Clinical Neurology and Neurosurgery 186 (2019) 105503

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Intraoperative neuromonitoring during microsurgical clipping for unruptured anterior choroidal artery aneurysm

Hyoung Soo Byoun[a], Chang Wan Oh[b], O-Ki Kwon[b], Si Un Lee[b], Seung Pil Ban[b], Sung Hoon Kim[b], Tackeun Kim[b], Jae Seung Bang[b,*,1], Sung Un Kim[c], Jongsuk Choi[c], Kyung Seok Park[c,**,1]

[a] Department of Neurosurgery, Chungnam National University Hospital, Daejeon, South Korea
[b] Department of Neurosurgery, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, South Korea
[c] Department of Neurology, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, South Korea

ARTICLE INFO

Keywords:
Aneurysm
Anterior choroidal artery
Ischemic complication
Intraoperative neuromonitoring
Microsurgical clipping

ABSTRACT

Objective: To investigate the safety and unexpected finding of the intraoperative neuromonitoring (IONM) including somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) during microsurgical clipping of an unruptured anterior choroidal artery (AChA) aneurysm.

Patients and methods: From January 2011 to March 2018, the neurophysiological, clinical, and radiological data of 115 patients who underwent microsurgical clipping for an unruptured AChA aneurysm under IONM were retrospectively analyzed. The incidence of ischemic complications after microsurgical clipping of unruptured AChA aneurysms as well as the false-negative rate, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IONM during surgery were calculated.

Results: Ischemic complications after the microsurgical clipping of an AChA aneurysm under IONM occurred in 7 of 115 patients (6.08%). Among them, 3 were symptomatic (2.6%). The false-negative rate of IONM for ischemic complications was 6.08% (7 patients). High specificity; 100% (95% confidence interval [95% CI] = 0.972–1.000), PPVs; 100% (95% CI = 0.055–1.000), and NPVs; 93% (95% CI = 0.945–0.973) with low sensitivity; 11.1% (95% CI = 0.006–0.111) were calculated.

Conclusions: IONM including transcranial MEP during microsurgical clipping of unruptured AChA aneurysm might have limited usefulness. Therefore, other MEP monitoring using direct cortical stimulation or modified transcranial methodology should be considered to compensate for it.

1. Introduction

Regardless of the current advances in endovascular techniques and devices, conventional surgical clipping for an intracranial aneurysm is indispensable. Complications after microsurgical clipping for unruptured intracranial aneurysms lead to morbidity and mortality; possible complications include cerebral infarction, intracerebral hemorrhage, seizure, hydrocephalus, wound infection, pulmonary and cardiac problems, systemic infection, and acute renal failure [1–4]. Morbidity and mortality rates after surgical clipping of unruptured intracranial aneurysms reported in meta-analyses ranged from 8% to 10.9% and from 1% to 2.6%, respectively [5,6].

Ischemic complications account for the largest portion of postoperative complications. Possible causes of cerebral ischemia during microsurgical clipping for unruptured aneurysms are parent artery stenosis or occlusion, temporary clipping, retraction injury, intraoperative aneurysm rupture, mechanical injury of the perforating artery, intraoperative vasospasm, embolic events, and a decrease in systemic blood pressure [7]. Tools to prevent ischemic complications by confirming the patency of parent vessels during microsurgical clipping

Abbreviations: AChA, anterior choroidal artery; CT, computed tomography; DM, diabetes mellitus; DSA, digital subtraction angiography; HTN, hypertension; IONM, intraoperative neuromonitoring; MEP, motor evoked potential; MRI, magnetic resonance image; mRS, modified Rankin Scale; NPV, negative predictive value; PPV, positive predictive value; SSEP, somatosensory evoked potential

* Corresponding author at: Department of Neurosurgery, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-Gu, Seongnam-Si, Gyeonggi-Do, South Korea.
** Corresponding author at: Department of Neurology, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-Gu, Seongnam-Si, Gyeonggi-Do, South Korea.
E-mail addresses: bang7842@snu.ac.kr (J.S. Bang), kpark78@naver.com (K.S. Park).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.clineuro.2019.105503
Received 14 February 2019; Received in revised form 18 August 2019; Accepted 26 August 2019
Available online 27 August 2019
0303-8467/

consist of mirrors, microvascular Doppler sonography, intraoperative digital subtraction angiography, intraoperative indocyanine green videoangiography, and intraoperative neurophysiology have developed [7–14].

The efficacy and safety of intraoperative neuromonitoring (IONM), including somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) have been reported and their importance has been emphasized [13,15–17]. Since regions supplied by the anterior choroidal artery (AChA) are associated with motor and sensory function, IONM is especially valuable during microsurgical clipping of aneurysms in this area. However, there are no tools without faults to prevent ischemic complication during aneurysm surgery.

In this study, we analyzed neurophysiological, clinical, and radiological data reguarding microsurgical clipping of the AChA aneurysms to investigate the safety of the IONM and to better prevent any devastating ischemic complications.

2. Materials and methods

2.1. Patient collection and baseline characteristics

The present study was approved by the institutional review board, which waived the need for informed consent. We retrospectively reviewed the medical records of 115 patients who underwent microsurgical clipping for an unruptured AChA aneurysm under IONM from January 2011 to March 2018 in our institution. We excluded the patients who were not followed up after surgery, had a ruptured aneurysm, or had intracranial pathologies such as an infection, tumor, vascular malformation, and a previous stroke at the surgical site that could produce confounding effects with IONM.

Baseline characteristics of the included patients were gathered using the clinical data warehouse system of our institution. Patient characteristics were age; sex; preoperative modified Rankin Scale (mRS) values; and history of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, heart disease, drug, and previous stroke. Aneurysm characteristics were the location of the aneurysm, maximal size, neck size, dome to neck ratio, daughter sac, and multiplicity. Operation characteristics were temporary clipping, duration of operation, re-operation, and simultaneous multiple treatments. The clinical outcome was evaluated using mRS values at discharge and at 6months after the operation. Postoperative complications were divided into 2 categories (radiological and clinical). Radiological complications could be ischemic, hemorrhagic, or functional while clinical complications were either symptomatic or asymptomatic.

2.2. Operative procedures and postoperative protocol

A standard pterional craniotomy and *trans-sylvian* approach was used to perform microsurgical clipping for the AChA aneurysms. Temporal lobe retraction before temporary or permanent clip application was avoided to prevent an intraoperative rupture of the aneurysm. Removal of the temporary clip, removal or repositioning of the permanent clip, relief of the brain retractor, and discontinuation of dissection were performed whenever a significant IONM change was detected. Also, the interval of temporary clipping was more than 5-minutes to allow the changed evoked potential to recover. Immediate postoperative brain computed tomography (CT) was performed to identify postoperative complications. Then, the patient was moved to the intensive care unit without being awakened from general anesthesia. If the patient showed no abnormalities in the immediate postoperative neurologic examination, extubation was performed. However, if neurologic deterioration was suspected, additional evaluations using magnetic resonance imaging (MRI) including diffusion-weighted image and/or digital subtraction angiography (DSA) were performed to detect and address any perioperative complications. If no neurologic deterioration was observed, routine follow-up brain CT and DSA or CT angiography was performed within 7 days postoperatively. Clinical outcomes of the patient were evaluated using the mRS scores [18] at 1 months and 6 months postoperatively.

2.3. Anesthesia

Total intravenous anesthesia with propofol (3–4 mg/mL) and remifentanil (1.5–4 mg/mL) was performed. Neuromuscular blockade was applied just before intubation (0.5–0.9 mg/kg rocuronium) to avoid potential confounding effects on MEP monitoring.

2.4. Transcranial motor evoked potentials and somatosensory evoked potentials

Transcranial electrical stimulation was delivered using needle electrodes. Multipulse transcranial electrical stimulation was applied using a commercially available electrical stimulator (Xltek protektor 32 IOM system; Natus Medical Inc, Ontario, Canada). In accordance with the international 10–20 electroencephalogram (EEG) system, the C1 anode and C2 cathode pairs or the C3 anode and C4 cathode pairs were used for stimulation of the left hemisphere, and the reverse arrangement was used for stimulation of the right hemisphere. Montage which elicited more prominent motor evoked potentials was chosen in each patient. A train of 5 square-wave stimuli was delivered with an individual pulse duration of 0.05 ms, an inter-stimulus interval of 2–4 ms, a time base of 100 ms, and a 10–1000 Hz filter. Stimulation intensities were set to levels to obtain motor evoked potentials of all recording muscles of the contralateral side. In case of significant amplitude decrease, stimulation intensities were increased within the limit of 30% of the baseline level. The overall intensities ranged from 250 to500 V. Motor evoked potentials were recorded by using subdermal insertion of needle electrodes placed in the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles for the upper extremities, whereas they were placed in the tibialis anterior (TA) and abductor halluces (AH) muscles for the lower extremities.

Our SSEP monitoring protocol has been described in a previously reported study of ours [19]. In order to obtain SSEPs, we administered square-wave 0.3-ms electrical pulses with an intensity of 15 mA for the upper extremities and 20 mA for the lower extremities at a frequency of 2.31 Hz. Needle-stimulating electrodes were placed at the wrist and ankle to stimulate the median and posterior tibial nerves, respectively. Recording needle electrodes were placed at C3' (2 cm posterior to C3), C4' (2 cm posterior to C4), Cz', the fifth cervical spine, Erb's point, and the popliteal fossa. In addition, a reference electrode was placed at Fpz. The frequency of the high-pass filter was 30 Hz and that of the low-pass filter was 1000 Hz.

2.5. Alarm criteria

We defined the alarm criteria for MEPs as a complete loss of or a reduction of more than 50% compared to the baseline MEP amplitudes. This alarm criteria applied to all muscles recorded. We defined the alarm criteria for SSEPs as a decrease in amplitude of more than 50% compared to the baseline SSEP amplitudes, and/or a 10% delay compared to the baseline SSEP latency. Two experienced electrophysiologists blinded to the patients' clinical information reviewed the IONM data.

2.6. Definition of a false-negative finding

False-negative cases were defined as the patients who had no significant evoked potential changes, or transient significant change for less than 13 min. Meaningful duration for significant EP changes were reported previous reports [20,21].

Also, such cases showed postoperative neurologic deterioration or had a newly developed brain lesion confirmed by postoperative brain

Table 1
Baseline characteristics for 115 patients performed microsurgical clipping of the anterior choroidal artery aneurysm.

Variable	Value
Age (year)	54.66 ± 9.12
Sex (n, %)	
Female	79 (68.7)
Side (left)	57 (49.6)
HTN	48 (41.7)
DM	7 (6.1)
Hyperlipidemia	32 (27.8)
Heart disease	6 (5.2)
Previous stroke history	8 (6.9)
Drug (Anti-platelet or anticoagulation)	1 (0.9)
Aneurysm characteristics	
Mean max size	3.47 ± 1.92
Mean neck size	2.69 ± 1.14
Mean dome to neck ratio	0.97 ± 0.36
Daughter sac	26 (22.6)
Multiplicity	49 (42.6)
Operation duration (min)	240.79 ± 90.60
Simultaneous multiple treatment	46 (40.0)
Temporary clipping	38 (33.0)
Preoperative mRS (0 – 1)	114 (99.9)

n, number; HTN, hypertension; DM, diabetes mellitus; min, minute; mRS, modified Rankin Scale.

CT or MRI. Then, sensitivity, specificity, the positive predictive value (PPV), and the negative predictive value (NPV) for each evoked potential and the overall SSEP and MEP changes were calculated.

2.7. Statistical analysis

Continuous variables are reported as the mean ± standard deviation using commercial software (IBM SPSS Statistics, version 22; IBM Corp, Armonk, NY). A Blaker exact 95% confidence interval using the PropCIs" package in R software version 3.1.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria) was used to calculate sensitivity, specificity, PPVs, and NPVs [22].

3. Results

One-hundred-fifteen patients underwent microsurgical clipping of an unruptured AChA aneurysm with IONM from January 2011 to March 2018. Demographic data and aneurysm characteristics of all 115 patients are shown in Table 1. The mean age of the patients was 54.66 years. Forty-nine patients had multiple aneurysms and simultaneous clipping for multiple aneurysms was performed in 46 patients. Due to a previous hemorrhagic stroke, 1 patient had a neurologic deficit (mRS score: 4).

Clinical and radiological outcomes are presented in Table 2. Mortality and morbidity at 6 months were 0% and 2.61%, respectively. The overall complication rate after microsurgical clipping was 12.17% (14 patients). Ischemic complications occurred in 7 patients (6.08%). Among them, symptomatic ischemic complications (Fig. 1) and silent ischemic complications (Fig. 2) occurred in 3 patients (2.6%) and 4 patients (3.5%), respectively. Two patients (1.74%) suffered permanent neurologic deficits. Three patients had hemorrhagic complications. However, these patients did not show any neurologic symptoms. Two patients suffered transient third nerve palsy that was improved within 6 months. One patient suffered permanent anosmia. Three patients underwent a re-operation. One patient suffered an infection at the surgical site. Clip repositioning was performed in the remaining 2 patients; among them, 1underwent clip repositioning within 6 h after initial clipping surgery because of postoperative neurologic deterioration including hemiparesis, facial palsy, and aphasia. That patient showed no significant changes on IONM throughout the surgery. Fortunately, the patient showed full recovery after the re-operation without any radiological abnormalities. However, the other patient who underwent a re-operation suffered permanent neurologic deficit including grade 3 hand motor weakness and ptosis. Post-operative brain CT results of this patient showed significant low density on left posterior limb of the internal capsule and corona radiata.

Table 2
Clinical and radiological outcomes.

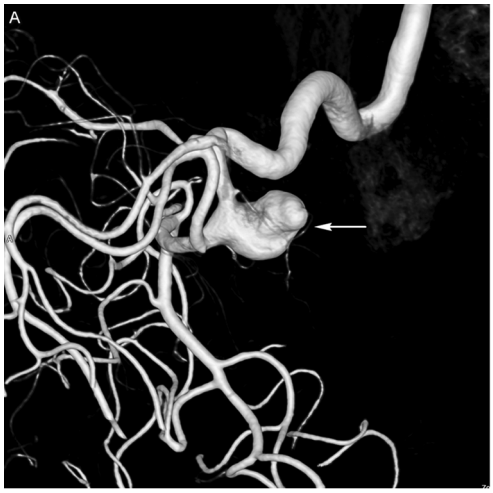
Variable	Value
Complications, n (%)	
Ischemic	7 (6.08)
Asymptomatic	4 (3.48)
Symptomatic	3 (2.61)
Permanent	2 (1.74)
Transient	1 (0.87)
Hemorrhagic	3 (2.61)
Asymptomatic	3 (2.61)
Symptomatic	0 (0)
Permanent	0 (0)
Transient	0 (0)
Functional and Miscellaneous	4 (3.48)
Third nerve palsy	2 (1.74)
Anosmia	1 (0.87)
Infection	1 (0.87)
Re-operation, n (%)	3 (2.61)
Clip reposition	2 (1.74)
Surgical site infection	1 (0.87)
mRS at discharge, n (%)	
0	87 (75.65)
1	21 (18.26)
2	4 (3.48)
> 2	3 (2.61)
mRS at 6months, n (%)	
0	104 (90.43)
1	7 (6.08)
2	1 (0.87)
> 2	3 (2.61)

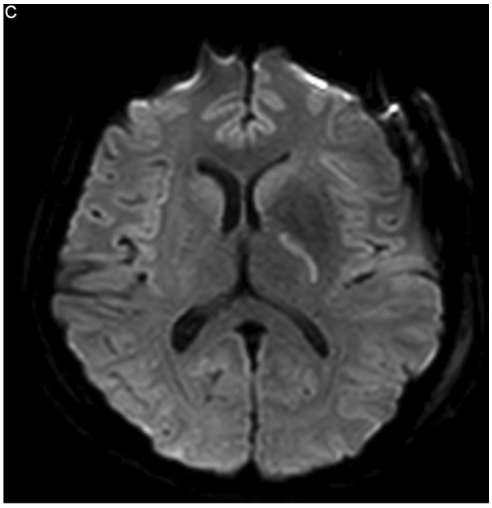
n, numbere; mRS, modified Rankin Scale.

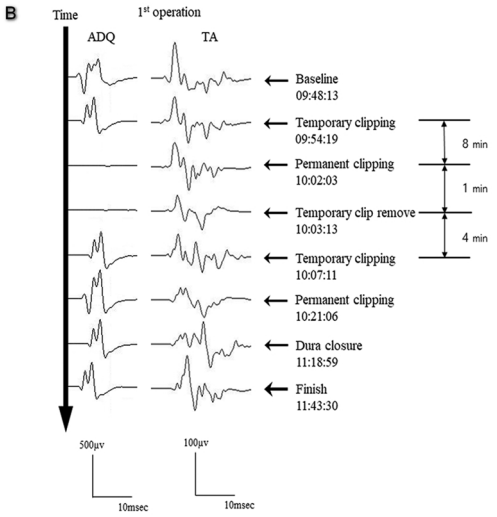
Significant changes in IONM were revealed in 5 patients. (Table 3). SSEP changes or MEP changes alone were shown in 1 patient (Case 3) and 2 patients (Cases 2 and 5), respectively. Both SSEP and MEP changes were evident in 2 patients (Cases 1 and 4) during surgery. The significant changes detected via IONM had recovered fully by the end of the surgery. Two patients (Case 2 and 5) suffered acute infarction in the AChA territory with significant neurologic deficits. (Fig. 3) Detailed information for the patients who suffered ischemic and hemorrhagic complications is shown in Table 4. IONM data for the patients who suffered ischemic and hemorrhagic complications revealed that there were no SSEP changes during surgery. The 2 patients who suffered ischemic complications showed transient MEP change during surgery. At the end of surgery, there were no abnormal intraoperative evoked potential changes in any patients who suffered ischemic or hemorrhagic complications.

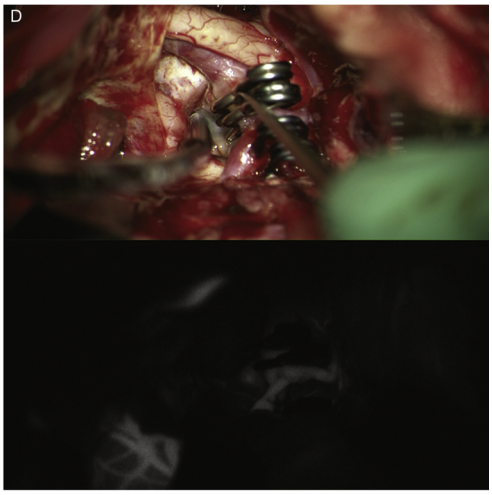
The most severe radiological complications associated with microsurgical clipping of the AChA aneurysms occurred in 6 patients. In these patients, data from brain CT or diffusion-weighted MRI performed within 7 days of the operation showed postoperative infarction in the territories of the AChA with different lesion sizes.

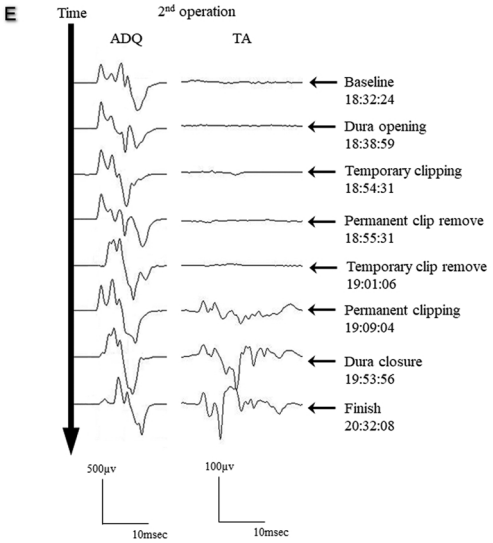
The false-negative rate of IONM for ischemic complications was 6.08% (7 patients: 6 patients who suffered ischemic complications, 1 patient who underwent clip repositioning and recovered fully without any radiological abnormalities). Furthermore, associated symptomatic complications occurred in 2.60% of the cases (3 patients). Sensitivity, specificity, PPVs, and NPVs of the SSEP and MEP changes are summarized in Table 5. Our data showed high specificity; 100% (95% confidence interval [95% CI] = 0.972–1.000), PPVs; 100% (95% CI = 0.055–1.000), and NPVs; 93% (95% CI = 0.945–0.973) with low











(caption on next page)

Fig. 1. (**A**) A 50-year-old woman had a 15.2 mm unruptured left anterior choroidal artery (AChA) aneurysm. The AChA arose from dome of the aneurysm (white arrow). After temporary clipping was performed at internal carotid artery, M1, and A1 segments, permanent clips were applied. Afterwards, the aneurysm was completely obliterated. (**B**) Motor evoked potentials (MEPs) were completely lost within 5 min after the temporary clipping. However, it recovered completely after the temporary clip was removed. Indocyanine green (ICG) videoangiography and Doppler sonography confirmed the complete obliteration of the aneurysm. We monitored any changes in somatosensory evoked potentials (SSEPs) and MEPs for 1 h after the permanent clipping without any surgical procedures. No evoked potential changes were noticed during the hour. Furthermore, there were no evoked potential changes through the end of the surgery. (**C**) An immediate post-operative neurologic examination showed right side hemiparesis (grade 2), central type facial palsy, left ptosis, and a left medial gaze limitation. Emergent brain magnetic resonance imageing with diffusion-weighted images revealed an acute infarction at the posterior limb of the left internal capsule. (**D**) Re-exploration and remodeling of the aneurysm by multiple clips was performed to maintain the flow of the AChA. ICG videoangiography and Doppler sonography confirmed the blood flow of the AChA. (**E**) The MEP amplitude before re-exploration had dropped more than 50%, so the clips were repositioned. The MEP amplitude was normalized after clip repositioning. After the re-operation, the neurologic deterioration of the patient improved and patent blood flow of the AChA was identified in post-operative digital subtraction angiography. However, the patient suffered neurologic deficits including right hand weakness, left ptosis, and mild dysarthria. Her modified Rankin Scale score at discharge and 6 months after discharge was a 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

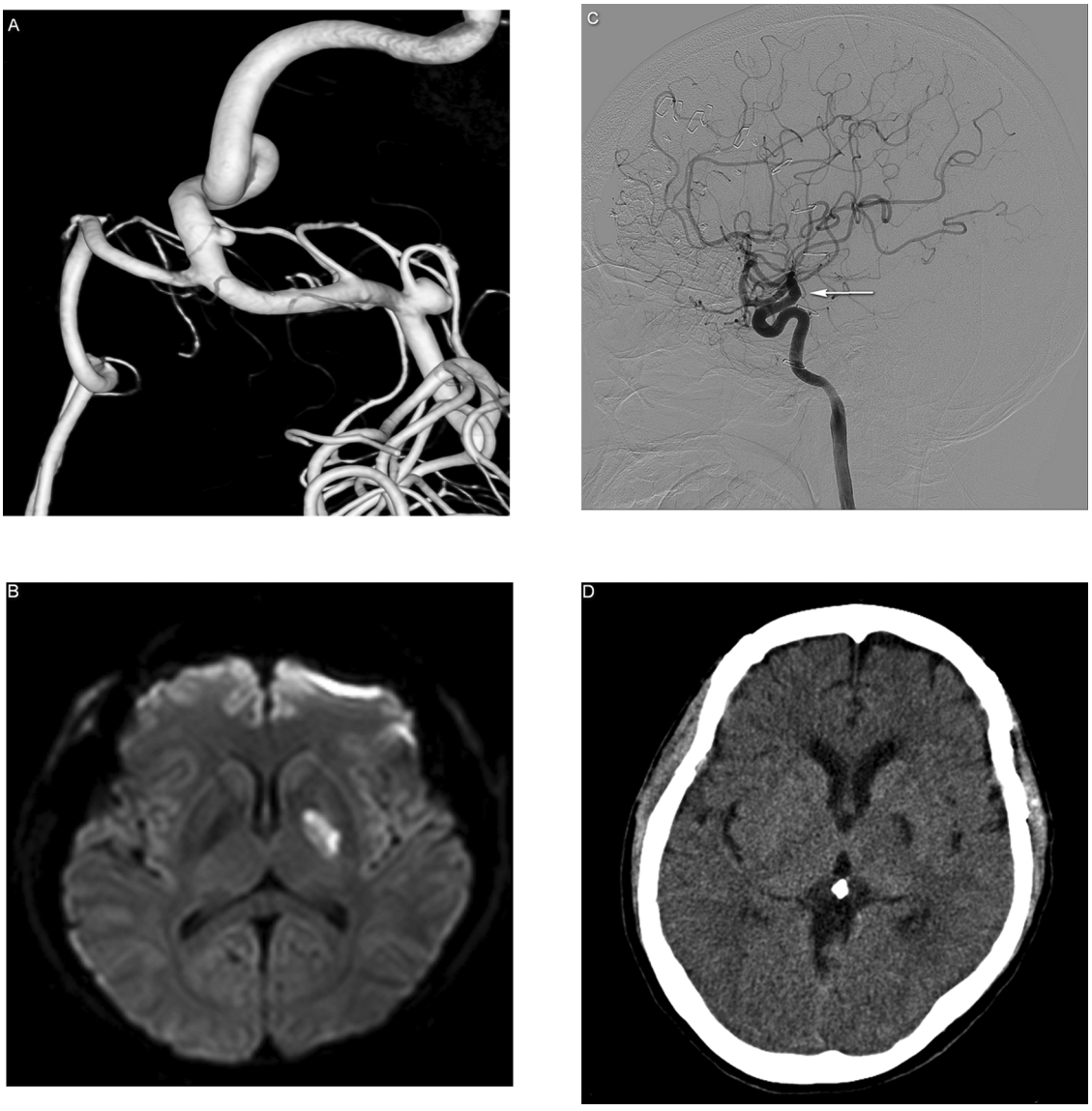


Fig. 2. (**A**) A 54-year-old woman had multiple unruptured intracranial aneurysms including in the left anterior choroidal artery (AChA) (2.4 mm) and both middle cerebral artery bifurcations (MCABs) (5.1 mm, left and 2 mm, right). The left AChA and MCAB aneurysms were clipped simultaneously. Then, the right MCAB aneurysm was clipped via a contralateral approach. No intraoperative evoked potential changes were noticed during the surgery. (**B**) Imediate postoperative neurologic examination revealed right side motor weakness (grade 4) and blurred vision without ptosis and external ocular movement limitation. Emergent brain magnetic resonance imageing (MRI) with diffusion weight images performed immediately showed a 2 cm sized acute infarction at the territory of the anterior choroidal artery including the left corona radiata, adjacent basal ganglia, and posterior limb of the internal capsule. (**C**) Subsequently, emergent digital subtraction angiography was performed. The left AChA was not compromised (white arrow). Postoperatively, an intravenous steroid injection and proper hydration was maintained for 3days and 7days respectively. (**D**) A follow-up brain computed tomography was performed 7 days after surgery, which showed an old infarction on the regions confirmed via the previous brain MRI. The patient was discharged 10 days postoperatively with blurred vision and a modified Rankin Scale score (mRS) of 2. The blurred vision improved 1 months after surgery and the mRS score changed to 1.

Table 3
Significant changes in intraoperative evoked potential monitoring during microsurgical clipping of anterior choroidal artery aneurysm.

SSEP changes

Case No.	Age / Sex	Duration of SSEP change	MNSEP change	Lo. MNSEP during surgery, % of baseline	PTSEP change	Lo. PTSEP during surgery, % of base line	Cause of SSEP change	Recovery	Radiological abnormality	Clinical Sx	mRS*
1	F/63	5	+	0	+	0	Permanent clipping	complete	None	None	0
2-1	F/50	NA	–	100	–	100	NA	NA	Acute infarction, posterior limb of the IC.	Right hand weakness facial palsy	3
2-2		NA	–	100	–	100	NA	NA			3
3	F/49	2	+	0	+	0	Temporary clipping	complete	None	None	0
4	F/51	8	+	0	+	0	Temporary clipping	complete	None	None	0
5	F/70	NA	–	100	–	100	NA	NA	Acute infarction, posterior limb of the IC, hippocampus, medial temporal lobe	Hemiparesis, homonymous hemianopsia	4

MEP changes

Case No.	Age / Sex	Duration of MEP change	TAMEP change	Lo. TAMEP during surgery, % of baseline	AHMEP change	Lo. AHMEP during surgery, % of baseline	ADQ or APBMEP change	Lo. ADQ or APBMEP during surgery, % of baseline	Cause of MEP change	Recovery	Radiological abnormaility	Clinical Sx	mRS
1	F/63	6	+	0	–	100	+	0	Permanent clipping	complete	None	None	0
2-1	F/50	5	–	100	–	100	+	0	Temporary clipping	complete	Acute infarction, posterior limb of the IC	Right hand weakness facial palsy	3
2-2		NA	+	0	–	100	+	18	initial	complete	Acute infarction, posterior limb of the IC	Right hand weakness facial palsy	3
3	F/49	NA	–	100	–	100	–	100	NA	NA	None	None	0
4	F/51	8	+	0	+	0	+	24	Temporary clipping	complete	None	None	0
5	F/70	17	+	11.6	+	0	+	0	Dura closure	complete	Acute infarction, posterior limb of the IC, hippocampus, medial temporal lobe	Hemiparesis, homonymous hemianopsia	4

SSEP, somatosensory evoked potential; MNSEP, median nerve somatosensory evoked potential; Lo., lowest; PTSEP, posterior tibial nerve somatosensory evoked potential; Sx, symptom; mRS, modified Rankin Scale; IC, internal capsule; MEP, motor evoked potential; TAMEP, tibialis anterior motor evoked potential; AHMEP, abductor hallucis motor evoked potential; ADQ, abductor digiti quinti; APBMEP, abductor pollicis brevis motor evoked potential; NA, not available.

* mRS score at 6 months after discharge.

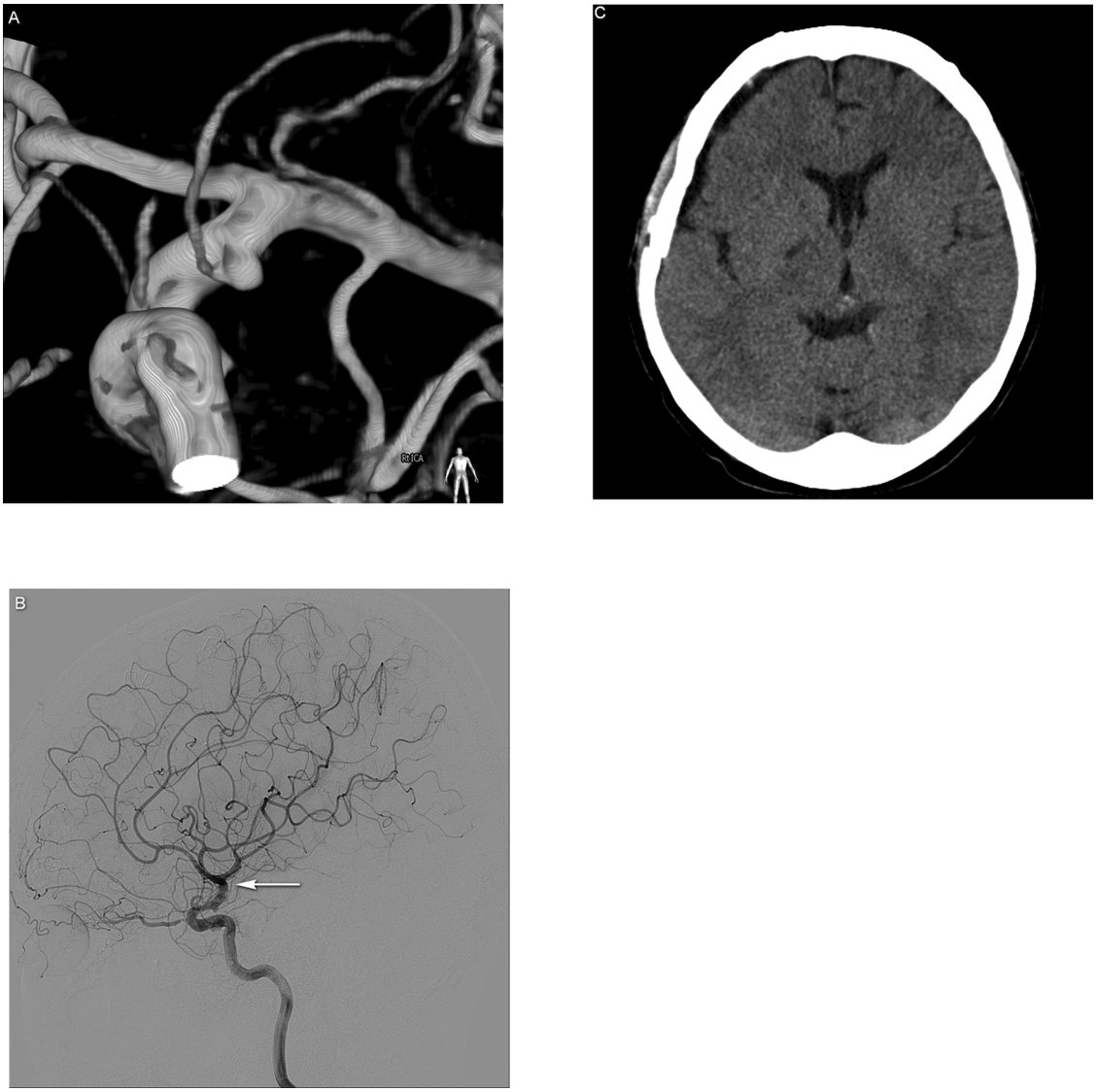


Fig. 3. (**A**) A 48-year-old woman had multiple unruptured intracranial aneurysms including in the right anterior choroidal artery (AChA) (2.8 mm), the right superior cerebellar artery (SCA) (2.3 mm), the left internal carotid artery bifurcation (ICAB) (1.2 mm), the M1 segment (3 mm), and basilar artery bifurcation (BABIF) (2.8 mm) aneurysms without any symptoms. The left ICAB and M1 aneurysms had been clipped 4 months before. The right AChA, SCA, and BABIF aneurysms were clipped simultaneously. There were no abnormal findings regarding the intraoperative evoked potential monitoring during microsurgical clipping. Immediate post-operative mobile brain computed tomography (CT) results showed no unusual findings. The patient recovered from general anesthesia without any neurologic deterioration. (**B**) The post-operative digital subtraction angiography performed 5 days after surgery showed no abnormal findings, including an intact flow of the right AChA (white arrow). (**C**) However, a follow-up brain CT performed 7 days after surgery revealed an old infarction at the territory of the AChA including the right posterior limb of the internal capsule and hippocampal head. The patient was discharged 8 days postoperatively without any neurologic deficits and a modified Rankin Scale score of 1.

sensitivity; 11.1% (95% CI = 0.006–0.111). However, due to the small sample size, there were no statistically significant findings.

4. Discussion

The incidence of ischemic complications after microsurgical clipping of unruptured intracranial aneurysms ranged from 1.0% to 13.2% in previous studies [3,6]. Reported incidence rates of ischemic complications after microsurgical clipping of AChA aneurysms ranged from 11.4% to 16% [23,24]. These incidence rates are higher than that in our study: 6.08% overall with 2.6% being symptomatic. Though ruptured AChA aneurysms were included in previous studies, the incidence of ischemic complications of this study was lower than previous studies.

The false-negative rate of IONM for ischemic complications after microsurgical clipping of an unruptured AChA aneurysm in present study was 6.08%. This result was higher than the previously reported false-negative rate of IONM for ischemic complications after microsurgical clipping of unruptured aneurysms (0-0.53%) [17,25]. Irie et al. reported false-negative rate of INOM for ischemic complications after microsurgical clipping of unruptured AChA aneurysm (2.85%).They used transcranial MEP monitoring like our study [16]. However, no false-negative finding and one case of false-positive finding were reported in another study that used MEP monitoring with direct cortical stimulation during microsurgical clipping of unruptured AChA aneurysm [26]. Our false-negative finding of IONM using our transcranial electrical stimulation protocol might be influenced by deep penetration of electrical stimulus applied transcranially. Nevertheless, high specificity and NPVs with low sensitivity of the SSEP and MEP changes were similar to previously reported results [13,15,17,25,27].

Table 4
Information for the patients suffered ischemic and hemorrhagic complications.

Case	Age (yr)/	Aneurysm characteristics				Intraoperative monitoring		Radiologic	Lesion	T-	Neurologic	mRS*
No.	Sex	Max size (mm)	Neck size (mm)	Type	Multiple Tx.†	SSEP change	MEP change	finding	Size (mm)	clip	deficit	
①	F/66	4.3	3.6	S	–	None	None	Infarction at right anterior temporal lobe	33	–	None	0
②§	F/50	15.2	7.6	F	–	None	Transient	Infarction at left posterior limb of the IC	20	+	Ptosis, hand weakness	3
③	M/53	2.1	2.1	S	–	None	None	Small infarction at right posterior limb of the IC	5.5	+	None	0
④	M/58	3.5	3.0	S	–	None	None	Small infarction at right posterior limb of the IC and GP	15	–	None	0
⑤¶	F/70	6.1	4.8	S	–	None	Transient	Infarction at right medial temporal lobe, hippocampus, and posterior limb of the IC	30	–	Hemiparesis Homonymous hemianopsia	4
⑥	F/48	2.8	2.8	S	+ SCA	None	None	Small infarction at right posterior limb of the IC and head of hippocampus	12	–	None	0
⑦	F/54	2.4	2.3	S	+ Both MCAB	None	None	Infarction at left CR, adjacent BG, and posterior limb of the IC	20	–	None (transient Sx: weakness and blurred vision)	0
⑧	F/56	2.3	2.0	S	–	None	None	ICH at right frontal and temporal lobe	10	–	None	0
⑨	M/43	6.8	3.9	S	+ PCoA	None	None	IVH at right lateral ventricle	NA	+	None	0
⑩	F/64	5.0	3.4	S	–	None	None	ICH at right temporal lobe	15	–	None	0

yr, year; T-clip, temporary clip; mRS, modified Rankin Scale; Tx, treatment; F, female; S, saccular; F, fusiform; IC. internal capsule; M, male; GP, globus pallidus; SCA, superior cerebellar artery; MCAB, middle cerebral artery bifurcation; CR, corona radiata; BG, basal ganglia; Sx, symptom; ICH, intracerebral hemorrhage; PCoA, posterior communicating artery; IVH, intraventricular hemorrhage.

* mRS score at 6 months after discharge.

† Simultaneous clipping of multiple aneurysm.

§ Same patient with case 2 of Table 3.

¶ Same patient with case 5 of Table 3.

Table 5
Sensitivity, specificity, PPV, and NPV for intraoperative SSEP and MEP monitoring.

Characteristic	MEP change with significant duration	SEP change with significant duration	Overall EP change with Significant duration (95% CI)
Sensitivity	0.125 (0.007–0.125)	0.125 (0.007–0.125)	0.111 (0.006–0.111)
Specificity	1.000 (0.991–1.000)	1.000 (0.991–1.000)	1.000 (0.991–1.000)
PPV	1.000 (0.055–1.000)	1.000 (0.055–1.000)	1.000 (0.055–1.000)
NPV	0.939 (0.930–0.939)	0.939 (0.930–0.939)	0.930 (0.922–0.930)

PPV, positive predictive value; NPV, negative predictive value; MEP, motor evoked potential; SEP, somatosensory evoked potential; CI, confidence interval; NA, not available.

4.1. Limitation of IONM and anatomical consideration

Thorough preparations such as a robust understanding of the course of the vessels near the aneurysm, careful manipulation of vessels during aneurysm surgery, and useful monitoring tools for blood flow insufficiency including IONM make it possible for surgeons to prevent devastating postoperative and perioperative ischemic complications. Especially, IONM detects insufficient blood flow quantitatively during an aneurysm surgery. The efficacy of IONM has been reported in several studies; IONM using SSEPs and MEPs had higher diagnostic accuracy in predicting blood flow insufficiency [13,17,28]. Therefore, it is considered a useful and reliable tool to prevent postoperative ischemic complications.

Although IONM is effective and reliable, surgeons should pay close attention to its applications and the interpretation of the data due to its limitations and faults. Unexpected postoperative motor deficits can occur eventuated from false-negative results that IONM failed to detect during aneurysm surgery. Possible causes of the false-negative results during aneurysm surgery include stimulus intensity, direct stimulation of deeper structures within the subcortical motor pathway, impairment in the supplemental motor area that was not located in the corticospinal pathway, sinking of the brain during surgery caused by excess cerebrospinal fluid drainage, delayed perfusion caused by hypotension, cerebral edema, and lacunar infarction after terminating the evoked potential monitoring were reported in previous studies [15,25]. Also, the alarm criteria of evoked potential changes and the influence of the duration of a significant decrease in evoked potentials were reported and interpreted differently in previous studies; thus, the safety margin of alarm criteria and duration of an evoked potentials change monitored to prevent postoperative neurologic deficits have been obscure [13,15,17,25,26,29,30].

IONM detected the injuries of regions located on the ascending sensory and descending motor tracts. Ischemic injuries not associated with those regions could not be found during surgery, which is a weak point of the IONM. Postoptic perforators of the AChA supply the posterior limb of the internal capsule containing ascending somatosensory fiber from the ventral posterior thalamic nucleus (the middle thalamic radiation) and descending motor fiber through the middle third of the cerebral peduncle, the origin of the optic radiations through the posterior optic tract, and the periphery of the lateral geniculate body. Damage to these perforators would result in definite contralateral hemiplegia, hemianesthesia, and homonymous hemianopsia. Contrary to postoptic perforators, preoptic perforators directed to the mesial temporal region have abundant anastomosis with the medial posterior choroidal artery, posterior communicating artery, and leptomeningeal arteries. Therefore, visual disturbances according to the damage of these perforators were often transient [31,32].

4.2. Mechanism of ischemia

In the present study, postoperative DSA of 3 patients revealed that they suffered immediate postoperative motor deficits evident via the occlusion of the AChA. One patient showed repeatedly significant MEP decreases during dura closures. The other patients showed no or transient MEP decreases during surgery.

Compromising of the AChA by permanent clipping and the torsion after releasing brain retraction, thromboembolism during manipulation of the AChA including temporary clipping, vasospasm, and glial edema were the main causes of postoperative ischemic complications [24,33]. Territories supplied by the AChA located along the corticospinal pathway, especially the posterior limb of the internal capsule, could receive some collateral flow from the perforating artery of the posterior communicating artery [34]. Therefore, reduced or occluded blood flow from the AChA by permanent clip torsion could be alleviated by the collateral flow to some degree. However, insufficient blood flow that does not to maintain adequate perfusion induces an ischemic condition; it also triggers local acidosis, glial edema, and decreased capillary perfusion that exacerbate compromised perfusion for the brain tissue [35,36].

Importantly, white matter of the brain has higher ischemic thresholds and greater resistance to ischemia than gray matter [37–40]. The posterior limb of the internal capsule containing the corticospinal tract is a white matter structure that contains both ascending and descending axons, going to and coming from the cerebral cortex. Therefore, it may temporarily withstand ischemic injury caused by a compromised AChA. Furthermore, a false-negative result during the microsurgical clipping of an AChA aneurysm in our study could be interpreted as this phenomenon.

4.3. Silent ischemia

The risk of silent ischemia associated with microsurgical clipping was 9.8% per treated aneurysm. Significant risk factors were age, the presence of thrombus, the number of permanent clips applied, number of temporary clips used, total time of temporary clip occlusion, and maximum time of temporary occlusion. The formation of new microthrombi or the detachment of existing thrombi due to frequent surgical manipulation using temporary or permanent clips was considered a possible cause of silent ischemia [41]. In the present study, postoperative infarction without any neurologic deterioration occurred in 4 patients (3.5%). Among them, postoperative infarctions correlated with the territory of the AChA occurred in 3 patients (2.6%). The reason why silent infarctions in the territory of the AChA occurred in 3 patients in present study requires further investigation.

Silent brain infarctions are not meaningless. They present as subtle deficits in physical and cognitive function that commonly go unnoticed. Especially, the risk of dementia and a steeper decline in cognitive function is higher in elderly patients with a silent brain infarction [42,43]. Therefore, prevention of both symptomatic and asymptomatic ischemic complications is needed and mandatory.

4.4. Limitations of this study

First, our study has a retrospectively design; therefore, it might have a potential selection bias. Second, the duration of temporary clipping, the number of permanent and temporary clipping attempts, and the condition of the internal carotid artery such as atherosclerotic changes, are not evaluated exactly due to imperfective medical records. Third,

there were a small number of patients with a lower rate of evoked potential changes. Therefore, statistical analysis could not be available to evaluate the factors associated with ischemic complications. Fourth, transcranial MEP monitoring might induce higher false-negative finding than direct cortical stimulation MEP monitoring due to deep penetration of stimulus.

5. Conclusions

Based on our results, IONM including transcranial MEP to prevent postoperative ischemic complications during microsurgical clipping of an AChA aneurysm shows higher false-negative rate and lower sensitivity. It means that this MEP methodology might have limited usefulness in this situation. Therefore, if neurosurgeons use transcranial MEP monitoring, it should be interpreted with great caution. Direct cortical stimulation MEP monitoring or modified transcranial MEP monitoring may be needed to reduce possible false-negative finding of IONM due to deep penetration of electrical stimulus. Also, surgeons should consider the anatomical characteristics of the AChA and pathophysiological consequences of brain white matter to reduce ischemic complications and false-negative results during microsurgical clipping of an AChA aneurysm.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-forprofit sectors.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] A. Alshekhlee, S. Mehta, R.C. Edgell, N. Vora, E. Feen, A. Mohammadi, S.P. Kale, S. Cruz-Flores, Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysm, Stroke 41 (2010) 1471–1476, https://doi.org/10.1161/STROKEAHA.110.580647.

[2] R. Gerlach, J. Beck, M. Setzer, H. Vatter, J. Berkefeld, R.D.M. De Rochemont, A. Raabe, V. Seifert, Treatment related morbidity of unruptured intracranial aneurysms: Results of a prospective single centre series with an interdisciplinary approach over a 6 year period (1999-2005), J. Neurol. Neurosurg. Psychiatry 78 (2007) 864–871, https://doi.org/10.1136/jnnp.2006.106823.

[3] P. Kerezoudis, B.A. McCutcheon, M. Murphy, T. Rayan, H. Gilder, L. Rinaldo, D. Shepherd, P.R. Maloney, B.R. Hirshman, B.S. Carter, M. Bydon, F. Meyer, G. Lanzino, Predictors of 30-day perioperative morbidity and mortality of unruptured intracranial aneurysm surgery, Clin. Neurol. Neurosurg. 149 (2016) 75–80, https://doi.org/10.1016/j.clineuro.2016.07.027.

[4] J. Song, B.S. Kim, Y.S. Shin, Treatment outcomes of unruptured intracranial aneurysm; experience of 1231 consecutive aneurysms, Acta Neurochir. (Wien) 157 (2015) 1303–1311, https://doi.org/10.1007/s00701-015-2460-2.

[5] A.A.T.W. Raaymakers, G.J. Rinkel, M. Limburg, Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis, Stroke 29 (1988) 1531–1538.

[6] C. Ruan, H. Long, H. Sun, M. He, K. Yang, H. Zhang, B. Mao, Endovascular coiling vs. surgical clipping for unruptured intracranial aneurysm: a meta-analysis, Br. J. Neurosurg. 29 (2015) 485–492, https://doi.org/10.3109/02688697.2015.1023771.

[7] M. Hokari, S. Kuroda, N. Nakayama, K. Houkin, T. Ishikawa, H. Kamiyama, Long-term prognosis in patients with clipped unruptured cerebral aneurysms - increased cerebrovascular events in patients with surgically treated unruptured aneurysms, Neurosurg. Rev. 36 (2013) 567–571, https://doi.org/10.1007/s10143-013-0465-y.

[8] J.M. Caplan, E. Sankey, W. Yang, M.G. Radvany, G.P. Colby, A.L. Coon, R.J. Tamargo, J. Huang, Impact of indocyanine green videoangiography on rate of clip adjustments following intraoperative angiography, Neurosurgery 75 (2014) 437–443, https://doi.org/10.1227/NEU.0000000000000468.

[9] B. Lane, B.N. Bohnstedt, A.A. Cohen-gadol, Cereb. Aneurysms 122 (2015) 618–626, https://doi.org/10.3171/2014.8.JNS14957.submitted.

[10] G. Neuloh, J. Schramm, Monitoring of motor evoked potentials compared with somatosensory evoked potentials and microvascular Doppler ultrasonography in cerebral aneurysm surgery, J. Neurosurg. 100 (2004) 389–399, https://doi.org/10.3171/jns.2004.100.3.0389.

[11] K. Roessler, M. Krawagna, A. Dorfler, M. Buchfelder, O. Ganslandt, Essentials in intraoperative indocyanine green videoangiography assessment for intracranial aneurysm surgery: conclusions from 295 consecutively clipped aneurysms and review of the literature, Neurosurg. Focus 36 (2014) E7, https://doi.org/10.3171/2013.11.FOCUS13475.

[12] P.D. Thirumala, R. Udesh, A. Muralidharan, K. Thiagarajan, D.J. Crammond, Y.F. Chang, J.R. Balzer, Diagnostic value of somatosensory-evoked potential monitoring during cerebral aneurysm clipping: a systematic review, World Neurosurg. 89 (2016) 672–680, https://doi.org/10.1016/j.wneu.2015.12.008.

[13] B. Thomas, D. Guo, The diagnostic accuracy of evoked potential monitoring techniques during intracranial aneurysm surgery for predicting postoperative ischemic damage: a systematic review and meta-analysis, World Neurosurg. 103 (2017) 829–840, https://doi.org/10.1016/j.wneu.2017.04.071 e3.

[14] C.W. Washington, G.J. Zipfel, M.R. Chicoine, C.P. Derdeyn, K.M. Rich, C.J. Moran, D.T. Cross, R.G. Dacey, Comparing indocyanine green videoangiography to the gold standard of intraoperative digital subtraction angiography used in aneurysm surgery, J. Neurosurg. 118 (2013) 420–427, https://doi.org/10.3171/2012.10.JNS11818.

[15] H.H. Choi, E.J. Ha, W.S. Cho, H.S. Kang, J.E. Kim, Effectiveness and limitations of intraoperative monitoring with combined motor and somatosensory evoked potentials during surgical clipping of unruptured intracranial aneurysms, World Neurosurg. 108 (2017) 738–747, https://doi.org/10.1016/j.wneu.2017.09.096.

[16] T. Irie, K. Yoshitani, Y. Ohnishi, M. Shinzawa, N. Miura, Y. Kusaka, S. Miyazaki, S. Miyamoto, The efficacy of motor-evoked potentials on cerebral aneurysm surgery and new-onset postoperative motor deficits, PubMed Commons 22 (2014) 1–2, https://doi.org/10.1097/ANA.0b013e3181de4eae.

[17] B. Staarmann, K. O'Neal, M. Magner, M. Zuccarello, Sensitivity and specificity of intraoperative neuromonitoring for identifying safety and duration of temporary aneurysm clipping based on vascular territory, a multimodal strategy, World Neurosurg. 100 (2017) 522–530, https://doi.org/10.1016/j.wneu.2017.01.009.

[18] J.D.K.G. Sulter, C. Steen, Use of the Barthel index and modified Rankin scale in acute stroke trials, Stroke 30 (1999) 1538–1541.

[19] H.S. Byoun, J.S. Bang, C.W. Oh, O.K. Kwon, G. Hwang, J.H. Han, T. Kim, S.U. Lee, S.R. Jo, D.G. Kim, K.S. Park, The incidence of and risk factors for ischemic complications after microsurgical clipping of unruptured middle cerebral artery aneurysms and the efficacy of intraoperative monitoring of somatosensory evoked potentials: a retrospective study, Clin. Neurol. Neurosurg. 151 (2016) 128–135, https://doi.org/10.1016/j.clineuro.2016.10.008.

[20] Z. Li, X. Fan, M. Wang, X. Tao, L. Qi, M. Ling, D. Guo, H. Qiao, Prediction of postoperative motor deficits using motor evoked potential deterioration duration in intracranial aneurysm surgery, Clin. Neurophysiol. 130 (2019) 707–713, https://doi.org/10.1016/j.clinph.2019.02.010.

[21] A. Szelényi, D. Langer, K. Kothbauer, A.B. de Camargo, E.S. Flamm, V. Deletis, Monitoring of muscle motor evoked potentials during cerebral aneurysm surgery: intraoperative changes and postoperative outcome, J. Neurosurg. 105 (2006) 675–681, https://doi.org/10.3171/jns.2006.105.5.675.

[22] M.P. Fay, Confidence intervals that match fisher's exact or blaker's exact tests, Biostatistics 11 (2010) 373–374, https://doi.org/10.1093/biostatistics/kxp050.

[23] B.N. Bohnstedt, W.J. Kemp, Y. Li, T.D. Payner, T.G. Horner, T.J. Leipzig, A.A. Cohen-Gadol, Surgical treatment of 127 anterior choroidal artery aneurysms: a cohort study of resultant ischemic complications, Neurosurgery 73 (2013) 933–940, https://doi.org/10.1227/NEU.0000000000000131.

[24] J.A. Friedman, M.A. Pichelmann, D.G. Piepgras, J.L.D. Atkinson, C.O. Maher, F.B. Meyer, K.K. Hansen, Ischemic complications of surgery for anterior choroidal artery aneurysms, J. Neurosurg. 94 (2001) 565–572, https://doi.org/10.3171/jns.2001.94.4.0565.

[25] J. Chung, W. Park, S.H. Hong, J.C. Park, J.S. Ahn, B.D. Kwun, S.-A. Lee, S.-H. Kim, J.-Y. Jeon, Intraoperative use of transcranial motor/sensory evoked potential monitoring in the clipping of intracranial aneurysms: evaluation of false-positive and false-negative cases, J. Neurosurg. (2018) 1–13, https://doi.org/10.3171/2017.8.JNS17791.

[26] K. Suzuki, N. Kodama, T. Sasaki, M. Matsumoto, Y. Konno, J. Sakuma, M. Oinuma, M. Murakawa, Intraoperative monitoring of blood flow insufficiency in the anterior choroidal artery during aneurysm surgery, J. Neurosurg. 98 (2003) 507–514, https://doi.org/10.3171/jns.2003.98.3.0507.

[27] K. Sahaya, A.S. Pandey, B.G. Thompson, B.R. Bush, D.N. Minecan, Intraoperative Monitoring for Intracranial Aneurysms, J. Clin. Neurophysiol. 31 (2014) 563–567, https://doi.org/10.1097/WNP.0000000000000093.

[28] J.Y. Yeon, D.W. Seo, S.C. Hong, J.S. Kim, Transcranial motor evoked potential monitoring during the surgical clipping of unruptured intracranial aneurysms, J. Neurol. Sci. 293 (2010) 29–34, https://doi.org/10.1016/j.jns.2010.03.013.

[29] K. Horiuchi, K. Suzuki, T. Sasaki, M. Matsumoto, J. Sakuma, Y. Konno, M. Oinuma, T. Itakura, N. Kodama, Intraoperative monitoring of blood flow insufficiency during surgery of middle cerebral artery aneurysms, J. Neurosurg. 103 (2005) 275–283, https://doi.org/10.3171/jns.2005.103.2.0275.

[30] K. Suzuki, T. Mikami, T. Sugino, M. Wanibuchi, S. Miyamoto, N. Hashimoto, N. Mikuni, Discrepancy between voluntary movement and motor-evoked potentials in evaluation of motor function during clipping of anterior circulation aneurysms, World Neurosurg. 82 (2014) E739–E745, https://doi.org/10.1016/j.wneu.2013.08.034.

[31] B.A. Craig, AD, M.C. Bushnell, E.T. Zhang, A thalamic nucleus specific for pain and temperature sensation, Nature 372 (1994) 770–773.
[32] N. Tanriover, B. Kucukyuruk, M.O. Ulu, C. Isler, B. Sam, B. Abuzayed, M. Uzan, H. Ak, S. Tuzgen, Microsurgical anatomy of the cisternal anterior choroidal artery with special emphasis on the preoptic and postoptic subdivisions, J. Neurosurg. 120 (2014) 1217–1228, https://doi.org/10.3171/2014.1.JNS131325.
[33] B.M. Kim, D.I. Kim, Y.S. Shin, E.C. Chung, D.J. Kim, S.H. Suh, S.Y. Kim, S.I. Park, C.S. Choi, Y.S. Won, Clinical outcome and ischemic complication after treatment of anterior choroidal artery aneurysm: comparison between surgical clipping and endovascular coiling, Am. J. Neuroradiol. 29 (2008) 286–290, https://doi.org/10.3174/ajnr.A0806.
[34] A.L. Rhoton Jr., The supratentorial arteries, Neurosurgery 51 (2002) S53–120 (n.d.).
[35] R.E. Anderson, W.K. Tan, F.B. Meyer, Brain acidosis, cerebral blood flow, capillary bed density, and mitochondrial function in the ischemic penumbra, J. Stroke Cerebrovasc. Dis. 8 (1999) 368–379, https://doi.org/10.1016/S1052-3057(99)80044-5.
[36] A.B.O. Kempski, F. Staub, M. Jansen, F. Schodel, Glial swelling during extracellular acidosis in vitro, Stroke 19 (1988) 385–392.
[37] S. Arakawa, P.M. Wright, M. Koga, T.G. Phan, D.C. Reutens, I. Lim, M.R. Gunawan, H. Ma, N. Perera, J. Ly, J. Zavala, G. Fitt, G.A. Donnan, Ischemic thresholds for gray and white matter: a diffusion and perfusion magnetic resonance study, Stroke 37 (2006) 1211–1216, https://doi.org/10.1161/01.STR.0000217258.63925.6b.
[38] M.S. Bristow, J.E. Simon, R.A. Brown, M. Eliasziw, M.D. Hill, S.B. Coutts, R. Frayne, A.M. Demchuk, J.R. Mitchell, MR perfusion and diffusion in acute ischemic stroke: human gray and white matter have different thresholds for infarction, J. Cereb. Blood Flow Metab. 25 (2005) 1280–1287, https://doi.org/10.1038/sj.jcbfm.9600135.
[39] C. Chen, A. Bivard, L. Lin, C.R. Levi, N.J. Spratt, M.W. Parsons, Thresholds for infarction vary between gray matter and white matter in acute ischemic stroke: a CT perfusion study, J. Cereb. Blood Flow Metab. (2017), https://doi.org/10.1177/0271678X17744453.
[40] A.L.E. Falcao, D.C. Reutens, R. Markus, M. Koga, S.J. Read, H. Tochon-Danguy, J. Sachinidis, D.W. Howells, G.A. Donnan, The resistance to ischemia of white and gray matter after stroke, Ann. Neurol. 56 (2004) 695–701, https://doi.org/10.1002/ana.20265.
[41] N. Krayenbühl, E. Erdem, M. Oinas, A.F. Krisht, Symptomatic and silent ischemia associated with microsurgical clipping of intracranial aneurysms: evaluation with diffusion-weighted MRI, Stroke 40 (2009) 129–133, https://doi.org/10.1161/STROKEAHA.108.524777.
[42] S.E. Vermeer, W.T. Longstreth, P.J. Koudstaal, Silent brain infarcts: a systematic review, Lancet Neurol. 6 (2007) 611–619, https://doi.org/10.1016/S1474-4422(07)70170-9.
[43] S.E. Vermeer, N.D. Prins, T. den Heijer, A. Hofman, P.J. Koudstaal, M.M.B. Breteler, Silent brain infarcts and the risk of dementia and cognitive decline, N. Engl. J. Med. 348 (2003) 1215–1222, https://doi.org/10.1056/NEJMoa022066.