a rongeur, the spinal cord was exposed. Right hemisection of the thoracic spinal cord was performed using a scalpel by removing a 0.2 cm segment from the right spinal cord. Bladder function was partially preserved after hemisection of the spinal cord. The right hind limb was initially flaccid, but became hypertonic within 21 days of the SCI.

Assessment of Muscle Tension by Passive Stretching of the Triceps Surae

Rats were anesthetized with 2% isoflurane and stabilized in a tube restrainer that allowed their hind limbs to protrude through holes on the bottom of the tube. The right knee was constrained by tape and the right foot was taped to a footplate, making an axis of the ankle joint along the rotational axis of the footplate. The footplate was connected to a torque transducer (TP-2KCE, Kyowa, Tokyo, Japan) and powered by a brushless DC motor (3268G024BX43692, Faulhaber, Schonaich, Germany) to produce repetitive ankle motion from 30° plantar flexion to 30° dorsiflexion (Fig. 2). The passive angular velocity was fixed at 75 rpm (450 deg/sec), at which setting the angular acceleration, and hence the inertia, were zero. The torque recorded during 0° ankle dorsiflexion was equal to the tension force from the triceps surae multiplied by the length between the ankle and tendon insertion [Torque (mNm) = Muscle tension (N) * level arm (mm)]. The level arm of the muscle was approximately 4 mm and was similar among rats of similar body size. Therefore, a torque of 4.0 mNm recorded by the transducer indicated a tension of 1.0 N from the triceps surae.

The passive stretching experimental procedure was designed to record muscle tension with minimal anesthetic effects and to allow consistent successive measurements. Specifically, once the rats were assembled on the instrument, the system was calibrated at a static value of 0° ankle dorsiflexion to remove the influence of the weight of the right hind limb. Isoflurane administration was stopped, and the torque produced by the passive movement of the ankle was recorded continuously. With each dorsiflexion movement from −30° to +30°, torque increased, and the peak value was measured around the 0° ankle position during a

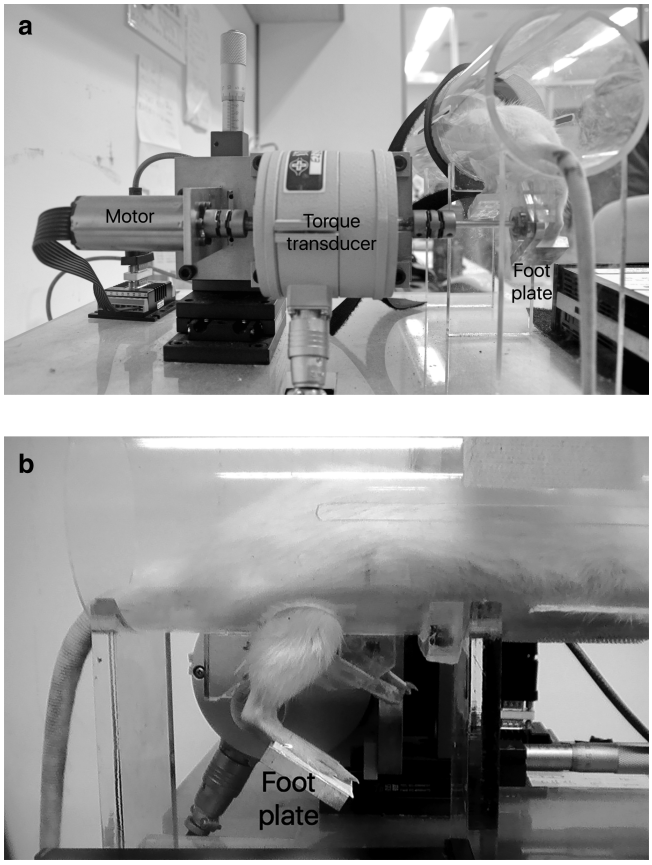

Figure 2. a. Instruments including brushless motor, torque transducer, and foot plate produced passive ankle motion and simultaneously measured resistant torque. b. Axis of the ankle joint was along with the rotational axis of the instruments.

plateau of angular velocity of 75 rpm (450 deg/sec). The peak torque increased gradually during the period in which the rat was waking up and a burst of resistance was recorded when the rat struggled against the footplate. The greater amount of torque that occurred during the 10 sec prior to the rat struggling against the instrumentation was sampled. The peak values of torque in these 10 sec were averaged to calculate muscle tension (Fig. 2).

Muscle Tension and Electromyography

Electromyography of the triceps surae was recorded using two percutaneous stainless steel needle (30 G) electrodes placed 1 cm apart. A ground electrode was placed into the left triceps surae. The signal was sampled at 2 KHz and amplified through a PXI1031 amplifier (National Instruments, Austin, TX, USA). A standard electromyography analysis device (KL-71001 Biomedical measurement system device; K&H Products, New Taipei City, Taiwan) filtered noise and detected signals between 100 and 1000 Hz (Fig. 3).

Locomotive Function Assessment

The Basso, Beattie, and Bresnahan (BBB) scores were taken to assess locomotive behavior of rats after neurological injury, according to established methods (33,34). This 21-point open field locomotive score was originally designed to assess sequential recovery from spinal injury, with higher scores indicating better locomotive function. In this study, we used BBB scores to first determine if neurologic recovery had reached a plateau state and then to assess locomotive function change after PRF treatment.

Pulsed Radiofrequency on the Dorsal Root Ganglion

PRF was administered using a bipolar electrode made of two stainless steel needles, as previously described. (30,35,36) One needle was bent at an angle of 105° upward and inserted into the spinal foramen, and the other was put into contact with the surrounding nonneural tissue as a reference electrode. The electrodes were connected to a PXI-5402 Function Generator (National Instruments, Austin, TX) to produce 5 V radiofrequency bursts at a frequency of 2 Hz for a total duration of 300 sec (i.e., 600 bursts). Each burst was composed of biphasic 500 kHz sinusoid radiofrequency waves for 25 μsec (36) (Fig. 4).

PRF was applied one time during open surgery. A right paraspinal incision was made over the lumbar spine to explore the L45 facet. The right L5 spinal nerve was exposed after removing the transverse process. The PRF electrode was made by two 32 g stainless steel needles. One needle tip was bended to be inserted into the foramen, and the other straight tip was in contact with the surrounding nonneural tissue as a grounding electrode (30). A burst of test stimulation (0.25–0.3 V at 0.5 msec, 2 Hz square wave pulses) was applied to produce ankle plantar flexion in order to confirm the nerve root level. PRF was applied to the foramen for 300 sec, and then the wound was closed. Rats in the sham operation group were also subjected to lumbar surgery, a burst of test stimulation to confirm the nerve root level, and insertion of the PRF electrode; however, power to the PRF electrode was not turned on.

Statistical Analysis

Muscle tension and BBB scores were assessed on pre-SCI, 28 days post-SCI, and 3, 7, and 14 days after PRF or sham operation. This series of data were analyzed using repeated measures analysis of variance (ANOVA) for intra-group comparisons, and post hoc analysis was performed using least significant difference tests. The intergroup comparisons between PRF rats and sham operation rats for the pre-treatment conditions and the changes from pre-treatment status at each time point were performed using independent t tests for muscle tension and Mann–Whitney tests for BBB scores. The statistical software used was IBM SPSS version 20.0 for Windows, and the level of significance was set at a p-value of <0.05.

RESULTS

Twenty-five Sprague–Dawley rats survived the right thoracic spinal cord hemisection and showed stable neurologic status 28 days after the injury. Muscle tension of the right triceps surae increased significantly from pre-SCI 1.04 ± 0.36 N to 2.58 ± 0.98 N 28 days after SCI. The locomotive function BBB scores decreased from 21 to 0–3 after SCI, and the scores gradually increased to a median of 10 (IQR 6–11) 28 days after SCI. The rats were separated randomly into PRF ($N = 13$) and sham ($N = 12$) groups. One rat in the sham group expired after the sham operation and one rat in PRF group expired nine days after PRF. Data of the two rats were not included in the repeat ANOVA test (Fig. 1).

Data on muscle tension of the 13 rats in the PRF group and the 11 rats in the sham group were plotted to show the course of

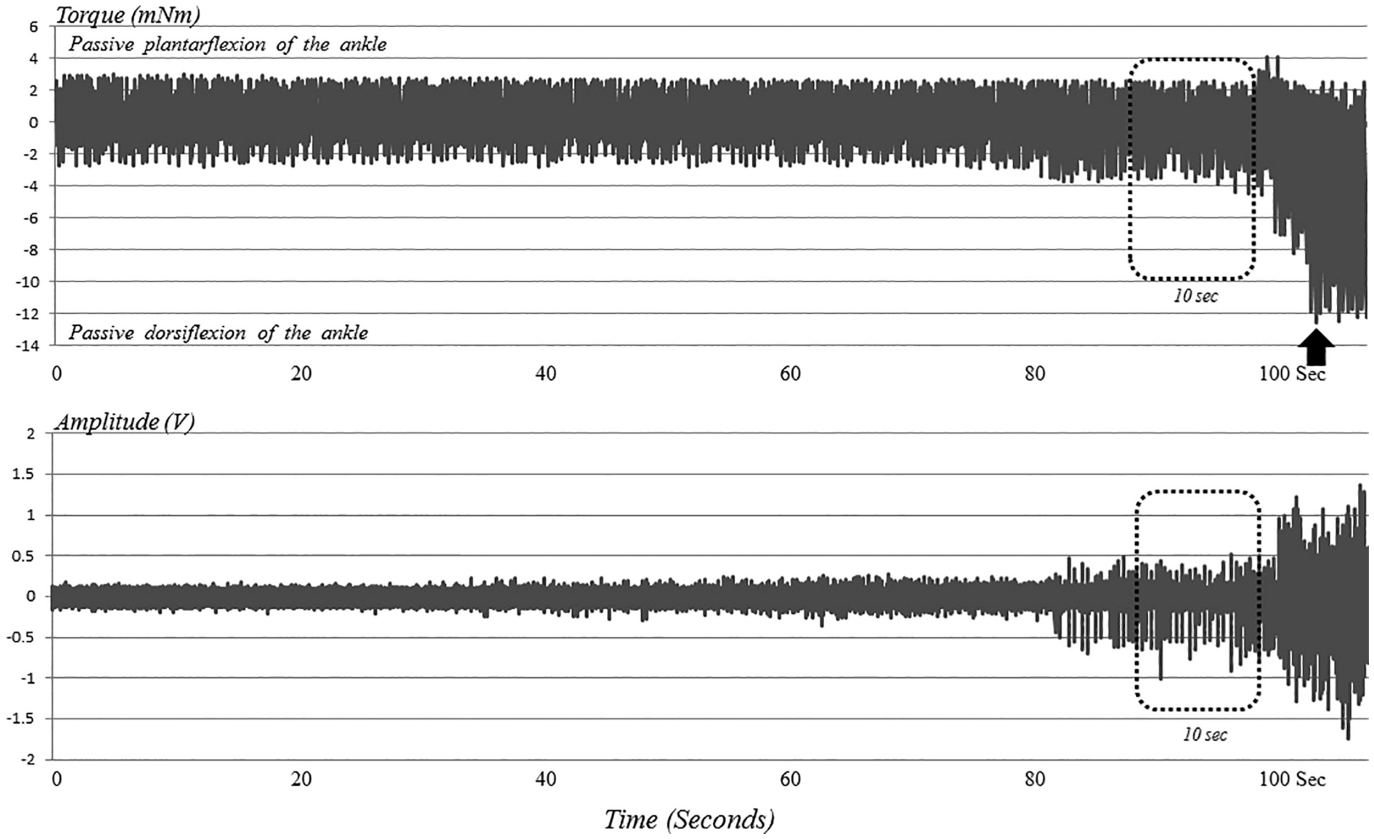

Figure 3. Continuous records of ankle torque and electromyography from triceps surae after turning off anesthesia gas. Torque values were sampled in the last 10 sec before the rat began to struggle against the device (arrow head).

each individual from pre-SCI to 14 days after treatment (Fig. 5). PRF produced a significant reduction in muscle tension from pre-treatment 2.58 ± 0.31 N to 1.19 ± 0.15 N more than three days. The suppression effect sustained for seven days, and then muscle tension recovered gradually to a level similar to pre-treatment status 14 days later. For sham-operated rats, the muscle tension increased gradually from pre-treatment 2.48 ± 0.27 N to 2.90 ± 0.34 N more than 14 days ($p = 0.002$), showing the typical progressive increase in muscle tension after SCI. Between the PRF and Sham groups, the pre-treatment condition was comparable ($p = 0.81$, independent t test). The PRF group had significantly less muscle tension than the sham group on post-treatment. Day 3 ($p < 0.001$) and Day 7 ($p = 0.048$; Table 1). The changes in muscle tension from pre-treatment status to Days 3, 7, and 14 were significantly different between the two groups (−2.01 ± 1.56 N vs. +0.26 ± 0.29 N on Day 3, $p < 0.001$; −0.48 ± 1.20 N vs. +0.53 ± 0.84 N on Day 7, $p < 0.01$; −0.10 ± 1.77 N vs. +1.39 ± 1.56 N on Day 14, $p < 0.05$; Fig. 6).

BBB scores (Fig. 7) indicated a sudden drop of locomotor function after SCI and a gradual recovery course until post-SCI 28 days. PRF produced a significant decrease in BBB scores from a pre-treatment median score of 10 (IQR 8–12) to a median score of 8 (IQR 6–9) over the three post-treatment time points ($p < 0.001$). Eleven of the 13 rats in the PRF group exhibited BBB score decreases of at least one. Then, scores increased to a median of 10 (IQR 9–12); similar to the pre-treatment status. For the rats in sham group, the BBB scores remained unchanged (Fig. 7). Between the PRF and Sham groups, the BBB scores were comparable at pre- and post-treatment Days 2, 7, and 14 on the Mann–Whitney test (Table 1).

DISCUSSION

This study used a rat model of SCI to demonstrate that the application of PRF on the dorsal root ganglion produced a desired suppressive effect on spasticity. However, there was also an

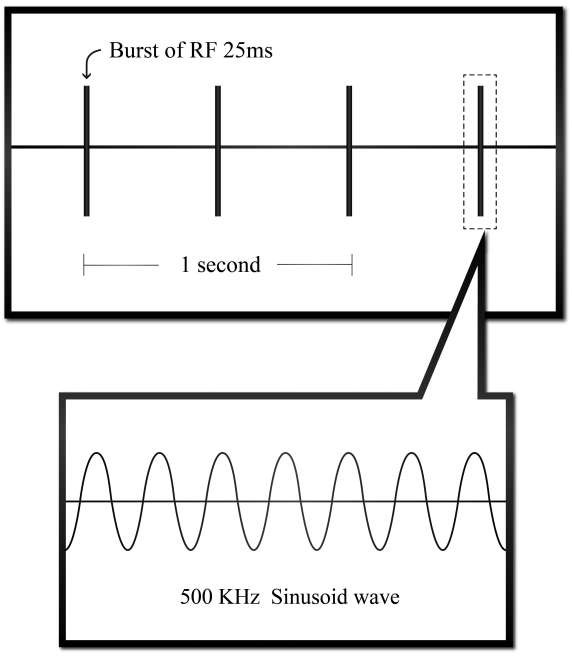

Figure 4. Electromagnetic waveforms of pulsed radiofrequency.

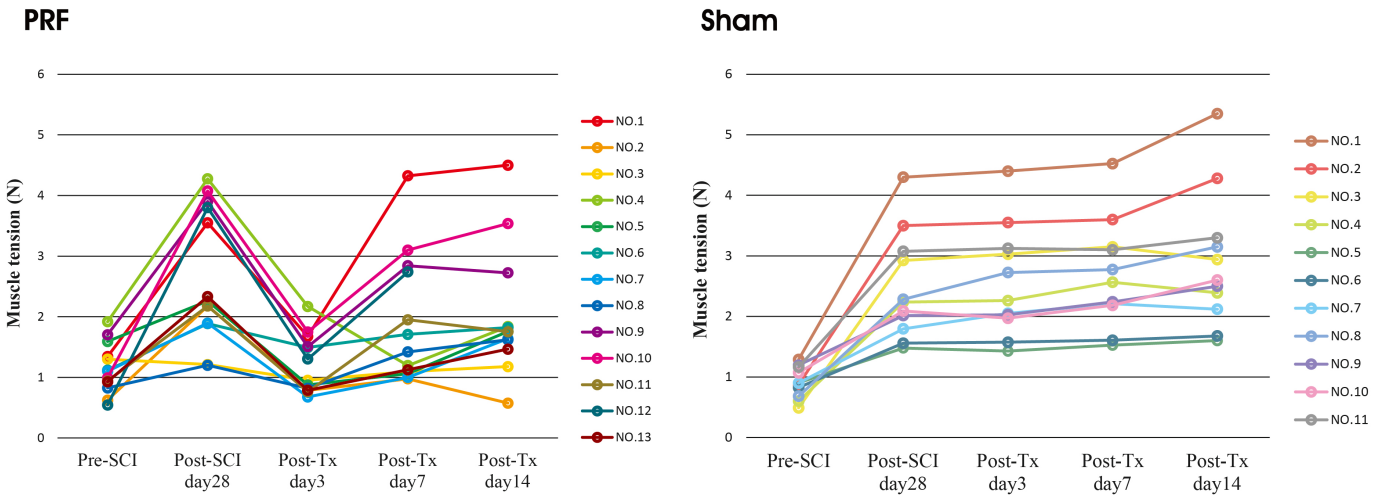

Figure 5. Muscle tension measured at pre-spinal cord injury, postinjury 28 days, and the first 14 days after pulsed radiofrequency (PRF) or sham operation. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Muscle Tension of the Triceps Surae Was Significantly Decreased After PRF Treatment and Increased Without PRF Treatment.

Post-SCI	Day 28 (A) Pre-Tx	Day 31 (B) Post-Tx Day 3	Day 35 (C) Post-Tx Day 7	Day 42 (D) Post-Tx Day 14	Repeat ANOVA *p* value	Post hoc test
Muscle tension (mean ± *SD*, Newton)						
PRF (*N* = 12)	2.58 ± 0.31	1.19 ± 0.15*	1.82 ± 0.31*	2.03 ± 0.31	<0.001	AB (<0.001) AC (0.02) BC (0.034) BD (0.006)
Sham (*N* = 11)	2.48 ± 0.27	2.56 ± 0.27	2.68 ± 0.27	2.90 ± 0.34	0.002	AC (0.002) AD (0.002)
BBB scores (median (IQR), scores 0–21)						
PRF (*N* = 12)	10(8~12)	8(6~9)	10(7~11)	10(9~12)	<0.001	AB (<0.001) AC (0.026) BC (<0.001) BD (<0.001)
Sham (*N* = 11)	7(6~11)	7(6~11)	7(6~11)	7(6~11)	0.341	

Numbers in parentheses are standard deviations.
*Significantly different between the PRF group and the sham group.

undesired effect of deteriorating locomotive function. The reversible effects of low amplitude PRF indicated a quick recovery of neurophysiology and that an implantable device is required for repeated administration of PRF. The decline in locomotive function suggested neuromodulation by any form of electromagnetic energy should be titrated to approximate the most desired dose for each patient's needs, balancing beneficial effects on spasticity with negative effects on locomotion.

In bringing PRF to the clinic, both the positive and potentially adverse effects need to be weighed against existing therapies. Highlighting the benefits of the short term, reversible actions of PRF, the permanent effects of rhizotomy is not completely desirable because patients may not be satisfied by the surgical results, which are irreversible. Conventional radiofrequency produces thermal lesions in surrounding tissue by intense and persistent electromagnetic energy. The thermal ablation around the dorsal root ganglion was used to alleviate severe spasticity for one to six months in nonambulant patients with quadriplegic cerebral palsy (23,25). The long term and significant suppression of spasticity improved pain and care giving, which was desirable for low

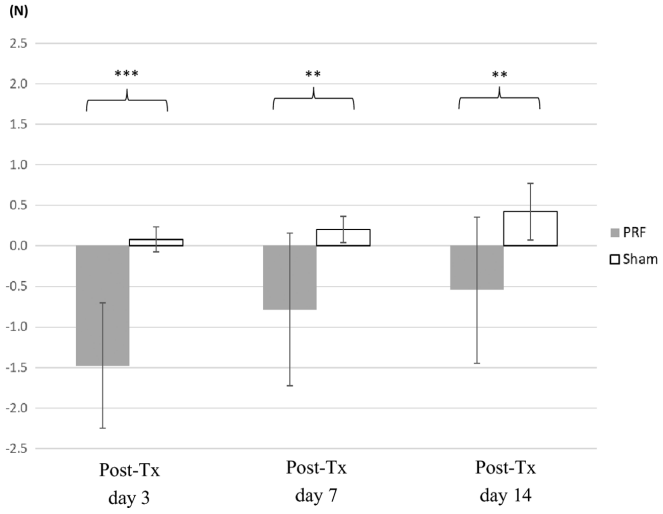

Figure 6. Comparison of the change in muscle tension from pre-treatment state. PRF altered the course of gradual increase in muscle tension shown in the sham operation group.

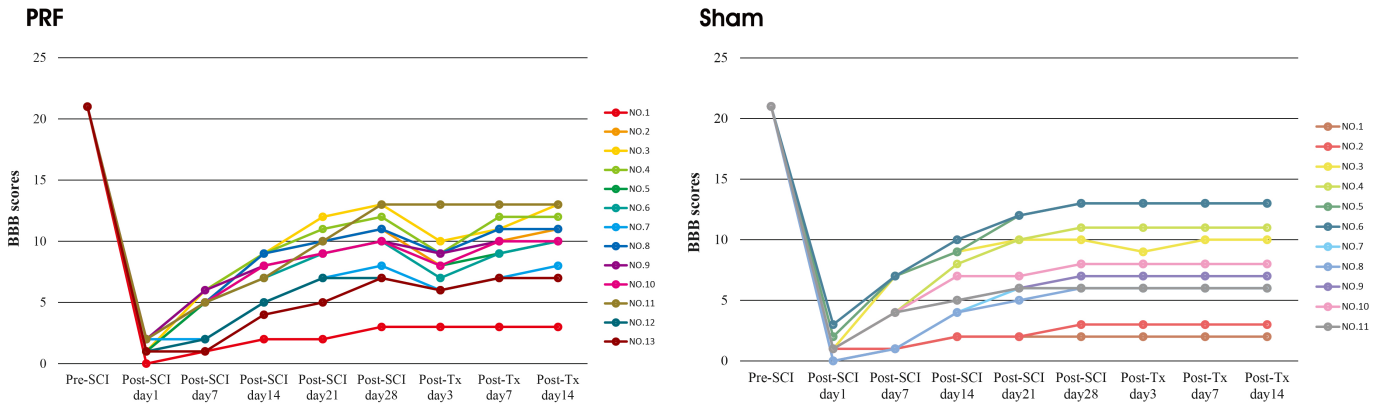

Figure 7. Basso, Beattie, and Bresnahan (BBB) scores were assessed to determine if neurologic recovery had reached a plateau state and then to assess locomotive function change after PRF treatment. [Color figure can be viewed at wileyonlinelibrary.com]

functioning patients who suffered from severe neuropathic symptoms. However, the risk of muscle weakness from one-shot percutaneous application of conventional or PRF may not be accepted by patients with ambulatory function. Even the low-intensity PRF used in this study still produced temporary locomotor deterioration. Thus, a titratable dose of PRF that allows an appropriate tradeoff between reducing muscle tone and preserving muscle strength is mandatory. A greater dose of spasticity suppression is desirable for bed-bound and wheelchair-bound patients who often exhibit more severe spasticity; the dose could be lowered for patients with ambulatory function.

The PRF used in this study was a short-duration (25 msec and 2 Hz) and low-intensity (5 V) electric field to alter cell physiology; therefore, quick recovery of neuroelectrical activity was noted within seven days after PRF administration. For sustainable suppression of spasticity, an implantable device to supply periodic and repeated PRF is feasible, as exemplified by the intracorporeal pump for intrathecal administration of baclofen. Comparing these two treatment modalities in spasticity management, intracorporeal PRF device has potential advantages over the baclofen pump in the form of reduced cost from avoiding Lioresal refilling, a smaller size due to the lack of need for a fluid container, and freedom from risk of respiratory suppression and drug withdrawal.

The passive resistance analysis of the triceps surae provided mixed result regarding neurological tone and tissue viscoelasticity. As PRF was applied around the dorsal root ganglion and could not affect the tissue viscoelasticity in the lower leg, only neurological tone could have been altered in this study and thereby been responsible for the reduction in muscle tension. Muscle tension was not reduced to the pre-SCI level by PRF treatment. Moreover, some soft tissue contracture might have developed at 28 days after SCI, especially in the rats with greater spasticity (Fig. 5).

Several experimental methods have been reported for the measurement of spasticity in rats with SCI (37–39). Muscle tension was not comparable among studies because different experimental models were used. Bose et al. (37) used a model of spinal cord contusion, and found the muscle tension in the triceps surae to be 1.20–1.38 N at an angular velocity of approximately 450 deg/sec. In our study, spinal cord hemisection produced greater muscle tension (2.58 $\pm$ 0.98 N) at a similar angular velocity. The different methods of measuring muscle tension could potentially have produced different results. In this study, the rats were anesthetized *by isoflurane* in order to achieve proper hindlimb position and carry out system calibration. Then, the torque in the last 10 sec before the rat struggled against the instrumentation was averaged to calculate muscle tension, which produced consistent results over repeated measurements. Isoflurane produces dose-dependent relaxation of skeletal muscles. Other anesthetic or sedative agents may produce different outcomes in terms of muscle tension.

There were several limitations to this study. First, the same dose of PRF was administered in this study. Therefore, further study is required to test if different PRF doses produce different effects on spasticity and motor function. Second, this study revealed the effects from single administration of PRF. Whether the spasticity suppression effects taper after repeat PRF administrations is unknown. Extracorporeal adjustment of doses and program of PRF treatment is feasible to control for tolerance of neurological responses. Third, the dorsal root ganglion is close to the motor axons. Suppression of neurophysiology of the motor axons may be partly responsible for muscle tension reduction. The exact mechanism of action requires further study. Fourth, the investigators were not completely blinded to the treatment given, as the decrease in muscle tension after PRF was sufficiently obvious that it could not be ignored by investigators. This could produce potential bias. Fifth, and most importantly, the study was limited in that it used an animal model. As a result, potential comorbidities that could occur in humans, such as sensory impairment and pain, could not be studied.

CONCLUSIONS

This is a study showing desirable and undesirable effects from neuromodulation. PRF on the dorsal root ganglion beneficially altered the course of progressive contracture compared to the sham operation group, but general locomotive function was also negatively affected by decreasing muscle tone. The quick recovery of neurophysiology after the low amplitude PRF suggested a new model of neuromodulation that should be titratable for an optimal resolution of spasticity suppression vs. muscle strength for individual needs.

Authorship Statements

Drs. C.H. Chang and C.W. Lin designed the study, executed data interpretation, drafted and revised the paper. K.H. Lu executed

animal operations, electromyography, and muscle tension measurement. W.T. Lin designed the instruments and executed pulsed radiofrequency treatment. W.P. Shih designed the instrumental system for measuring muscle tension. S.C. Chen revised and added clinical relevance to the paper.

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