

**Application of tetanic stimulation of unilateral tibial nerve
prior to transcranial stimulation can augment the amplitudes of myogenic motor
evoked potentials from the muscles in bilateral upper and lower limbs.**

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Implication

Since myogenic motor evoked potentials (MEPs) are very sensitive to suppression by anesthetic and neuromuscular blocking agents, the techniques to augment MEP responses are desirable under anesthesia. In the present study, we report that the application of tetanic stimulation to left tibial nerve prior to transcranial stimulation augmented the amplitudes of MEPs from the muscles without tetanic nerve stimulation as well as those with tetanic nerve stimulation.

Abstract

Background: Recently, we reported a new technique to augment motor evoked potentials (MEPs) under general anesthesia, called as post-tetanic MEP (p-MEP), in which tetanic stimulation of peripheral nerve prior to transcranial stimulation enlarged amplitudes of MEPs from the muscle innervated by the nerve subjected to tetanic stimulation. In the present study, we tested whether tetanic stimulation of left tibial nerve can also augment amplitudes of MEPs from the muscles, which are not innervated by the nerve subjected to tetanic stimulation.

Methods: Thirty patients undergoing spinal surgery under propofol-fentanyl anesthesia with partial neuromuscular blockade were examined. For conventional MEP (c-MEP) recording, transcranial stimulation with train-of-five pulses was delivered to C3-C4, and the compound muscle action potentials were bilaterally recorded from the abductor pollicis brevis (APB), abductor hallucis (AH), tibialis anterior (TA), and soleus (S) muscles. For p-MEP recording, tetanic stimulation (50Hz, 50mA of stimulus intensity) with a duration of 5 sec was applied to the left tibial nerve at the ankle 1 sec prior to transcranial stimulation. Transcranial stimulation and recording of compound muscle

action potentials were performed in a same manner as c-MEP recording. Amplitudes of c-MEP and p-MEP were compared by using Wilcoxon signed rank test.

Results: Amplitudes of p-MEPs from the left AH muscle innervated by the left tibial nerve with tetanic stimulation were significantly larger compared with those of c-MEPs. Amplitudes of p-MEPs from the bilateral APB and S muscles and right AH and TA muscles, which were not innervated by the left tibial nerve with tetanic stimulation, were also significantly larger compared with those of c-MEPs.

Conclusion: In patients under propofol and fentanyl anesthesia with partial neuromuscular blockade, the application of tetanic stimulation to left tibial nerve augmented the amplitudes of MEPs from the muscles without tetanic nerve stimulation as well as those with stimulation.

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Key Words:

motor evoked potentials, monitoring, tetanic stimulation, nerve, spinal cord

Introduction

Intraoperative monitoring of myogenic motor evoked potential (MEP) to transcranial stimulation of the motor cortex has become a commonly used technique for the early detection and reversal of spinal cord injury during operations in which there is a risk for spinal cord injury (1-3). However, clinical and experimental use of these techniques has shown that the elicited responses are very sensitive to suppression by most anesthetics and muscular blockade (4-10). Furthermore, patients with preoperative neuropathy, such as spinal cord tumor, Chiari malformation and scoliosis may have very poor baseline MEPs. Although multipulse stimulation setups have been proposed to improve monitoring reliability (11-13), further improvements in technique for reliable MEP recording will be helpful.

Recently, we reported a new technique for MEP recording, called as post-tetanic MEP (p-MEP) (Figure 1), in which MEP amplitude can be enlarged by tetanic stimulation of the peripheral nerve prior to transcranial stimulation compared with that of conventional MEP (c-MEP) (14). Using this technique, we can successfully enlarge MEP amplitudes under general anesthesia with partial neuromuscular blockade.

Originally, we proposed that MEP augmentation by tetanic stimulation of peripheral nerve might be limited in the muscles innervated by the nerve with tetanic stimulation (TS-muscle). For examples, tetanic stimulation of left tibial nerve was considered to augment only the muscles innervated by left tibial nerve, including left abductor hallucis (AH) muscle, but not other muscles, which are not innervated by left tibial nerve. However, we have unexpectedly found out that tetanic stimulation of peripheral nerve at one site also augmented MEP amplitudes from other muscles, which are not innervated by the nerve with tetanic stimulation (non-TS muscles). To our best knowledge, this is the first report to show that tetanic stimulation of peripheral nerve at one site can augment MEP amplitudes from not only TS muscle, but also non-TS muscles. The present study was therefore conducted to investigate whether tetanic stimulation of left tibial nerve can augment MEP amplitude from the non-TS muscles including bilateral abductor pollicis brevis (APB), tibialis anterior (TA), and soleus (S) muscles and right AH muscle.

METHODS

After Institutional approval at Nara Medical University, Nara, Japan, written informed consent was obtained from each patient. Thirty patients undergoing elective spine and spinal cord surgery at Nara Medical University, Nara, Japan were enrolled in the study. Patients ranged in age from 17 to 85 years (mean 58 years). There were 15 males and 15 females. Disease in these patients included cervical spinal stenosis (n=6), cervical spinal tumor (n=4), lumbar spinal stenosis (n=13), lumbar spinal tumor (n=4) and others (n=3). Patients with preoperative motor dysfunction, seizures, implanted atrial or ventricular pacemakers, and other implanted neural stimulators or pumps were precluded from the study. Patients with moderate to severe sensory deficits were also precluded from the study, while patients with mild sensory deficits including numbness and intermittent claudication were included in the study. Anesthesia was standardized in all patients. No premedication was given before anesthesia. Anesthesia was induced with 2-4 mcg/kg of fentanyl, 0.1-0.15 mg/kg of vecuronium and propofol. Target-controlled infusion was used for propofol administration at a target plasma concentration of 4-6mcg/ml. Anesthesia was maintained using a regimen of propofol and fentanyl with neuromuscular blockade. Propofol was maintained at a target plasma concentration of

3-5 mcg/ml. After the trachea was intubated, the lungs were ventilated mechanically to maintain the partial pressure of end tidal carbon dioxide between 30 and 40 mmHg. A mixture of air and oxygen at a fractional inspired concentration of 40-50% was administered. Fentanyl for pain relief was administered as required to mitigate heart rate and blood pressure increase. The rectal temperature was maintained between 35.5 and 37.0 degrees C. The level of neuromuscular blockade was assessed by M-response from the abductor pollicis brevis (APB) muscle in response to electrical stimulation of the median nerve at 50 mA. Twitch height of M-response was maintained at a level of 2-5 mV by a continuous administration of vecuronium at 0.04-0.06 mg/kg/h.

Techniques for c-MEP and p-MEP recording

c-MEP

Multipulse transcranial electric stimulation was performed using a multipulse stimulator (D-185; Digitimer, Welwyn Garden City, United Kingdom). A train-of-five pulses stimulation was delivered at 2 msec interstimulus intervals (500Hz). The stimulating electrodes consisted of a pair of 14.5mm silver-plated disk electrodes at C3 (cathode) and C4 (anode) (international 10-20 System) affixed with conductive paste. The stimulus intensity of transcranial stimulation was determined at the beginning of MEP

recording as supramaximal (approximately 500V). The compound muscle action potentials were bilaterally recorded from the skin over the APB, abductor hallucis (AH), tibialis anterior (TA), and soleus (S) muscles. A ground electrode was placed on the left or right arm proximal to the elbow. Evoked myographic responses were amplified with a 0.3- to 3-kHz bandpass filter. An intraoperative MEP measurement system (Neuropack MEB-2208; Nihon Koden, Tokyo, Japan) was used for MEP monitoring.

p-MEP

Tetanic stimulation (50Hz, 50mA of stimulus intensity) with a duration of 5 sec was applied to the left tibial nerve, which innervates the left AH muscle, at the ankle 1 sec prior to transcranial electric stimulation. Transcranial electric stimulation was automatically triggered after the application of tetanic stimulation. Transcranial electrical stimulation was performed in a same manner mentioned in c-MEP recording. The compound muscle action potentials were recorded from the same muscles as c-MEP recording.

Study protocol

Assessments of c-MEPs and p-MEPs were performed before any surgical interventions

that might have resulted in impaired spinal cord functioning. First, control c-MEPs were recorded. Then p-MEPs were recorded. In our preliminary study, we determined that 2-min interval after p-MEP recording did not affect subsequent MEP responses, so that an interval of p-MEP recordings was set at more than 2 min. Peak-to-peak amplitude was determined from the average of two individual responses. When average MEP amplitude is less than 30 mcV, MEP response was defined as “no response”. Since the left tibial nerve at the ankle mainly innervates left AH muscle, but not other muscles used in this study, we defined left AH muscle as “TS muscle” and bilateral APB, TA, and S muscles and right AH muscles as “non-TS muscles”.

Statistical Analysis

Sample size in the current study was determined based on the data in our previous and preliminary studies. We assumed that it was clinically important if MEP amplitude was augmented by 75% after the application of tetanic stimulation of peripheral nerve. Based on the formula for normal theory and assuming a type I error of 0.05 and a power of 0.8, 30 patients were required for each comparison. Comparisons of amplitudes of c-MEP and p-MEP at each recording site were performed using Wilcoxon signed rank test. P values less than 0.05 were considered significant.

RESULTS

There were no complaints of seizures or skin burns postoperatively. Success rates of MEP recording from all muscles were shown in table 1. MEP amplitudes from all recording sites could be obtained reliably in 24 of 30 patients (80%) by c-MEP, and 29 of 30 patients (97%) by p-MEP. The patients without reliable MEP responses by p-MEP also had no reliable responses by c-MEP.

Comparisons of amplitudes of c-MEP and p-MEP were shown in a box plot (figure 2). MEP amplitude from the left AH muscle (TS muscle) was significantly increased by the application of tetanic stimulation to the left tibial nerve compared with those of c-MEP. Similarly, MEP amplitudes from the bilateral APB, right AH, right TA and bilateral S muscles (non-TS muscles) were significantly increased by the application of tetanic stimulation to the left tibial nerve compared with those of c-MEP. Only MEP amplitude from the left TA muscle (non TS muscle) was not significantly augmented by p-MEP, although MEP amplitude tended to increase with a p value of 0.0532. The representative c-MEP and p-MEP recordings of the same patient were shown in figure 3. Note that MEP amplitudes from the bilateral APB, AH, TA, and S muscles were increased after

the application of tetanic stimulation to the left tibial nerve.

DISCUSSION

The results in the present study show that the application of tetanic stimulation to the left tibial nerve at the ankle prior to transcranial stimulation significantly augmented the amplitudes of MEPs recorded from the bilateral APB, AH and S muscles and right TA in patients under propofol and fentanyl anesthesia with partial neuromuscular blockade. Since left tibial nerve at the ankle mainly innervate only the left AH muscle (TS-muscle), but not other muscles (non-TS muscles), the results indicated that myogenic MEPs from the non-TS muscles, as well as TS-muscle, were significantly augmented by using p-MEP.

Tetanic stimulation of peripheral nerve has been widely used as a method to potentiate muscle response during neuromuscular blockade (15,16). During the administration of nondepolarizing neuromuscular blocking agent, tetanic nerve stimulation at 50-100 Hz is followed by a posttetanic increase in twich tension (i.e., posttetanic fasciculation of transmission). The posttetanic count after TS at 50 Hz for 5 sec has therefore become an accepted technique to quantify the degree of intense neuromuscular blockade under the conditions in which response to single-twitch stimulation are no longer obtained (17-19).

We originally hypothesized that tetanic stimulation of peripheral nerve prior to transcranial stimulation may enhance the amplitude of MEPs from the muscles (TS-muscle), which are innervated by the nerve with tetanic stimulation, during the administration of neuromuscular blockade under general anesthesia.

Kakimoto et al. (14) investigated whether tetanic stimulation of peripheral nerve before transcranial electrical stimulation can enlarge amplitudes of MEPs in patients under propofol and fentanyl anesthesia with neuromuscular blockade. They evaluated MEP augmentations by tetanic stimulation at different levels of duration, posttetanic interval, and stimulus intensity. The results indicated that the application of tetanic stimulation to the tibial nerve at a stimulus intensity of 25-50 mA with a duration of 3-5 sec and a posttetanic interval of 1-5 sec significantly augmented the amplitudes of MEPs from the AH muscle at the ipsilateral side to tetanic stimulation. In the present study, we therefore used tetanic stimulation at a stimulus intensity of 50 mA with a duration of 5 sec and a posttetanic interval of 1 sec in order to obtain maximal augmentation of MEPs.

In the report by Kakimoto et al. (14), the application of tetanic stimulation only

augmented the MEP amplitudes at the ipsilateral side to tetanic stimulation, but not at the contralateral side. However, after gaining the experience regarding p-MEP recording, we found out that MEP amplitudes at the contralateral side to tetanic stimulation were also augmented in addition to the ipsilateral side in some cases. In the current study, we therefore hypothesized that the application of tetanic stimulation of peripheral nerve prior to transcranial stimulation might augment the amplitudes of MEPs recorded from the non-TS muscles as well as TS muscle. As a result, tetanic stimulation of peripheral nerve significantly enhanced MEP amplitudes from not only the TS muscle, but also non-TS muscles.

The results obtained in this study are contradictory to those by Kakimoto et al. (14), in which tetanic stimulation of tibial nerve at the ankle augmented MEPs from the TS-muscle, but not from non-TS muscles. The reasons of these contradictory results are unknown. However, possible explanation is as follows. In the study by Kakimoto et al. (14), patients with preoperative moderate to severe sensory deficits were also enrolled. In contrast, in this study, in order to exclude any influences of preoperative neurological conditions on MEP augmentations, the patients with preoperative motor dysfunction and moderate to severe sensory deficits were precluded. Patient's profile might therefore

have affected the results. In fact, although we did not show the data in this study, our preliminary results showed that existence of preoperative sensory and motor deficits might attenuate the MEP augmentations by the application of tetanic stimulation.

Of interest is that tetanic stimulation of peripheral nerve prior to transcranial stimulation augmented the MEPs from non-TS muscles, that is, the phenomenon which induced “remote augmentation of MEPs by peripheral stimulation”. To our best knowledge, this is the first report to show the remote augmentations of MEPs by tetanic stimulation of peripheral nerve. The mechanisms of remote augmentations of MEPs are not clear. However, central mechanisms at the levels of spine and brain may be involved in this remote augmentation. Peripheral stimulation has been reported to modulate corticomotoneuronal excitability (20-23). Kaelin-Lang et al. (21) demonstrated that ulnar nerve stimulation at the wrist for 2 h enhanced MEP amplitudes to transcranial magnetic stimulation from abductor digiti minimi muscles in humans, and this effect was blocked by the gamma-aminobutyric acid type A agonist lorazepam, suggesting that somatosensory stimulation elicited an increase in corticomotoneuronal excitability, probably at the level of cortex. Andersson et al. (23) demonstrated that a train of stimuli to the foot sole within the receptive field of the withdrawal reflex of the tibialis anterior

muscle prior to transcranial stimulation augmented MEP responses, indicating that the cortically elicited responses were spatially facilitated probably at the level of spine. However, further investigations would be required to clarify the mechanisms of MEP augmentations by peripheral nerve stimulation.

There are several limitations to merit comments in this study. First, in this study, only the patients without preoperative motor dysfunction and moderate to severe sensory deficits were enrolled. So it is unknown whether remote augmentations of MEPs by peripheral stimulation would be observed in patients with preoperative motor and/or moderate to severe sensory deficits. Second, this study was performed under propofol and fentanyl anesthesia with partial neuromuscular blockade. Although we believe that this is a standard anesthetic regime during the monitoring of MEPs, it is unknown whether remote augmentations of MEPs would be induced under the different anesthetic conditions. Third, in the present study, we used tetanic stimulation at a stimulus intensity of 50 mA with a duration of 5 sec and a posttetanic interval of 1 sec in order to obtain maximal augmentation of MEPs, based on the results in the previous study. However, these settings were optimal for augmentations of MEPs from the TS muscle. The optimal setting for augmentations of MEPs from the non-TS muscles might be

different. Finally, based on the data obtained in the current study, it is unclear whether p-MEPs can really reflect motor function as conventional MEPs do. Extensive studies to assess the usefulness of p-MEPs would be required.

In summary, we investigated whether tetanic stimulation of peripheral nerve prior to transcranial stimulation can augment myogenic MEPs from non-TS muscles as well as TS muscle in patients under propofol and fentanyl anesthesia with partial neuromuscular blockade. The results showed that the application of tetanic stimulation prior to transcranial stimulation induced augmentations of MEPs from not only the TS-muscle, but also non-TS muscles, indicating “the remote augmentations of MEPs by peripheral stimulation”. The relevance of this phenomenon in clinical situations remained undetermined. However, considering that MEP responses are very sensitive to anesthetic agents and neuromuscular blocking agents, the methods to augment MEP responses are still desirable. Since the application of peripheral nerve stimulation at one site enhanced MEP responses from most of muscles in upper and lower limbs, p-MEP may be applied as a method to augment MEP responses in cases, in which MEP responses are poor or absent. In addition, transcranial stimulation can induce patient’s movement, which may put patients at a risk of injury of spinal cord, neck, eye, tongue

and lip. Yamamoto et al. (24) demonstrated that MEP recording was feasible without any patient' movement under the deep level of neuromuscular blockade as long as p-MEP was used. Furthermore, the results in this study may provide a key for the techniques to augment MEP responses through the central facilitation. However, the data in clinical validity and usefulness of p-MEP are still limited. In order to use p-MEP as a routine monitor, further studies would be required.

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Figure legends

Figure 1

Technique to record post-tetanic motor evoked potential (p-MEP) and conventional MEP (c-MEP). For c-MEP recording, transcranial stimulation was performed by train-of-five pulses with an interstimulus interval of 2 ms to C3 and C4 (international 10-20 System) and the compound muscle action potentials were recorded. For p-MEP recording, tetanic stimulation of left tibial nerve with a duration of 5 sec and a stimulus intensity of 50 mA at 50 Hz was performed prior to transcranial stimulation with a posttetanic interval of 1 sec.

Figure 2

Comparisons of amplitudes of c-MEPs and p-MEPs from the bilateral abductor pollicis brevis (APB), abductor hallucis (AH), tibialis anterior (TA), and soleus (S) muscles. For p-MEP recording, tetanic stimulation of left tibial nerve at the ankle with a duration of 5 sec and a stimulus intensity of 50 mA at 50 Hz was performed prior to transcranial stimulation with a posttetanic interval of 1 sec. Since the left tibial nerve mainly innervate left AH muscle, but not other muscles, left AH muscle was defined as tetanic stimulated muscle. * $p < 0.05$ (c-MEP vs. p-MEP).

Figure 3

Representative c-MEP (a) and p-MEP (b) recordings in the same patient without preoperative motor and sensory deficits. For p-MEP recording, tetanic stimulation of left tibial nerve at the ankle with a duration of 5 sec and a stimulus intensity of 50 mA at 50 Hz was performed prior to transcranial stimulation with a posttetanic interval of 1 sec. Note that amplitudes of p-MEPs from the bilateral abductor pollicis brevis (APB), abductor hallucis (AH), tibialis anterior (TA), and soleus (S) muscles were augmented compared with those of c-MEPs.