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Predictive value of IOM in clipping of unruptured intracranial aneurysms – A prospective study from the surgeon's point of view

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ABSTRACT

Introduction: Intraoperative neuromonitoring (IOM) of motor/somatosensory evoked potentials is a well-established approach for reducing ischemic complications after aneurysm clipping.
Research question: To determine the predictive validity of IOM for postoperative functional outcome and its perceived added value for intraoperative real-time feedback of functional impairment in the surgical treatment of unruptured intracranial aneurysms (UIAs).
Material and methods: Prospective study of patients scheduled for elective clipping of UIAs between 02/2019–02/2021. Transcranial motor evoked potentials (tcMEP) were used in all cases, a significant decline was defined as loss of ≥50% in amplitude or 50% latency increase. Clinical data were correlated to postoperative deficits. A surgeon's questionnaire was conceived.
Results: 47 patients were included, median age 57 years (range 26–76). IOM was successful in all cases. In 87.2%, IOM was stable throughout surgery, although 1 patient (2.4%) demonstrated a permanent postoperative neurological deficit. All patients with an intraoperatively reversible tcMEP-decline (12.7%) showed no surgery-related deficit, regardless of the decline duration (range 0.5–40.0 min; mean: 13.8). Temporary clipping (TC) was performed in 12 cases (25.5%), with a decline in amplitude in 4 patients. After clip-removal, all amplitudes returned to baseline. IOM provided the surgeon with a higher sense of security in 63.8%.
Discussion and conclusion: IOM remains invaluable during elective microsurgical clipping, particularly during TC of MCA and AcomA-aneurysms. It alerts the surgeon of impending ischemic injury and offers a way of maximizing the time frame for TC. IOM has highly increased surgeons' subjective feeling of security during the procedure.

1. Introduction

Unruptured intracranial aneurysms (UIAs) are surgically clipped to reduce risk of rupture and subsequent subarachnoid hemorrhage (SAH) which may result in substantial morbidity (Choi et al., 2017; Etminan et al., 2020; Etminan and Rinkel, 2016; Rinkel and Algra, 2011; Wiebers, 2003; Ishibashi et al., 2009; Nieuwkamp et al., 2009). The 5-year risk of rupture ranges from 0.25 to more than 15% (Greving et al., 2014). Given this risk, the morbidity rate after elective clipping should be lower to justify the preventive treatment (Choi et al., 2017; Wiebers, 2003; Ishibashi et al., 2009; Greving et al., 2014; Gonda et al., 2014; Foreman et al., 2018). Often, intraoperative inspection alone is insufficient to detect imminent ischemia, and must be supplemented with additional monitoring (Neuloh and Schramm, 2004; Szelényi et al., 2006).

In neurovascular surgery, intraoperative neuromonitoring (IOM) is a well-established instrument for reducing morbidity (Choi et al., 2017; Szelényi et al., 2003, 2006; Greve et al., 2019; Fehlings et al., 2009, 2010). It encompasses a plethora of electrophysiological modalities, and provides real-time feedback of motor and sensitive function. IOM is utilized to detect the eventual shift in nerve conduction in the reversible phase, and is thus aimed at preventing postoperative neurological impairments (Choi et al., 2017; Wiebers, 2003; Neuloh and Schramm, 2004). Therefore, IOM became an essential part of the neurosurgical armamentarium (Ishibashi et al., 2009; Fehlings et al., 2009).

The predictive validity of IOM in clipping of UIAs, especially during TC, is still under discussion and lacks prospective data. The relationship

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between TC and declines in amplitude, as well as the maximum time of TC without a postoperative neurological deficit remains controversial. It must further be noted that part of the value and utility of IOM stems from its potential impact on the surgeon's strategy during different surgical steps, which is largely unexplored (Nasi et al., 2020; Kombos et al., 2001, 2009; Krieg et al., 2012).

This study aimed to determine the predictive validity of IOM in the surgical treatment of UIAs and to assess its subjective intraoperative value for the surgeon.

2. Methods

2.1. Ethical declaration

This study was designed and performed in accordance with the Declaration of Helsinki from 1964 and approved by the local ethics committee of our university (no. 18/19s). All patients gave written informed consent before study inclusion.

2.2. Study design and outcome parameters

This is a prospective observational study. The objective was to investigate the predictive validity of IOM in the microsurgical clipping of UIAs, by assessing its predictive values in addition to its sensitivity for detecting intraoperative ischemic injury to motor-eloquent territories by correlating intraoperative changes of the evoked potentials with the postoperative neurological status.

2.3. Patient population

We screened patients ≥18 years undergoing elective microsurgical aneurysm clipping performed under IOM at our Department between 02/2019–02/2021. A cohort of 47 patients with UIAs was enrolled. Patients with a history of aneurysmal SAH of the index UIA or prior endovascular treatment of the index UIA were excluded.

2.4. Preoperative examination

Preoperative neurological status was assessed on the day of admission, including limb motor strength, sensory function, and cranial nerve function. Motor strength was graded from 0 (plegia) to 5 (full motor strength). For assessments of functional status, the modified Rankin scale (mRS) was obtained. A digital subtraction angiography (DSA) was conducted, in addition to cranial magnetic resonance tomography. Each case was discussed in an interdisciplinary neurovascular board.

2.5. Anesthesia

In all 47 cases, total intravenous anesthesia with propofol was used, as volatile aesthetics have been shown to interfere with IOM (Krieg et al., 2012; Deletis et al., 2001). Rocuronium was exclusively used for intubation because it blocks neuromuscular transmission and makes IOM impossible (Krieg et al., 2012; Deletis et al., 2001).

2.6. IOM setup

Transcranial motor evoked potentials (tcMEPs) served as the primary IOM modality. In addition, auditory evoked potentials (AEP) and facial nerve electromyography (EMG) were performed for aneurysms of the posterior circulation.

For tcMEPs, an *ISIS stimulator* (Inomed, InomedMedizintechnik, Germany) was used. IOM setup, recordings, and analysis were conducted by a neurophysiological specialist. A pair of transcranial subdermal needle electrodes (Inomed 27-gauge bipolar needle electrode, Inomed Medizintechnik®) were placed at C3, C4 and at C3′ and C4′ positions in accordance with the 10–20 system. Recording electrodes were placed over the M. abductor pollicis brevis and brachial biceps for the upper extremity and the anterior tibial muscle and flexor hallucis brevis for the lower limb, contralateral to the side of transcranial stimulation. For SSEPs, anodal square-wave pulses of 200 μs duration were applied to stimulate the median nerve. For recording of SSEPs, electrodes were placed at C3′, C4′ and Erb's point with reference to Fz.

The initial stimulation parameters were predetermined and modified, to avoid disruptive extremity movements or undetectable tcMEPs. A first response was recorded with an intensity of 90 mA. The stimulation intensity was then tapered until loss of signal, and then increased again by 10% to achieve a baseline response, this protocol for our IOM setup was recently published (Wagner et al., 2022). For TES, the train of five stimulation technique was used (Krieg et al., 2012; Taniguchi et al., 1993).

During surgery, continuous monitoring was performed. The amplitude, latency and duration of EPs were analyzed. Declines in amplitudes were categorized as reversible or irreversible. Cut-off criteria were defined as an amplitude diminishment over 50% or an increase in latency by 50% of the respective baselines recorded immediately after dural opening. The time until recovery of amplitude was documented (Fig. 1). The TC of proximal vessels as a precautionary or facilitating surgical step and its relation to the duration and declines of IOM received particular attention in this study.

2.7. Surgeon questionnaire

Operating surgeons were handed a questionnaire aimed at gauging various intraoperative aspects related to the use and utility of IOM. The surgeon answered questions about their perceived impact of IOM on the course of the procedure as well as its added value on surgical and functional outcome compared to not having used this modality.

2.8. Postoperative clinical course

Patients underwent postoperative DSA. Neurological status was evaluated in the Peri Anesthesia Care Unit (PACU), at postoperative day (POD) 1, 5 and DOD. Postoperative neurological deficit was defined as the occurrence of new neurological dysfunction that were either temporary or permanent. The postoperative mRS was compared with the preoperative mRS. Complications were documented.

2.9. Statistical analysis

Baseline characteristics were compared via Chi square test. The primary endpoint was the correlation of postoperative neurological deficits with abnormalities in IOM. Differences between groups, stratified by stable vs decline in IOM were tested with the Mann-Whitney-U test. A secondary endpoint was defined as the occurrence of amplitude changes of the tcMEP monitoring in relation to the duration of TC occlusion of parent vessels. Calculations were made with IBM SPSS statistics version 28. Results are presented as mean ± SD. Median and range were also calculated. Values of $p < .05$ were considered significant.

3. Results

3.1. Baseline characteristics

47 patients met the inclusion criteria (Table 1). For cardiovascular risk factors, 40.4% had arterial hypertension and 42.6% were smokers. Familial aneurysms occurred in 5 patients (10.6%), 31.9% had suffered from an aneurysmal SAH in the past. Preoperative mRS ranged from 0 to 4. Most commonly was mRS of 0 (72.3%). Baseline characteristics are displayed in Table 1 (Table 1). Due to multiple aneurysms, 61 aneurysms were clipped. Mean aneurysm size was 5.1 mm (SD ± 3.7) (Table 2). The most common location was MCA, followed by AcomA (Fig. 2). Median PHASES Score was 5 (±2.5) (range 0–12). Extremely high PHASES scores

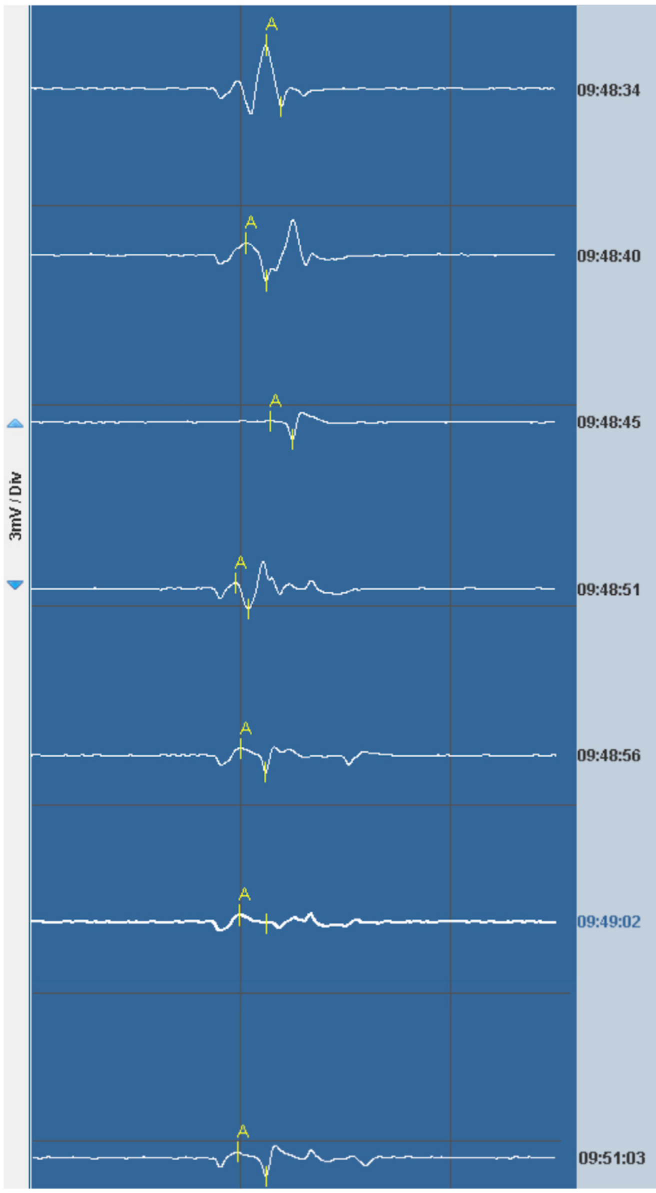

Fig. 1. tcMEPs of a patient with microsurgical clipping of an AcomA aneurysm. At 09:48:34: regular MEP amplitude; decreasing decline in amplitude of tcMEPs until 09:49:02 (>50% of the baseline amplitude: 0.365 mV–0.046 mV) 8 min after temporary clipping of the ICA. The temporary clip was subsequently removed at 09:49:02. At 09:51:03 beginning recovery of tcMEP amplitude 2 min after removal of the temporary clip.

≥10 were rarely seen (4.2%). Primary symptoms were very various, from headache (14.9%), vertigo (6.4%), previous SAH (31.9%) to other neurological symptoms, while 29.8% were asymptomatic. In preoperative clinical examination, 7 patients (14.9%) presented with a motor deficit, 1 patient (2.1%) had a sensory deficit, and 2 patients (4.3%) had a cranial nerve deficit.

3.2. IOM

IOM was technically successful in all 47 cases. Stable parameters (tcMEPs, SSEPs, AEPs, facial nerve EMG) throughout surgery were seen in 87.2%. In 6 cases (12.8%), there was a temporary decline in amplitude, all of them in tcMEP.

The recovery time ranged from 0.5 to 40 min (mean: 13.8 ± 18.5) (Table 3). In 2 of these cases, surgery was interrupted immediately, and

Table 1
Baseline characteristics of patients, risk factors and medical history.

Demographics	All patients (n = 47) N (%) or median (±SD)
Sex	F 36 (76.6)
	M 11 (23.4)
Age	57 (IQR 47–67)
Modified Rankin Scale (mRS)	
Preoperative mRS = 0	34 (72.3)
Preoperative mRS = 1	9 (19.2)
Preoperative mRS ≥2	4 (8.5)
Postoperative mRS = 0	33 (70.2)
Postoperative mRS = 1	9 (19.2)
Postoperative mRS ≥2	5 (10.6)
Risk factors	
Smoking	20 (42.6)
Former Smoking	7 (14.9)
Hypertension	19 (40.4)
Alcohol consumption (regularly)	4 (8.5)
Familial aneurysms	5 (10.6)
Medical history	
Previous SAH	15 (31.9)
Previous surgical clipping	7 (14.9)
Previous endovascular coiling	10 (21.3)

Table 2
Aneurysm characteristics regarding number, size, and associated PHASES Score.

PHASES Score	All patients (n = 47) N (%) or median (±SD)
Median PHASES Score	5 (range: 0–12)
Number of aneurysms	
1	28 (59.6)
2	10 (21.3)
3	5 (10.6)
>3	4 (8.5)
Size of aneurysms	
<5 mm	37 (55.2)
5–9.9 mm	24 (35.8)
10–19.9 mm	4 (6)
>20 mm	2 (3)
Mean size (mm)	5.1 (±3.7)
Median size (mm)	4 (±3.7)
Number of aneurysms treated	
1	37 (78.7)
2	7 (14.9)
3	2 (4.3)
>3	1 (2.1)

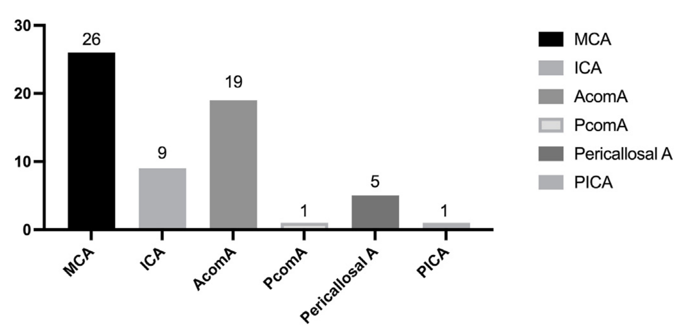

Fig. 2. Locations of Aneurysms clipped. MCA – Middle cerebral artery; ICA – Internal carotid artery; AcomA – Anterior communicating artery; PcomA – Posterior communicating artery; Pericallosal A – Pericallosal artery; PICA – Posterior inferior cerebellar artery.

the surgeon irrigated with a solution of nimodipine in saline. In 5 of 6 cases, disruptive factors could be identified: Circulatory deficits, aneurysm/vessel rupture and TC. In one case (patient:39), a temporary hypotension (blood pressure: 90/45 mmHg, mean arterial pressure: 60 mmHg) was the reason for the decline. After raising the blood pressure with noradrenaline, the amplitude recovered. In two cases (patients: 7,

Table 3
Patients with a transient tcMEP decline and their postoperative neurological status. Patient and aneurysm characteristics are presented. Furthermore, intraoperative data, including the modality of IOM that showed a decline in evoked potentials, the duration until recovery (min), the performance of temporary clipping and the number of declines in IOM. Postoperative focal neurological deficits are depicted. f = female, m = male, MCA = A. cerebri media, AcomA = A. communicans anterior.

Transient decline in IOM										
Patient			Aneurysm			Surgery				PostOP
ID	Sex	Age	PHASES	Location	Size (mm)	IOM decline: modality	Duration until recovery (min)	Temporary clipping (duration in min)	Number of declines (IOM)	New neurol. deficit postop
7	f	59	10	MCA	22	tcMEP	35	yes (18)	1	no
12	f	59	4	AcomA	6	tcMEP	40	yes (6)	1	no
37	f	57	5	MCA	3	tcMEP	0.5	yes (2)	2	no
39	f	70	9	Pericallosal A.	7	tcMEP	3	no	1	no
40	f	76	8	MCA	9	tcMEP	2	yes (3,5)	1	no
41	m	60	5	AcomA	5	tcMEP	2	yes (8)	1	no

12), the aneurysm ruptured during clipping resulting in tcMEP decline. After clipping, the amplitude returned to baseline.

In two other cases (patients: 37,41), the decrease was caused by TC of the parent artery. The EPs recovered after the temporary clip was removed. In one case (patient:40), there was no explanation found. There were no postoperative neurological deficits in the group with reversible tcMEP depletion. In the group with stable IOM, one patient developed a facial nerve palsy in the PACU. Facial nerve EMG, which is not able to monitor brainstem or cortical lesions, was performed in this case (Fig. 3).

3.3. *Validity of IOM in clipping of UIA*

NPV of 97.6% was calculated for IOM (including MEP, AEP, Facial nerve EMG). Furthermore, specificity was 87% for the included patients. As there are no patients with postoperative neurological deficit after transient decline of IOM, the Sensitivity and PPV are described with 0.

3.4. *Temporary clipping*

TC was performed in 12 cases (25.5%). The duration of TC ranged from 2 to 18 min (median 6 min ± 4.1). In 4 of 12 cases (33.3%), there was a decline in EPs during TC, all were reversible. Postoperative neurological outcome was uneventful. Patients with a reversible amplitude decline during TC can be further divided: In 50%, the decline was caused by application of the temporary clip. In the other 50%, a rupture of the aneurysm has occurred. Temporary clips were also applied here. In the first group, the decrease occurred 1.5 and 8 min after application of the temporary clip. After temporary clip removal, the amplitude returned to baseline. In the second group, the ruptured aneurysm was treated, by application of a permanent clip.

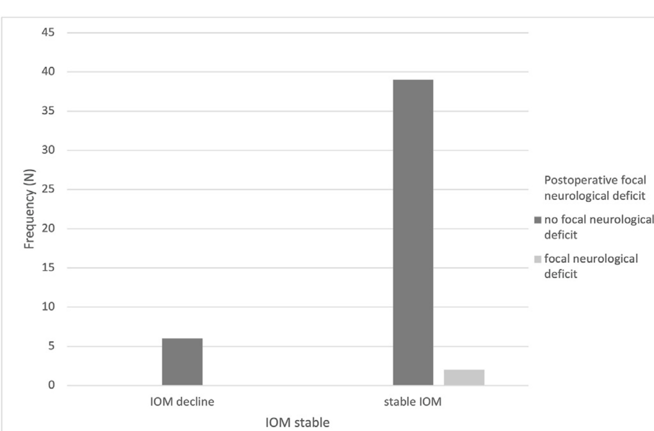

Fig. 3. Postoperative deficit of patients with stable IOM (tcMEP, SSEP, AEP, facial nerve EMG) and patients with decline in amplitude.

3.5. *Surgeon questionnaire*

Using IOM granted the surgeon a higher sense of security in 63.8% compared to the imagination of not having used IOM. There were no occasions in which the IOM had a negative impact. Especially during the clipping of MCA aneurysms, the surgeon reported a higher subjective feeling of security (Fig. 4).

In aspects of surgical outcome, in 80.9%, the surgeons considered the effect of IOM as neutral. In 19.1% IOM was identified as a positive impact on surgical outcome. Regarding the locations, a positive impact on the surgical outcome was observed especially after clipping of MCA (46.2% of all MCA aneurysms clipped) and AcomA (30.8%)

3.6. *False negative results*

There was one patient with aneurysm of PICA, who developed a facial nerve palsy (House and Brackmann III) in the PACU, still present at DOD. IOM was stable during surgery and postoperative DSA was uneventful. False negative cases must be divided into true and putative false negative cases. In a true false negative case, there is intraoperative diminished perfusion of an eloquent area monitored by IOM. Consequently, there should be a decrease in amplitude. On the other hand, secondary events (edema, hemorrhage, ischemia) can cause a postoperative neurological deficit, that could have not been predicted by IOM, as IOM measures the function during surgery. Further examination revealed that the neurologic deficit in our case was due to subacute ischemic complications after surgery (secondary event). Therefore, no true false-negative results were reported.

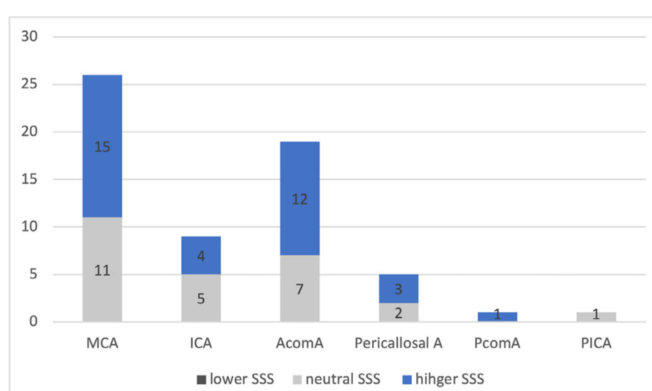

Fig. 4. Locations of aneurysms and the surgeons' subjective sense of security (SSS) using IOM compared to the imagination of not having used IOM during microsurgical aneurysm clipping at this location. Higher SSS: IOM provided the surgeon with a higher SSS during surgery compared to the hypothetical case of not having used IOM.

3.7. Postoperative evaluation

In 76.6%, there was an uneventful postoperative course. Adverse events (AEs) occurred in 23.4%, involving postoperative delirium, disorientation, decreased level of consciousness and neurological deficits. However, 90.9% recovered completely by DOD. Most AEs occurred either in the PACU (45.5%) or on POD 1 (36.4%).

4. Discussion

Our study shows a case series with a very low rate of postoperative neurological deficits. The results indicate, that for elective clipping of UIAs, IOM can prevent neurological deficits, by granting the surgeon information about the functionality of motor eloquent brain areas (Krieger et al., 1992). Furthermore, the study demonstrates that TC for up to 18 min may be possible without causing postoperative neurological deficits in our patient population. However, only the use of IONM can inform the surgeon on the tolerability of TC in the individual patient in terms of the development of new sensorimotor deficits. Yet, neuropsychological aspects, i.e. postoperative delirium, have not been subjected to our assessment and may still very well be second to transient ischemia below the hypoxic threshold.

4.1. IOM

EP acquisition was successful in all cases (100%), demonstrating IOM to be of exemplary easy-of-use without technical hindrances. This finding is in accordance with the previous literature (Choi et al., 2017; Szelényi et al., 2003; Krieg et al., 2012; Gläsker et al., 2006; Neuloh et al., 2007).

4.2. Temporary clipping

Our study proved TC, to be a potential reason for reversible amplitude drop. This causal relationship is in accordance with recent studies, showing that patients with TC, have a significantly higher risk of ischemic lesions in the vascular territory of the parent artery. (Park et al., 2021; Woertgen et al., 2008). Our study shows that TC with a duration of 18 min is possible without causing postoperative neurological deficits. Lavine et al. reports that patients only tolerate TC for 10 min (Lavine et al., 1997). According to Ogilvy et al. patients with TC < 20 min have a significantly lower risk for brain ischemia compared to patients with longer TC (Ogilvy et al., 1996).

Due to the real time feedback of IOM, the surgeon was always able to react immediately in the reversible phase of structural injury. Therefore, especially during TC, IOM is able to prevent neurologic impairments (Choi et al., 2017; Gonda et al., 2014). This crucial role of IOM in TC has not been described in previous literature in this way. Especially during TC of MCA and AcomA aneurysms our study revealed IOM to be highly advantageous.

4.3. False negative cases

In our study, there was one patient (PICA aneurysm), who developed a permanent facial nerve palsy in the PACU, even though IOM was uneventful. Few previous studies confirmed false negative cases in their reports. Greve et al. described five false negative cases in a cohort of 274 patients (Greve et al., 2019). Chung et al. observed eight cases with false negative IOM in a retrospectively collected patient cohort of 1514 patients (Chung et al., 2019). No mechanistic explanation was provided as for the origin of the false negative decline (Greve et al., 2019; Chung et al., 2019).

Neuloh et al. also reported a patient with a new transient facial nerve palsy. Analysis revealed that this case was not a real false negative case (Neuloh et al., 2007). In our case, the neurological deficit resulted from subacute ischemic complications after surgery. Therefore, this case in our study must be rated as putative false negative case. Additionally, regarding AEs after surgery, the importance of observation in the PACU is clearly demonstrated, as most of AEs were observed here.

We have made similar observations on false-negative measurements in a recent study elucidating IOM in glioma surgery. There, we reported five patients with new and permanently deteriorated motor function despite uneventful intraoperative recordings of tcMEPs. On closer analysis, all five cases were sequelae of adverse events secondary to the tumor resection (increased edema in one case, ischemia at the resection cavity border in two cases, postoperative hemorrhage needing revision surgery in two cases), As such, formally no true false negative cases were observed (Krieg et al., 2012). We therefore believe that genuine false-negative cases are an exception and commonly related to technical errors and secondary events.

4.4. Predictive value of IOM

Our study demonstrated that IOM has a high NPV. In cases where IOM remains stable or only exhibits temporary declines, the probability of a postoperative motor deficit is highly unlikely. The predictive value has frequently been under dispute (Nasi et al., 2020; Kombos et al., 2001, 2009; Krieg et al., 2012). In our study PPV and sensitivity were null, as there were no postoperative neurological deficits recorded after transient IOM decline. Therefore, the statistical value of the NPV and the specificity is very limited in our study. Recent studies have shown a high specificity and NPV, while sensitivity and PPV were low (Szelényi et al., 2003; Park et al., 2021; Chung et al., 2019).

4.5. Surgeons' perspective

In our investigations, IOM granted the surgeon a higher sense of security compared to conducting the procedure without IOM. A higher sense of security can encourage the surgeon during surgery (Gläsker et al., 2006). This is also reflected by the controlling of TC by tcMEPs.

In accordance to the literature, our study also demonstrated that IOM provides the surgeon with more confidence concerning the procedures' outcome for the patient (Krieg et al., 2012; Gläsker et al., 2006). There were no occasions in which IOM had a negative impact on surgeon's confidence.

By contrast, there was a discrepancy between the positive effects on the sense of security (63.8%) and the impact on objective surgical outcome (19.1%). The latter of which is a function of the overall surgical performance with IOM as one of the corner stones within the intraoperative decision-making framework. The surgeon's sense of security, however, is highly variable and may be unfounded during the course of surgery. A facet of the surgeon's persona, some may be unsure even without any clear indication of intraoperative injury or insult; it is in these cases that IOM may deliver a much-needed confirmation of the absence of injury and thus provide pivotal sense of security. This has not yet been examined in literature, and we hope to spark discourse with our study.

Naturally, a certain familiarity with IOM is critical to achieving the optimal outcome for the patient, particularly since the intraoperative signal changes may be difficult to interpret. The modality certainly presents a learning curve, often requiring a form of trial and error for the more ambiguous findings.

4.6. Study limitations

Limitation of the study is the number of patients ($N = 47$) included. To have a higher statistical power, a larger patient cohort is needed, as there would be a better distribution regarding the patients with stable IOM, transient decline and permanent decline in IOM. Furthermore, neuropsychological aspects, including postoperative delirium, were not included in this study.

5. Conclusions

IOM of tcMEPs remains invaluable during elective microsurgical clipping, particularly during TC of MCA and AcomA aneurysms. It provides reliable real-time information on the functionality of motor eloquent brain areas. Thus, it alerts the surgeon of impending ischemic injury and offers a way of maximizing the time frame for TC. Due to the different cerebral supply areas of the arteries, it is crucial to adapt the electrophysiological examination area to the arterial supply to obtain a reliable result. Furthermore, IOM has highly increased surgeons' subjective feeling of security during the procedure.

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Disclosures

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Declaration of competing interest

The study was financed from institutional grants. SK is consultants for Ulrich Medical (Ulm, Germany) and Need Inc. (Santa Monica, CA, USA); he received honoraria from Medtronic (Meerbusch, Germany), Nexstim Plc (Helsinki, Finland) and Carl Zeiss Meditec (Oberkochen, Germany). SI, SK and BM received research grants and are consultants for Brainlab AG (Munich, Germany). BM received honoraria, consulting fees, and research grants from Medtronic (Meerbusch, Germany), icotec ag (Altstätten, Switzerland), and Relievant Medsystemy Inc., Sunnyvale, CA, USA), honoraria, and research grants from Ulrich Medical (Ulm, Germany), honoraria and consulting fees from Spineart Deutschland GmbH (Frankfurt, Germany) and DePuy Synthes (West Chester, PA, USA), and royalties from Spineart Deutschland GmbH (Frankfurt, Germany).

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Not applicable.

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