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CLINICAL ARTICLE

Effects of intraoperative motor evoked potential amplification following tetanic stimulation of the pudendal nerve in pediatric craniotomy

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OBJECTIVE Monitoring the intraoperative motor evoked potentials (MEPs) in pediatric craniotomy is challenging because of its low detection rate, which makes it unreliable. Tetanic stimulation of the peripheral nerves of the extremities and pudendal nerves prior to transcranial electrical stimulation (TES) or direct cortical stimulation (DCS) amplifies the MEPs. The authors investigated the effects of MEP amplification following tetanic stimulation of the median and tibial nerve or the pudendal nerve in pediatric patients undergoing craniotomy.

METHODS This prospective observational study included 15 patients ≤ 15 years of age (mean age 8.9 ± 4.9 years) undergoing craniotomy. MEPs were obtained with TES (15 cases) or DCS (8 cases)—conventional MEP without tetanic stimulation (c-MEP) and MEP following tetanic stimulation of the unilateral median and tibial nerves (mt-MEP) or following tetanic stimulation of the pudendal nerve (p-MEP) were used. Compound muscle action potentials were elicited from the abductor pollicis brevis, gastrocnemius, tibialis anterior, and abductor hallucis longus muscles. The authors compared the identification rate and the rate of amplitude increase of each MEP.

RESULTS For both TES and DCS, the identification and amplitude increase rates were significantly higher in cases without preoperative hemiparesis for p-MEPs than in those for c-MEPs and mt-MEPs. In comparison to patients with preoperative hemiparesis, p-MEPs displayed a higher identification rate, with fewer false negatives in DCS cases.

CONCLUSIONS In pediatric craniotomy, the authors observed the amplification effect of MEPs with pudendal nerve tetanic stimulation and the amplification effect of DCS on MEPs without increasing false negatives. These findings suggested the likelihood of more reliable intraoperative MEP monitoring in pediatric cases.

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KEYWORDS amplification; intraoperative motor evoked potential; pediatric craniotomy; pudendal nerve; tetanic stimulation; surgical technique

The detection rate of intraoperative motor evoked potentials (MEPs) is poor in pediatric neurosurgery, and it declines with decreasing age. Motomura et al. reported intraoperative MEP detection rates of 60% and 10% for transcranial electrical stimulation (TES) and direct cortical stimulation (DCS), respectively, in children younger than 5 years.[1] This phenomenon may be attributed to the immature myelination of the pyramidal tracts, insufficient functional differentiation of the cortex, and the lack of defined function. Despite limited reports regarding detection of electrical stimulation in children upon increasing the stimulation intensity, the stimulation supposedly reaches not only the pyramidal tract area to be evaluated but also the brainstem and spinal cord.[2,3] More-

ABBREVIATIONS AH = abductor hallucis longus muscle; APB = abductor pollicis brevis muscle; BCR = bulbocavernosus reflex; c-MEP = conventional MEP without tetanic stimulation; CMAP = compound muscle action potential; DCS = direct cortical stimulation; GABA = γ-aminobutyric acid; $GABA_A$ = γ-aminobutyric acid-A; Gc = gastrocnemius muscle; MEP = motor evoked potential; MMT = manual muscle testing; mt-MEP = MEP following tetanic stimulation of the unilateral median and tibial nerves; p-MEP = MEP following tetanic stimulation of the pudendal nerve; TA = tibialis anterior muscle; TES = transcranial electrical stimulation.

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over, it poses a risk of neuronal damage, electrochemical damage, and burns due to electrical stimulation, thus warranting a safe and reliable monitoring method.[4–6] In our hospital we use tetanic stimulation of the unilateral median and tibial nerves (mt-MEP) to amplify MEPs in pediatric patients experiencing difficulty in inducing MEPs with conventional MEP without tetanic stimulation (c-MEP); however, it exerts limited effects. Recently, Takatani et al. reported that the use of tetanic stimulation of the pudendal nerve (p-MEP) in pediatric lumbosacral surgery can amplify MEPs, and the effect is greater at younger ages.[7] However, there are no studies examining the effect of MEP amplification by p-MEP in pediatric craniotomy. Thus, we aimed to evaluate if transcranial and direct MEP with pudendal nerve tetanus exerts an amplifying effect in pediatric craniotomy. In addition, we intended to compare and investigate mt-MEPs, c-MEPs, and p-MEPs with respect to their success and MEP amplification rates. To our knowledge, this is the first study examining whether MEPs can accurately identify paralysis following tetanic stimulation.

Methods

Standard Protocol Approval, Registration, and Patient Consent

This prospective observational study was approved by the medical ethics committee of the Nara Medical University. The study was registered in a public trial registry (https://www.umin.ac.jp/ctr/), and its registration number is UMIN000047998. Written consent was obtained from all patients and their parents.

Study Design and Patient Data

Between 2021 and 2022, we enrolled 15 pediatric patients ≤ 15 years of age who underwent craniotomy requiring intraoperative MEP monitoring at the Nara Medical University. MEPs in all 15 patients were elicited from the abductor pollicis brevis (APB), tibialis anterior (TA), gastrocnemius (Gc), and abductor hallucis longus (AH) muscles. These muscles were divided into four groups for TES and into two groups (APB, AH) for direct cortical stimulation (DCS), contralateral to anodal stimulation. We applied tetanic stimulation of the median and tibial nerves on one side; i.e., to the contralateral side of the anodal stimulation. The pudendal nerve was stimulated using electrodes placed for monitoring the bulbocavernosus reflex (BCR). We documented the success rate of recording each type of MEP in all 92 muscles (i.e., the TES groups in all 15 patients and DCS groups in 8 patients). Successful monitoring of MEPs was defined as the ability of TES to evoke compound muscle action potentials (CMAPs) with an amplitude of at least 30 μV. First, we compared the monitoring success for c-MEPs, mt-MEPs, and p-MEPs. Second, we compared the mean amplitudes of mt-MEPs and p-MEPs with those of c-MEPs for each of the four muscle groups. Third, the amplification rates were compared between p-MEPs and mt-MEPs. The amplification rates were compared in cases with c-MEPs > 30 μV. We assessed the amplification rates in a similar manner for all four muscle groups.

Anesthetic Protocol

Anesthesia was maintained with propofol (target effect-site concentration of 2–5 μg/mL) and remifentanil (0.25 μg/kg/min). No muscle relaxant agents were administered following anesthesia induction and the insertion of the endotracheal tube.

Motor Evoked Potentials

We induced transcranial MEPs after confirming that the effects of muscle relaxants had disappeared by the recovery of the train-of-four ratio to 0.8. Following craniotomy and before microscopic manipulation, we performed suprathreshold stimulation at a stimulus intensity up to 500 V, which was used as baseline. Stimulation was performed with train-of-five pulses at a stimulation interval of 2 msec between two electrodes located at C3 and C4, as the anode and cathode, respectively. For transcranial MEPs, the stimulating electrode was defined as the anode.

Following transcranial MEP induction, we placed a strip electrode on the brain surface toward the precentral gyrus to induce direct MEPs by DCS. Suprathreshold stimulation was performed at a stimulus intensity up to 30 mA before microscopic manipulation, and was used as the baseline. Stimulation was performed with train-of-five pulses with a stimulation interval of 2 msec. Strip electrodes and those placed on the Fpz were used as the anodes and cathodes, respectively.

The ground electrode was placed proximally at either the left or right elbow. Myoelectric signals were amplified with a 0.3- to 3-kHz bandpass filter and displayed on a monitor (Neuromaster MEE-2032G1; Nihon Kohden). MEP amplitude was defined as the range between the maximum positive and maximum negative peaks of the multiphasic CMAPs.

Tetanic Stimulation Before TES or DCS

In mt-MEPs, we stimulated the median nerve at the contralateral wrist and the tibial nerve at the ankle simultaneously, 1 second before TES or DCS to elicit MEPs (50 Hz; stimulation intensity 50 mA for median nerve, 30–40 mA for tibial nerve; duration 5 seconds). In the C3-anode/C4-cathode arrangement, tetanic stimulation was applied to the right median and tibial nerves. Similarly, it was applied to the left median and tibial nerves in the C4-anode/C3-cathode arrangement. Surface electrodes arranged for BCR were used to elicit p-MEPs (cathode in the proximal penis or clitoris, anode in the distal penis or labia majora). We applied tetanic stimulation to the pudendal nerve in the penis or clitoris 1 second before TES or DCS (50 Hz; stimulation intensity 20–40 mA; duration 5 seconds). TES or DCS was automatically triggered following tetanic stimulation and was performed using a method similar to the c-MEP measurements; CMAPs were recorded from the identical muscles used for c-MEP recordings.

Statistical Analyses

To compare the success rates of monitoring c-MEPs, mt-MEPs, and p-MEPs, we performed the McNemar test with Bonferroni adjustment. We performed the paired t-test or Wilcoxon signed-rank test for comparing the

TABLE 1. Characteristics of 15 consecutive pediatric patients undergoing craniotomy

Case No.	Age (yrs)	Sex	Diagnosis	Side	Lesion Location or Surgical Approach	Surgery	DCS	Motor Sxs	
								Preop	Postop
1	3	F	Brain tumor	Rt	Parietal lobe	Removal	–	–	–
2	14.5	M	MMD	Rt	Frontal & temporal lobe	Revasc	–	–	–
3	13.3	F	CM	NA	Posterior fossa	FMD	–	Hemiparesis (MMT 3)	Improved (MMT 5)
4	13.3	F	MMD	Rt	Frontal & temporal lobe	Revasc	–	–	–
5	4.1	M	Refractory focal epilepsy	Rt	Total hemisphere/vertical approach	Hemispherotomy	+	Hemiparesis (MMT 2)	Not deteriorated
6	7.3	F	MMD	Rt	Frontal & temporal lobe	Revasc	–	–	–
7	5.3	F	Brain tumor	Rt	Temporal lobe	Removal	+	–	–
8	3.2	F	Brain tumor	Rt	BG/FT approach	Removal	+	Hemiparesis (MMT 4)	Not deteriorated
9	14	M	Refractory gen epilepsy	Rt	Interhemispheric approach	Callosotomy	+	–	Transient motor weakness
10	15	F	Refractory gen epilepsy	Rt	Interhemispheric approach	Callosotomy	+	Hemiparesis (MMT 3)	Not deteriorated
11	11.2	F	CM	NA	Posterior fossa	FMD	–	–	–
12	12.7	M	Brain tumor	Rt	Pineal body/occipital transtentorial approach	Removal	–	–	–
13	1.4	F	Refractory gen epilepsy	Rt	Interhemispheric approach	Callosotomy	+	–	–
14	8.1	M	Brain tumor	Lt	BG/FT approach	Removal	+	–	Transient motor weakness
15	6.6	M	Brain tumor	Rt	Temporal lobe	Removal	+	–	–

BG = basal ganglia; CM = Chiari malformation; FMD = foramen magnum decompression; FT = frontotemporal; gen = generalized; MMD = moyamoya disease; NA = not applicable; revasc = revascularization; Sxs = symptoms; + = positive; – = negative.

mean amplitude of c-MEPs with those of mt-MEPs and p-MEPs, and the ratio of the mean amplitude of p-MEPs or mt-MEPs to the mean amplitude of c-MEPs. The Friedman test was conducted to compare the mean amplitudes of c-MEPs, mt-MEPs, and p-MEPs in DCS; multiple comparisons were performed using the Bonferroni method. We conducted Fisher's exact test to compare the MEP identification rates between hemiparesis and nonhemiparesis cases. All statistical analyses were performed using EZR version 1.55 software (Saitama Medical Centre, Jichi Medical University), a graphical user interface for R (R Foundation for Statistical Computing).[8] The significance value was set at $p < 0.05$.

Results

Patient Characteristics and Intraoperative Findings

We evaluated 15 pediatric patients undergoing craniotomy; the cohort included 6 boys and 9 girls, with a mean age of 8.9 ± 4.9 years (Table 1). The diseases comprised brain tumors, refractory epilepsy, moyamoya disease, and Chiari malformation in 6, 4, 3, and 2 cases, respectively. Tumor resection, corpus callosotomy, revascularization, foramen magnum decompression, and hemispherotomy was performed in 6, 3, 3, 2, and 1 case, respectively. We observed preoperative hemiparesis to manual muscle testing (MMT), grade ≤ 4 in 4 patients; the causes were cortical dysplasia, the lesion being in the basal ganglia, and symptoms of Chiari malformation in 2, 1, and 1 patient, respectively. One of these patients recovered postoperatively. Two other patients exhibited transient postoperative hemiparesis up to MMT grade 4, which improved to the similar level as preoperative within 1 week. Transcranial MEP monitoring was performed contralaterally and bilaterally in 7 and 8 patients, respectively. Direct MEP monitoring was performed in 8 patients. There were no complications related to intraoperative monitoring, burns, or skin symptoms due to electrode placement on the pubic area during the intraoperative, postoperative, or follow-up periods.

Success Rates of MEP Monitoring

The success rates of c-MEP, mt-MEP, and p-MEP monitoring of 80 muscles without preoperative paralysis (4 or 8 muscles each in 15 patients) with amplitudes > 50 μV were 37.5%, 53.8%, and 63.8%, respectively. The McNemar analysis demonstrated that all two-group comparisons revealed three types of statistically significant differences between the MEPs ($p < 0.01$ for c-MEPs vs mt-MEPs and c-MEPs vs p-MEPs; $p < 0.05$ for mt-MEPs vs p-MEPs) (Fig. 1).

Amplitudes of MEPs in Each Muscle Group Following Tetanic Stimulation

The mean amplitudes of c-MEPs, mt-MEPs, and p-MEPs from all 80 muscles without preoperative paralysis were 117.9 ± 259.9 μV, 185.7 ± 357.4 μV, and 372.9 ± 757.3 μV, respectively. The Wilcoxon signed-rank test revealed that each MEP pair displayed statistically significant differences ($p < 0.01$, all-muscle group). c-MEPs and mt-MEPs demonstrated statistically significant differences

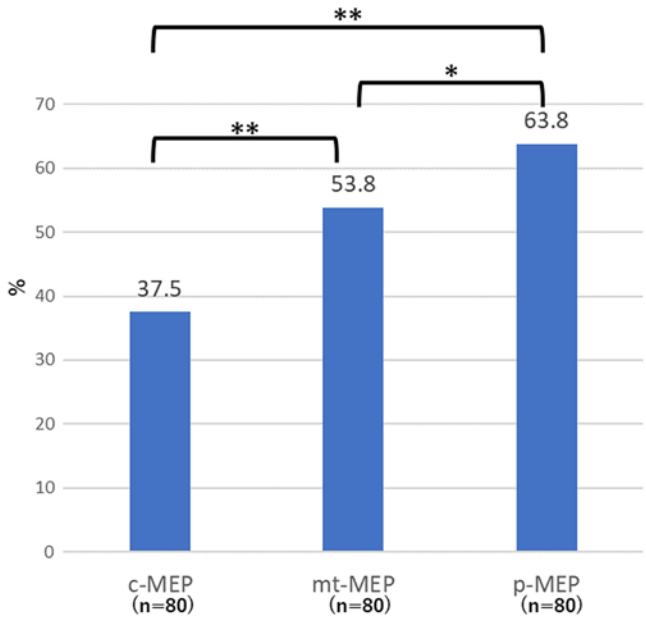

FIG. 1. Bar graph showing the respective MEP success rates in c-MEPs, mt-MEPs, and p-MEPs. *p < 0.05, **p < 0.01. Figure is available in color online only.

in the mean amplitudes observed in APB, Gc, and AH (Fig. 2). In contrast, we observed statistically significant differences in the mean amplitudes in all four muscles for c-MEPs and p-MEPs (Fig. 2).

Increased Ratios

Of the 15 patients, APB, TA, Gc, and AH c-MEPs were able to elicit amplitudes > 30 μV in 12, 9, 7, and 12 muscles, respectively. Increases in the ratios of the mean amplitudes of mt-MEPs and p-MEPs to that of c-MEPs in each of the four muscle groups are depicted in Fig. 3. The mean increase in the ratio of p-MEPs to c-MEPs for the all-muscles group was significantly greater than the ratio of c-MEPs to mt-MEPs (3.54 ± 3.36 vs 1.87 ± 2.30, $p < 0.01$). For each muscle group, the increase in the ratio of p-MEP to c-MEP amplitudes in APB (3.54 ± 3.21 vs 1.66 ± 1.07, $p < 0.01$); TA (2.92 ± 3.03 vs 1.43 ± 0.69, $p < 0.05$); and AH (4.85 ± 4.09 vs 2.72 ± 3.99, $p < 0.05$) was significantly greater than that of mt-MEP to c-MEP amplitudes (Fig. 3).

Success Rates and Amplitude Amplification Rates in Direct MEP Measurements

We examined 10 muscles from 5 patients without

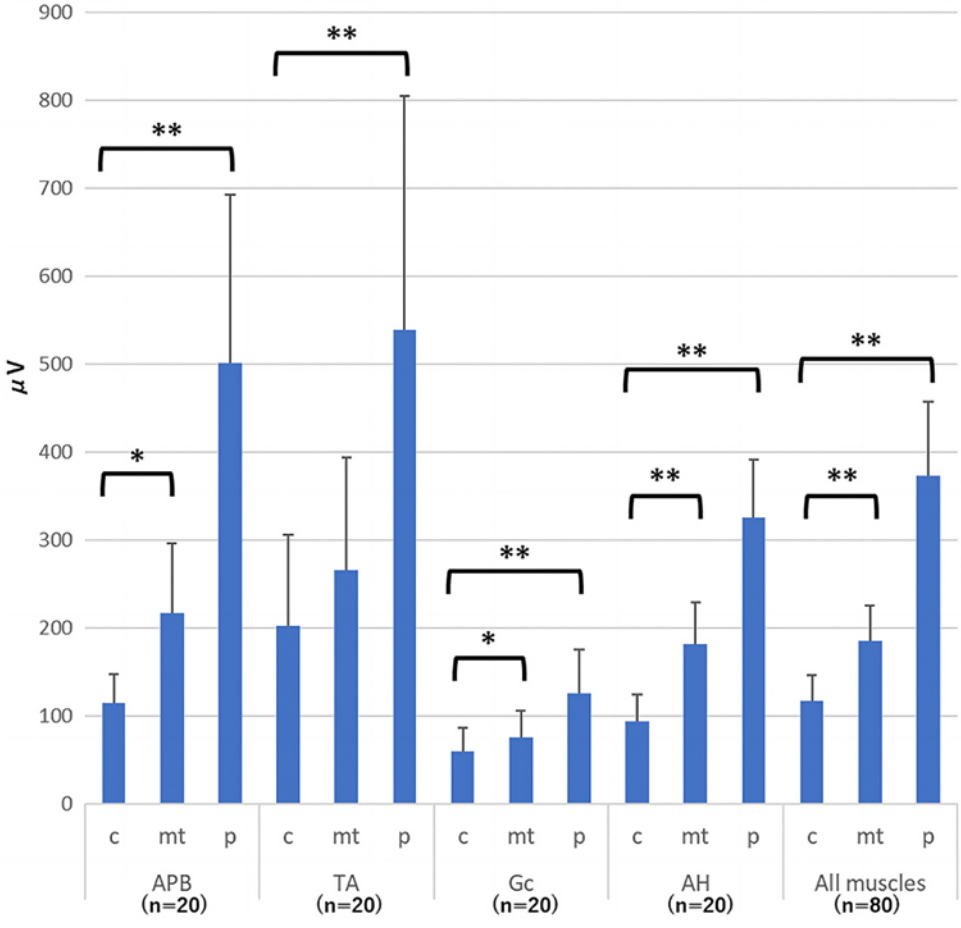

FIG. 2. A comparison of the mean amplitudes between c-MEPs (c), mt-MEPs (mt), and p-MEPs (p) in each muscle group. *p < 0.05, **p < 0.01. Figure is available in color online only.

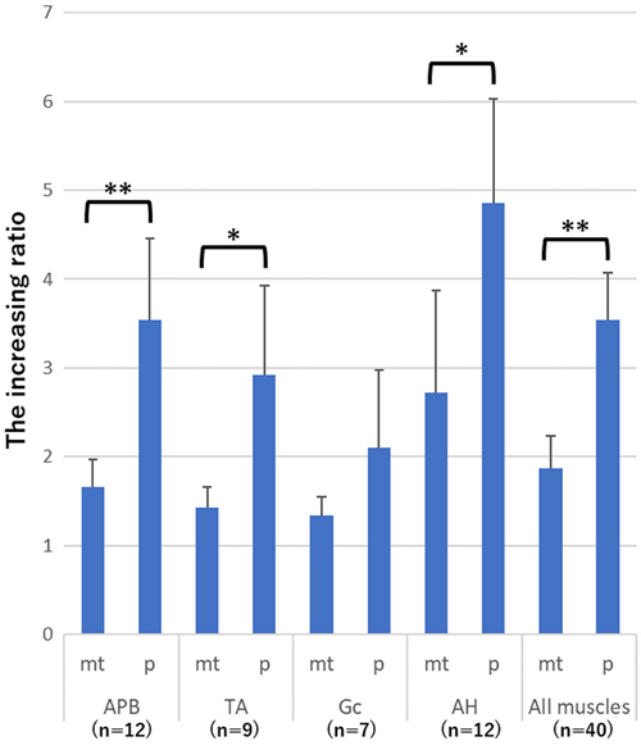

FIG. 3. A comparison of the increases in the ratios of mean amplitudes between mt-MEPs (mt) to c-MEPs and p-MEPs (p) to c-MEPs in each muscle group and all muscles. *p < 0.05, **p < 0.01. Figure is available in color online only.

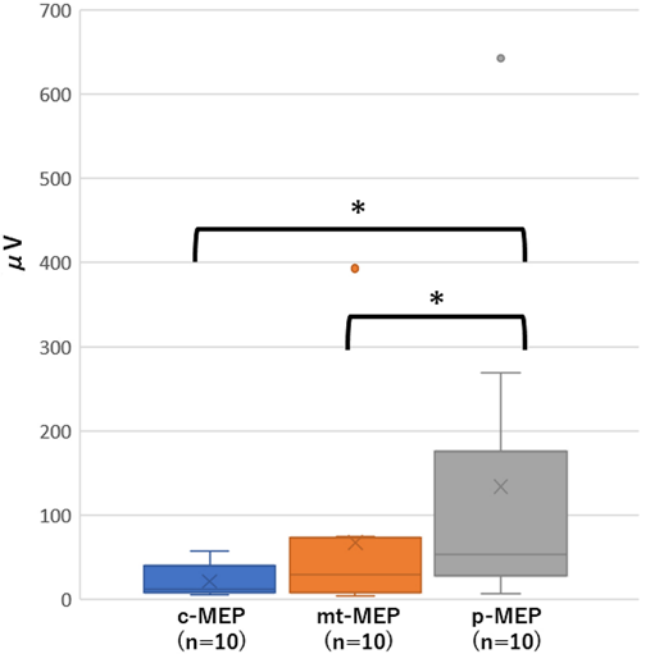

FIG. 4. A comparison of the mean amplitudes of direct MEPs between c-MEPs, mt-MEPs, and p-MEPs, with or without tetanic stimulation in all muscles. *Circles* represent outliers. *p < 0.05. Figure is available in color online only.

preoperative paralysis. c-MEPs, mt-MEPs, and p-MEPs obtained amplitudes > 30 μV in 40%, 60%, and 80% of cases, respectively. There were no statistically significant differences. c-MEPs, mt-MEPs, and p-MEPs demonstrated a mean amplitude of 21.5 ± 19.4 μV, 67.39 ± 117.2 μV, and 133.9 ± 195.3 μV, respectively. A comparison of the c-MEPs with p-MEPs and of the mt-MEPs with p-MEPs revealed statistically significant differences in the mean amplitude (both $p < 0.05$). In contrast, there were no statistically significant differences between c-MEPs and mt-MEPs (Fig. 4).

Comparison With Hemiparesis Cases

We examined the identification rate with APB and AH (16 muscles) in 8 patients (5 nonparalyzed and 3 paralyzed) who underwent both transcranial and direct MEPs. Fisher's exact test revealed a significant difference in the identification rate between direct MEPs, with and without paralysis in the tetanic stimulation group (mt-MEPs $p < 0.05$, p-MEPs $p < 0.01$) (Table 2).

Discussion

This novel prospective observational study demonstrated that the tetanic stimulation of both peripheral nerves of the extremities and the pudendal nerve increased the MEP amplitude following both TES and DCS in pediatric craniotomy. The amplification effect of pudendal nerve tetanic stimulation was significantly greater than that of the extremity peripheral nerve tetanic stimulation. Furthermore, p-MEPs in DCS displayed a significantly higher identification rate than that of c-MEPs and mt-MEPs; there were fewer false negatives. Kakimoto et al. first reported on a significant increase in MEP amplitude during general anesthesia following tetanic stimulation of the peripheral nerves.[9] Thereafter, researchers have demonstrated the usefulness of the MEP amplification effect following peripheral nerve tetanic stimulation in spine surgery, principally at that institution.[10–13] Subsequently, Takatani et al. reported on the effects of MEP amplification following pudendal nerve tetanic stimulation in pediatric lumbosacral surgery.[7] However, to our knowledge, no studies have reported on tetanic stimulation to augment the MEP amplitude obtained with suprathreshold stimulation in pediatric craniotomy cases.

TABLE 2. Comparison of MEP success rates by transcranial versus direct stimulation

Stimulation	Hemiparesis Status	MEP Success Rate		
		c-MEPs	mt-MEPs	p-MEPs
Transcranial MEP	–	70% (7/10)	70% (7/10)	80% (8/10)
	+	16.7% (1/6)	50% (3/6)	66.7% (4/6)
Direct MEP	–	40% (4/10)	60% (6/10)*	80% (8/10)†
	+	0% (0/6)	0% (0/6)*	0% (0/6)†

* $p < 0.05$.
† $p < 0.01$.

In transcranial MEPs, we confirmed the effect of MEP amplification by pudendal nerve tetanic stimulation even after craniotomy. Results similar to those of previous studies were obtained for the amplitude and ratio increases.[7] The identification rate was generally lower than that in previous studies, which may be attributed to the need to shift the transcranial electrodes due to an overlap between the transcranial stimulating electrodes and the operative field, in addition to a brain shift caused by the drainage of CSF.[14] The previous study measured MEPs with supramaximal stimulation, whereas in our study we measured MEPs with suprathreshold stimulation, with APB and AH as the main targets of intraoperative monitoring, and TA and Gc as secondary assessments. Therefore, regarding the identification rate of MEPs, we believe that the identification rate values were lower than usual because all muscle groups were evaluated together.

In this study, both transcranial MEPs and direct MEPs showed an amplification effect by pudendal tetanic stimulation in patients without preoperative paralysis, whereas in patients with preoperative paralysis, direct MEPs showed no amplification effect. The absence of distinct amplification effects in patients with preoperative paralysis suggested that researchers can assess greater localized motor function with pudendal nerve tetanic stimulation, without increasing false negatives. Direct MEP measurement assesses the pyramidal tract function more accurately in studies of intraoperative monitoring in adults comparing transcranial MEPs with direct MEPs.[15,16] Taken together, with the addition of pudendal nerve tetanic stimulation, intraoperative motor function monitoring may be more accurate in pediatric craniotomy than it was in the past.

The exact mechanism underlying the MEP amplification effects of peripheral nerve stimulation remains unknown. Tetanic stimulation of the peripheral nerves induces acetylcholine at the neuromuscular junction, which enhances pyramidal tract excitation.[17] A recent analysis of F waves suggested the enhanced excitation of anterior horn cells in the spinal cord, thus indicating an involvement in the upper portion of the spinal cord.[18] This phenomenon was consistent with previous studies demonstrating that the tetanic stimulation of one limb can exert an amplifying effect on MEPs in all four limbs.[19] Takatani et al. considered the involvement of sensory stimulation to be due to the higher potentiating effect of tetanic stimulation of the pudendal nerve, a pure sensory nerve.[7] The pudendal nerve originates from the sacral nerve and innervates a large part of the perineum. Its afferent fibers do not form a monosynaptic circuit with the alpha motor neurons innervating the muscles of the upper and lower limbs; tetanic stimulation of the pudendal nerve would purely reflect sensory stimulation. A previous animal study demonstrated that stimulation of the dorsal root of the spinal cord can exert an MEP amplification effect.[20] The mechanism underlying substantial MEP enhancement by stimulation of the pudendal nerves is unclear; nonetheless, this phenomenon may be attributed to differences in the sensitivity of the pudendal and peripheral nerves in the limbs.

Furthermore, we suggested a response to the MEP amplification effect of tetanic stimulation, particularly at the basal ganglia–cerebral cortex level. In animal studies, pubic stimulation suppressed the source of γ-aminobutyric acid (GABA)–mediated inhibition in the thalamus and increased thalamic activity.[21,22] The M1 cortex layer 6 is connected to all thalamic nuclei and is involved in pain regulation by the GABAergic pathway.[23] This feature may have resulted in enhanced interactions between the sensory and motor cortices via the GABA system in the thalamus. This phenomenon is consistent with reports stating that the administration of the γ-aminobutyric acid-A ($GABA_A$) receptor agonist lorazepam suppressed the MEP amplification effect of peripheral nerve stimulation.[24] In rats, the intracortical microstimulation of M1 neurons did not normally induce locomotion until day 35 of life; however, local inhibition with the $GABA_A$ antagonist bicuculline induced locomotion from day 13 of life onward.[25] Thus, corticospinal neurons cannot directly induce movement in the early postnatal period, consistent with the expansion of corticospinal axons in the spinal cord.[26,27] The application of tetanic stimulation may have caused a similar phenomenon in humans, thereby resulting in an amplification of MEPs.

In this study the pudendal nerve was stimulated 1 second before TES or DCS, which was at a frequency of 50 Hz, an intensity of 20–40 mA, and a duration of 5 seconds. Even though the electrical charge of these stimulation conditions was greater than the electrical charge of the BCR, we have not observed any complications related to electrical stimulation, such as burns, skin problems, or seizures, which is consistent with the findings of a previous study.[7] The technique is simple: surface electrodes placed at defined locations on the pubis and tetanic stimulation as per the protocol can produce the same MEP amplification effect as in the present study. In addition, a study of patients without preoperative hemiparesis showed that the procedure could be performed in patients whose pyramidal tracts were not affected, irrespective of the type of disease. However, its usefulness in clinical practice has naturally not been fully proven. Furthermore, there are drawbacks, such as the difficulty of performing emergency surgery given the complexity of the setting, and the fact that some patients or their parents want to avoid stimulation of the pubic region even under general anesthesia. Therefore, it is recommended that p-MEP monitoring should be performed as an adjunctive procedure with preoperative consent in cases of planned surgery involving operations around the pyramidal tract, where sufficient amplitude cannot be obtained with c-MEP monitoring.

Limitations

Our prospective study has provided new insights into the amplification effect of MEPs with pudendal nerve tetanic stimulation during surgery in pediatric populations. However, our study has some limitations, including the relatively small sample size and numerous etiologies per case. For this reason, our study did not show differences in complications or disease-specific outcomes, but new findings and problems may be encountered as more cases are added in the future. In addition, we covered a broad age range. Therefore, an adequate statistical analysis of age-related differences in the MEP amplification effect of tetanic stimulation was not possible. Furthermore, we could

not prove whether MEP monitoring with pudendal nerve stimulation is useful in patients younger than 5 years of age. This warrants larger cohort studies in the future to determine whether p-MEPs can be truly useful in clinical practice.

Conclusions

In pediatric craniotomy cases, we confirmed the amplification effects of MEPs by pudendal nerve tetanic stimulation for both TES and DCS. Particularly, we observed the amplification effects of DCS on MEPs without increasing false negatives, thus suggesting the possibility of highly accurate intraoperative motor function monitoring that could enable safe surgery with preserved motor function in future cases of pediatric craniotomy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tamura, Sasaki, Hayashi, Motoyama, Kawaguchi, Nakase. Acquisition of data: Sasaki, Kim, Takatani, Park. Analysis and interpretation of data: Sasaki, Takatani, Hayashi. Drafting the article: Sasaki. Critically revising the article: Tamura, Hayashi, Motoyama, Kawaguchi. Reviewed submitted version of manuscript: Tamura, Sasaki, Kim, Takatani, Hayashi, Motoyama, Nakagawa, Park, Kawaguchi, Nakase. Approved the final version of the manuscript on behalf of all authors: Tamura. Statistical analysis: Sasaki. Administrative/technical/material support: Tamura, Yamazaki, Takatani. Study supervision: Tamura, Nakagawa, Park, Kawaguchi, Nakase.

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