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# Intraoperative Combined Use of Somatosensory Evoked Potential, Microvascular Doppler Sonography, and Indocyanine Green Angiography in Clipping of Intracranial Aneurysm

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**Background:** The aim of this study was to evaluate the effect of combining application of somatosensory evoked potential (SEP), microvascular Doppler sonography (MDS), and indocyanine green angiography (ICGA) in intracranial aneurysm clipping surgery.





**Material/Methods:** A total of 158 patients undergoing an intracranial aneurysm clipping operation were recruited. All patients were evaluated with intraoperative SEP and MDS monitoring, and 28 of them were evaluated with intraoperative combined monitoring of SEP, MDS, and ICGA.

**Results:** The SEP waves dropped during temporary occlusion of arteries in 19 cases (12.0%), and returned to normal after the clips were repositioned. After aneurysms were clipped, the vortex flow signals were detected by MDS in 6 cases. The aneurysm neck remnants were detected by ICGA in 2 cases of olfactory artery (OA) and in 1 case of middle cerebral artery (MCA), which disappeared after the clips were repositioned. Postoperative CTA or DSA showed that aneurysms were clipped completely and parent arteries and perforating vessels were patent. GOS at 1 month after the surgery was good in 111 cases (70.3%), mild disability in 22 cases (13.9%), severe disability in 14 cases (8.9%), vegetative state in 5 cases (3.2%), and death in 6 cases (3.8%).

**Conclusions:** Intraoperative combining application of SEP, MDS, and ICGA can reduce brain tissue ischemia and damage and disability and mortality rate after effective clipping of intracranial aneurysms, thereby improving surgical outcomes.

**MeSH Keywords:** **Evoked Potentials, Somatosensory • Indocyanine Green • Intracranial Aneurysm • Monitoring, Intraoperative • Ultrasonography, Doppler**

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## Background

Intracranial aneurysm is a common cerebrovascular disease with the incidence rate of about 2.3% to 6% [1]. The major onset mode of intracranial aneurysm is subarachnoid hemorrhage (SAH) [2], and the incidence rate of SAH reaches 10 000~20 000 cases per year [3], with a fatality rate of 50%. About 30% of patients can return to normal life after active treatment [4].

In recent years, vascular interventional materials endovascular interventional treatment of intracranial aneurysms have developed rapidly, however, clipping of intracranial aneurysm is still adopted as the long-term method in treating intracranial aneurysms. Intraoperative temporary blocking of parent artery of aneurysms and application of cross-vascular clip are the most common techniques used to facilitate the separation, clipping and re-molding of the aneurysm neck. However, these techniques could cause cerebral vasospasm and parent artery stenosis, and they would lead to cerebral ischemic damage [5]. The incorrect operations such as perforating artery damage or faulty clipping, excessive stretching of the lobe could also cause the corresponding regional cerebral ischemic damage and neurological deficits. In addition, incomplete clipping of the aneurysm sac and aneurysm neck remnants are also issues worthy of great concern. In order to avoid irreversible damage to brain tissue and improve the safety of surgical procedures, taking standard, effective intraoperative neurological monitoring measures becomes extremely important.

Somatosensory evoked potential (SEP), a neurological electrophysiological monitoring method, has been increasingly used for monitoring cerebral aneurysm surgery, which can give warning when apparent cerebral ischemia and brain damage occurred. Microvascular Doppler sonography (MDS) can detect the parent artery stenosis directly and whether aneurysm is clipped completely. Akdemir et al. [6] demonstrated that intraoperative MDS is a feasible, safe, and very reliable technique in aneurysm surgery, and suggested that intraoperative MDS should be used routinely in cerebral aneurysm surgery, especially for large, complicated, and giant aneurysms. In addition, indocyanine green angiography (ICGA), a developing agent with good spatial and temporal resolution, can clearly show arteries, capillaries, and small blood vessels with a diameter of less than 1 mm. ICGA is superior to digital subtraction angiography (DSA) and can assess whether an aneurysm is clipped completely, whether the parent artery is unobstructed, and whether the peripheral arteries are involved.

We found that in their clinical application, SEP is superior to MDS in monitoring cortical and subcortical ischemic, as well as brain function damage; MDS is superior to SEP in monitoring hemodynamics; ICGA has the advantage of evaluating the patency situation of the perforated artery. In this study, we

investigated intraoperative combined application value of SEP, MDS, and ICGA in clipping of intracranial aneurysms, which has rarely been reported in previous studies.

## Material and Methods

### Patients and ethnic consideration

The study was approved by and registered with Sichuan Provincial People's Hospital in November 2011. The Ethics Committee approved related screening, treatment, and data collection of these patients, and all subjects signed written informed consent. All work followed the provisions of the Declaration of Helsinki.

The patients were selected from the Neurology Department, who presented with main symptoms of sudden severe headache, nausea, vomiting, and unconsciousness. After patients were diagnosed by imaging examination, a total of 158 patients who were suitable for intracranial aneurysm resected operations were recruited in our study from January 2012 to June 2012 at our hospital. The enrolled patients included 65 males and 93 females, their age range was 28~72 years (mean, 51.6±9.5 years). During the operation, the clipping of intracranial aneurysms was performed in these patients.

### Imaging examination

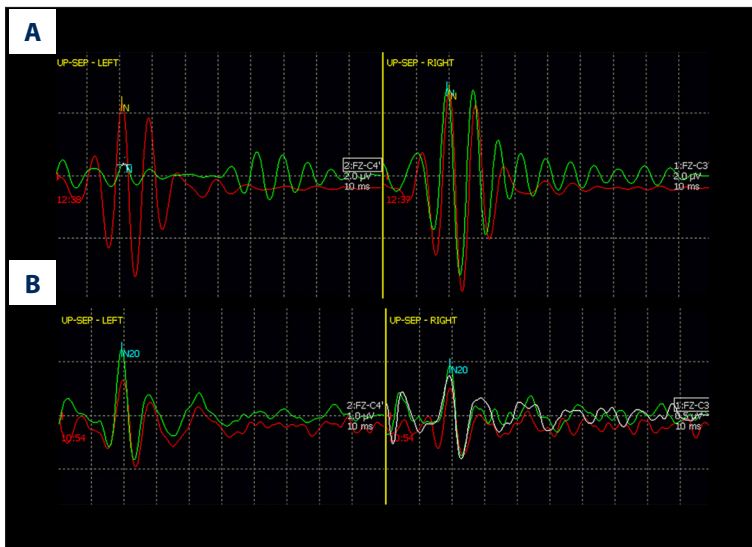
Cranial CT was performed in these patients, result showed SAH combined with intra-cerebral hematoma occurred in 16 cases, and hematoma rupturing into ventricle occurred in 8 cases. The patients were graded by Fisher Grade methods [7]: there were 10 cases in grade I, 53 cases in grade II, 68 cases in grade III and 27 cases in grade IV. The patients underwent CT angiography (CTA) or digital subtraction angiography (DSA) when CTA could not show aneurysm clearly.

In addition, the Hunt-Hess grade [8] was used to evaluate the situation of SAH or intra-cerebral hematoma. Result showed that 55 cases were evaluated as grade I, 66 as grade II, 25 as grade III, and 12 as grade IV.

### Surgery procedure

The surgery was performed after aneurysm rupturing in these patients; 48 cases were performed within 3 days (early stage), 75 cases were performed within 14 days (metaphase), and 35 cases were performed 14 days later (late stage).

Surgery was performed via the pterional approach, and then the cristae sphenoidalis was gnawed off or ground off. The lateral fissure cistern was separated ecto-entad and dissected



**Figure 1.** The SEP waveforms changed during the monitoring process. **(A)** The SEP amplitude reduced caused by prolonged occlusion time of ICA; **(B)** SEP waveforms returned to baseline level after the occlusion was suspended.

sharply. During the operation process, the basic principle was to reduce brain tissue traction and expose the proximal fragment of parent artery as early as possible. Vascular temporary occlusion technology was used to reduce “immature” rupture of aneurysm and damage of those vessels around the aneurysm, thereby achieving satisfactory clipping. During the operation, intra-cristae hematomyelia was removed as much as possible. For intra-ventricular hemorrhage and intra-cerebral hematoma, evacuation of hematoma was performed. Cerebral vasospasm was prevented and treated actively.

#### Intraoperative monitor of SEP, MDS and ICGA

Intraoperative SEP monitoring was performed with an EpochXP Neurological Electrophysiology Monitoring Workstation (AXON, NY, USA). SEP of median nerve was recorded at C3' and C4' by stimulation of contralateral scalp and N20 and P25 waves were observed. SEP of the posterior tibial nerve was recorded at Cz, and P40 and N45 waves were observed. The SEP waveform before separating lateral fissure cistern was used as baseline, and changes in intraoperative SEP amplitude and latency were observed. According to current international standards, a more than 50% reduction in amplitude or a more than 10% prolongation in latency was determined as abnormal. In such a case, vascular occlusion was suspended until the waveform returned to normal condition.

We used a DIGI-LITE Doppler blood flow analyzer (RIMED Ltd., Israel), supplied with a probe diameter of 1 mm, working at a frequency of 16 MHz, and M-mode depth bounds of 0.8~13.6 mm for MDS monitoring. Monitoring contents included blood flow spectrum and velocity of proximal and distal fragments of parent artery. The aneurysm sac and important perforating vessels before and after the aneurysms were clipped. A more than 10% change in mean blood flow velocity indicated

the occurrence of stenosis or vasospasm. Cerebral vasospasm could be improved through repositioning the aneurysm clip, applying papaverine cotton pads, or immersion of the parent artery in a nimodipine saline.

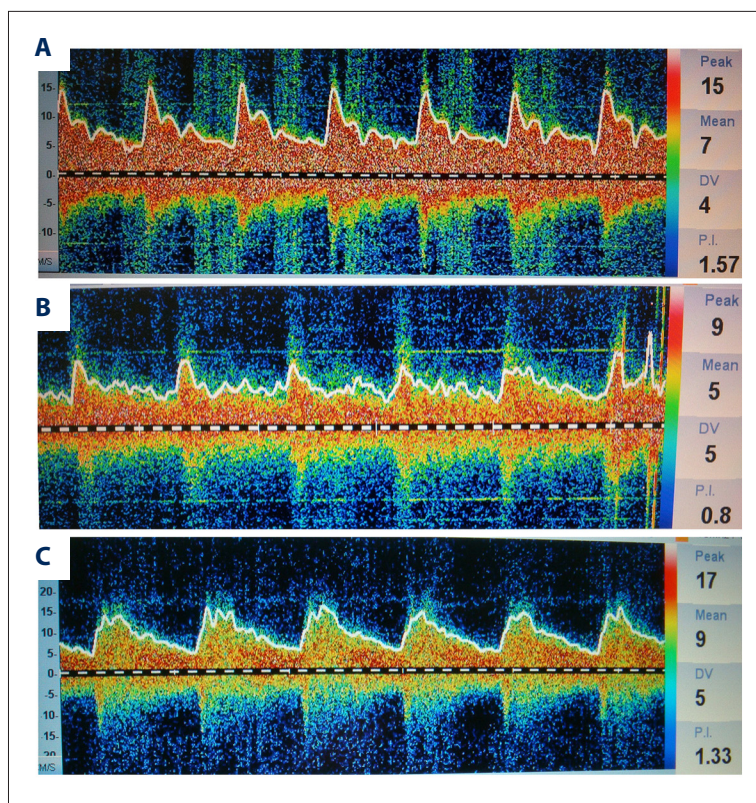
A Zeiss fluorescence microscope was used for ICGA monitoring before and after the aneurysm was clipped, the angle and focal length of the microscope and the operative field was adjusted, the microscope was switched to the fluorescence mode, and then 25 mg ICG was quickly dissolved in 2mL sterile water for rapid injection via peripheral vein or central venous catheter, and about 5~20 s later, aneurysms, parent artery, and adjacent vessels were observed through fluorescence angiography video; monitored contents included whether aneurysm was completely occluded, whether the parent artery was unobstructed, and whether the peripheral artery was involved or not. When an abnormal condition occurred, appropriate measures such as repositioning the aneurysm clip were taken to deal with it.

## Results

#### Intracranial aneurysms in these patients

Internal carotid artery (ICA)-posterior communicating artery (PCOA) aneurysm was diagnosed in 58 cases (36.7%), anterior communicating (ACOA) aneurysm was diagnosed in 49 cases (31.0%), middle cerebral artery (MCA) aneurysm was diagnosed in 26 cases (16.5%), ICA-ophthalmic artery (OA) aneurysm was diagnosed in 21 cases (13.3%), and internal carotid bifurcation aneurysm was diagnosed in 4 cases (2.5%). In these patients, ACOA aneurysm combined with PCOA aneurysm occurred in 6 cases, PCOA aneurysm combined with cerebral aneurysm occurred in 4 cases, ACOA aneurysm combined





**Figure 2.** The MDs waveforms changed during monitoring process. (A) ICA blood flow demonstrated by MDS before the OA aneurysm is clipped. (B) After the aneurysm sac is clipped, blood flow velocity declines. (C) After the clip is repositioned, blood flow velocity of ICA returns to normal level.

with OA aneurysm occurred in 2 cases, and ACOA aneurysm combined with PCOA aneurysm and multiple MCA aneurysms occurred in 1 case.

CT imaging result demonstrated that there were 19 cases with the size of aneurysm sac <5 mm, 112 cases with size  $\geq$ 5 mm and <15 mm, 22 cases with size  $\geq$ 5 mm and <25 mm, and 5 cases with size  $\geq$ 25 mm.

### SEP and MDS monitoring

All 158 patients underwent SEP and MDS monitoring. The SEP waves dropped during temporary occlusion of parent arteries in 19 cases (12.0%); the temporary occlusion was suspended and surgery was continued after SEP waves returned to normal level (Figure 1A, 1B). MDS detected 9 cases (5.7%) of SEP amplitude changes and a greater than 10% increase in flow velocity of parent arteries, and the SEP and MDS returned to baseline levels after the aneurysm clip was repositioned. After the aneurysm was clipped, 10 patients with MCA aneurysm presented with perforating vessel occlusion, 12 patients with ACOA aneurysm, and 8 patients with olfactory artery (OA) aneurysm presented with a greater than 10% increase in flow velocity of parent arteries (Figure 2A, 2B). MDS returned to baseline level after the aneurysm clip was repositioned (Figure 2C). After aneurysms were clipped in 6 cases of PCOA, an apophysis occurred in the residual part of the initial point of PCOA, where there was a

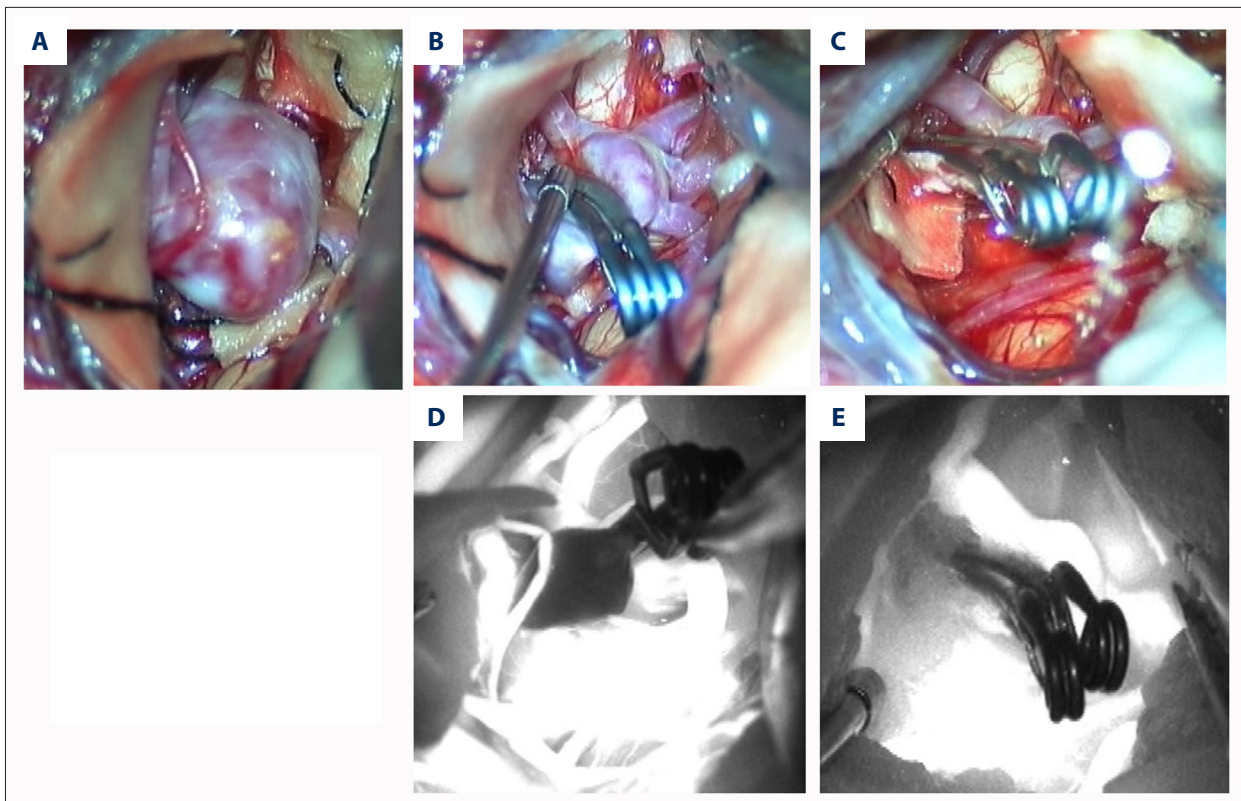
vortex flow signal detected by MDS. The parent artery flow velocity was significantly improved and returned to normal level and SEP showed no significant changes after the aneurysm clip was repositioned or sarcoplasmic wrapping was performed.

### ICGA monitoring

There were 28 patients who underwent ICGA monitoring. Before the aneurysms were clipped, contrast examination was performed 15 times; results showed that the aneurysm, as well as the proximal and distal fragments of parent artery and branch vessels, were displayed clearly. After the aneurysms were clipped, contrast examination was performed 36 times. The aneurysm neck remnants were detected in 2 cases of OA aneurysm and 1 case of MCA aneurysm (Figure 3), which disappeared after the aneurysm clip was repositioned. The PCOA in 2 cases of PCOA aneurysm and the perforating artery in 1 case of ACOA aneurysm were occluded and returned to patency after the aneurysm clip was repositioned.

### Postoperative examination and follow-up

Postoperative CTA or DSA showed that aneurysms were clipped completely; the parent arteries and perforating vessels were patent. There were 21 patients with hydrocephalus after surgery, which was improved by external drainage of the lumbar cistern (7 cases) or ventriculoperitoneal shunt (14 cases).



**Figure 3.** Indocyanine green angiography during clipping of a middle cerebral artery aneurysm. (A) Image of the middle cerebral artery aneurysm before clipping. (B) Clipping of the middle cerebral artery aneurysm. (C) Intraoperative ICGA demonstrating the neck remnants. (D) The clip was revised under guidance of the ICGA image. (E) Postoperative ICGA showed no residual neck.

One month after the surgery, we performed Glasgow outcome scale (GOS) evaluation, result showed 111 cases (70.3%) were good; 22 cases (13.9%) were mild disability; 14 cases (8.9%) were severe disability; 5 cases (3.2%) were vegetative state and 6 cases (3.8%) dead.

The 4 months to 1.2 years follow-up (mean 0.9 years) in other 152 patients showed these patients lived well without re-hemorrhaging.

## Discussion

Nowadays, clipping is the most used therapeutic approach for ruptured aneurysms and in all the 158 cases in this study, clipping of intracranial aneurysm was applied. During the surgeries, temporary clipping of intracranial vessels was conducted electively during surgery on giant aneurysms and during immediate surgery, when dissection of the aneurysm was often difficult and the incidence of rerupture is high during the dissection and clip application [9]. The temporary occlusion of parent arteries can easily lead to cerebral angiospasm and tissue ischemia, and sometimes causes cerebral ischemic injury and neurological dysfunction due to aneurysm misclipping,

artery injury, residue aneurysm, or overstretching of brain tissues. Therefore, intraoperative monitoring is very relevant and useful during aneurysm surgery.

In the development of acute cerebral ischemia, abnormal patterns or disappearance of brain electrical activity often can be detected before the depletion of ionic pumps in the nerve cells. Monitoring brain electrical activity can detect ischemia-associated changes in nerve cell function in early stages, thereby alerting the surgeon to take appropriate measures to prevent irreversible neurological damage caused by cerebral ischemia. Presently, neurological electrophysiological monitoring techniques used in intracranial aneurysm surgery mainly include scalp electroencephalogram (EEG), cortex EEG, SEP, and motion evoked potential, auditory evoked potential [10]. In 1965, Perez-Borja et al. [4] initially used scalp EEG monitoring the clipping of intracranial aneurysm. However, EEG has low sensitivity in detecting brain ischemia. Moreover, EEG is easily influenced by incision site, brain tissue collapse after the release of cerebrospinal fluid, and anesthetic drugs. In contrast, SEP monitoring is easy to learn, is highly relevant to cerebral ischemia, and can monitor infarction, which is an excellent indicator of intraoperative acute brain ischemia. SEP is elicited by stimulation of peripheral sensory nerves in limbs [11] (commonly, the

median nerve and tibial nerve). The electrical responses could be recorded in any part of nerve conductive pathway (from sensory nerve endings to the somatosensory cortex) to reflect the integrity of the somatosensory conductive pathway function. Due to differences in artery territory, median nerve SEP is commonly used for monitoring ICA and MCA aneurysms, and the tibial nerve SEP is commonly used for monitoring the anterior cerebral artery and ACOA aneurysms [10,12]. On the other hand, it should be noted that SEP monitoring may be affected by some anesthetic drugs. SEP monitoring also changes intraoperative body temperature and blood pressure. In the actual clinical operations, we should pay attention to SEP baseline setting; bilateral SEP waveforms comparison could avoid some false-positive results.

Langborde et al. [13] initially reported MDS used for intraoperative monitoring of large intracranial aneurysms. Before the aneurysm is clipped, MDS can detect the direction and hemodynamics of parent arteries, and can detect the vortex flow or thrombus in the aneurysm sac. After the aneurysm is clipped, MDS monitoring could assess whether the aneurysm sac is clipped completely, and whether parent or perforating arteries are stenosed or clipped by mistake, especially in giant and complicated aneurysm surgery. With the development of the high-frequency micro-probe, MDS can detect all vessels in the Willis ring and its branches, even some vessels with a diameter of less than 1 mm [14]. MDS has been widely applied in intracranial aneurysm surgery [6,14,15]. MDS is a simple, quick examination tool for diagnosis of cerebral vasospasm, especially for perforating arteries, which could be detected by MDS before abnormal change of SEP. The limitations of MDS are that MDS is easily affected by detection angle and depth, fluid around vessels and tractor, and MDS cannot detect the rear of the aneurysm or small remnants of the aneurysm neck [16–18].

ICGA is a simple and safe monitoring method in help improve the quality of aneurysm surgery [19–21]. In 2003, Raabe [22] initially reported ICGA could display the vessels within the operative field with clear vision and high resolution. ICGA is used for assessing the remnants of aneurysm neck, patency of parent artery and its branches. However, the tissue penetration of ICG fluorescence is weak; as a result, it can only display the blood flow of vessels in the surface of the operative field and cannot display the blood flow of vessels occluded by obstacles such as brain tissue, aneurysm clips, or thrombus in the aneurysm. The vessels cannot be observed well when there are atherosclerotic plaques and calcifications in the artery wall and thrombus in the aneurysm. Thus, combining application of real-time ICGA and MDS could significantly reduce the residual rate of aneurysm neck and improve the quality of aneurysm clipping

surgery. ICGA could also be combined with endoscopy [23] and served as a useful adjunct in aneurysm surgery, which might have the potential to further improve operative results.

In recent years, improvements in preoperative imaging and intraoperative visualization have led to a refinement in surgical techniques. Many new concepts and approaches have been put forward. Compared with the traditional pterional approach used in our study, Fischer et al. [24] reported application of the keyhole technique in aneurysm surgery and found the overall outcome, rate of retreatment, and approach-related complications with keyhole approaches for the management of aneurysms were comparable to those in a recently published conventional surgical aneurysm series. Besides the new surgery approach, they also proposed that use of an endoscope before, during, and after microsurgical aneurysm occlusion might enhance the visual field and increase the quality of treatment [25].

For the treatment of aneurysm, besides neurosurgical clipping, endovascular coiling is also a recommended strategy and now is used commonly in many medical centers. According to European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage [26], aneurysm patients with a wide neck, branching vessels out of the aneurysm sack, middle cerebral artery aneurysms, or patients with intracerebral hematoma are recommended to be treated by clipping, while aneurysms of the basilar artery or in elderly patients (patients >70 years, small aneurysm neck, posterior circulation) should be coiled. The possibility of recanalization and the need for retreatment are the most important drawbacks of intracranial aneurysm embolization, and aneurysm neck diameter and sac-to-neck ratio are independently related to the residual flow in embolized ruptured aneurysms at early follow-up [27]. In addition to elderly patients, a report also proposed the feasibility of endovascular embolization treatment in pediatric aneurysm patients [28], but the conclusion needs further evidence.

## Conclusions

Our study indicated that intraoperative combined application of SEP, MDS, and ICGA can effectively reduce brain tissue ischemia, damage, disability, and mortality rates after clipping of intracranial aneurysm, thereby improving surgical outcomes.

## Conflict of interest

There is no conflict of interest in this work.



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