Motor evoked potential monitoring can evaluate ischemic tolerance to carotid artery occlusion during surgery

Yoshiaki Takamura, MD[1], Yasushi Motoyama, MD, PhD[1], Tsunenori Takatani, PhD[2], Yasuhiro Takeshima, MD, PhD[1], Ryosuke Matsuda, MD, PhD[1], Kentaro Tamura, MD, PhD[1], Shuichi Yamada, MD, PhD[1], Fumihiko Nishimura, MD, PhD[1], Ichiro Nakagawa, MD, PhD[1], Young-Su Park, MD, PhD[1], Hiroyuki Nakase, MD, PhD[1]

[1] *Department of Neurosurgery, Nara Medical University, Kashihara, Japan*

[2] *Department of Central Laboratory, Nara Medical University, Kashihara, Japan*

Address reprint requests to: Yoshiaki Takamura, MD, Department of Neurosurgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

Phone Number : +81-744-22-3051

Fax Number : +81-744-29-0818

E-mail: ytakam@hotmail.co.jp

Abstract

Balloon test occlusion (BTO) is a useful examination for evaluating ischemic tolerance to internal carotid artery (ICA) occlusion. The aim of this study was to investigate the relationships between intraoperative motor evoked potential (MEP) monitoring and the results of preoperative BTO. Between 2013 and 2017, 32 patients undergoing surgery under general anesthesia with intraoperative MEP monitoring, in whom preoperative BTO was performed, were identified. A receiver operator characteristic (ROC) analysis was performed to determine the appropriate cutoff value of MEP amplitude for BTO-positive. Furthermore, the accuracy of MEP monitoring for BTO-positive was compared with electroencephalogram (EEG) and somatosensory evoked potential (SEP) monitoring. Four of 32 (12.5%) patients were BTO-positive. The cutoff value of MEP amplitude for BTO-positive was a >80% reduction from the baseline level, which showed sensitivity of 100% and specificity of 100%. Thus, the sensitivity and specificity for BTO-positive were significantly higher for MEP than for EEG (100% and 72.0%, $p = 0.02$) in 28 patients, but they were not significantly different compared with SEP (33.3% and 100%, $p = 0.48$) in 21 patients. MEP monitoring might be one of the alternatives for evaluating ischemic tolerance to ICA occlusion during surgery. The cutoff value of MEP amplitude was a >80% reduction.

Keywords Balloon test occlusion, Carotid artery occlusion, Intraoperative neurophysiological monitoring, Ischemic tolerance, Motor evoked potential

Declarations

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Conflict of interest None of the authors has potential conflicts of interest to be disclosed.

Ethical approval Ethical approval was obtained for this study from the Nara Medical University Clinical Research Ethics Board (approval number: 1219). All study procedures were performed in accordance with the ethical standards of this institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Author contributions Study design: YT, YM, HN. Recording data: TT. Interpreting data: YT, YM, TT. Data analysis: YT, YM. Writing manuscript: YT, YM. Reading and reviewing manuscript: YM, YT, RM, KT, SY, FN, IN, YP, HN.

1 Introduction

It is difficult to directly measure cerebral blood flow (CBF) during surgery under general anesthesia. Therefore, when intraoperative occlusion of the internal carotid artery (ICA) is required, various intraoperative monitoring techniques have been used to detect cerebral ischemia, such as transcranial Doppler, carotid stump pressure, near-infrared spectroscopy, electroencephalogram (EEG), somatosensory evoked potential (SEP), and motor evoked potential (MEP) monitoring. However, these techniques monitor certain aspects of cerebral hemodynamics or cerebral metabolism in a limited area, or a certain cerebral function, which reflects reduced CBF only indirectly or partially.

On the other hand, balloon test occlusion (BTO) is a useful examination for evaluation of ischemic tolerance to ICA occlusion [1]. Based on the results of BTO, we can identify patients who require carotid artery shunting during carotid endarterectomy (CEA), or decide whether to use a low-flow or high-flow extracranial-intracranial bypass for ICA occlusion during large or giant ICA aneurysm surgery.

However, we sometimes encounter patients in whom ICA occlusion is required transiently or permanently during surgery, even though preoperative BTO cannot be performed. These patients include, for example, those who undergo aneurysmal surgery and the ICA must be sacrificed due to unexpected neck laceration. Awake surgery for CEA or aneurysms has been reported, but it is impossible to perform in all patients for all age ranges and varieties of conditions and severities. Considering such situations, it would be very useful to determine the relationships between intraoperative monitoring and the results of preoperative BTO. However, there have been no previous reports comparing intraoperative monitoring with preoperative BTO.

The aim of the present study was to evaluate the reliability of intraoperative neurophysiological monitoring (IONM), including MEP, EEG, and SEP monitoring, compared with preoperative BTO and to investigate whether MEP monitoring can evaluate ischemic tolerance to ICA occlusion during surgery.

2 Methods

This study was approved by the medical ethics committee of Nara Medical University Hospital (approval number: 1282). The medical ethics committee approved a waiver of consent for the collection of data as part of routine clinical care and quality control.

2.1 Study design and patient data

The medical records of 32 patients who underwent surgery with IONM including MEP, EEG, or SEP monitoring, in whom preoperative BTO was performed between 2013 and 2017 were retrospectively reviewed. The patients included 26 men and 6 women, with a mean age of 69.9 years, ranging in age from 41 to 85 years. The diagnosis was ICA stenosis in 28 patients, ICA aneurysm in 3, and brain tumor in 1.

Intraoperative MEP monitoring was performed in all 32 patients in whom BTO was performed preoperatively; during surgery, EEG and SEP monitoring were performed in 28 and 21 patients, respectively.

First, the reduction rate of MEP amplitude was reviewed to compare the result of BTO with receiver operating characteristic (ROC) analysis to determine the cutoff value. Second, the accuracy of MEP monitoring for BTO-positive was assessed based on its sensitivity and specificity. Third, the accuracy of MEP monitoring for BTO-positive was compared with EEG and SEP monitoring among the groups. Additionally, the times that significant changes were observed from ICA occlusion during surgery were compared between MEP and EEG monitoring.

2.2 Balloon test occlusion

BTO was performed under local anesthesia and minimal intravenous conscious sedation, ensuring that the patient could be examined neurologically during the test occlusion. In the case of carotid stenosis with plaque, the common carotid artery and external carotid artery were occluded using a double balloon catheter. In the other cases, a single balloon catheter was used to occlude the cervical ICA. Complete occlusion was confirmed by an angiogram through the balloon catheter demonstrating stagnation of the iodine contrast agent inside the proximal part of the ICA. The patient then underwent continuous neurological evaluation throughout the examination. The procedure was terminated if the patient developed any clinical signs of ischemia, including consciousness disturbance, motor weakness, or speech disturbance. In such cases, the BTO was judged to be positive. The BTO was considered negative when the patient tolerated 20-min occlusion.

During the procedure, systemic blood pressure was measured intermittently and maintained at a maximum systolic pressure under 140 mmHg.

2.3 Anesthesia protocol

Anesthesia was induced with a bolus injection of propofol (1-2 mg/kg body weight), fentanyl (2 µg/kg body weight), and vecuronium (0.1 mg/kg body weight) or rocuronium (0.5-0.6 mg/kg body weight), and maintained with 40% oxygen, propofol (2.3-3.0 g/mL of target-controlled infusion), fentanyl (total dose of 0.3-0.5 mg), and remifentanil (0.05-0.2 mg/kg/min). No muscle relaxant agents were used after induction and insertion of the endotracheal tube. After the trachea was intubated, the lungs were mechanically ventilated to maintain the partial pressure of arterial carbon dioxide between 35 and 40 mmHg. Rectal temperature was maintained between 35.5 and 37.0°C. The other physiological monitoring parameters included electrocardiography, intra-arterial continuous blood pressure, and oxygen saturation measurement by pulse oximetry.

2.4 Intraoperative neurophysiological monitoring

For eliciting MEPs, corkscrew electrodes were placed over the primary motor cortex bilaterally (locations C3 and C4 in the International 10-20 system). To record compound muscle action potentials from the upper and lower extremities, surface electrodes were placed on the abductor pollicis brevis and abductor hallucis muscles. Five-train stimulation with an inter-stimulus interval of 2 msec was used. Intraoperatively, stimulation intensity was set at 20% more than the threshold level to ensure that MEPs of at least 50 μV in amplitude could be stably obtained. Threshold levels were rechecked every 30 minutes, and baseline levels for MEPs were renewed.

EEG was recorded using needle electrodes placed on the scalp. An anterior-to-posterior montage using the following eight channels was used: Fp1-F7, F7-T3, Fp1-F3, F3-C3, Fp2-F4, F4-C4, Fp2-F8, and F8-T4 according to the international 10-20 system (EEG1224, Nihon Kohden, Tokyo, Japan). The 60-Hz notch filter was used, and band pass filtering was set from 0.53-60 Hz. Sensitivity varied between 5 and 10 microvolts/mm, and a time base of 30 mm/sec was used.

For the generation of SEPs, the median and tibial nerves of both sides were independently stimulated at the wrist and ankle using surface electrode pairs (Nihon Kohden). Scalp electrodes were placed at CPi/CPc/Fz for the upper extremity and CPz/iCPi/iCPc/Fz for the lower extremity to record the cortical

SEPs (N20/P25) for the upper extremity and (P38/N46) for the lower extremity. CPi and CPc were CP3 or CP4 ipsilateral and contralateral to the stimulated nerve, and iCPi and iCPc were CP1 or CP2 intermediate centro-parietal sites ipsilateral and contralateral. Ipsilateral and contralateral sites were switched. Constant current stimulation at intensities sufficient to evoke a consistent and supra-maximal peripheral nerve response was used for SEP generation. The stimulation frequency was set at 4.37 Hz, with a pulse duration of 0.2-0.5 msec. Band pass filters were set at 10-2000 Hz for cortical recording. MEPs and SEPs were elicited and recorded by the same device (MEE1232, Nihon Kohden).

Significant MEP changes were defined as a reproducible greater than 50% reduction in amplitude from the baseline. Significant EEG changes were defined as a decrease in the amplitude of fast frequency activity or an increase in theta or delta activity. Significant SEP changes were defined as a persistent and consistent prolongation of latency of 10% or of a 50% decrease in amplitude. These decisions were made by at least two or more independent examiners, including one neurosurgeon and one experienced medical technologist.

While IONM was performed, the systemic blood pressure remained constant and was similar to the average pressure during BTO.

2.5 Statistical analysis

For the assessment of the accuracy of MEP monitoring, receiver operating characteristic (ROC) analysis was performed. Using an ROC curve, the cutoff value for MEP amplitude was determined. Contingency tables were constructed for each modality, and sensitivity and specificity were calculated. The sensitivity and specificity of the two different modalities were compared using the McNemar test. The Mann-Whitney U test was used to compare data between the two groups. The relationships between two variables were investigated using Pearson's correlation analysis. $P < 0.05$ was considered significant. For statistical analysis, EZR Ver.1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used.

3 Results

Table 1 shows the clinical summary of the 32 patients included in this study. Four (12.5%) of 32 patients were BTO-positive. Of them, 3 developed ischemic symptoms including consciousness disturbance (cases 18, 25), speech disturbance (cases 17, 18), and motor weakness (case 25) immediately after carotid artery occlusion, and another patient (case 32) developed speech disturbance after 6 minutes. The MEP amplitude decreased significantly to <50% of the control in 6 (18.8%) of 32 patients. MEP changes occurred at a mean time of 13.5 minutes (range 3-27 minutes). In all 4 BTO-positive cases, MEP amplitude disappeared completely at a mean time of 11.5 minutes. There was no positive correlation between the time to onset of neurological deficits in the BTO-positive patients and the time to MEP changes ($r = -0.511$, $p = 0.489$). These MEP changes were followed by complete recovery to the control level after declamping of the ICA or insertion of the internal shunt. Significant EEG changes were observed in 10 (35.7%) of 28 patients, and significant SEP changes were seen in 1 (4.8%) of 21 patients. EEG changes occurred with a mean time of 4.5 minutes (range 0-24 minutes), significantly earlier than MEP changes ($p = 0.02$).

Two BTO-negative patients who underwent CEA developed transient monoparesis of the hand or arm after surgery. Both patients were diagnosed with a focal cerebral infarct due to embolism, because diffusion-weighted magnetic resonance imaging showed a high-intensity spot lesion in the motor cortex. One of them showed significant MEP changes during ICA cross-clamping without EEG/SEP changes. The other one showed no significant MEP changes intraoperatively, which was recognized as a false-negative finding. In both patients, the symptoms improved rapidly.

The sensitivity and specificity of MEP monitoring for BTO-positive were 100% and 92.9%, respectively. The cutoff value of MEP amplitude using the ROC curve was a >80% reduction from the baseline level, which showed sensitivity of 100% and specificity of 100% (Table 2). Thus, the sensitivity and specificity for BTO-positive were higher for MEP than for EEG monitoring (100% and 72.0%, $p = 0.02$) in 28 patients (Table 3). However, they were not significantly different compared with SEP (33.3% and 100%, $p = 0.48$) in 21 patients (Table 4).

4 Discussion

The aim of this investigation was to determine whether MEP monitoring is capable of identifying patients without ischemic tolerance during surgery. MEP monitoring has become common in neurosurgery [2, 3]. MEP monitoring has been reported to be more sensitive than SEP monitoring for detecting cerebral ischemia [4-7] and has been used to help prevent ischemic complications during surgery [8]. There is increasing evidence that MEP monitoring is quite valuable for identifying critical cerebral ischemia during CEA [9, 10]. In the present study, the relationship between intraoperative MEP monitoring and preoperative BTO, which has been established as a useful examination to evaluate tolerance to ICA occlusion[1], was investigated. To the best of our knowledge, this is the first study comparing preoperative BTO and IONM.

There is little consensus regarding the evaluation of the amplitude change and the threshold in MEP monitoring [11]. Generally, as the alarm point, more than a 50% reduction in amplitude is adopted for MEP monitoring during brain surgery targeting supra- and infratentorial lesions. Therefore, in the present study, significant MEP changes were defined as >50% reductions in amplitude. According to this criterion, the sensitivity and specificity of MEP monitoring for BTO-positive were 100% and 92.9%, respectively. Using ROC analysis, the cutoff value for MEP amplitude was a >80% reduction. These results are consistent with previous reports that an 80% reduction in amplitude was the threshold for irreversible motor palsy on MEP monitoring [8, 12]. If the threshold were defined as a >80% amplitude reduction, in the present study, the sensitivity and specificity of MEP monitoring for BTO-positive were 100% and 100%, respectively. The significant changes in MEP amplitudes were consistent with the results of BTO. Accordingly, a >80% reduction in MEP amplitude is considered to indicate lack of tolerance to ICA occlusion. The present data clearly support the hypothesis that MEP monitoring might be one of the alternatives for evaluating ischemic tolerance during surgery.

However, some limitations must be considered in the application of MEP monitoring. MEP monitoring is not always possible, especially in patients with moderate or severe motor deficits. There is a time delay until changes of MEP amplitude appear. Furthermore, MEP changes occur with not only hemodynamic ischemia due to ICA occlusion, but also focal ischemia of the pyramidal tract due to embolism. In the present study, one BTO-negative patient had significant MEP change due to a focal cerebral infarct related to embolism. Therefore, the other monitoring modalities are necessary to complement MEP monitoring.

EEG and SEP monitoring have been used frequently to detect cerebral ischemia during surgery [13-16]. The previous studies reported the high sensitivity and specificity of SEP monitoring for detecting cerebral ischemia [17, 18], comparable to those of EEG monitoring. However, false-negative SEP changes associated with postoperative motor deficits have also been reported [6, 7, 18-20]. In 3 patients, there were significant changes in MEPs that depended on ICA occlusion without significant depression of SEP responses in the present study. The present results indicated that SEP changes have a strong specificity of 100%, but a weak sensitivity of 33.3% for BTO-positive. Since SEP monitoring has more false-negatives and less accuracy than MEP, we believe it is less reliable for detection of ischemic tolerance. On the other hand, EEG monitoring had a strong sensitivity of 100% for BTO-positive. EEGs are difficult to interpret and easily affected by anesthesia, although EEG monitoring has the advantage of being continuous. Furthermore, EEG changes were noted to occur earlier than MEP changes. EEG is a rapid indicator of cerebral ischemia and is probably a useful alarm.

There have been no reports of the relationship between MEP changes and CBF. On the other hand, the relationship between EEG changes and CBF has been demonstrated previously [21-25]. Changes in EEG such as loss of fast beta frequencies occurred when CBF dropped below 25 to 35 mL/100 g/min. A further reduction was shown to provoke slowing of the background activity to theta rhythms, and a drop in CBF to below 18 mL/100 g/min has been associated with slowing to delta activity. Suppression of all frequencies was associated with neuronal cell death and a CBF below 10 to 15 mL/100 g/min. Regarding SEP monitoring, animal models indicate that a drop in CBF below 16 to 20 mL/100 g/min causes a reversible decrease in SEP amplitude. SEPs disappear for CBF values less than 12 mL/100 g/min [26, 27]. In humans, persistent reduction of SEP amplitude by 50% is observed when CBF decreases below 14 mL/100 g/min [28]. Moreover, the previous studies reported that the CBF threshold of ischemic symptoms is 15 to 20 mL/100 g/min [29, 30]. Based on the previous reports and the present study, we could suggest the following as the possible reason for the time lag in the appearance of changes in each modality. After ICA occlusion, EEG changes occur when CBF falls below 25 to 35 mL/100 g/min. As CBF decreases below 15 to 20 mL/100 g/min, ischemic symptoms occur, and it is possible that MEP changes may also appear at around these CBF values. Finally, SEP changes occur with a further decrease of CBF below 14 mL/100 g/min.

In summary, MEP monitoring was a reliable indicator for evaluating ischemic tolerance to ICA occlusion during surgery. In patients in whom it is difficult to perform preoperative BTO, MEP monitoring may be used instead of BTO. Since MEP monitoring has some limitations, as described previously, combining it with EEG and SEP monitoring provides complementary information. When ICA occlusion is required, we should pay attention to the EEG first. EEG change is a prompt warning sign for MEP change. Then, if MEP amplitude decreases to >80% of the control, we consider that the patient cannot tolerate ICA occlusion. SEP change requires rapid correction (i.e. temporary clip removal, internal shunt placement, or an increase of cerebral perfusion).

The present study had limitations in its retrospective nature, the small number of subjects, and the single-center design. A large patient population and further studies are needed to obtain more definitive values. Furthermore, there are other limitations to this study. One cannot be absolutely certain that the results of intraoperative monitoring in patients undergoing surgery under general anesthesia are comparable to the results of BTO under local anesthesia. There are reports that patients under general anesthesia may tolerate cerebral ischemia more than patients who received local anesthesia because of the possible protective effect of the anesthetic [31]. Finally, one of the essential benefits of preoperative BTO is that it can evaluate ischemic tolerance before the surgery, whereas MEPs can only be checked during the surgery. After all, even if there could be a close relationship between these 2 tests, intraoperative MEP monitoring cannot be a real alternative or replace preoperative BTO. To validate the accuracy of intraoperative MEP monitoring for evaluation of ischemic tolerance to ICA occlusion, it will be necessary to search for concordance between the final intraoperative MEP findings and the sequelae after ICA sacrifice.

5 Conclusions

MEP monitoring might be one of the alternatives for evaluating ischemic tolerance to carotid artery occlusion during surgery. A >80% reduction in MEP amplitude should be considered to indicate lack of tolerance of ICA occlusion. Combining MEP monitoring with EEG and SEP monitoring may be useful to overcome the disadvantages of each modality.

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Table 1. Summary of Clinical Data of the 32 Patients Included in this Study

Case No.	Age (yrs)	Sex	Diagnosis	Method	BTO (Time to onset of deficits)	Intraoperative monitoring	MEP change (Time from clamp to change)	EEG change (Time from clamp to change)	SEP change (Time from clamp to change)	Postoperative neurological deficits
1	61	M	ICA stenosis	CEA	Negative	MEP, EEG	-10%	-	NA	-
2	78	M	ICA stenosis	CEA	Negative	MEP, EEG	-25%	-	NA	-
3	75	M	ICA stenosis	CEA	Negative	MEP, EEG	-15%	-	NA	-
4	75	M	ICA stenosis	CEA	Negative	MEP, EEG	-10%	-	NA	-
5	76	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	-	-	-
6	67	M	ICA stenosis	CEA	Negative	MEP, EEG	0%	+ (immediately)	NA	-
7	76	F	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-20%	-	-	-
8	73	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-15%	-	-	-
9	76	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-30%	-	-	-

10	74	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	-	-	-
11	63	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-80% (20mins)	-	-	+ (transient)
12	67	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	-	-	-
13	66	M	ICA stenosis	CEA	Negative	MEP, EEG	-20%	+ (15mins)	NA	-
14	74	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-20%	-	-	-
15	69	F	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-40%	-	-	-
16	65	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-80% (15mins)	+ (3mins)	-	-
17	69	M	ICA stenosis	CEA	Positive (immediately)	MEP, EEG, SEP	-100% (27mins)	+ (immediately)	-	-
18	77	M	ICA stenosis	CEA	Positive (immediately)	MEP, EEG, SEP	-100% (12mins)	+ (2mins)	Disappeared (8mins)	-

19	75	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-10%	-	-	-
20	85	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	+ (immediately)	-	+ (transient)
21	79	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-20%	+ (immediately)	-	-
22	69	M	ICA stenosis	CEA	Negative	MEP, EEG	-10%	+ (immediately)	NA	-
23	72	F	ICA stenosis	CEA	Negative	MEP, EEG	-45%	-	NA	-
24	80	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	-40%	-	-	-
25	75	M	ICA stenosis	CEA	Positive (immediately)	MEP, EEG, SEP	-100% (4mins)	+ (1min)	-	-
26	65	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	-	-	-
27	62	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	-	-	-
28	73	M	ICA stenosis	CEA	Negative	MEP, EEG, SEP	0%	+	-	-

								(24mins)		
29	57	F	ICA aneurysm	Clipping	Negative	MEP	-20%	NA	NA	-
30	41	M	ICA aneurysm	Clipping	Negative	MEP, SEP	-45%	NA	-	-
31	69	F	ICA aneurysm	Clipping	Negative	MEP	0%	NA	NA	-
32	53	F	Pituitary tumor	Removal	Positive (6mins)	MEP	-100% (3mins)	NA	NA	-

BTO = balloon test occlusion; CEA = carotid endarterectomy; EEG = electroencephalogram; ICA = internal carotid artery; MEP = motor evoked potential; NA = not available; SEP = somatosensory evoked potential

Table 2. Results of Validating Reduction in MEP Amplitude for BTO-positive

MEP	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	AUC	95% CI
>50%	100%	92.9%	66.7%	100%	0.96	0.92 - 1
>80%	100%	100%	100%	100%	1	1 - 1

AUC = area under the curve; BTO = balloon test occlusion; CI = confidence interval; MEP = motor evoked potential

Table 3. Diagnostic Accuracy Parameters of MEP and EEG in 28 patients

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	P Value
MEP (>80% reduction in amplitude)	100%	100%	100%	100%	
EEG	100%	72%	30%	100%	0.0233

EEG = electroencephalogram; MEP = motor evoked potential

Table 4. Diagnostic Accuracy Parameters of MEP and SEP in 21 patients

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	P Value
MEP (＞80% reduction in amplitude)	100%	100%	100%	100%	
SEP	33.3%	100%	100%	90%	0.48

MEP = motor evoked potential; SEP = somatosensory evoked potential