Tetanic Stimulation of the Peripheral Nerve before Transcranial Electrical Stimulation Can Enlarge Amplitudes of Myogenic Motor Evoked Potentials during General Anesthesia with Neuromuscular Blockade

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Background: Neuromuscular blockade can suppress myogenic motor evoked potentials (MEPs). The authors hypothesized that tetanic stimulation (TS) of the peripheral nerve before transcranial stimulation may enhance myogenic MEPs during neuromuscular blockade. In the current study, the authors evaluated MEP augmentations by TS at different levels of duration, posttetanic interval, neuromuscular blockade, and stimulus intensity.

Methods: Thirty-two patients undergoing propofol–fentanyl–nitrous oxide anesthesia were examined. Train-of-five stimulation was delivered to C3–C4, and MEPs were recorded from the abductor hallucis muscle. In study 1, TS with a duration of 1, 3, or 5 s was delivered at 50 Hz to the tibial nerve 1, 3, or 5 s (interval) before transcranial stimulation, and the effects of TS on MEP amplitude were evaluated. In study 2, TS-induced MEP augmentations were evaluated at the neuromuscular blockade level (%T1) of 50% or 5%. In study 3, MEP augmentations by TS at stimulus intensities of 0, 5, 25, and 50 mA were evaluated.

Results: The application of TS significantly enlarged the amplitudes of MEPs at the combinations of duration (3, 5 s) and interval (1, 3, 5 s) compared with those without TS. TS-induced MEP augmentations were similarly observed at %T1 of both 50% and 5%. TS-induced MEP augmentations were observed at stimulus intensities of 25 and 50 mA.

Conclusions: The results indicate that TS of the peripheral nerve before transcranial stimulation can enlarge the amplitude of MEPs during general anesthesia with neuromuscular blockade. TS of the peripheral nerve can be intraoperatively applied as a method to augment myogenic MEP responses.

Materials and Methods

After institutional approval at Nara Medical University, Nara, Japan, written informed consent was obtained from all patients. The institutional review board at Nara Medical University, Nara, Japan, approved the research protocol. All patients were adults undergoing general anesthesia with neuromuscular blockade. The authors monitored the amplitudes of myogenic MEPs during general anesthesia with neuromuscular blockade. The current study was conducted to evaluate the TS-induced MEP augmentations during different levels of neuromuscular blockade and to evaluate the MEP augmentations by TS of peripheral nerve at different levels of stimulus intensity.
from each patient. Thirty-two patients undergoing elective spinal surgery were enrolled in the studies. Anesthesia was standardized in all patients. All patients were premedicated with 75 mg roxatidine orally 2 h preoperatively. Anesthesia was induced with 1–2 mg/kg propofol, 1–2 μg/kg fentanyl, and 0.1 mg/kg vecuronium and was maintained with 50% nitrous oxide in oxygen, 4–8 mg · kg⁻¹ · h⁻¹ propofol, and fentanyl (total doses of 0.3–0.5 mg). After the trachea was intubated, the lungs were ventilated mechanically to maintain the level of partial pressure of arterial carbon dioxide between 35 and 40 mmHg. The level of neuromuscular blockade was assessed by recording the twitch height (T1) of muscle response from the abductor pollicis brevis (APB) muscle in response to supramaximal electrical stimulation of the median nerve at the wrist. T1 of muscle response from the abductor hallucis (AH) muscle in response to supramaximal electrical stimulation of tibial nerve at lateral malleolus was also recorded. To elicit the muscle response, a square wave pulse of 0.2 ms in duration was administered through a pair of adhesive gel Ag/AgCl electrodes. The level of neuromuscular blockade was described as percentage of T1 of control value before induction of anesthesia (awake state) without neuromuscular blockade. %T1 of control from the APB muscle was controlled at 50% in study 1, 5% and 50% in study 2, and 5% in study 3 by titrating vecuronium infusion rate. Physiologic monitoring included electrocardiography, intraarterial pressure monitoring, oxygen saturation measurement by pulse oximetry, end-tidal carbon dioxide concentration monitoring, and rectal temperature monitoring.

**Study 1: MEP Augmentations by TS at Different Levels of Duration and Posttetanic Interval**

Ten patients were included in this study. Demographic variables are shown in table 1. Disease in these patients included cervical spondylosis (n = 5), ossification of the posterior spinal ligament (n = 2), and others (n = 3). For recording MEPs, transcranial electrical stimulation was performed by using a multipulse stimulator (D-185; Digitimer, Welwyn Garden City, United Kingdom). Stimulation was performed by train-of-five pulses with an inter stimulus interval of 2 ms. The outputs were delivered to the scalp by a single pair of 14.5-mm silver disk electrodes applied to C3 (cathode) and C4 (anode) (International 10-20 System). The stimulus intensity of transcranial stimulation was determined at the beginning of MEP monitoring and was set just supramaximal to each stimulus. The MEPs were recorded from the skin over the AH muscle at the side ipsilateral to TS of the tibial nerve. 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 and were displayed on oscilloscopes (MEB-5508; Nihon Kohden, Tokyo, Japan).

Tetanic stimulation (50 Hz, 50 mA) with a duration of 1, 3, or 5 s was delivered to the tibial nerve at the ankle 1, 3, or 5 s (posttetanic interval) before transcranial electrical stimulation. The same electrodes as used for stimulation to assess the level of neuromuscular blockade were used for TS. Transcranial stimulation was automatically triggered after performing TS. MEPs with TS at each combination of duration (1, 3, or 5 s) and posttetanic interval (1, 3, or 5 s) were then recorded and compared with those without TS. The order of the combinations of duration and posttetanic interval was randomized to eliminate time-course bias. Three minutes were allowed for interrecording intervals. These recordings were performed at least 20 min after the skin incision was made but before any surgical interventions that might have resulted in impaired spinal cord functioning. Peak-to-peak amplitude was determined from the average of two individual responses, and the amplitudes of MEPs with TS were converted to percentages of the MEP amplitudes without TS.

**Study 2: TS-induced MEP Augmentations at Different Levels of Neuromuscular Blockade**

Twelve patients were examined in study 2. Demographic data are shown in table 1. Disease in the patients included spinal tumor (n = 5), cervical disc herniation (n = 3), and others (n = 4). To evaluate TS-induced MEP augmentations at the different levels of neuromuscular blockade, T1 from the APB muscle was controlled at approximately 5% or 50% of control in random order. For MEP recording, transcranial stimulation was performed as mentioned in study 1. Myogenic MEPs were recorded from the AH muscles at both sides. TS (50 Hz, 50 mA) with a duration of 5 s was delivered to the tibial nerve 1 s before transcranial electrical stimulation for recording the posttetanic MEPs. The MEPs with and without TS were recorded from the AH muscles at the sides ipsilateral and contralateral to TS at each level of neuromuscular blockade (%T1 of 5% and 50%). Peak-to-peak amplitude was determined from the average of two individual responses, and MEP amplitudes with and without TS were compared.

**Study 3: MEP Augmentations by TS at Different Levels of Stimulus Intensity**

Ten patients were examined in study 3. Demographic data are shown in table 1. Disease in the patients in-
cluded cervical disc herniation (n = 2), cervical spondylosis (n = 2), spondylolisthesis (n = 2), and others (n = 4). The level of neuromuscular blockade was controlled at %T1 of 5% of control values as mentioned above. To evaluate TS-induced MEP augmentations at the different levels of stimulus intensity of peripheral nerve stimulation, the stimulus intensity was set at 0, 5, 25, and 50 mA in random order. These levels of stimulus intensity were determined by the preliminary study in the 10 healthy volunteers, which indicated that 5 mA is the level of subthreshold (no muscle response), 25 mA is the level between the threshold and supramaximum (muscle response, but not maximum), and 50 mA is the level of supramaximum (maximal muscle response).

Myogenic MEPs were recorded from the AH muscles as mentioned above. TS (50 Hz) with a duration of 5 s was delivered to the tibial nerve 1 s before transcranial electrical stimulation for recording the posttetanic MEPs. The MEPs with and without TS were recorded from the AH muscles at the side ipsilateral to TS at each level of stimulus intensity (5, 25, or 50 mA). Peak-to-peak amplitude was determined from the average of two individual responses, and MEP amplitudes with and without TS were compared.

Statistical Analysis
Sample sizes in the current study were determined based on the data in our previous and preliminary studies. We assumed that it was clinically important if MEP amplitude was augmented by 100% after the application of tetanic stimulation of peripheral nerve. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.8, 10–12 patients were required for each comparison. Demographic variables and the level of neuromuscular blockade are shown as mean ± SD. The levels of neuromuscular blockade were analyzed using a paired t test. MEP data are expressed as median with interquartile range in parentheses. Differences in MEP amplitudes and percentage MEP amplitudes of control were analyzed using the Wilcoxon signed rank test. P values less than 0.05 were considered significant.

Results
Effects of Duration and Posttetanic Interval (Study 1)
Control myogenic MEPs could be recorded without TS in all patients. Percentage changes in MEP amplitudes after the application of TS of the peripheral nerves are shown in figure 1. TS of the tibial nerve significantly enlarged MEP amplitudes from the AH muscle to 156–256% (median) at the combinations of 3 and 5 s of duration and 1, 3, and 5 s of posttetanic interval (P < 0.05). Of these settings, we selected a combination of 5 s of duration and 1 s of posttetanic interval for further assessments in studies 2 and 3.

Effect of Neuromuscular Blockade Levels on TS-induced MEP Augmentation (Study 2)
At %T1 of 50%, the amplitudes of muscle response from the APB and AH muscles were 50 ± 9 and 49 ± 31%, respectively, and there were no significant differences between these values. At %T1 of 5%, the amplitudes of muscle response from the APB and AH muscles were 7 ± 2 and 10 ± 10%, respectively, and there were no significant differences between these values. At %T1 of 50%, MEPs could be recorded in all patients regardless of the application of TS. At %T1 of 5%, MEPs from the AH muscles could be recorded in 10 of 12 patients (83%) without TS. However, after TS was applied, MEPs could be recorded in all patients.

Motor evoked potential amplitudes with and without TS at %T1 of 50% and 5% are shown in figure 2. At %T1 of both 50% and 5%, MEP amplitudes at the side ipsilateral to TS were significantly higher compared with those without TS (P < 0.05). In contrast, MEP amplitudes with and without TS were similar at the side contralateral to TS. The representative MEP recordings without and with TS at %T1 of 50% and 5% are shown in figure 3.

Effects of Stimulus Intensity on TS-induced MEP Augmentation (Study 3)
In all patients, MEPs could be recorded regardless of stimulus intensity of TS. MEP amplitudes from the AH muscles with TS at each stimulus intensity and without TS are shown in figure 4. MEP amplitudes with TS at 25 and 50 mA were significantly higher compared with those without TS (P < 0.05). The enlargement rates of MEP amplitudes by TS at 25 and 50 mA were 265 and 904%, respectively. The representative MEP recordings with TS at stimulus intensities of 0, 5, 25, and 50 mA are shown in figure 5.
Discussion

The results in the current study showed that TS of the peripheral nerve before transcranial electrical stimulation significantly enlarged myogenic MEP amplitude during partial neuromuscular blockade with propofol–fentanyl–nitrous oxide anesthesia. In cases of monitoring of the spinal cord by recording MEPs from the AH muscles, TS of the tibial nerve at a stimulus intensity of 25–50 mA with a duration of 3–5 s and a posttetanic interval of 1–5 s produced MEP augmentations. Posttetanic MEP augmentations were similarly observed at %T1 of both 50% and 5% (P < 0.05). NS = not significant; %T1 = percentage amplitude of muscle response of control values before the induction of anesthesia without neuromuscular blockade.

Induction of multipulse stimulation allowed us to monitor myogenic MEPs during general anesthesia, although most anesthetics and neuromuscular blockade still affect the MEPs to multipulse stimulation.4–11 For example, our previous studies have demonstrated that propofol, an anesthetic commonly used during the monitoring of MEPs, suppressed MEP responses in a dose-dependent manner, although the application of multipulse stimulation can augment MEP amplitudes.10 To monitor myo-

Fig. 2. Box plot of changes in motor evoked potential amplitude from the abductor hallucis muscle with and without tetanic stimulation (TS) at %T1 of 50% (A) and 5% (B). Motor evoked potentials were recorded at the ipsilateral and contralateral sides to TS. TS (50 Hz, 50 mA) with a duration of 5 s was applied on the tibial nerve 1 s before transcranial stimulation. At the side ipsilateral to TS, motor evoked potential amplitudes were significantly enlarged after the application of TS at %T1 of both 50% and 5% (P < 0.05). NS = not significant; %T1 = percentage amplitude of muscle response of control values before induction of anesthesia without neuromuscular blockade.

Fig. 3. Representative motor evoked potentials from the abductor hallucis muscle without and with tetanic stimulation (TS) at %T1 of 50% and 5%. TS (50 Hz, 50 mA) with a duration of 5 s was applied on the tibial nerve 1 s before transcranial stimulation. Motor evoked potential amplitudes were increased after the application of TS at %T1 of both 50% and 5%. %T1 = percentage amplitude of muscle response of control values before induction of anesthesia without neuromuscular blockade.

Fig. 4. Box plot of changes in motor evoked potential amplitude from the abductor hallucis muscle after tetanic stimulation at stimulus intensities of 0, 5, 25, and 50 mA at %T1 of 5%. Motor evoked potentials were recorded at the ipsilateral side to tetanic stimulation. Tetanic stimulation (50 Hz, 50 mA) with a duration of 5 s was applied on the tibial nerve 1 s before transcranial stimulation. Motor evoked potential amplitudes were significantly higher with tetanic stimulation at stimulus intensities of 25 and 50 mA compared with control values (0 mA). * P < 0.05 versus control (0 mA).

Fig. 5. Representative motor evoked potentials from the abductor hallucis muscle with tetanic stimulation at stimulus intensities of 0, 5, 25, and 50 mA at %T1 of 5%. Tetanic stimulation (50 Hz, 50 mA) with a duration of 5 s was applied on the tibial nerve 1 s before transcranial stimulation. The motor evoked potential amplitude was enlarged after the application of tetanic stimulation at stimulus intensities of 25 and 50 mA.
genic MEPs, the levels of anesthesia must therefore be controlled within the narrow ranges in which patients were asleep but not deeply anesthetized, and signal/noise ratios of MEP responses are relatively high for the possibility of MEP monitoring. In addition, the level of neuromuscular blockade has been controlled to a level around 50% of baseline T1 as a concept of partial neuromuscular blockade. As a result, we frequently encounter the situations in which the patients can move in response to transcranial stimulation. However, during surgery with a risk of spinal cord injury, any patient movements can be harmful, so their avoidance may be an important anesthetic challenge. One of the strategies for this purpose is the development of MEP and anesthetic techniques in which no movements are induced in response to transcranial stimulation. This can improve the quality of treatment for patients during the monitoring of myogenic MEPs. The results of the current study clearly indicate that the application of TS of peripheral nerve before transcranial stimulation can enlarge myogenic MEP amplitudes during general anesthesia with neuromuscular blockade, which allows us to use neuromuscular blockade at the deeper levels (i.e., %T1 of 5%) compared with those for conventional MEPs without TS. This is the first report to demonstrate posttetanic augmentation of MEPs as a possible technique for MEP augmentation during general anesthesia with neuromuscular blockade.

The mechanisms by which TS of the peripheral nerve before transcranial electrical stimulation augmented MEP amplitudes are unclear. However, possible explanations are as follows. First, potentiation of neuromuscular transmission at the neuromuscular junctions can be a primary mechanism for posttetanic MEP augmentation. Tetanic or high-frequency rates of stimulation at 50 Hz or more have been widely recognized to induce augmentation of subsequent muscle response to peripheral nerve stimulation, and this phenomenon is known as posttetanic potentiation. Mobilization and enhanced synthesis of acetylcholine can continue during and after cessation of TS so that after the end of TS, there is an increase in fractional release of acetylcholine from the nerve ending. In general, TS at 50 Hz for 5 s is used in clinical situations during general anesthesia. Theoretically, it is possible that TS of the peripheral nerve at 50 Hz could augment the subsequent myogenic MEP to transcranial stimulation. Second, peripheral nerve stimulation may modulate corticomotoneuronal excitability. Kaclin-Lang et al. demonstrated that ulnar nerve stimulation at the wrist for 2 h enhanced MEP amplitudes to transcranial magnetic stimulation from the abductor digitii minimi muscles in humans, and this effect was blocked by the γ-aminobutyric acid type A agonist lorazepam, suggesting that somatosensory stimulation elicited an increase in corticomotoneuronal excitability, probably at the level of cortex. Hamdy et al. also indicated that electrical stimulation of pharyngeal sensory nerves for at least 30 min increased MEP amplitudes recorded from pharyngeal muscles in humans. Although the stimulation paradigms are different between these studies and our study, we cannot deny the possibility that TS of peripheral nerve might increase motor excitability at the brain or spinal cord, resulting in an augmentation of MEP amplitudes.

The size of MEPs elicited by transcranial magnetic stimulation can increase soon after a nonexhaustive voluntary contraction of the target muscle in the awake state, and this phenomenon, called postexercise facilitation, may mimic posttetanic augmentation of MEPs observed in this study, although the main mechanism of postexercise facilitation has been considered to be due to changes in motor cortex excitability. Balbi et al. investigated the effects of duration (5, 15, and 30 s) and intensity (10, 25, and 50% of maximal voluntary contraction) of voluntary muscle contraction and the interval between muscle contraction and transcranial magnetic stimulation (1–60 s) on MEP augmentation to transcranial magnetic stimulation in awake, healthy subjects. As a result, the maximal MEP facilitation by voluntary muscle contraction was observed at 1-s postexercise recordings, using a duration of 5 s and the strongest intensity. These conditions are similar to those obtained in the current study (1- to 5-s posttetanic interval, 3-5 s in duration, and maximal intensity), although these phenomena may be different in various ways.

Because this is the first report to demonstrate posttetanic MEPs, there may be a number of ways to improve the method and a number of limitations to clarify in the current study. First, as posttetanic intervals, we only assessed 1, 3, and 5 s because of the limitations of the equipment. A shorter posttetanic interval might have produced better MEP augmentations. Further study would be required to clarify the best posttetanic interval. Second, we also used 1, 3, and 5 s as durations of TS. Similarly, a longer duration might have produced better MEP augmentation. However, a longer duration might not be practical because of the longer waiting time and might induce muscle fatigue, resulting in the depression of MEP responses. Third, the efficacy of repetitive use of posttetanic MEP is not clear. Repetitive application of TS might induce fatigue of muscle responses, resulting in less MEP augmentation. Further study would be required to assess the efficacy and limitations in cases in which posttetanic MEPs are repetitively used. Fourth, the target muscles for MEP recording might be limited by the concept of posttetanic MEPs because TS should be performed at the nerves that innervate the target muscles. In the current study, we selected the tibial nerve at the lateral malleolus for MEPs from the AH muscles because electrical stimulation can be applied easily. Although routine MEP monitoring is feasible with these muscles, in situations in which MEP monitoring from other muscles is
required, techniques to stimulate nerves that innervate the target muscles should be developed. Fifth, we used %T1 from the APB muscle for monitoring the level of neuromuscular blockade because the MEP and %T1 from the APB muscle (as muscles in the upper extremities) are clinically used as controls for the monitoring of spinal cord function at our institution. However, for assessments of MEPs from the AH muscle, %T1 from the AH muscle might be more accurate. In the current study, because there were no significant differences between the values of %T1 from the APB and AH muscles, we believe that its influence was small. Finally, based on the data obtained in the current study, it is unclear whether posttetanic MEPs can really reflect motor function as conventional MEPs do. Extensive studies to assess the usefulness of posttetanic MEPs would be required.

In summary, we investigated the effects of TS of the peripheral nerve before transcranial electrical stimulation on MEP amplitudes during propofol–fentanyl–nitrous oxide anesthesia with neuromuscular blockade. The results indicated that TS of the peripheral nerve induced an augmentation of MEP amplitudes at both relatively deep and moderate levels of neuromuscular blockade (%T1 of 5% and 50%). Because this is the first trial, the number of patients was small, and the MEP data had high variability, we cannot determine the optimal settings for posttetanic MEP augmentations. However, the data obtained in the current study suggest that TS with a duration of 3–5 s and a posttetanic interval of 1–5 s at a stimulus intensity of 50 mA can be applied for this purpose. Although its clinical usefulness is still under study, posttetanic augmentation of MEPs can be used in cases in which MEP responses are small or absent because of the suppression by anesthetic agents and neuromuscular blockade. Application of this technique may also allow us to use neuromuscular blockade to the level at which no movements of patients in response to transcranial stimulation are observed. Therefore, the application of posttetanic MEPs may improve the anesthetic status of patients during monitoring of MEPs. We hope that the data obtained by this study will provide key information for further improvement in intraoperative monitoring of myogenic MEPs, although there are a number of points to be clarified regarding the validity and usefulness of posttetanic MEPs.

References