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Case Report

Effects of repetitive peripheral magnetic stimulation on a patient with severe lower limb muscle weakness due to coronavirus disease-2019

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ABSTRACT
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Introduction: A patient developed severe lower limb muscle weakness and gait disturbance after receiving mechanical ventilation in the intensive care unit (ICU) due to coronavirus disease 2019 (COVID-19). We describe the effect of repetitive peripheral magnetic stimulation (rPMS) to strengthen his lower limb muscles.
Case: A 70-year-old man was mechanically ventilated due to COVID-19-related breathing difficulties. He was weaned off mechanical ventilation after 54 days, and the tracheostomy was closed after 225 days. However, his lower limbs remained significantly weak, and he was wheelchair-bound for daily activities. Despite approximately 6 months of functional training at a day-service center, his physical function and movement abilities did not improve. Therefore, 30-Hz rPMS was applied to both quadriceps for 20 minutes/day, three times a week, for 4 weeks (12 times). Knee extensor torque (KET) during maximum voluntary contraction (MVC) was greater after (right: 42.1 Nm, left: 40.7 Nm) than before the intervention (right: 33.7 Nm, left: 36.2 Nm). Before the intervention, KET induced by rPMS (rPMS-induced torque) was 0 Nm on both sides, the 30-second chair stand test (CS-30) was challenging to perform, and the walking item score of the Functional Independence Measure (FIM) was 2 points (endurance 30 m). Post-intervention, rPMS-induced torque was 6.5 Nm on the right and 4.7 Nm on the left side, CS-30 could be performed once, and the FIM walking score was improved to 6 points (endurance 60 m).
Discussion: The use of rPMS improved lower limb muscle strength in a patient who developed ICU-acquired muscle weakness after COVID-19.
Key words: repetitive peripheral magnetic stimulation, skeletal muscle, peripheral nerve, muscle strengthening, COVID-19.

Introduction

Severe muscle weakness that develops after receiving mechanical ventilation in the intensive care unit (ICU) due to coronavirus disease 2019 (COVID-19) is defined as ICU-acquired weakness (ICU-AW) [1]. Recent studies investigating the pathophysiology of COVID-19 have revealed that a cytokine storm, high C-reactive protein levels, and certain pro-inflammatory cytokines contribute to the mechanism underlying this muscle weakness [2, 3]. These factors may cause endothelial damage and mitochondrial autophagy, leading to myofibrillar breakdown [4]. This induces muscle atrophy and muscle weakness in the lower limbs, causing persistent impairment [5]. These symptoms increase the risk of falls, impede independence in activities of daily living (ADL), and reduce quality of life [6, 7]. Therefore, special measures should be taken to increase muscle strength in patients with COVID-19.

While resistance exercise is recognized to be effective in improving muscle weakness, very few resistance exercises are realistically effective when muscle strength has severely decreased. In particular, methods that use the body's own weight to strengthen

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the muscles of the lower limbs can often not be performed effectively. Furthermore, performing resistance exercises requires the patient's own active participation and is dependent on their motivation. Therefore, it is necessary to adopt methods that can strengthen their muscles even when their motivation is decreased. Conversely, for patients discharged from acute or subacute hospitals, the amount of time that they can receive functional training at medical facilities is limited. Currently, patients having difficulty walking independently have few opportunities to receive sufficient strengthening exercise training to improve their symptoms.

In recent years, the use of repetitive peripheral magnetic stimulation (rPMS) has become popular in clinical practice and has been reported to be effective in increasing muscle strength in the lower limbs [8−11]. Some reports state that it improves muscle strength, walking endurance [8], walking speed, and movement abilities [10, 11].

We encountered a patient with COVID-19 who was left with severe muscle weakness in the lower limbs after long-term ICU treatment, which reduced his ability to walk and compelled him to use a wheelchair for daily activities. We administered rPMS at a day-service center to improve muscle strength in the lower limbs, standing and walking ability, and other movement abilities. Herein, we report the significant beneficial effects obtained in this manner.

Case

Patient: A 70-year-old man.
Diagnosis: COVID-19
Patient background: The patient had retired from working for a company. Before contracting COVID-19, he was able to drive a car, go on trips with his family, and play at pachinko parlors, despite having high blood pressure and renal failure.
Chief complaint: Desire to improve reduced walking ability.
History of present illness: After contracting COVID-19 on X month Y day 2022, the patient rested at home. The next day, he developed difficulty breathing and was urgently admitted to the ICU of Hospital A. Findings of pneumonia were observed, and he was diagnosed as severe according to the severity classification of COVID-19 proposed by the Japanese Ministry of Health, Labour and Welfare. He was immediately placed on mechanical ventilation. Chronic obstructive pulmonary disease was noted as a comorbidity. He was weaned off the ventilator on day X+54, and the tracheostomy was sutured on day X+225. He was discharged home without being transferred to a Kaifukuki rehabilitation ward. He was compelled to use a wheelchair for daily activities, as severe muscle weakness remained in his lower limbs. Disuse syndrome was co-existent. After he applied for Certification of Needed Long-Term Care under the long-term care insurance system of Japan, he was certified as requiring nursing care level 3. Utilization of a day-service center began on day X+239, and functional training was scheduled for 20 minutes a day, three times a week. However, no improvement in physical function or movement abilities was observed even after approximately 6 months.
Physical findings at the time of starting the use of the day-service center were as follows: 1) Manual muscle testing (MMT): bilateral hip flexion 3, bilateral hip extension 2, bilateral knee flexion 2, bilateral knee extension 2, bilateral ankle dorsiflexion 4, bilateral ankle plantar flexion 3, all bilateral upper limbs 5. 2) Sensory function: both surface and deep sensory function were normal. 3) Reflexes: bilateral upper limbs normal, bilateral patellar tendon reflex decreased, and bilateral Achilles tendon reflex decreased. 4) Pathological reflexes: The Hoffmann, Tremner, Babinski, and Chaddock reflexes were all absent. 5) Range-of-motion (ROM) was normal. 6) ADL: His indoor locomotion (home, day-service center) was independent, but required use of a wheelchair, while his outdoor locomotion was dependent on assistance. 7) Functional Independence Measure (FIM): his total FIM score was 99 (motor items 64, cognitive items 35); the locomotion (walking) item score was 2 points.
Physical examinations: Because the day-service center is not a medical institution, electrophysiological examinations (nerve conduction study and needle electromyography) could not be performed.

rPMS Methods and Treatment Plans

The patient was suspected to have peripheral neuropathy, but it was determined to be in the chronic stage, because considerable time had passed since the onset of COVID-19. Therefore, a method of muscle strengthening using rPMS was planned. The purpose, methods, and safety of rPMS, and the results of a study presented at an academic conference were explained to him in detail both orally and in writing. He voluntarily agreed to receive rPMS after understanding the explanation of the treatment.

While muscle strengthening using rPMS was planned approximately 6 months after starting utilization of the day-service center, a 4-week period from the planning date to the start of the intervention was set as the control period. During the control period, the patient was given regular functional training, including ROM exercises in the supine position and strengthening exercises in the weight-free position, for 20 minutes/day. The intervention using rPMS was then carried out for 4 weeks. Although regular functional training was not performed during the intervention period, his own independent practice was not prohibited. After completing the intervention,

regular functional training was resumed for 4 weeks. During this period, standing and walking exercises were added, depending on his physical function and movement abilities. Functional evaluations were scheduled on the first day of the intervention using rPMS and on the first visit after completing the intervention. Measurement of maximal voluntary contraction (MVC) was performed 4 weeks before the start of the intervention and 4 weeks after the end of the intervention.

The stimulator used for rPMS was an oil-cooled device (Talent Pro®; ReMed Co., Ltd., Republic of Korea; sold by OG Wellness Co. Ltd., Okayama, Japan). Stimulation was performed using a large circular coil (radius: 7.8 cm). The vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM) of the bilateral quadriceps femoris were stimulated. Stimulation was performed after searching for the optimal stimulation site for each muscle to induce stable and strong muscle contraction [12, 13]. The optimal stimulation site for the VL was between the proximal one-third and distal one-third of the line connecting the anterior superior iliac spine and the lateral superior margin of the patella. For the RF, the center of the line connecting the anterior superior iliac spine and the central superior margin of the patella was stimulated. For the VM, the center of the muscle belly was stimulated. The total stimulation time for one session was 20 minutes, so that each muscle was stimulated for the same amount of time (3 minutes and 20 seconds). The stimulation frequency was 30 Hz. Stimulation was administered for 3 seconds, followed by 6 seconds of rest; this process was repeated. The stimulation intensity was set at 80% of the maximum output of the device (1.47 Tesla) based on a previous report [14]; the pain felt by the patient was within the acceptable range. The number of visits to the day-service center was set to three times a week, and the intervention period was 4 weeks (i.e., 12 sessions in total). Approval for the use of Talent Pro® on an older person in the day-service center for the purpose of muscle strengthening was obtained from the Ethics Committee of Kawasaki University of Medical Welfare prior to the study (approval number: 21−088).

Functional Evaluations

1. Measurement of knee extensor torque during maximum voluntary contraction

Bilateral knee extensor torque (KET) during MVC was measured in a chair-sitting position using a handheld dynamometer (μ-Tas F-1®, manufactured by Anima Co., Ltd., Tokyo, Japan). A folded towel was placed in the popliteal fossa, and the sensor pad was attached to the distal end of the lower leg with a hook-and-loop fastener. A fixation belt was used to connect the sensor pad and a bed foot so that the knee extensors could contract isometrically. The length of the belt was adjusted to maintain the knee-joint angle at 90° when the knee extensors contracted. The KET was measured during 3 seconds of MVC. Measurements were taken twice with a 5-second interval, and the mean value was used for analysis. The torque value (Nm) was calculated by multiplying the measured value (N) by the distance from the knee-joint space to the center of the sensor pad.

2. Measurement of muscle torque induced by magnetic stimulation

KET induced by rPMS (rPMS-induced torque) was also measured using the μ-Tas F-1®. The posture and position of the limbs during measurement were the same as for KET during MVC. The bilateral VLs were selected as the muscles to measure rPMS-induced torque [8, 10, 13, 14]. The optimal stimulation site that could induce maximal contraction was explored using 60% of the maximum output of the device. It was determined by approximately five explorations between the proximal one-third and distal one-third of the line connecting the anterior superior iliac spine and the lateral superior margin of the patella [12, 13].

During the measurement of rPMS-induced torque, the patient was instructed to relax his whole body as much as possible to avoid voluntary contraction of the quadriceps femoris. The center of the probe containing the coil was carefully and exactly aligned with the optimal stimulation site, and the long axis of the probe was held parallel to the long axis of the thigh. The stimulation frequency was 30 Hz. The stimulation intensity was the maximum output of the device, and the stimulation time was 3 seconds [11−14]. Measurements were performed twice with an interval of 5 seconds.

3. Evaluation of pain during magnetic stimulation

On the first and last day of rPMS intervention, the patient self-rated the pain level during rPMS using a visual analog scale (VAS). The patient was instructed to place an “x” mark on a 100-mm-long line drawn on a piece of paper. The left end (0 mm) of the line was set as “no pain” and the right end (100 mm) as “pain too intense to be tolerated.”

4. Pulmonary function tests

Ventilation function was measured using an electronic spirometer (HI-801, CHEST M.I., Inc., Tokyo, Japan). Before measurements, the nasal airflow sensor was firmly attached to the respiratory muscle sensor to prevent exhaled or inspired air from leaking through gaps in the device. We measured vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1). The FEV1/FVC ratio (FEV1.0%) was calculated by dividing the FEV1 by the FVC. Measurement using the spirometer was performed twice, and the maximum value was used as data.

5. Other functional evaluations

Based on past reports, we evaluated the following functional evaluations.

1) Timed-Up-and-Go Test (TUG)
2) The 30-second chair-stand test (CS-30)
3) The comfortable 5-m walking time
4) Walking endurance (the distance until the patient could no longer walk, even when using a circle walker)
5) The Functional Reach Test (FRT)
6) Thigh circumference (measured immediately above, 5 cm above, 10 cm above, and 15 cm above the patella)
7) The walking item of the FIM.

Results

The KET obtained during MVC are shown in **Figure 1**. KET during MVC remained unchanged between the 4 weeks before and on the first day of rPMS intervention. The mean values of KET during MVC on the first day of rPMS intervention were 33.7 Nm on the right and 36.2 Nm on the left side, but increased to 42.1 Nm on the right and 40.7 Nm on the left side after the end of intervention. The KET during MVC continued to increase after the intervention was completed, with mean values of 43.9 Nm on the right and 47.1 Nm on the left side observed 4 weeks after intervention completion. In MMT, the extension force of both knee joints had increased to 4 after completion of the intervention.

rPMS-induced torque was 0 Nm on both sides on the first day of rPMS intervention, but increased to 6.5 Nm on the right and 4.7 Nm on the left side by the end of rPMS intervention. No significant changes were observed in the thigh circumference immediately above, 5 cm above, 10 cm above, or 15 cm above the patella (**Table 1**).

On the first day of rPMS intervention, the VAS value was 70 mm, the TUG was 25.4 seconds, the CS-30 was difficult to perform, the comfortable 5-m walking time was 8.6 seconds, and the walking endurance was 30 m. The patient was able to walk independently up to 10 m using a walker, but beyond that he required minimal assistance and was unable to walk more than 30 m. Thus, the walking item of the FIM was scored as 2 points. After completing the rPMS intervention, the VAS value decreased to 14

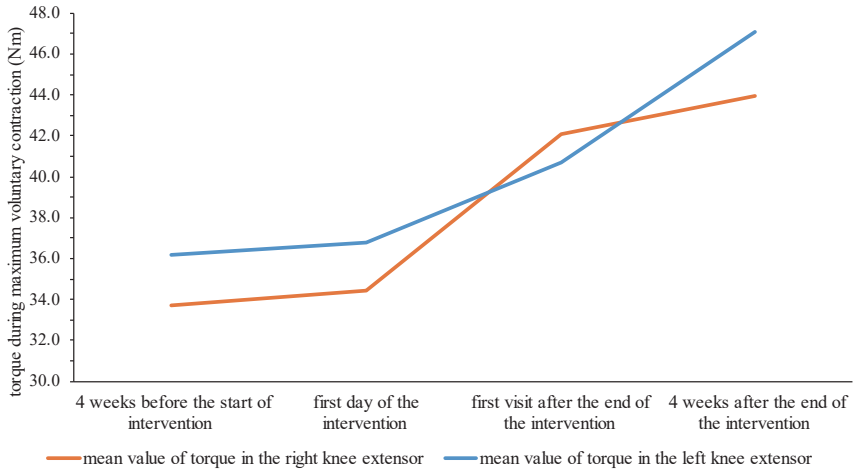

Figure 1. Changes in torque during maximum voluntary contraction.

Table 1. Torque induced by rPMS and thigh circumference.

		Right		Left	
		(1)	(2)	(3)	(4)
rPMS-induced torque (Nm)		0	6.5	0	4.7
Thigh circumference	Immediately above the patella (cm)	39.0	39.0	39.5	39.0
	5 cm above the patella (cm)	40.0	40.0	40.0	40.0
	10 cm above the patella (cm)	41.0	41.0	41.5	41.0
	15 cm above the patella (cm)	43.5	43.5	45.5	45.5

rPMS: repetitive peripheral magnetic stimulation.
(1) 4 Weeks before the start of intervention.
(2) First day of the intervention.
(3) First visit after the end of the intervention.
(4) 4 Weeks after the end of the intervention.

Table 2. Comparison of functions before and after rPMS intervention.

		Before intervention	After intervention
VAS value during rPMS (mm)		70	14
Pulmonary function test	VC (ℓ)	2.17	1.89
	FVC (ℓ)	1.87	1.84
	FEV1 (ℓ)	1.53	1.37
	FEV1.0 % (%)	81.82	74.46
TUG (s)		25.4	19.7
CS-30 (times)		0	1
Comfortable walking time for 5 m (s)		8.6	6.9
Walking endurance (m)		30	60
FRT (cm)		25.5	27.2

rPMS, Repetitive peripheral magnetic stimulation; VAS, Visual analogue scale; VC, Vital capacity; FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second; FEV1.0 %, FEV1/FVC ratio; CS-30, Chair stand test; TUG, Timed Up and Go Test; FRT, Functional Reach Test.

mm, the TUG shortened to 19.7 seconds, CS-30 could be performed once, the comfortable 5-m walking time improved to 6.9 seconds, and walking endurance increased to 60 m. The walking item of the FIM was scored as 6 points, because the patient became able to walk independently for more than 50 m while using a walker.

No significant changes in the results of the pulmonary function test (FVC before intervention: 1.87 L, FVC after intervention: 1.84 L, FEV1 before intervention: 1.53 L, FEV1 after intervention: 1.37 L) and FRT before and after the intervention were noted (**Table 2**).

Discussion

After confirming that long-term regular functional training did not improve muscle strength in the lower limbs of a patient with severe impairment after contracting COVID-19, rPMS of the bilateral quadriceps femoris was performed. After the intervention, the patient's MVC increased significantly; CS-30, a functional evaluation of lower limb muscle strength, could be measured; and motor functions and walking ability parameters, such as the TUG, comfortable 5-m walking time, and walking endurance, improved. These findings were similar to those of previous studies using rPMS for other diseases [8, 10, 11], supporting the usefulness of rPMS.

It has been reported in a previous study that sufficiently long stimulation time and high stimulation frequency are imperative for muscle strengthening using rPMS [9]. The Talent Pro® device used in this case did not generate high heat, even if stimulation was continued for more than 60 minutes at 30 Hz. In this case, the program was carried out three times a week for a total of 4 weeks, resulting in approximately 144,000 stimulations to both lower limbs (30 Hz × 400 seconds × three times a week × four weeks). In previous studies reporting the success of muscle strengthening in the lower extremities, 22,500−108,000 magnetic stimulations were administered to participants during an intervention period of 2−8 weeks [8−11]. Although the disease involved was different, we supposed that the greater number of stimulations in this study compared to previous reports led to effective muscle strengthening.

Although the thigh circumference did not change in this case, improvements were observed in items related to muscle strength in the lower limbs, such as the MVC and CS-30. Severe muscle weakness due to COVID-19 has been reported to be a type of ICU-AW [1]. Because an electrophysiological examination was not performed in our case, we could not confirm the presence of peripheral nerve or muscle lesions, but the involvement of ICU-AW was suspected due to decreased reflexes and significant muscle weakness. However, it is inappropriate to conclude that neurogenic or myogenic changes were directly repaired by rPMS. It seems reasonable to conclude that rPMS was effective against disuse changes from long-term muscle weakness caused by ICU-AW.

The muscle-strengthening effects of rPMS on disuse changes have been reported to result from a combination of nervous system adaptations, muscle histochemical changes, and muscle fiber hypertrophy [9]. Gondin et al. stated that nervous system adaptations occurred in 4 weeks, whereas changes in muscle mass required 8 weeks [15]. Since the rPMS intervention period was 4 weeks in this case, we assume that there was no change in muscle mass, and as a result, no increase in thigh circumference was observed. Therefore, the changes in muscle strength that occurred after the 4-week intervention are considered to be

adaptations of the nervous system. The continued increase in MVC, even after the end of rPMS, was supposed to be due to the recovery of muscle strength to the extent that strengthening exercises using his own body weight could be performed. We consider that rPMS accelerated the increase in muscle strength to some extent, after which more effective resistance exercise became possible. Increased patient motivation may also have been an important factor in MVC increase after the intervention. The improved muscle strength and motivation presumably made it possible for him to perform exercises independently, resulting in further muscle-strengthening effects.

rPMS-induced torque increased from 0 Nm before intervention to 6.5 Nm in the right and 4.7 Nm in the left lower limb after intervention, providing sufficient knee joint extension. A previous study reported that rPMS-induced torque was related to MVC [14]. Thus, if muscle strength is decreased, it may be difficult to induce strong muscle torque by rPMS. It is not clear whether the cause of the increase in rPMS-induced torque was related to the peripheral nerves, the neuromuscular junction, or the muscle itself, but since thigh circumference remained unchanged, it may not have been related to muscle mass. Given that rPMS-induced torque increased after 4 weeks of intervention, functional changes are assumed to have occurred in the nervous system. Nevertheless, future detailed studies are required to elucidate the mechanism.

In this case, improvements were also observed in the TUG, an indicator of balance ability, as well as in the 5-m walking time and walking endurance. A previous study stated that balance ability improved because of using rPMS on the quadriceps femoris [10]. The improvement in the TUG that occurred in our case seems to be considerably due to muscle strengthening in both lower limbs. Furthermore, walking speed has been reportedly improved by applying rPMS to necessary muscles [11]. Furthermore, a previous study reported that the minimum increase of muscle torque required to improve walking endurance in COPD patients was 7.5 Nm [16]. In this case, the KET during MVC of the right lower limb increased by 8.4 Nm, which suggests that the muscle strength needed to improve walking endurance may have been achieved, supporting previous studies [8]. In the future, studies should investigate whether it is effective to use rPMS in combination with strengthening exercises to improve motor abilities further.

Conclusion

We described the effectiveness of using rPMS for a patient who had developed significant muscle weakness in the lower limbs and had gait disturbance after mechanical ventilation in the ICU for COVID-19. rPMS treatment in this case led to increased muscle strength in the quadriceps femoris. rPMS is an easy-to-use treatment that has the potential to improve standing and walking abilities in patients with muscle weakness in the lower limbs.

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