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Research paper

Quadripulse transcranial magnetic stimulation inducing long-term depression in healthy subjects may increase seizure risk in some patients with intractable epilepsy

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ABSTRACT

Objective: This study aimed to assess the efficacy and safety of quadripulse transcranial magnetic stimulation-50 (QPS-50) in patients with intractable epilepsy.
Methods: Four patients were included in the study. QPS-50, which induces long-term depression in healthy subjects, was administered for 30 min on a weekly basis for 12 weeks. Patients' clinical symptoms and physiological parameters were evaluated before, during, and after the repeated QPS-50 period. We performed two control experiments: the effect in MEP (Motor evoked potential) size after a single QPS-50 session with a round coil in nine healthy volunteers, and a follow-up study of physiological parameters by repeated QPS-50 sessions in four other healthy participants.
Results: Motor threshold (MT) decreased during the repeated QPS-50 sessions in all patients. Epileptic symptoms worsened in two patients, whereas no clinical worsening was observed in the other two patients. In contrast, MT remained unaffected for 12 weeks in all healthy volunteers.
Conclusions: QPS-50 may not be effective as a treatment for intractable epilepsy.
Significance: In intractable epilepsy patients, administering repeated QPS-50 may paradoxically render the motor cortex more excitable, probably because of abnormal inhibitory control within the epileptic cortex. The possibility of clinical aggravation should be seriously considered when treating intractable epilepsy patients with non-invasive stimulation methods.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is widely used to modulate cortical excitability. The direction of long-term effects depends on the stimulation frequency and pattern. In conventional repetitive stimulation, low- and high-frequency rTMS induces long-term depression (LTD)- and long-term potentiation (LTP)-like effects, respectively (Chen et al., 1997; Muellbacher et al., 2000; Pascual-Leone et al., 1994). Quadripulse transcranial magnetic stimulation (QPS), a patterned rTMS performed over the primary motor area (M1), also induces LTP- or LTD-like effects on the excitability of motor or somatosensory cortices in healthy

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subjects with a high efficiency and stability across subjects (Hamada et al., 2007, 2008; Nakatani-Enomoto et al., 2012, 2016).

In intractable epilepsy patients, motor cortical areas are usually hyperexcitable (Badawy et al., 2013; Tassinari et al., 2003), and rTMS patterns that induce LTD-like effects have been proposed as potential treatment options. Several studies have shown that low-frequency rTMS reduces seizure frequency or improves electroencephalographic (EEG) features (Fregni et al., 2006; Hsu et al., 2011; Sun et al., 2012; Üstün Özek et al., 2020), whereas other studies have reported no beneficial effects of low-frequency rTMS (Cantello et al., 2007; Seynaeve et al., 2016). One case report described rebound seizure aggravation after transient improvement induced by low-frequency rTMS (Seynaeve et al., 2016). Therefore, the efficacy of rTMS in epilepsy patients remains unclear. In this study, we evaluated the efficacy of QPS in the treatment of intractable epilepsy, because QPS is more effective and stable for inducing synaptic plasticity compared with other methods of plasticity-induction (Tiksnadi et al., 2020).

1.1. Subjects

***Patients*:** We studied four patients with intractable epilepsy (aged 17, 26, 32, and 36 years). Ideally, we should have included many more patients with the same pathological abnormalities; however, we were unable to enroll more patients with intractable epilepsy who had the same underlying pathogenesis. All patients had multiple bilateral epileptic foci. Disease duration in these patients was >14 years. Qualified epileptologists had treated the patients for years; however, all participants still experienced seizures more than twice a month despite being treated with a combination of various antiepileptic drugs (AEDs). All the patients fulfilled the International League Against Epilepsy criteria for drug-resistant epilepsy (Kwan et al., 2010). All patients kept a seizure diary for several years.

Patient 1: A 36-year-old woman with focal impaired awareness seizures. Magnetic resonance imaging (MRI) of the brain showed no structural abnormalities. The patient sometimes noticed a brief loss of consciousness (LOC). EEG showed multiple spikes in the bilateral frontotemporal and left occipital areas. A combination of several AEDs, including carbamazepine (CBZ), phenytoin (PHT), clobazam (CLB), clonazepam (CZP), zonisamide and topiramate, had been administered to the patient; nevertheless, LOC episodes increased in frequency. CBZ (660 mg/day), PHT (215 mg/day), CZP (0.5 mg/day), and CLB (20 mg/day) were prescribed when she joined this study in 2007.

Patient 2: A 26-year-old man with focal to bilateral tonic-clonic seizures. The patient was born with asphyxia and mild left-sided hemiparesis. Brain MRI revealed cortical atrophy in the right hemisphere. EEG showed bilateral spikes in the frontal cortices. The patient was treated with CBZ (700 mg/day), PHT (150 mg/day), and phenobarbital (90 mg/day) when he joined this study in 2006.

Patient 3: A 36-year-old man with hippocampal sclerosis and focal aware seizures (FASs). FASs still occurred even after resection of the temporal lobe and fusiform gyrus. EEG showed a residual focus in the ipsilateral posterior temporal lobe and an epileptic focus in the contralateral temporal lobe. The patient was treated with CBZ (600 mg/day), CLB (30 mg/day), and valproic acid (VPA; 1600 mg/day) when he joined this study in 2006.

Patient 4: A 17-year-old boy with tuberous sclerosis presented with focal atonic seizures, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures produced by bilateral multiple foci. Brain MRI revealed cortical tubers in the bilateral inferior to middle temporal lobes and subependymal nodules. EEG showed multiple spikes in the bilateral frontotemporal and parietal areas. The patient was treated with VPA (1200 mg/day) and PHT (300 mg/day) when he joined this study in 2007.

***Healthy volunteers*:** Thirteen healthy volunteers were enrolled in this study. All previous QPS studies had used a figure-of-eight coil for the intervention. However, we used a round coil to treat our patients because they had multiple epileptic foci. Therefore, we studied the effects of QPS-50 performed with a round coil in nine healthy volunteers between the ages of 29 and 68 years. The motor thresholds (MTs) were followed up under the repeated QPS-50 interventions in four other healthy volunteers (aged 39, 40, 48, and 50 years) who did not participate in the previous experiment, for comparison with those from the patients. Ideally, we should have studied control subjects whose age range was similar to that of the included patients. However, we had difficulty in recruiting healthy teenagers who were able to be followed up for three months.

2. Methods

The study protocol was approved by the Ethics Committees of Fukushima Medical University (Fukushima, Japan; No. 713 for epilepsy patients and No. 2175 for healthy subjects). Written informed consent was obtained from all the participants before the experiments.

2.1. QPS-50 with a round coil in healthy subjects

Nine healthy volunteers participated in this experiment. During the QPS-50 intervention, the center of a round coil was placed over the vertex. The quadruple stimuli were delivered using four magnetic stimulators (Magstim 200^2; The Magstim Co. Ltd.) connected to a combining module (The Magstim Co. Ltd.; Hamada et al., 2008). The QPS-50 intensity was set at 90% of the lower active motor threshold (AMT) of both hemispheres measured using a round coil on the same day. Each burst consisted of four monophasic TMS pulses fixed at 90% AMT. A single QPS session consisted of 360 bursts (1440 pulses) for 30 min, and each burst was administered every 5 s. The intracranial current direction was reversed by overturning the coil in the middle of the session (sides A and B up, for 15 min).

Motor evoked potentials (MEPs) elicited by a figure-of-eight coil were recorded from the first dorsal interosseous (FDI) muscle, with an active electrode placed over the muscle belly and a reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified through filters set at 100 Hz and 3 kHz (Neuropack μ, Nihon-Kohden, Japan), stored at a sampling rate of 10 kHz, and analyzed offline (TMS BiStim tester; Medical Try System, Japan). The direction of the induced current in the brain was adjusted as posterolateral to anteromedial at a 45° angle. The participants were asked to keep the FDI muscle relaxed during the measurement. Ten MEPs were measured twice with a 2-min intersession interval using single pulse TMSs at random intervals between 5 s and 10 s. The stimulus intensity was adjusted to provoke MEPs with a peak-to-peak amplitude of approximately 0.5 mV. MEPs contaminated with voluntary EMG activities were discarded from the analyses. Peak-to-peak amplitudes of the residual MEPs were averaged. The MEPs were recorded at four time points: before QPS-50, and at 10, 30, and 60 min after the intervention (Tpre, T10, T30, and T60, respectively). The stimulus intensity on M1 was kept constant throughout the experiment. The amplitudes of the average MEPs recorded after QPS-50 were normalized to the baseline MEP (before QPS).

2.2. QPS-50 in the patients

A session of QPS-50 using a round coil as described above was repeated once a week for a maximum of 12 weeks.

2.3. Experiment 1

The main purpose of this study was to investigate the beneficial effects of QPS-50 with a round coil in intractable epilepsy patients. The protocol is illustrated in Fig. 1. The observation periods were set before and after the QPS period for 12 weeks. We evaluated patients' physical conditions and seizure diaries during all visits. The AED regimen was not changed during the entire duration of the experiment (36 weeks). The QPS-50 protocol could not be completed in patients 1 and 2 because of clinical aggravation. Patient 4 participated in two different intervention periods preceded and followed by observation periods (observation for 12 weeks – intervention for 12 weeks – observation for 12 weeks – intervention for 12 weeks – observation for 12 weeks) for 60 weeks in total, having provided informed consent for a second period of repeated QPS intervention.

At the first QPS session, both AMT and resting motor threshold (RMT) were measured before and after the session in all participants to confirm the previous result of no threshold changes after a single QPS session (Hamada et al., 2007). In patients with epilepsy, we measured AMT before each session of repeated QPS using a figure-of-eight coil. The RMT was also measured before and after QPS at the first and last sessions of the repeated QPS period. In healthy subjects, AMT and RMT were measured with both a round and a figure-of-eight coil throughout the repeated QPS sessions (Fig. 1).

The threshold measured with a round coil was used as the reference intensity in the QPS-50, and the threshold measured with a figure-of-eight coil was used to follow the time course of the MTs. Participants maintained a slight voluntary contraction of the FDI muscle during AMT measurement, and the FDI muscle was relaxed during RMT measurement. AMT was defined as the lowest intensity that evoked an MEP of peak-to-peak amplitude >100 μV at a 50% rate. RMT was defined as the lowest intensity that elicited an MEP, with a peak-to-peak amplitude >50 μV in half of the trials. Stimulus intensity was changed in steps of 1% of the maximum stimulator output (Hamada et al., 2008).

2.4. Experiment 2

We studied the time course of MTs for 12 weeks in four healthy volunteers as controls exposed to the same repeated QPS-50 protocol (Fig. 1). During the 12-week preparation period before QPS-50 intervention, the participants were instructed to avoid any kinds of non-invasive brain stimulations. Bilateral AMT and RMT were measured 13 times in total, immediately before every QPS-50 session.

2.5. Statistical analyses

Statistical analyses were performed using SPSS 17.0 for windows (SPSS, Chicago, IL, USA). For the round coil QPS experiment in healthy subjects, each MEP size after single QPS-50 at T10, T30, and T60 was compared with that at Tpre. For non-parametric analyses, we used Friedman's test for Analysis of variance and Kruskal–Wallis test for multiple comparisons. The time course of the effect was depicted as the size ratio over time. The AMTs of the experimental patients and healthy subjects were compared using Mann–Whitney U tests. The significance level for all analyses was set at $p < 0.05$.

3. Results

In healthy subjects, a single QPS-50 session with a round coil (sides A and B up, for 15 min) suppressed MEPs at 10, 30, and 60 min after the intervention. The size of MEP recorded after QPS-50 were normalized against the MEP size obtained before QPS-50 (size ratio). Mean size ratios after the intervention were 0.59 at T10, 0.60 at T30, and 0.50 at T60. These values were almost in the same range as in previous results obtained using a figure-of-eight coil (Hamada et al., 2007, 2008). A non-parametric test

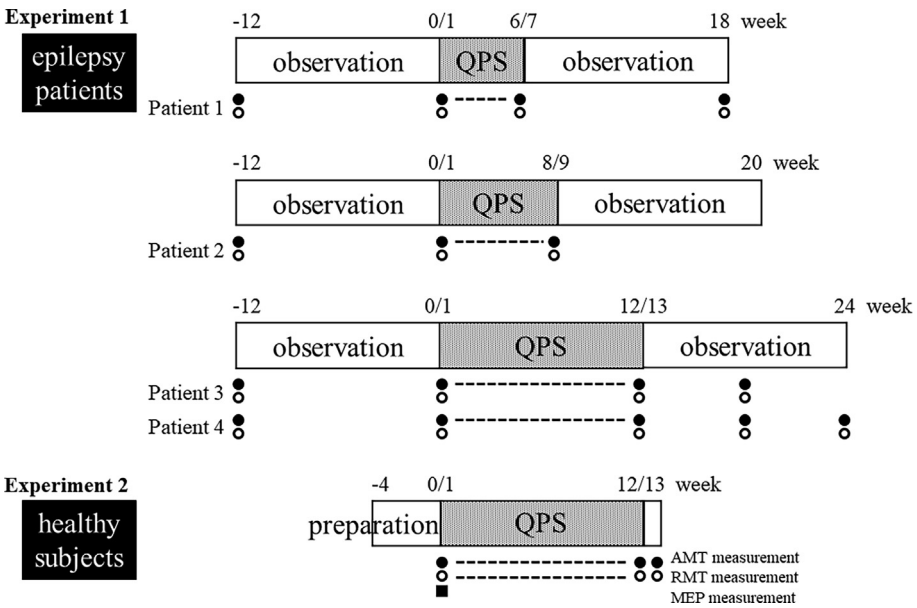

Fig. 1. Protocol of the experiment. Quadripulse transcranial magnetic stimulation (QPS) with an interpulse interval of 50 ms (QPS-50) was performed with a round coil once a week on the same day of the week for 12 weeks. *Patients*: Patients were observed for 12 weeks before and after the repeated QPS-50 period. The antiepileptic drug regimen did not change during the experimental period. The active motor threshold (AMT) and resting motor threshold (RMT) in both hemispheres were measured with a figure-of-eight coil on the first day of the observation period. The bilateral AMTs were measured before each session of repeated QPS-50 interventions. RMTs were measured at the first and last QPS-50 sessions of the entire repeated QPS-50 period. Patients 3 and 4 completed the scheduled protocol. For patients 1 and 2, the QPS-50 protocol was stopped prematurely owing to the deterioration of epilepsy symptoms. *Healthy volunteers*: QPS-50 was administered for 12 weeks. None of the subjects received any medications or other non-invasive transcranial stimulation for 17 weeks during the entire experiment. AMT and RMT were measured before every repeated QPS-50 session, and again a week after the final QPS-50 session.

(Friedman's test) showed a significant effect of time (chi-square = 23.257, $p < 0.001$). The Kruskal–Wallis test revealed that MEP sizes at T10, T30, and T60 were significantly smaller compared to those at Tpre (Tpre vs T10, $p = 0.013$; Tpre vs T30, $p = 0.011$; Tpre vs T60, $p < 0.001$).

In experiment 1, no seizures were provoked during the each single QPS-50 session in any of the patients. However, in patient 1, seizure frequency increased during the repeated QPS-50 interventions. Seizures occurred 1.1 times per week on average before the repeated QPS-50 stimulation, but the mean seizure frequency increased to 4.0 times per week during the repeated QPS-50 period. Therefore, the QPS-50 intervention was stopped after 6 weeks. Even after cessation of the repeated QPS-50 intervention, average seizure frequency did not return to the baseline level for over 12 weeks, which was 4.6 times per week. In patient 2, the average proportion of severe convulsion was 14.2% before the repeated QPS-50 stimulation. However, severe convulsion rate increased to 50% during the repeated QPS-50 period. Furthermore, seizure attacks always occurred on the next day following the QPS-50 stimulation session. The intervention was stopped after 7 weeks. Fortunately, the frequency of severe convulsions returned to the baseline level after cessation of the repeated QPS-50 intervention. No clinical worsening was observed in patients 3 and 4. Neither AMT nor RMT differed significantly before and immediately after the first single QPS-50 session in any of the patients. However, AMTs and RMTs gradually decreased bilaterally during the repeated QPS-50 period in all the patients. In patient 4, bilateral AMTs was reduced reproducibly for the first and second QPS sessions (Fig. 2). In contrast, no significant changes were observed in healthy volunteers (Fig. 3).

In healthy volunteers, neither AMT nor RMT differed significantly before and immediately after the first single QPS-50 session. The baseline AMTs of the healthy controls were 34, 38, 40, 43, 46, 46, 48, 50, 50, 51, 52, 68, and 72. Neither AMT nor RMT changed during the entire repeated QPS-50 sessions for a period lasting 13 weeks (Fig. 3). The Mann–Whitney *U* test showed no significant differences in AMT between experimental patients and healthy volunteers ($Z = 1.238$, $p = 0.260$).

4. Discussion

This study confirmed that a single QPS-50 intervention with a round coil induced an LTD-like effect on the primary motor cortex in healthy volunteers. Neither AMT nor RMT changed after a single session of QPS-50 stimulation in patients and healthy volunteers, which is in agreement with the findings of previous studies on rTMS (Cincotta et al., 2003; Ziemann et al., 1998) and QPS (Hamada et al., 2008). AMT and RMT were stable during the repeated QPS-50 period for 13 weeks in healthy volunteers, whereas MTs decreased during the intervention period in all patients. Seizure episodes may have worsened in parallel with threshold reductions in two out of the four patients. However, we are not able to exclude the possibility of accidental threshold reductions, because we studied only four patients.

Several prior studies have reported that the risk of crude seizure in patients receiving rTMS treatment is 1.4% or 2.9% (Bae et al., 2007; Pereira et al., 2016). Adverse events are generally mild (Bae et al., 2007), and rTMS is considered safe for patients with epilepsy (Bae et al., 2007; Chen et al., 2016; Pereira et al., 2016). Although some studies have reported no beneficial effects of rTMS (Cantello et al., 2007; Seynaeve et al., 2016), other studies have shown favorable effects of low-frequency rTMS on patients with focal epilepsy (Fregni et al., 2006; Hsu et al., 2011; Misawa et al., 2005; Theodore et al., 2002), as well as in multifocal epilepsy patients (Üstün Özek et al., 2020). However, in the present investigation, seizures may have worsened in two out of the four patients with intractable epilepsy with multiple foci after repeated QPS-50 interventions. In this study, AMT and RMT gradually decreased during the repeated QPS-50 period in all the patients, whereas MTs did not change throughout the entire repeated QPS-50 period in healthy volunteers. Decreased MTs are considered to reflect an increase in

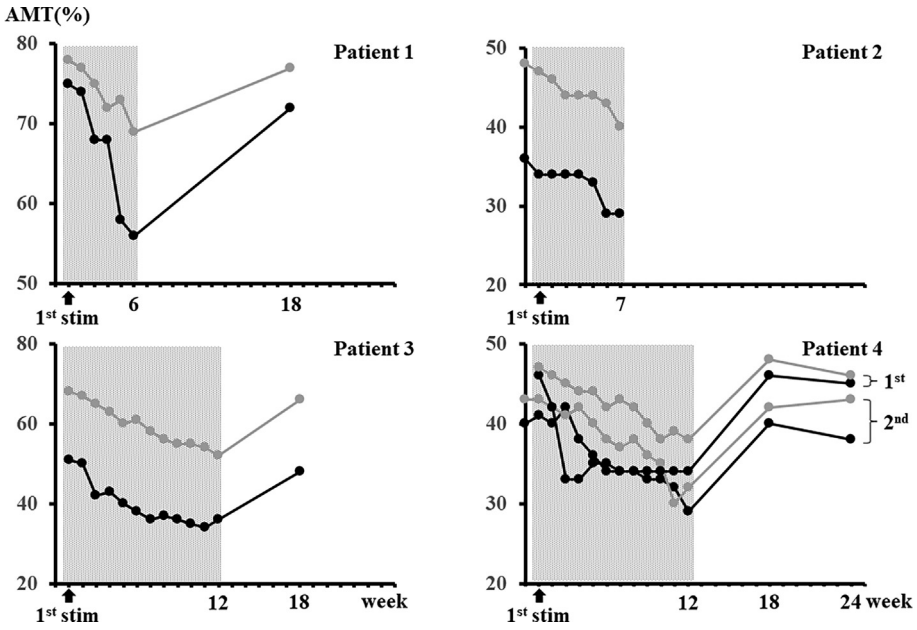

Fig. 2. Time courses of the bilateral AMTs measured using a figure-of-eight coil during the repeated QPS-50 period in patients. The AMTs of both hemispheres decreased during the repeated QPS-50 period in all the patients (*black, lower side; gray, higher side*). The planned 12 QPS-50 sessions were not performed in patients 1 and 2 because of clinical aggravation. The time courses of the two repeated QPS-50 periods in patient 4 are superimposed. AMT, active motor thresholds; QPS-50, quadripulse transcranial magnetic stimulation with an interpulse interval of 50 ms.

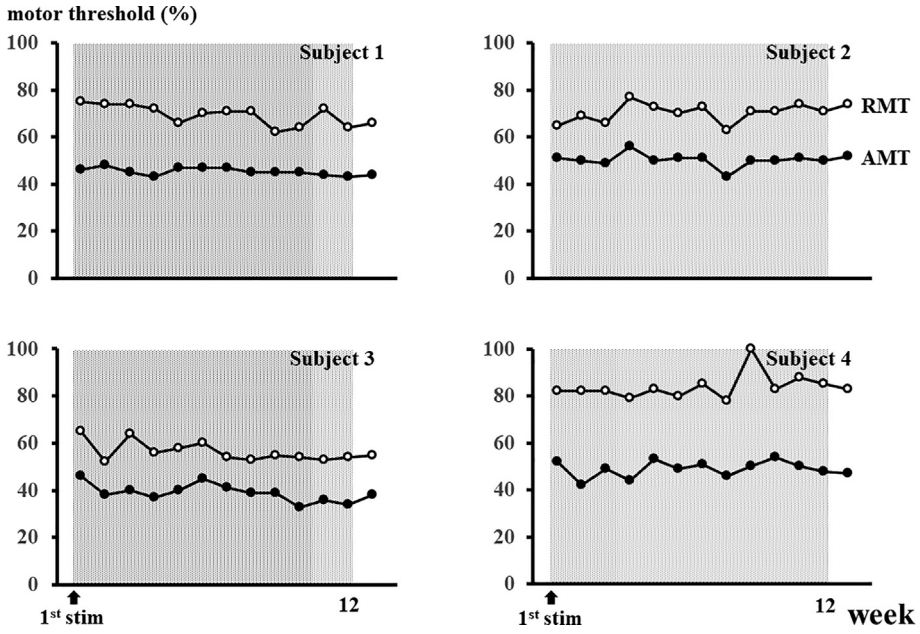

Fig. 3. Time courses of AMT and RMT during the repeated QPS-50 sessions in healthy volunteers. No changes were observed in either the AMT (*dots*) or RMT (*circles*) in healthy volunteers. AMT, active motor thresholds; QPS-50, quadripulse transcranial magnetic stimulation with an interpulse interval of 50 ms; RMT, resting motor threshold.

seizure risk (Mufti et al., 2010; Reutens et al., 1993). MT levels are elevated after AED intake (Reutens et al., 1993; Ziemann et al., 1996), which is consistent with the anti-seizure effect. Based on the above hypothesis that MT may be a marker of seizure risk, the MT reduction observed in all four patients may indicate an increase in the seizure risk after repeated QPS-50 interventions, even though we are not able to completely exclude the possibility that the MT reduction may have been an accidental finding due to the small number of enrolled patients. In two patients, clinical symptoms worsened in parallel with threshold reductions. In the other two patients, seizures did not worsen despite threshold reduction.

The most important difference between our results and those of previous studies was the target patients. We studied intractable epilepsy patients with multiple epileptic foci, whereas most previous studies have examined patients with only mildly or moderately severe epilepsy. Moreover, one study reported that the frequency and severity of seizures were reduced in patients with a single focus, but these variables were not changed in patients with multiple foci (Daniele et al., 2003). Repeated QPS-50 stimulation may have a beneficial effect in patients with a single focus; and if effective, adverse effects may be rarely observed. Another possibility is that a single session of QPS, but not repeated stimulations, may be effective for patients with multiple foci or with a single focus. These issues are beyond the scope of the present study, and they may be worthwhile projects for future investigations using QPS with a figure-of-eight coil or a round coil.

Another possible factor is the difference in the stimulation protocol. Patients in our study received repeated QPS-50 once a week for 12 weeks as a long-term treatment strategy. However, previous studies were short- to moderate-term, that is, five consecutive days per week (Cantello et al., 2007; Fregni et al., 2006; Üstün Özek et al., 2020), 10 days in two weeks (Seynaeve et al., 2016), or a second straight week (Sun et al., 2012). Low-frequency rTMS performed biweekly for four consecutive weeks showed limited effects. Stimulations on consecutive days may have been the reason for the successful results in previous studies. Therefore, QPS-50 administered five days per week, or similar stimulation protocols with a short-term design, may have a beneficial effect on seizure symptoms. Optimizing the protocol for effective QPS-50 strategies is a future target for QPS study. Other factors that should be considered are the coil type used in the repeated QPS-50 intervention, and the reversal of current direction during the intervention. Previous QPS studies used a figure-of-eight coil for focal stimulation in one current direction. However, in this study, we used a round coil and two current directions. The effect induced by a round coil stimulation is more complex than that induced by a figure-of-eight coil, because many cortical areas may simultaneously modulate a certain cortex (Ishikawa et al., 2007). Stimulation of wide areas using a round coil in patients with intractable epilepsy with multifocal spikes induces unexpected results. Additional possibilities include a lack of GABAergic function (Treiman, 2001), the absence of an LTD-like mechanism (Lippman-Bell et al., 2016), or a shift in the transition point of the Bienenstock–Cooper–Munro curve in patients with epilepsy. Whichever mechanisms explain the present results, QPS-50, which induces an LTD-like effect in healthy individuals, may possibly increase the risk of seizures in patients with intractable epilepsy.

5. Limitations

The first limitation of this study is that it included only four patients. Therefore, we may not be able to exclude the possibility of accidental observations in our results. The second limitation is that we did not study beneficial effects on patients with a focal lesion. Thirdly, effectiveness of a single session of QPS in patients with a single focus or multiple lesions was also not verified. We cannot conclude that any non-invasive stimulation interventions have no beneficial effects in any epilepsy patients. Here, we can only state that repeated QPS-50 session is not useful for intractable epilepsy patients with multiple foci.

6. Conclusion

In patients with intractable epilepsy with multiple epileptic foci, weekly repeated QPS-50 intervention may worsen epileptic clinical symptoms in association with threshold reduction, or

may induce MT reduction without worsening of symptoms. In contrast, the threshold was not affected by repeated QPS-50 intervention for 12 weeks in healthy volunteers. The results suggest that the possibility of clinical aggravation should be seriously considered when treating intractable epilepsy patients with non-invasive stimulation methods.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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