Feasibility of adjunct facial motor evoked potential monitoring to reduce the number of

false-positive results during cervical spine surgery

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Abstract

Object: False-positive intraoperative muscle motor evoked potential (mMEP) monitoring results due to systemic effects of anesthetics and physiological changes continue to be a challenging issue. Although control MEPs recorded from the unaffected side are useful for identifying a true positive signal, there are no muscles on the upper or lower extremities to induce control MEPs in cervical spine surgery. Therefore, this study was conducted to clarify if additional MEPs derived from facial muscles can feasibly serve as controls to reduce false-positive mMEP monitoring results in cervical spine surgery.

Methods: Patients who underwent cervical spine surgery at our institution who did not experience postoperative neurologic deterioration were retrospectively studied. mMEPs were induced with transcranial supramaximal stimulation. Facial MEPs (fMEPs) were subsequently induced with suprathreshold stimulation. mMEP and subsequently recorded fMEP waveforms were paired during each moment during surgery. The initial pair was regarded as the baseline. A significant decline in mMEP and fMEP amplitude was defined as >80% and >50% decline compared with baseline, respectively. All mMEP alarms were considered false-positives. Based on two different alarm criteria, mMEP alone or both mMEP and fMEP, rates of false-positive mMEP monitoring results were calculated.

Results: Twenty-three patients were included in this study, corresponding to 102 pairs of mMEPs and fMEPs. This included 23 initial and 79 subsequent pairs. Based on the alarm criterion of mMEP alone, 17 false-positive results (21.5%) were observed. Based on the alarm criterion of both mMEP and fMEP, 5 false-positive results (6.3%) were observed, which was significantly different compared to mMEP alone (difference, 15.2%; 95% confidence interval, 7.2–23.1%; p<0.01).

Conclusions: fMEPs might be used as controls to reduce false-positive mMEP monitoring results in cervical spine surgery.

<u>Introduction</u>

Complex spinal surgery is associated with a significant risk of neurological injury. Thus, preventing postoperative neurologic deficits is a major concern for spine surgeons. Many reports[6,7,14,30,32,37] have indicated the effectiveness of intraoperative neuromonitoring. It is currently becoming a required assistive technique for detecting impending neural damage during neurological surgery, including spine surgery. Muscle motor evoked potential (mMEP) monitoring, developed to monitor the functional integrity of the descending motor pathways,[4,13] allows for early detection and reversal of spinal cord injury during complex spine surgery.[12] Nevertheless, concerns about the reliability of intraoperative mMEP monitoring in daily clinical practice remain. The main cause of concern is intraoperative instability of the mMEP waveform due to various non-surgical interventions such as anesthetic agents, fluctuations in blood pressure or body temperature, among others.[24,25] Instability of the mMEP waveform causes false-positive results[22]; thus, the reliability of intraoperative mMEP monitoring becomes questionable.

Control mMEPs from the unaffected side, which are not influenced by surgical manipulation, are useful for identifying truly positive signals by excluding possible indicators of the systemic effects of anesthetic agents and physiological changes during surgery. In general neurosurgical practice, once a significant decrease in mMEP amplitude has been detected intraoperatively on the affected side, we can refer to the control mMEP amplitude derived from the unaffected side to check for systemic effects before giving the surgeon alarm. For example, in lumbar spine surgery, we can refer to mMEP waveforms from

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the upper extremities as a control. However, in cervical spine surgery, there are no muscles in the extremities suitable for inducing control mMEPs (Fig. 1) (Fig. 1).

Transcranial MEPs evoked from the muscles innervated by the facial, vagus, or hypoglossal nerves have been used in intraoperative neuromonitoring of cranial nerve functional integrity in skull base surgery.[2,8,33] These muscles have recently attracted attention as sources of controls for mMEPs in cervical spine surgery. Therefore, this retrospective study focused on the potential of muscles innervated by the facial nerve to serve as controls during cervical spine surgery. The aim of this study is to clarify if the addition of facial motor evoked potential (fMEP) monitoring to mMEP monitoring of muscles in the extremities is feasible for reducing the number of false-positive results in cervical spine surgery.

Materials and Methods

All experiments were conducted according to the Declaration of Helsinki. All research protocols were approved by the institutional review board of Nara Medical University. The need for informed consent was waived (approval number: 1678). We retrospectively studied the medical records of all patients who underwent cervical spine surgery with intraoperative spinal cord monitoring using mMEPs derived from muscles in the extremities and facial muscles in department of neurosurgery at Nara Medical University Hospital from January 2015 to December 2016.

Exclusion criteria were: (1) insufficient fMEP amplitude for all monitored facial muscles (<10 µV), (2) postoperative neurologic deterioration (>1° of difference on the manual muscle test), and (3) insufficient mMEP amplitude (<10 µV).

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Clinical data were gathered retrospectively from medical records, radiographic images, anesthetic charts, and preoperative and postoperative neurologic examinations. We evaluated patient characteristics and intraoperative neuromonitoring data when the same anesthetic management and techniques documented below were used.

Anesthetic Management

No medications were given before anesthesia. Induction of anesthesia was achieved with propofol (target-controlled infusion dose, 4.0–6.0 μg/mL), remifentanil, fentanyl, and rocuronium. Anesthesia was maintained with propofol (target-controlled infusion dose, 2.0–4.0 μg/mL), remifentanil (0.2–0.4 μg/kg/min), and intermittent fentanyl boluses. Neuromuscular blockade was not used for maintenance of anesthesia. After tracheal intubation, the lungs were ventilated mechanically to maintain a partial end-tidal carbon dioxide pressure of 30 to 40 mmHg. Anesthetic depth was measured with a bispectral index monitor and maintained between 40 and 60. Mean arterial pressure was maintained between 70 and 100 mmHg throughout the operation. Core body temperature was maintained between 35.5°C and 37.0°C.

Stimulation and Recording Techniques for mMEPs from the Extremities and fMEPs

mMEPs from the Extremities. Transcranial electric stimulation was performed using an intraoperative monitoring system (Neuromaster MEE-1232; Nihon Kohden Corp., Tokyo, Japan). The stimulating electrodes consisted of a pair of scalp corkscrew electrodes (NM-480B; Nihon Kohden Corp.) at C3 (cathode) and C4 (anode; international 1–20 system). Stimulation consisting of a train of five pulses was delivered with an interstimulus interval of 2 ms and duration of 0.2 to 0.5 ms. Stimulus intensity was

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determined at the beginning of surgery and was set to be just supramaximal to each stimulus. A constant

current stimulator (MS-120B; Nihon Kohden Corp.) was initially used up to 200 mA. When the mMEP

amplitude was sufficient, constant voltage stimulation was used instead (SEN4100; Nihon Kohden Corp.),

up to 500 V. When the mMEP amplitude was insufficient, a post-tetanic motor evoked potential[10] was

also used. Compound muscle action potentials (CMAPs) were recorded from the skin over the abductor

pollicis brevis, tibialis anterior, gastrocnemius, and abductor hallucis bilaterally using disposable surface

electrodes (Vitrode V; Nihon Kohden Corp.). The settings of the low and high cut filters were 1 to 5 Hz,

and 1.5 to 3.0 kHz, respectively.

Facial Motor Evoked Potentials (fMEPs). Transcranial stimulation with the same apparatus was

performed for fMEPs. For fMEP monitoring, stimulation consisting of a train of four pulses was delivered

with an interstimulus interval of 1.5 to 1.7 ms; suprathreshold stimulation was used. Since facial muscles

and muscles in the extremities have different reactivity to muscle relaxants,[3,5] confirmation of recovery

from muscle relaxants was required. CMAPs were recorded from the skin over the orbicularis oculi

(Oculi) and orbicularis oris (Oris) bilaterally using needle electrodes (NM-31; Nihon Kohden Corp). For

Oculi and Oris, the anode and cathode were set on the lateral and medial sides of the muscle just below

the orbit or mouth, respectively. Transcranial electrical fMEP stimulation was performed immediately

after mMEP stimulation.

Criteria to check MEPs during the surgery. After induction of anesthesia, it was confirmed that

neuromuscular blockade have adequately deactivated. If it was inadequate below 80% in train-of-four

monitoring, neuromuscular blockade reversal was achieved with sugammadex. Then, baseline mMEP and fMEP were recorded. After the start of surgery, MEPs were evoked in the beginnings of each surgical phase and the end of surgery.

Data Collection and Analysis of mMEP and fMEP Waveforms

All mMEP and fMEP data derived intraoperatively were collected by a neurosurgeon and an anesthesiologist who were not involved in data interpretation of the study. For evaluation of fMEP, the amplitudes of fMEPs derived from Oris were preferentially evaluated in each patient. If fMEPs derived from Oris were unstable, they were replaced by Oculi fMEPs. mMEP and subsequently recorded fMEP waveforms, evoked in combination as described above, were paired. The initial pair was regarded as the baseline for each patient. Rates of change in amplitude from baseline were calculated for each mMEP and fMEP.

Details about Two Different Alarm Criteria

A significant decline in mMEP or fMEP amplitude was defined as a decline of >80% or >50% compared to the baseline amplitude, respectively. All mMEP alarms were considered false-positive, because the patients included in this study had no observed neurological deterioration after cervical spine surgery. Two different alarm conditions, including alarms based on mMEP alone or mMEP and fMEP in combination, were used to evaluate the feasibility of using fMEPs as controls.

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Using the alarm criterion based on mMEP alone, the false-positive rate was calculated based on only the criterion for mMEP. Using alarm criterion based on mMEP and fMEP in combination, once a decline in mMEP amplitude met the alarm criterion for mMEP alone, the change in fMEP amplitude recorded at the same moment was assessed using the alarm criterion for fMEP. Next, the decline in mMEP amplitude was determined to be a true false-positive result when the change in fMEP amplitude did not meet the fMEP alarm criterion. The decline in mMEP amplitude was determined to be a false false-positive result when the change in fMEP amplitude met the fMEP alarm criterion.

Statistical Analysis

All statistical comparisons were performed using PASW software, version 18 (IBM SPSS, Armonk, New York, USA). The false-positive rate for mMEP monitoring based on the two different diagnostic techniques was calculated separately. The difference in false-positive rates based on the two different diagnostic techniques was compared using the McNemar test to assess the feasibility of adding fMEP monitoring to eliminate systemic effects.

<u>Results</u>

Clinical Characteristics

Although cervical spine surgery was performed with both intraoperative mMEP and fMEP monitoring in 31 patients during this period, 23 patients without postoperative neurologic deterioration

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were ultimately included in this study (Fig. 2). In the 23 patients, 102 trials of combined mMEP and fMEP monitoring, including 23 initial and 79 subsequent trials, were evaluated.

The characteristics of the study patients who did not have postoperative neurologic deterioration are presented in Table 1. The study population included 15 males and 8 females aged 43–83 years (mean ± SD, 65.5 ± 12.1 years). Most patients had cervical canal stenosis (34.8%). Five (22%) underwent surgery via an anterior approach. Mean preoperative and postoperative Japanese Orthopedic Association scores at discharge were 11.9 ± 2.9 and 14.4 ± 2.2, respectively.

Relationship between the Number of Alarms based on mMEP and fMEP Alarm Criteria

The relationship between the number of alarms based on the mMEP alarm criterion and the addition of the fMEP alarm criterion is shown in Table 2. Based on the mMEP alarm criterion, 17 alarms were observed. Based on the fMEP alarm criterion, 15 alarms were observed. Since the fMEP alarm was issued simultaneously in 12 of 17 alarms based on the mMEP alarm criterion, 12 alarms based on the mMEP alarm criterion satisfied the combined mMEP and fMEP alarm criterion, which was identified as arising from systemic effects such as anesthetic agents and physiologic changes. As a result, there were five true false-positive results for mMEP monitoring when fMEP was used as a control.

In terms of the number of patients, 13 patients were affected by at least one of each alarm. In details, 7 of 23 patients involved the alarms based on the mMEP alarm criterion. Based on the additional fMEP criterion, 6 of the 7 patients had the "false" false-positive results, and 4 of the 7 patients also had the "true" false-positive results.

Impact of Adding fMEP Monitoring as a Control for mMEP Monitoring

A flow chart showing the diagnosis of true false-positive mMEP monitoring results based on the alarm criterion for combined mMEP and fMEP is shown in (Figure 3). The false-positive rate for intraoperative mMEP monitoring based on the mMEP alarm criterion alone was 21.5% (17 of 79 trials), whereas the false-positive rate of intraoperative mMEP monitoring based on the combined mMEP and fMEP alarm criterion was 6.3% (5 of 79 trials). The difference in the rate of false-positive detection between the two alarm criteria was 15.2% (95% confidence interval (CI), 7.2–23.1%; p<0.01).

Discussion

This is the first study to evaluate the feasibility of adding fMEPs as controls in order to reduce false-positive mMEP monitoring results during cervical spine surgery. The false-positive rate decreased significantly from 21.5% to 6.3% when fMEPs were used as controls. Since mMEPs are sensitive to anesthetic agents, neuromuscular blockade, and fading (gradually decreasing amplitudes and rising thresholds over time during surgery), a valid baseline should be selected accordingly for each proper part during operation.[26] It would be difficult to define multiple mMEP baselines intraoperatively, especially when surgical phases transition seamlessly (e.g., during long intramedullary tumor surgeries). Therefore, adding fMEP as a control is highly recommended because the added information would be very important.

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False-positive Results as a Major Issue in Intraoperative mMEP Monitoring

Although mMEPs have been widely used in neurologic surgery,[20,21] intraoperative instability of

the mMEP waveform presents a major issue that sometimes causes critical problems such as

false-positive results.[24] Sakaki et al. reported that false-positives occurred in 54 of 350 (15.4%) patients

with cervical compression myelopathy when transcranial mMEP monitoring was used; the alarm criteria

in this report was defined as waveform dissappearance.[31] Kim et al. also conducted a study in which 5 of

52 (9.6%) patients undergoing surgery for cervical myelopathy had false-positive results; the alarm

criterion consisted of an 80% decline in amplitude.[16] These false-positive results should be avoided

because they may lead surgeons to make an error in intraoperative judgment or surgical strategy.

Intraoperative mMEP waveforms are impacted by physiological changes (e.g., temperature, blood

pressure)[24,27] as well as systemic effects of anesthetic agents and neuromuscular blockade. To overcome

these systemic effects, one technique consists of neuromonitoring potentials directly evoked from the

spinal cord, known as D-waves. Since the D-wave does not involve any synaptic responses and is

relatively insensitive to anesthesia,[22] combined mMEP and D-wave monitoring is recommended to reduce

the number of false-positive results.[11,17,35] However, since the D-wave might reflect some physiological

changes, another approach to overcome this issue has been recommended.

Need for a Reference MEP as a Control in Cervical Spine Surgery

To overcome the instability of intraoperative mMEPs, setting a reference MEP as a control is

another popular and effective approach. There are few reports demonstrating the usefulness of concurrent

ipsilateral and contralateral MEP monitoring during brain and spinal surgery.[24,27,36] In these reports,

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analyzing waveforms elicited from the affected and unaffected hemispheres during surgery allows for the detection of general effects (e.g., anesthesia, hypotension) on mMEPs,[36] reduces false-positive observations,[23] and achieves high sensitivity and specificity.[1] Even though monitoring rostral or contralateral MEPs concurrently as controls whenever possible is highly recommended,[26] the practical effects of adding unaffected MEPs as controls on the rate of false-positive results in brain and spinal surgery are not well understood. Moreover, in upper cervical spine surgery, it is extremely difficult to set a reference value based on muscles in the extremities because there are no suitable muscles above the affected level. Therefore, control MEPs recorded as cranially as possible are highly recommended in cervical spine surgery.

Other options for reference muscles as controls in cervical spine surgery include the sternocleidomastoid and muscles of the face and tongue.[15,29] The sternocleidomastoid may be useful as a reference for cervical spinal disorders only below the C6 level, because its innervation is dominated by the accessory nerve arising from the medulla oblongata to the fifth or sixth segment of the cervical spinal cord. On the other hand, the facial nerve is not involved in spinal cord function. Facial muscles are promising candidates because transcranial fMEP monitoring has recently become recognized and established as a valid method for quantitative monitoring of facial nerve function in skull base surgery, including surgery for vestibular schwannoma.[7-9,33] One interesting report suggested the possibility of using transcranial MEPs from tongue muscles as controls in cervical spine surgery.[15] However, there is relatively poor evidence regarding mMEPs from muscles innervated by the hypoglossal nerve.

At our institution, we have empirically adopted fMEPs as controls. We feel it has been beneficial in cervical spinal and craniovertebral junction surgery for many years. Adding fMEP needs only a few time; electrode placement on facial muscles needs 5 minutes, and additional electrical stimulation for

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fMEP needs only a second or less. The leads for fMEP do not get in the way of any operative procedure of cervical spine. Therefore, we planned this study to confirm the benefit of adding fMEPs as controls in cervical spinal surgery.

Criteria Regarding Amplitude Decline for Spinal Cord Monitoring

The definition of a significant decline in fMEP and mMEP amplitude in the present study was based on past reports. For spinal cord monitoring, MacDonald proposed that a 50% decline based on supramaximal transcranial electric stimulation is too sensitive and a more marked decline is required, such as >80%, in a review paper.[26] However, this cutoff still results in a positive predictive value of only 0.6; a substantial proportion of false-positives remain.[18,19,22,28] For brain surgery, it was also noted that a mild (>50%) amplitude decline may be a major alarm criterion. For facial nerve monitoring, a 50% decline is considered a major alarm criterion based on published data.[8]

Possible Adverse Effects of Adding fMEP Monitoring on True-positive Results

In this study, adding fMEP monitoring significantly reduced the number of false-positive results. However, there is concern that adding fMEP monitoring might negatively affect the reliability of mMEP monitoring. Since only patients without postoperative neurological deterioration were included in this study, the impact of adding fMEP monitoring on the number of true-positive results could not be analyzed. Thus, there is a possibility that adding fMEP monitoring could conversely reduce the number of true-positive results, but it was not possible to assess this phenomenon in the present study.

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However, this might be a minor issue because many studies have demonstrated that fMEP monitoring has a high degree of reliability.[2,33,34] Akagami et al. reported that facial MEPs predicted immediately satisfactory postoperative facial functioning with a final-to-baseline ratio of 50%. There was a strong correlation between the final-to-baseline MEP ratio and immediate postoperative clinical facial nerve outcome. Moreover, the sensitivity and specificity for the criterion of 50% reduction in fMEP amplitude were 90% and 89%, respectively.[2] Therefore, this highly reliable and established method is unlikely to affect true-positive results in the present study.

Limitations

Our study had some limitations. First, this was a retrospective study with a small number of patients. Since we decided to survey MEP waveforms using electronic medical records over the entire surgical procedure, measurement bias was possible. Second, to the best of our knowledge, no specific complications associated with adding fMEP monitoring have been reported, such as slight scratches or bleeding from the facial recording needles. Third, only false-positive results were assessed in this study. For a comprehensive analysis of intraoperative neuromonitoring, false-positive and false-negative rates, sensitivity, and specificity are all essential endpoints. Moreover, this study did not include the patient developing new postoperative neurological deficits. Therefore, further investigation will be needed to assess the utility of using fMEPs as controls using data collected from patients who had postoperative neurological worsening.

In addition, specific care would be needed to derive fMEP. Because amplitude of fMEP is very low due to suprathreshold stimulation, meticulous attention not to suppress potentials from facial

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muscles would be needed for maintain of anesthesia. Neuromonitoring technologist should also avoid direct stimulation of facial muscles by stray current, which is induced by strong electrical stimulation. Therefore, it is very important to intensity surgeon's communications with anesthesiologist and neuromonitoring technologist.

Despite these limitations, the present study showed for the first time that mMEP monitoring using fMEPs as controls might lower the false-positive rate in upper cervical spine surgery.

Conclusions

Adding fMEP monitoring to control for the systemic effects of anesthetic agents and physiological changes might be feasible. Adjunct fMEP monitoring might help reduce the number of false-positive results associated with mMEP monitoring during cervical spine surgery.

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None

<u>Disclosures</u>

Conflicts of Interest:

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Figure legends

Figure 1. Schematic drawing of control muscle MEPs. a, b) During brain or thoracolumbar spine surgery, we can interpret waveforms derived from the *unaffected* contralateral side or upper extremities as controls. However, in upper cervical spinal surgery, such *unaffected* control muscles in the extremities typically do not exist.

Figure 2. Flowchart showing the patient selection process of this study. Eight of 31 patients were excluded for various reasons; 23 patients were included in the analysis.

mMEP, muscle motor evoked potential; fMEP, facial motor evoked potential; MEP, motor evoked potential.

Figure 3. Flowchart for diagnosing true false-positive mMEP monitoring results. 79 combined trials of mMEPs and fMEPs were evaluated. False-positive results were observed in 17 trials with mMEP assessment alone. The addition of fMEP assessment led to false-positive results in only five trials.

MEP, motor evoked potential; fMEP, facial motor evoked potential; mMEP, muscle motor evoked potential.

Figure 1. Schematic drawing of control muscle MEPs. a, b) During brain or thoracolumbar spine surgery, we can interpret waveforms derived from the unaffected contralateral side or upper extremities as controls. However, in upper cervical spinal surgery, such unaffected control muscles in the extremities typically do not exist.

Figure 1

a) Brain surgery

transcranial electrical stimulation

surgical site

upper limb

lower limb

b) Thoraco-lumbar spine surgery

transcranial electrical stimulation

surgical site

upper limb

lower limb

c) Cervical spine surgery

transcranial electrical stimulation

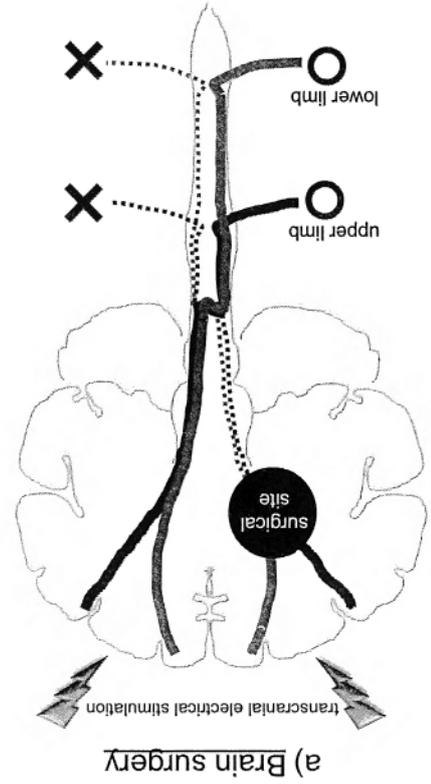surgical site

upper limb

lower limb

facial muscles

facial muscles
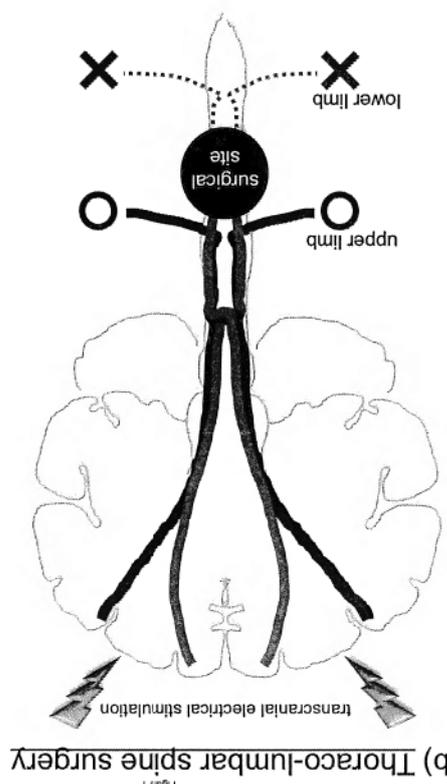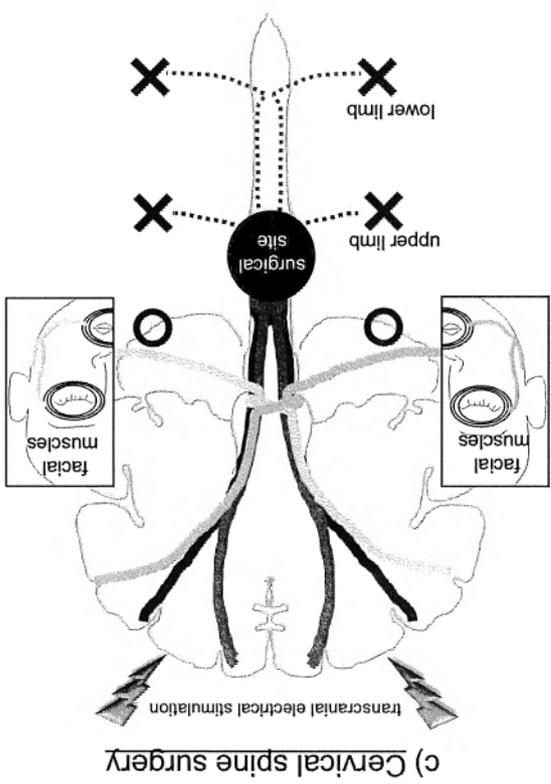
Figure 2. Flowchart showing the patient selection process of this study. Eight of 31 patients were excluded for various reasons; 23 patients were included in the analysis. mMEP, muscle motor evoked potential; fMEP, facial motor evoked potential; MEP, motor evoked potential.

Figure 2

31 patients underwent mMEP and fMEP monitoring in cervical spine surgery

→ 1 patient excluded, fMEP was not able to be derived

30 patients with fMEPs

→ 1 patient excluded, with postoperative neurologic deterioration

29 patients with fMEPs and no postoperative neurologic deterioration

→ 3 patients excluded, insufficient MEP amplitude

→ 3 patients excluded, too few MEPs with the same stimulation setting for evaluation

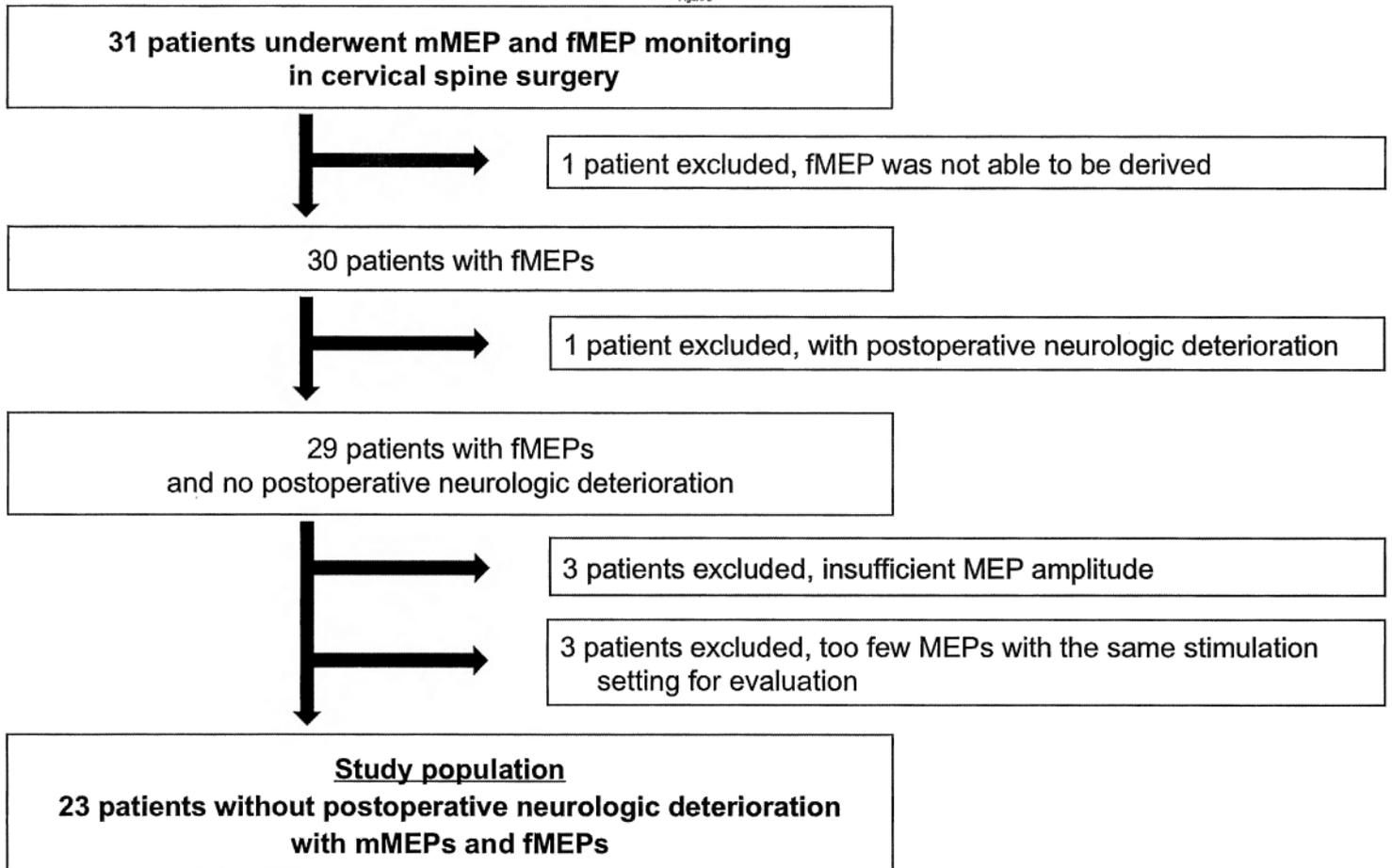| **Study population** 23 patients without postoperative neurologic deterioration with mMEPs and fMEPs |
| --- |

Figure 3. Flowchart for diagnosing true false-positive mMEP monitoring results. 79 combined trials of mMEPs and fMEPs were evaluated. False-positive results were observed in 17 trials with mMEP assessment alone. The addition of fMEP assessment led to false-positive results in only five trials. MEP, motor evoked potential; fMEP, facial motor evoked potential; mMEP, muscle motor evoked potential.

Figure 3

79 MEPs were evaluated
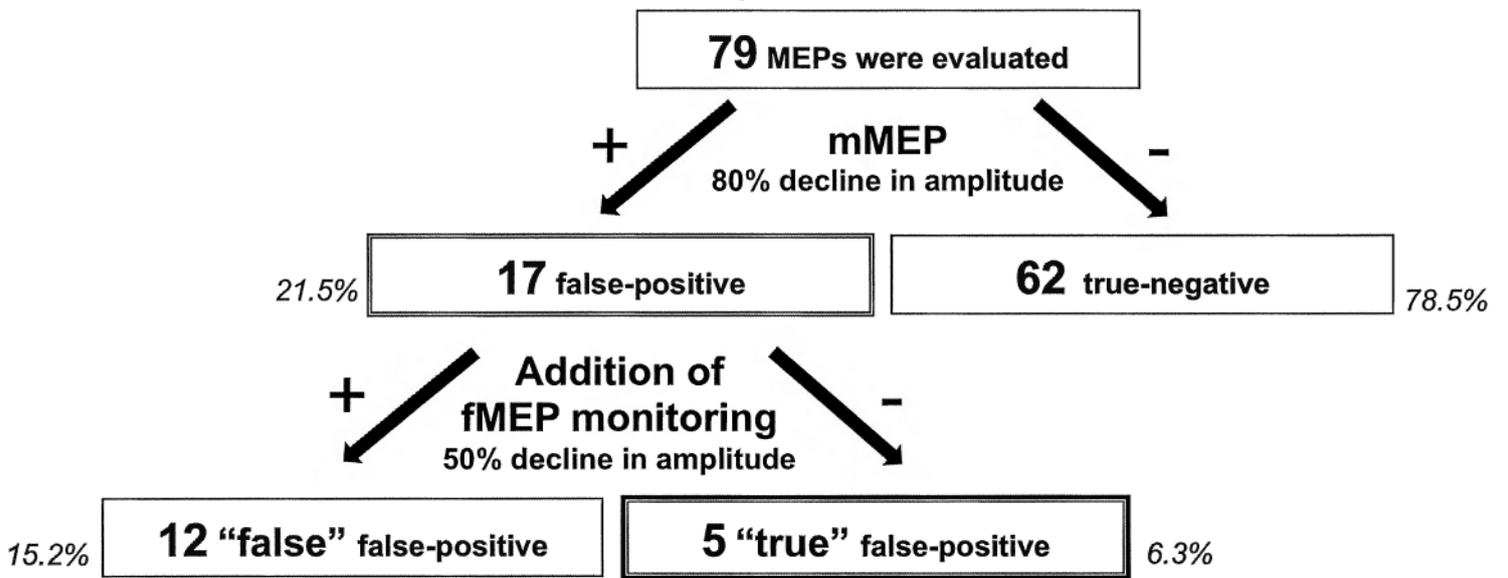
+ mMEP **‒**
80% decline in amplitude

21.5% **17** false-positive

62 true-negative 78.5%

+ Addition of
fMEP monitoring **‒**
50% decline in amplitude

15.2% **12** "false" false-positive

5 "true" false-positive 6.3%

Table 1. Clinical characteristics of the study participants ($n = 23$)

Characteristic	
Age, y	65.5 ± 12.1
Male sex, n	15 (65.2%)
Disease, n	
Cervical canal stenosis	8 (34.8%)
Ossification of the posterior longitudinal ligament	6 (26.1%)
Cervical disc herniation	4 (17.4%)
C1/2 subluxation	4 (17.4%)
C2 fracture	1 (4.3%)
Surgical approach, n	
Posterior	18 (78.3%)
Anterior	5 (21.7%)
Highest level, n	
C1	6 (26.1%)
C2	0 (0%)
C3	6 (26.1%)
C4	5 (21.7%)
C5	5 (21.7%)
C6	0 (0%)
C7	1 (4.3%)
JOA score for cervical myelopathy	
Before surgery	11.9 ± 2.9
At discharge	14.4 ± 2.2

JOA, Japan Orthopedic Association

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Table 2. Relationship between the number of alarms based on mMEP alarm criterion and the addition of fMEP alarm criterion

		>50% decline in fMEP amplitude		
		(+)	(-)	Total
>80% decline in extremity mMEP amplitude	(+)	12	5	17
	(-)	3	59	62
	Total	15	64	79

MEP, motor evoked potential; mMEP, muscle motor evoked potential; fMEP, facial motor evoked potential.