A comparison between threshold criterion and amplitude criterion in transcranial motor evoked potentials during surgery for supratentorial lesions

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OBJECTIVE The aim of this study was to compare sensitivity and specificity between the novel threshold and amplitude criteria for motor evoked potentials (MEPs) monitoring after transcranial electrical stimulation (TES) during surgery for supratentorial lesions in the same patient cohort.

METHODS One hundred twenty-six patients were included. All procedures were performed under general anesthesia. Craniotomies did not expose motor cortex, so that direct mapping was less suitable. After TES, MEPs were recorded bilaterally from abductor pollicis brevis (APB), from orbicularis oris (OO), and/or from tibialis anterior (TA). The percentage increase in the threshold level was assessed and considered significant if it exceeded by more than 20% on the affected side the percentage increase on the unaffected side. Amplitude on the affected side was measured with a stimulus intensity of 150% of the threshold level set for each muscle.

RESULTS Eighteen of 126 patients showed a significant change in the threshold level as well as an amplitude reduction of more than 50% in MEPs recorded from APB, and 15 of the patients had postoperative deterioration of motor function of the arm (temporary in 8 cases and permanent in 7 [true-positive and false-negative results]). Recording from TA was performed in 66 patients; 4 developed postoperative deterioration of motor function of the leg (temporary in 3 cases and permanent in 1), and showed a significant change in the threshold level, and an amplitude reduction of more than 50% occurred in 1 patient. An amplitude reduction of more than 50% occurred in another 10 patients, without a significant change in the threshold level or postoperative deterioration. Recording from OO was performed in 61 patients; 3 developed postoperative deterioration of motor function of facial muscles (temporary in 2 cases and permanent in 1) and had a significant change in the threshold level, and 2 of the patients had an amplitude reduction of more than 50%. Another 6 patients had an amplitude reduction of more than 50% but no significant change in the threshold level or postoperative deterioration.

Sensitivity of the threshold criterion was 100% when MEPs were recorded from APB, OO, or TA, and its specificity was 97%, 100%, and 100%, respectively. Sensitivity of the amplitude criterion was 100%, 67%, and 25%, with a specificity of 97%, 90%, and 84%, respectively.

CONCLUSIONS The threshold criterion was comparable to the amplitude criterion with a stimulus intensity set at 150% of the threshold level regarding sensitivity and specificity when recording MEPs from APB, and superior to it when recording from TA or OO.

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KEYWORDS threshold criterion; amplitude criterion; intraoperative monitoring; motor evoked potentials; threshold level; motor pathways; diagnostic technique

INTRAOPERATIVE monitoring has become a standard technique to predict postoperative neurological function during cranial and spinal surgery.^{7,9,11,14} There is evidence that monitoring of motor evoked potentials (MEPs) is useful in preventing and predicting postoper-

ative motor deficit during surgery for supratentorial lesions.^{11,31} Two stimulation modalities have been established to elicit MEPs—transcranial electrical stimulation (TES) and direct cortical stimulation. Two kinds of warning criteria have been developed to evaluate the intraop-

ABBREVIATIONS APB = abductor pollicis brevis; GTR = gross-total resection; KPS = Karnofsky Performance Scale; MEP = motor evoked potential; MRC = Medical Research Council; NPV = negative predictive value; OO = orbicularis oris; PPV = positive predictive value; SMA = supplementary motor area; TA = tibialis anterior; TES = transcranial electrical stimulation.

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erative change in MEPs. The most well-known one is the amplitude criterion, which depends on measurement of amplitude change during surgery. A postoperative neurological deterioration can be anticipated when an amplitude reduction of more than 50% takes place.^{23,33} The second one is the threshold criterion, which has been primarily developed during spine surgery,^{5,6} and relies on the trend of the threshold level (i.e., the change in the stimulus intensity needed to elicit MEPs during surgery). An increase in the threshold level of more than 100 V during at least 1 hour was proposed to be predictive for postoperative motor deficit during spine surgery.⁵

We recently developed a novel threshold criterion for MEP monitoring during surgery for supratentorial lesions, based on a bilateral evaluation of the threshold level that was defined as the minimum voltage needed to evoke a stable response from the muscle being monitored. An increase in the threshold level on the affected side of more than 20% beyond the increase on the unaffected side was considered a significant alteration.² This concept allows practitioners to distinguish between changes in the threshold level caused by damage to the motor pathway and changes attributed to other factors, leading to a significant reduction in false-negative and false-positive results. The stimulus intensity required to elicit MEPs using the amplitude criterion varies in the literature and there is no clear recommendation on how to adjust the stimulation intensity to incorporate MEP changes resulting from factors unrelated to surgical compromise of the motor pathway. In a study that was undertaken to investigate these factors, we found that the threshold level on the affected side can rise up to 48%, without being predictive of a postoperative paresis, as long as the difference between the affected and the unaffected side is less than 20%.¹ Based on this finding, we hypothesized that the amplitude criterion might incorporate MEP changes unrelated to surgical compromise of the motor pathway when MEPs are elicited with a stimulus intensity of 150% of the threshold level set for each muscle. By this we mean an amplitude measurement applying a stimulus intensity that is 50% higher than the lowest threshold level needed to evoke a stable muscle response.

To investigate this hypothesis, we designed this study comparing sensitivity and specificity between threshold and amplitude criteria during MEP monitoring for resection of supratentorial lesions in the same patient cohort.

Methods

Patient Population

Between November 2015 and November 2016, TES was performed to elicit MEPs in 126 patients during surgery for unilateral supratentorial lesions in subcortical motor-eloquent brain areas identified on preoperative MRI scans. The lesions did not involve the primary motor cortex and the craniotomies performed did not have to expose this area. In tumors involving the primary motor cortex, direct cortical stimulation would be the appropriate monitoring modality.

A clinical examination to assess motor deficits was performed in all patients preoperatively, at 24 hours after surgery, at discharge, and at the 3-month follow-up. Strength

of arm and leg muscles was evaluated according to the British Medical Research Council (MRC) grading system and facial function was described either as normal function, asymmetry, moderate dysfunction, or severe dysfunction. The postoperative deterioration of motor function was considered temporary if it resolved before the last follow-up and permanent if it lasted beyond the last follow-up. Postoperative paresis that took place following resection of the supplementary motor area (SMA) and resolved within days to weeks after surgery was considered SMA syndrome^{8,27} and was not considered in the final analysis. Informed consent was obtained from all patients prior to the surgical procedure. The data were collected prospectively according to the local ethical standards.

The primary endpoint of the study was to determine whether the sensitivity and specificity of the amplitude criterion in monitoring of transcranial MEPs elicited with a stimulus intensity set at 150% of the threshold level are comparable to the sensitivity and specificity of the novel threshold criterion in detecting postoperative motor deficits in different muscles in the same patient cohort. A secondary endpoint was to investigate the relationship between the range of change in MEPs and the degree of postoperative deterioration of motor function.

Anesthesia

All procedures were performed under general intravenous anesthesia, applying the same protocol for all patients, and muscle relaxants (rocuronium bromide) were applied for intubation. Anesthesia was induced using propofol, and analgesia was applied using sufentanil for the intubation and continued with remifentanyl. Invasive measurement of blood pressure was performed during all procedures to maintain stable systolic and mean blood pressure. The detailed protocol containing rates of anesthesia and analgesia was presented in a previous study.¹

Stimulation and Warning Criterion

For the surgical procedure, all patients were put in the supine position. Motor evoked potential monitoring was started before pin fixation of the head. Corkscrew-like electrodes were placed subcutaneously at C1, C2, C3, C4, and Cz according to the international 10–20 electroencephalography system. Metal pins were used for head fixation, and proximity to the installed electrodes was avoided if possible. Skin incision was tailored to avoid interfering with the installed electrodes and, if necessary, the electrodes were placed close to the skin incision.

Bilateral stimulation was performed in all patients: C4 to Cz stimulation for right-sided lesions and C3 to Cz for left-sided lesions. To reach a proper monitoring of the leg muscles in lesions located adjacent to the falx cerebri, C2 to C1 stimulation or C1 to C2 stimulation was performed (Fig. 1). Motor evoked potentials were recorded bilaterally from the abductor pollicis brevis (APB), tibialis anterior (TA), and orbicularis oris (OO) muscles by using subdermal needle electrodes. For both stimulation and recording of MEPs, we used the Endeavor system (Natus Europe GmbH, previously CareFusion). Transcranial electrical stimulation applied a constant-voltage stimulation by us-

FIG. 1. Schematic drawing refers to the placement of the electrodes on the scalp according to the international 10–20 electroencephalography system. C4 to Cz stimulation was used to evoke MEPs on the left side and C3 to Cz stimulation was used to evoke MEPs on the right side. For a specific recording of MEPs from the leg muscles, C2 to C1 stimulation or C1 to C2 stimulation was performed.

ing a repetitive anodal 5-train stimulation with pulse duration of 500 μ sec and interstimulus interval of 2 msec. Motor evoked potentials of the affected APB were evoked continuously and MEPs of TA and OO were evoked every minute. Motor evoked potentials of the unaffected muscles were recorded at the beginning, following every change in the MEPs of the affected muscles, and after finishing tumor resection.

Threshold Criterion

We defined the threshold level as the minimum voltage needed to evoke a stable motor response from each of the muscles being monitored. The threshold level was determined for each muscle and the percentage increase in the threshold level from the baseline set after craniotomy before dural opening was assessed on both sides. An increase in the threshold level was considered significant if it exceeded 20% on the contralateral side (i.e., in muscles contralateral to the affected hemisphere), beyond the percentage increase on the ipsilateral side (i.e., in muscles ipsilateral to the affected hemisphere). If a significant increase in the threshold level took place, resection of the lesion was halted and only continued using other strategies if the increase in the threshold level recovered, whereas the lesion resection was stopped if there was persisting significant increase in the threshold level. The expected recovery time of MEPs was 15 minutes, during which warm irrigation was applied and the position of brain retraction was changed. The final change in the threshold level was assessed when tumor resection was finished.

Amplitude Criterion

Motor evoked potentials were also elicited with a stimulus intensity that was set at 150% of the threshold level determined for each muscle before dural opening. The same stimulus intensity was applied again to elicit MEPs when significant changes in the threshold level took place and after completion of the tumor resection. The resulting amplitudes were recorded in microvolts and the percentage change between opening and closure was assessed for each muscle. The maximum stimulus intensity was limited through the stimulating device to 400 V.

Installation and analyses of MEP monitoring were performed by a medical technologist experienced in the field of neuromonitoring who was blinded to the postoperative motor function of the patients. For intraoperative imaging, ultrasound was used in all procedures.

Statistical Analysis

For all tests, a *p* value less than 0.05 was considered significant. Statistical analysis and graphics were performed using IBM SPSS Statistics (v20, IBM Corp.), Microsoft Excel (2013, Microsoft Inc.), and SigmaPlot (v12.5, Systat Software Inc.). The Student *t*-test and Kruskal-Wallis 1-way test were used to compare threshold levels and amplitudes of different muscles. Logistic regression was used to study the association between range of MEP changes and range of changes in postoperative muscle strength and whether they were temporary or permanent.

Results

Between November 2015 and November 2016, 126 patients underwent resection of supratentorial lesions located in motor-eloquent brain areas, and TES-MEPs were successfully elicited in all these procedures. Clinical and demographic characteristics of the patients and tumors are presented in Table 1. Thirty-six patients (29%) presented with a recurrent tumor. Thirty-four patients (27%) had a preexisting motor deficit of the arm (MRC grades 4, 3, and 2 in 23, 10, and 1 patients, respectively); 12 patients (10%) had a preexisting facial paresis (asymmetry in 7 patients and moderate dysfunction in 5 patients); and 15 patients (12%) had a preexisting leg weakness (MRC grade 4 in 9 patients and grade 3 in 6 patients). Of these patients, 8 had a hemiparesis (affecting face, arm, and leg), 4 had a brachiofacial paresis, and 3 had an arm-leg paresis. No MEP changes due to head positioning were detected and no intraoperative seizures were reported.

Primary Threshold Levels and Amplitudes

Recording from the APB was performed in all patients, with a threshold level that ranged from 48 to 350 V and a median of 124 V. Recording from the TA was appropriate for only 66 patients, and the threshold level ranged from 80 to 308 V with a median of 216 V. Recording from the OO was performed in 61 patients, with a threshold level that ranged from 52 to 300 V and a median of 140 V.

Measurement of the amplitude was performed with a stimulus intensity set at 150% of the threshold level defined for each muscle—except for 5 muscles in 5 patients (3 TA, 1 OO, and 1 APB) in whom the threshold level

TABLE 1. Clinical and demographic characteristics of the 126 patients and tumors and a comparison between patients with and without a postoperative deterioration of motor function

Characteristic	Age (yrs)	Sex		Preop KPS	Preop Median (range)	Preop Motor Deficit	Tumor Localization					Side Rt Lt	Rate of GTR	Pathology			
		M	F				Frontal Lobe	Parietal Lobe	Temporal Lobe	Insula	Gliomas*						
											I			II	III	IV	
																	Metastases
All patients	52 ± 16	81	45	100% (60–100)	38	54	31	23	18	78	48	63.5%	9	11	21	60	25
No postop deterioration	53 ± 16	71	37	100% (60–100)	30	48	28	20	12	67	41	64.1%	6	11	18	52	21
Postop deterioration of motor function	46 ± 17	10	8	100% (70–100)	8	6	3	3	6	11	7	61%	3	0	3	8	4
p values	0.119†	0.569‡	0.096†	0.216‡	0.532‡	0.583‡	0.888‡	0.888‡	0.033‡	0.970‡	0.970‡	0.970‡	0.230‡	0.334‡	0.733‡	0.971‡	0.964‡

* Graded according to WHO criteria (Louis et al.).

† Mann-Whitney rank-sum test.

‡ Chi-square statistic.

was 308, 296, 296, 300, and 350 V, respectively, and the maximum limit of stimulus intensity (400 V) was applied. The amplitudes recorded from the APB ranged from 50 to 2000 μ V with a median of 1000 μ V, amplitudes recorded from the TA ranged from 40 to 1500 μ V with a median of 725 μ V, and amplitudes recorded from the OO ranged from 30 to 1000 μ V with a median of 200 μ V.

Threshold and Amplitude Changes and Postoperative Motor Deficits

When tumor resection was achieved, the threshold level was unchanged in 42%, 44%, and 35% of the hand, facial, and leg muscles, respectively. The amplitude was unchanged in 73%, 72%, and 67% of the hand, facial, and leg muscles, respectively. The range of changes in threshold levels and amplitudes in addition to the median values for each muscle are reported in Table 2.

Significant changes in the threshold level and amplitude as well as the degree of postoperative paresis in hand, face, and leg muscles are presented in Tables 3–5. One patient had an SMA syndrome with no MEP changes. Eighteen of 126 patients showed a significant change in the threshold level as well as an amplitude reduction of more than 50% in the MEPs recorded from APB, and 15 of the patients had a postoperative deterioration of motor function of the arm, which was temporary in 8 cases and permanent in 7 cases (Table 3). Four patients developed a postoperative deterioration of motor function of the leg, which was temporary in 3 cases and permanent in 1 case; all showed a significant change in the threshold level of the TA; and an amplitude reduction of more than 50% took place in one of them. An amplitude reduction of more than 50% occurred in 10 more patients who had no significant change in the threshold level and did not develop a postoperative leg paresis (Table 5). Three patients developed a postoperative deterioration of motor function of the facial muscles, which was temporary in 2 cases and permanent in 1 case; all had a significant change in the threshold level of OO; and 2 of them had an amplitude reduction of more than 50%. Another 6 patients had an amplitude reduction of more than 50% but had no significant change in the threshold level and did not develop a postoperative facial paresis (Table 4).

Transient MEP Changes

Transient significant changes in the threshold level that were higher than the final values took place in 12 muscles (10 patients). After halting tumor resection, these changes recovered slightly in 2 muscles in 2 patients (OO in case E and TA in case AA), but the difference between affected and unaffected sides was still higher than 20% and these patients had a postoperative deterioration of motor function. In the remaining 10 muscles, the threshold level recovered and the difference between both sides was less than 20%, and no postoperative deterioration of motor function was observed. A transient amplitude reduction of more than 50% took place in 2 muscles (OO in case AL and APB in case AN) (Supplemental Table 1). All values of threshold levels and amplitudes are presented in Supplemental Tables 2–4.

TABLE 2. Range and median values of threshold levels and amplitudes in patients with intraoperative MEP changes

Muscle	Changes in TL			Changes in Amp		
	No. of Pts	Range	Median	No. of Pts	Range	Median
APB	73 (58%)	-20% to 165%	10%	34 (27%)	5% to 100%	62%
OO	34 (56%)	-11% to 83%	9%	17 (28%)	3% to 100%	50%
TA	43 (65%)	-22% to 59%	9%	22 (33%)	7% to 100%	53%

Amp = amplitude; pts = patients; TL = threshold level.

Analysis

When analyzing the primary threshold levels, we found that there was no significant difference between the threshold levels of APB and OO, whereas both were significantly lower than the threshold levels of TA ($p \leq 0.001$). The amplitudes of APB were found to be the highest, followed by amplitudes of TA and then by those of OO ($p \leq 0.001$). Patients with preoperative paresis had a higher threshold level of APB than those without preoperative paresis (median 180 μ V and 116 μ V, respectively; $p \leq 0.001$), whereas no significant difference was found regarding the amplitude (median 1000 μ V, $p = 0.810$). We found no significant correlation between preoperative paresis and the threshold level or amplitude of TA or OO.

The increase in the threshold level (affected side minus unaffected side) and the amplitude reduction in patients

who developed a postoperative deterioration in motor function of 1 MRC grade in the APB was significantly lower than in those who developed a deterioration of more than 1 MRC grade (threshold level increase: median 24% and 90%, respectively [$p = 0.009$]; amplitude reduction: mean 78% and 96%, respectively [$p = 0.018$]). A significant difference was also found between patients with temporary paresis and those with permanent paresis (threshold level increase: mean 34% and 110%, respectively [$p \leq 0.001$]; amplitude reduction: median 75% and 100%, respectively [$p = 0.008$]) (Fig. 2).

Preoperative paresis had no significant influence on false-negative or false-positive results when recording MEPs from OO or TA ($p = 0.590$ and $p = 0.217$, respectively; Fisher exact test). Age, sex, preoperative Karnofsky Performance Scale (KPS) score, preoperative motor defi-

TABLE 3. Patients with significant change in threshold level or amplitude and postoperative motor function of APB

Pt ID	Age (yrs)	TL in Contralat Muscles (V)			TL in Ipsilat Muscles (V)			Difference*	Amp in Contralat Muscles (μ V)			Preop Muscle Strength†	Postop Muscle Strength†		
		Start	End	% Change	Start	End	% Change		Start	End	% Change		After 24 Hrs	At Discharge	After 3 Mos
A	43	116	148	28%	76	80	5%	23%	800	200	75%	5	4	4	5
B	72	128	272	113%	144	188	31%	82%	500	0	100%	3	1	2	‡
C	39	80	212	165%	92	92	0%	165%	1000	0	100%	5	1	1	3
D	59	80	112	40%	88	96	9%	31%	1000	450	60%	5	4	4	5
E	64	188	400	113%	80	92	15%	98%	1000	0	100%	3	1	1	2
F	16	76	94	24%	84	84	0%	24%	1000	40	96%	5	4	4	5
G	23	220	400	82%	168	220	31%	51%	400	0	100%	5	3	3	4
H	43	130	196	51%	124	124	0%	51%	1000	200	80%	5	4	5	5
I	52	152	200	32%	132	136	3%	29%	400	0	100%	3	2	2	3
J	36	196	240	22%	130	130	0%	22%	1000	300	70%	5	3	3	3
K	27	84	152	81%	88	88	0%	81%	1000	0	100%	5	3	4	5
L	50	190	400	111%	124	124	0%	111%	1000	0	100%	4	1	2	3
M	33	116	296	155%	112	112	0%	155%	1000	0	100%	5	0	1	2
N	63	224	270	21%	180	180	0%	21%	50	15	70%	4	3	4	4
O	66	208	244	17%	276	260	-6%	23%	1000	300	70%	4	3	4	4
P	73	116	172	48%	80	84	5%	43%	900	100	89%	5	5	5	5
Q	46	240	332	38%	128	140	9%	29%	900	30	97%	5	5	5	5
R	78	112	160	43%	120	128	7%	36%	1000	20	98%	5	5	5	5

True-positive results in cases A–O and false-positive results in cases P–R.

* Percentage change in threshold level in the contralateral muscles minus percentage change in threshold level in the ipsilateral muscles.

† British MRC grading system (0, no contraction; 1, flicker/trace contraction; 2, active movement with gravity eliminated; 3, active movement against gravity; 4, active movement against resistance; 5, normal muscle strength).

‡ Patient died 1 month after the procedure following a myocardial infarction.

TABLE 4. Patients with significant change in threshold level or amplitude and postoperative motor function of OO

Pt ID	Age (yrs)	TL in Contralat Muscles (V)			TL in Ipsilat Muscles (V)			Difference*	Amp in Contralat Muscles (μ V)			Preop Facial Function†	Postop Facial Function†		
		Start	End	% Change	Start	End	% Change		Start	End	% Change		After 24 Hrs	At Discharge	After 3 Mos
E	64	140	185	32%	76	84	11%	21%	80	70	13%	2	1	1	2
L	50	230	400	74%	120	120	0%	74%	200	0	100%	3	1	2	3
M	33	116	212	83%	128	128	0%	83%	55	0	100%	4	2	3	3
S	72	104	128	23%	148	188	27%	-4%	850	50	94%	5	5	5	5
T	66	160	180	13%	168	168	0%	13%	500	200	60%	5	5	5	5
U	66	208	244	17%	108	108	0%	17%	300	120	60%	5	5	5	5
V	54	124	132	6%	112	112	0%	6%	700	50	93%	5	5	5	5
W	62	88	100	14%	104	108	4%	10%	220	90	59%	3	5	5	5
X	40	268	284	6%	260	260	0%	6%	200	80	60%	4	5	5	5

True-positive results (threshold criterion) in cases E, L, and M; false-negative results (amplitude criterion) in case E; and false-positive results (amplitude criterion) in cases S–X.

* Percentage change in threshold level in the contralateral muscles minus percentage change in threshold level in the ipsilateral muscles.

† Facial function described as follows: normal, 5; asymmetrical, 4; moderate dysfunction, 3; severe dysfunction, 2; and no contraction, 1.

cits, rate of gross-total resection (GTR), and tumor pathologies did not correlate with postoperative deterioration of motor function and did not influence its recovery. Tumor location in the insula was correlated with a higher rate of postoperative deterioration of motor function ($p = 0.033$, Table 1), but had no significant influence on its recovery.

Multiple regression showed that if an increase in the threshold level of more than 50% beyond the increase on the unaffected side or an amplitude loss took place, pa-

tients were at higher risk of a postoperative deterioration of motor function of more than 1 MRC grade (OR 42, 95% CI 2–885 [$p = 0.016$] and OR 52, 95% CI 2–1371 [$p = 0.018$], respectively) and of experiencing a permanent deterioration (OR 19, 95% CI 1.3–288.4 [$p = 0.034$] and OR 18, 95% CI 1.3–257 [$p = 0.033$], respectively). Postoperative motor function of TA and OO showed a similar correlation with the intraoperative changes in the threshold level but not with the amplitude reduction (Tables 4 and 5).

TABLE 5. Patients with significant change in threshold level or amplitude and postoperative motor function of TA

Pt ID	Age (yrs)	TL in Contralat Muscles (V)			TL in Ipsilat Muscles (V)			Difference*	Amp in Contralat Muscles (μ V)			Preop Muscle Strength†	Postop Muscle Strength†		
		Start	End	% Change	Start	End	% Change		Start	End	% Change		After 24 Hrs	At Discharge	After 3 Mos
M	33	252	400	59%	276	280	1%	58%	400	0	100%	5	0	1	2
Y	25	184	236	28%	196	200	2%	26%	1000	1000	0%	5	4	5	5
Z	27	208	296	42%	196	200	2%	40%	200	175	13%	5	4	5	5
AA	69	228	300	32%	196	216	10%	21%	400	300	25%	4	3	4	4
F	15	188	250	33%	200	308	54%	-21%	500	100	80%	5	5	5	5
AB	28	112	160	43%	108	136	26%	17%	600	200	67%	5	5	5	5
AC	62	236	252	7%	276	292	6%	1%	900	350	61%	3	5	5	5
AD	40	232	272	17%	230	230	0%	17%	800	50	94%	4	5	5	5
AE	39	172	216	26%	204	224	10%	16%	500	50	90%	3	5	5	5
AF	38	172	196	14%	170	170	0%	14%	500	50	90%	3	5	5	5
AG	35	300	350	17%	340	340	0%	17%	500	200	60%	5	5	5	5
AH	66	256	288	13%	276	288	4%	8%	1000	80	92%	5	5	5	5
AI	54	300	400	33%	350	400	23%	10%	700	200	71%	5	5	5	5
AJ	42	200	216	8%	164	176	7%	1%	700	100	86%	5	5	5	5

True-positive results (threshold criterion) in cases M, Y, Z, and AA; false-negative results (amplitude criterion) in cases Y, Z, and AA; and false-positive results (amplitude criterion) in cases F and AB–AJ.

* Percentage change in threshold level in the contralateral muscles minus percentage change in threshold level in the ipsilateral muscles.

† British MRC grading system (see Table 3 for description of grades).

FIG. 2. Box plot showing the range of change in the threshold level and amplitude in patients with postoperative deterioration of motor function. Change in the threshold level always describes the increase on the affected side minus the increase on the unaffected side.

Both the threshold criterion and the amplitude criterion had a sensitivity of 100% and a specificity of 97% when MEPs were recorded from APB. Recording from the leg and face muscles, the threshold criterion had a 100% sensitivity and specificity, whereas the amplitude criterion had a sensitivity of 25% and 67% and a specificity of 84% and 90% (leg and face, respectively). Table 6 presents sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for all postoperative deteriorations, temporary deterioration, and permanent loss of motor function, which were determined by applying the threshold criterion as well as the amplitude criterion for the APB, TA, and OO muscles.

Discussion

In this study we performed a comparison between the novel threshold criterion and the amplitude criterion for monitoring of MEPs elicited by TES during resection of unilateral supratentorial lesions. Motor evoked potentials were recorded from APB in all 126 patients, from OO in 61 patients, and from TA in 66 patients. Before dural opening, the threshold level was determined for each muscle on the affected and unaffected sides. Amplitude measurement from each monitored muscle on the affected side was performed after determining its threshold level with a stimulus intensity set at 150% of the threshold level. The percentage change in the threshold level was evaluated bilaterally until completion of tumor resection, and the percentage change in amplitude was calculated between baseline and dural closure. The main finding of this study is that the amplitude criterion, with a stimulus intensity

set at 150% of the threshold level, achieved high sensitivity and specificity similar to the threshold criterion when MEPs were recorded from APB. This finding allows the application of the amplitude criterion as an alternative to the threshold criterion, or when the unaffected side needed as a reference for the threshold criterion is not available, as in the case of surgery for infratentorial lesions in which motor pathways of both hemispheres might be involved or close to the site of surgery. Noteworthy is the fact that the threshold criterion always uses the minimum stimulus intensity and therefore does not necessarily provoke intraoperative patient movement unless the threshold level increases significantly during tumor resection. In contrast, using a stimulus intensity of 150% of the threshold level to monitor the amplitude is likely to result in patient movement that might make continuous monitoring uncomfortable for the neurosurgeon.

Interpretation of intraoperative MEP changes remains a challenge for neurophysiologists and neurosurgeons. Measurement of the MEP amplitude has long been the standard warning criterion in intraoperative monitoring. Disadvantages of this warning criterion during cranial surgery include being dependent on the evaluation of the affected side, and thus unable to detect and incorporate general changes resulting from anesthesia, altered blood pressure, or pneumocephalus, all of which affect both hemispheres. A further disadvantage is the missing recommendation for the stimulus intensity required to elicit an appropriate MEP amplitude that allows for reliable anticipation of postoperative motor function. The stimulus intensity required to elicit MEPs by using the amplitude

TABLE 6. Sensitivity, specificity, PPV, and NPV for all postoperative deteriorations, temporary deterioration, and permanent loss of motor function

Muscle	Postop Motor Function	Criterion	True-Positive Results	True-Negative Results	False-Positive Results	False-Negative Results	Sensitivity	Specificity	PPV	NPV
APB*	All deteriorations	TL ↑ >20%†	15	107	3	0	100%	97%	83%	100%
		Amp ↓ >50%	15	107	3	0	100%	97%	83%	100%
	Temporary	TL ↑ 20–50%	6	114	3	2	75%	97%	67%	98%
		Amp ↓ 50–99%	6	114	3	2	75%	97%	67%	98%
	Permanent	TL ↑ >50%	6	116	2	1	86%	98%	75%	99%
		Amp loss	6	116	2	1	86%	98%	75%	99%
TA	All deteriorations	TL ↑ >20%†	4	62	0	0	100%	100%	100%	100%
		Amp ↓ >50%	1	52	10	3	25%	84%	9%	95%
	Temporary	TL ↑ 20–50%	3	63	0	0	100%	100%	100%	100%
		Amp ↓ 50–99%	0	53	10	3	0%	84%	0%	95%
	Permanent	TL ↑ >50%	1	65	0	0	100%	100%	100%	100%
		Amp loss	1	65	0	0	100%	100%	100%	100%
OO	All deteriorations	TL ↑ >20%†	3	58	0	0	100%	100%	100%	100%
		Amp ↓ >50%	2	52	6	1	67%	90%	25%	98%
	Temporary	TL ↑ 20–50%	1	59	0	1	50%	100%	100%	98%
		Amp ↓ 50–99%	0	53	6	2	0%	90%	0%	96%
	Permanent	TL ↑ >50%	1	59	1	0	100%	98%	50%	100%
		Amp loss	1	59	1	0	100%	98%	50%	100%

↑ = increase beyond the increase on the unaffected side; ↓ = reduction.

The threshold criterion as well as the amplitude criterion was applied for APB, TA, and OO.

* One patient had an SMA syndrome and was excluded from the analysis.

† TL ↑ >20% was the standard warning criterion used intraoperatively.

criterion varies in the literature between near-threshold intensity;²² slightly suprathreshold level;¹² 5%, 10%, and up to 20% above the motor threshold^{29,30} for TES-MEPs; and the maximal stimulus intensity with no body motion for MEPs elicited by direct cortical stimulation.²⁶ In the current study, we applied the amplitude criterion using a stimulus intensity of 150% of the threshold level and achieved high sensitivity and specificity, thus improving its performance significantly compared to previous studies.^{13,16,24,25,29} The combined use of the threshold and amplitude criteria, as also discussed in previous studies,^{10,20,29} might enable more accurate judgment of MEPs in supratentorial surgery.

Range of MEP Change and Postoperative Paresis

Predicting postoperative deterioration of motor function is a major task of intraoperative monitoring. The information delivered to the neurosurgeon, especially the degree of expected deterioration, is likely to influence the decision on whether or not to proceed with tumor resection. In this study the increase in the threshold level of more than 20% beyond the increase on the unaffected side was used as a warning criterion to detect all deteriorations of motor function, and showed the best results regarding sensitivity and specificity (Table 6). However, based on our findings, an increase in the threshold level of more than 50% beyond the increase on the unaffected side, or an amplitude loss, were associated with a significantly higher risk of a postoperative deterioration of motor function of

more than 1 MRC grade and subsequently with a permanent deterioration. In other words, when the threshold level on the affected side increases between 20% and 50% beyond the increase on the unaffected side, a mild deterioration is rather to be expected, which gives the surgeon the option of continuing tumor resection as long as the increase in the threshold level is still less than 50%. This applies also for a range of amplitude reduction between 50% and 100%. Transient changes in the threshold level were not predictive of postoperative paresis if the difference in the threshold level between affected and unaffected sides recovered during the procedure to a level less than 20%. The correlation between intraoperative MEP changes and postoperative paresis has been reported in the literature;³³ however, without an accurate prediction of the degree of postoperative deterioration or whether a temporary or permanent paresis should be expected.

The difference between patients with and without postoperative deterioration of motor function regarding age, sex, preoperative KPS score, rate of preoperative motor deficits, rate of GTR, and tumor pathologies was not significant (Table 1). The only difference we found was that the rate of postoperative deterioration of motor function was significantly higher in patients in whom tumor was in the insula ($p = 0.033$, Table 1). Furthermore, none of these factors had a significant influence on whether the postoperative deterioration of motor function was temporary or permanent. It also must be said that the influence on long-term recovery of other factors like postoperative adjuvant

treatment (chemotherapy or radiotherapy) and tumor progress after surgery was not investigated in this study.

Monitoring of Face and Leg Muscles

In this series, we report a dedicated bilateral MEP recording from face and leg muscles after TES during surgery for supratentorial lesions. Motor evoked potentials were recorded from the OO, a facial muscle that has been widely used for electromyography monitoring as well as MEP monitoring during surgery for infratentorial lesions.^{3,4,17,32} The threshold criterion had a 100% sensitivity and specificity, whereas the amplitude criterion was false negative in 1 case and false positive in 6 cases, which means that amplitude measurement cannot be recommended for monitoring of facial MEPs, at least during supratentorial surgery. Postoperative deterioration of facial function occurred in 3 patients (cases E, L, and M; Table 4), in whom postoperative deterioration of hand/arm muscle strength also took place, which is not surprising due to the anatomical correlation between hand and face areas on the motor cortex. For recording from the leg we used the TA, which has been used as a standard muscle for MEP monitoring during spine surgery.^{15,19,28} The threshold criterion had a 100% sensitivity and specificity, whereas the amplitude criterion was false negative in 3 cases and false positive in 10 cases, meaning that using a higher stimulus intensity, as we did, was not able to improve the performance of the amplitude criterion regarding false-positive results, which has been described as fading MEPs during monitoring of leg muscles in spine surgery.^{19,21} Postoperative deterioration of leg function occurred in 4 patients (cases M, Y, Z, and AA; Table 5), and postoperative deterioration of hand/arm muscle strength took place in 1 of the patients (case M). A full recovery of leg function took place in all 3 patients who had isolated postoperative leg paresis.

Limitations

This study and previous studies that applied the novel threshold criterion used constant voltage and included patients who were in the supine position during the procedure. Also, as is known, eliciting MEPs from the TA in the prone position can be technically challenging, in addition to the phenomenon of fading MEPs, which are described mainly during testing in the prone position.¹⁹ Therefore, investigation of our findings on threshold and amplitude criteria during spine surgery and using constant current will be a scope of further studies.

Conclusions

In transcranial MEPs during surgery for supratentorial lesions, the threshold criterion was comparable to the amplitude criterion with a stimulus intensity set at 150% of the threshold level regarding sensitivity and specificity when recording MEPs from APB, and superior to it when recording from TA or OO.

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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: Abboud. Acquisition of data: Abboud, Schwarz. Analysis and interpretation of data: Abboud. Drafting the article: Abboud. Critically revising the article: Abboud, Westphal, Martens. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Abboud. Statistical analysis: Abboud. Administrative/technical/material support: Schwarz. Study supervision: Abboud, Martens.

Supplemental Information

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Supplemental material is available with the online version of the article.

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