Dual-Channel Endoscopic Indocyanine Green Fluorescence Angiography for Clipping of Cerebral Aneurysms

Won-Sang Cho¹, Jeong Eun Kim¹, Hyun-Seung Kang¹, Eun Jin Ha¹, Minwoong Jung², Choonghee Lee², Il hyung Shin², Uk Kang²

OBJECTIVE: Neuroendoscopy is useful for assessing status of perforators, parent arteries, and aneurysms beyond the straight line of microscopic view during aneurysm clipping. We aimed to evaluate the clinical usefulness of our endoscopic indocyanine green angiography (ICGA) system, which can simultaneously display visible light and indocyanine green fluorescent images.

METHODS: Surgical clipping of 16 unruptured aneurysms in 10 patients was performed via the keyhole approach. Using our endoscopic ICGA and commercial microscopic ICGA systems, we prospectively compared 10 targeted cerebral aneurysms at the posterior communicating (n = 4) and anterior choroidal (n = 6) arteries.

RESULTS: Microscopic ICGA and endoscopic ICGA were feasible during surgery. Microscopic ICGA displayed 50% of branch orifices, 100% of branch trunks, and 20% of exact clip positions, whereas endoscopic ICGA showed 100% of these. Based on endoscopic ICGA findings such as incomplete clipping and compromise of parent arteries or branches, clips were repositioned in 2 cases, and additional clips were applied in 2 cases. Complete occlusion and residual neck states were achieved in 6 and 4 aneurysms after surgery. There were no neurologic deficits within 3 months after surgery except for frontalis palsy and anosmia in each patient.

CONCLUSIONS: The endoscopic ICGA system with dual imaging of visible light and indocyanine green fluorescence was very useful for assessing geometry of aneurysms and surrounding vessels before clipping and for evaluating completeness of clip position after clipping.

INTRODUCTION

In the treatment of cerebral aneurysms, novel surgical skills and devices such as keyhole approaches, fluorescence imaging, neuroendoscopy, intraoperative neurophysiologic monitoring, and cerebral angiography are rapidly being introduced because they help to reduce surgical morbidity and mortality. One such technique, using indocyanine green (ICG) fluorescence, is microscopic indocyanine green angiography (ICGA), which since its introduction by Raabe et al. has been widely used to detect and readjust the compromise of perforators and parent arteries and incomplete clipping of cerebral aneurysms. However, the microscopic ICGA system has some limitations in visualizing vascular structures beyond the line of microscopic view and deeply seated structures with weak illumination. Neuroendoscopy is helpful to overcome such microscopic drawbacks, magnify the areas of interest, and obtain longer ICG fluorescence. When a keyhole approach is used, the limitations of the microscope and the need for a neuroendoscope become more profound. We have already reported a prototype of a dual-channel endoscopic ICGA system to combine the advantages of microscopic ICGA and neuroendoscopy. Thereafter, the system was improved with a smaller camera size, higher display resolution, and fine modifications. Although there are 3 clinical
reports about the usefulness of the endoscopic ICGA system, our system has the distinguishing features of simultaneous imaging and real-time merging of ICG fluorescence and visible light. The aim of this study was to evaluate the safety and usefulness of our endoscopic ICGA system in clinical circumstances.

**MATERIALS AND METHODS**

**Patient Selection**

This study was prospectively performed in patients undergoing surgical clipping of unruptured cerebral aneurysms arising at the internal carotid artery (ICA)—posterior communicating artery (PCoA) and the anterior choroidal artery (AChA) between August 2015 and July 2016. Institutional review board approval was received. Inclusion criteria were as follows: 1) adult patients 20—80 years old; 2) medical conditions tolerating general anesthesia and surgical clipping; 3) unruptured cerebral aneurysms arising at the ICA-PCoA and AChA, the orifices of which were expected to be difficult to identify with the microscope; 4) aneurysms >3 mm in maximal diameter, aneurysms <3 mm with which other multiple aneurysms were scheduled to be simultaneously clipped through the same corridor, or aneurysms that patients were eager to have treated regardless of the size or shape; 5) no previous history of porphyria or hypersensitivity to ICG; 6) no use of drugs that influence the effect of ICG, such as photosensitizers; and 7) patient provision of informed consent. Surgical clipping of 16 cerebral aneurysms in 10 patients was performed; among the patients, 6 had single aneurysms, 3 had 2 aneurysms each, and 1 had 4 aneurysms. Patients consisted of 3 men and 7 women with a median age of 60 years (range, 52—75 years). Targeted cerebral aneurysms arose from the ICA-PCoA in 4 patients and the ICA-AChA in 6 patients. Of the lesions, 4 were left-sided, and 6 were right-sided, with a median maximal diameter of 4.4 mm (range, 2.4—8.6 mm) (Table 1).

**Microscopic ICGA and Endoscopic ICGA Systems**

Using a microscopic ICGA system (Leica M720 OH5 and FL800; Leica Microsystems, Wetzlar, Germany) and the endoscopic ICGA system (LAP-2C; Korea Electrotechnology Research Institute, Seoul, Korea) that our team previously developed, the safety and usefulness of endoscopic ICGA were compared with microscopic ICGA. Our endoscopic ICGA system was upgraded with a smaller camera, similar in size to commercial cameras for neuroendoscopes, and the resolution of the display was much improved (Figure 1). The merits of our endoscopic ICGA system are simultaneous display and real-time merging of visible light and fluorescent imaging through the dual-channel camera and software. Commercial 2.7-mm neuroendoscopes were used (HOPKINS Straight Forward Telescope o° and Forward-Oblique Telescope 30°; KARL STORZ GmbH & Co., Tuttlingen, Germany). ICG was intravenously injected as a bolus of 0.3—0.4 mg/kg (25 mg dissolved in 5 mL of sterile normal saline).

First, identification of the ICA as a parent artery, the orifice and trunk proper of the PCoA and AChA as branches, other perforators, the aneurysm, and the clip blade was attempted with the microscope and endoscope in a visible light mode before and immediately after clipping. Second, ICG was injected when clipping was considered satisfactory. The structures were

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Table 1. Basal Characteristics and Surgical Outcomes

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/Sex</th>
<th>Location of Target Aneurysm</th>
<th>Maximal Diameter (mm)</th>
<th>Approach</th>
<th>Locations of Other Aneurysms</th>
<th>Operation Time (minutes)</th>
<th>Surgical Results</th>
<th>Postoperative Complications</th>
<th>Modified Rankin Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72/F</td>
<td>AChA, left</td>
<td>4</td>
<td>LSO</td>
<td>None</td>
<td>120</td>
<td>Complete occlusion</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>52/M</td>
<td>AChA, left</td>
<td>5.8</td>
<td>LSO</td>
<td>PCoA, MCA (M1, M2)</td>
<td>250</td>
<td>Residual neck</td>
<td>Transient third nerve palsy</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>56/M</td>
<td>AChA, right</td>
<td>2.4</td>
<td>SSO</td>
<td>None</td>
<td>140</td>
<td>Complete occlusion</td>
<td>Frontalis palsy</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>59/F</td>
<td>AChA, right</td>
<td>4.1</td>
<td>FL</td>
<td>None</td>
<td>145</td>
<td>Complete occlusion</td>
<td>Transient third nerve palsy</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>58/F</td>
<td>PCoA, right</td>
<td>2.4</td>
<td>LSO</td>
<td>MCA</td>
<td>100</td>
<td>Complete occlusion</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>73/F</td>
<td>PCoA, left</td>
<td>8.6</td>
<td>LSO</td>
<td>None</td>
<td>130</td>
<td>Residual neck</td>
<td>None</td>
<td>0</td>
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<tr>
<td>7</td>
<td>73/F</td>
<td>PCoA, left</td>
<td>4.7</td>
<td>FL</td>
<td>ACoA</td>
<td>280</td>
<td>Complete occlusion</td>
<td>Transient frontalis palsy, anosmia</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>59/M</td>
<td>AChA, left</td>
<td>6.5</td>
<td>LSO</td>
<td>None</td>
<td>140</td>
<td>Residual neck</td>
<td>Delayed asymptomatic left post IC infarction</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>61/F</td>
<td>PCoA, left</td>
<td>3</td>
<td>FL</td>
<td>MCA</td>
<td>120</td>
<td>Complete occlusion</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>75/F</td>
<td>PCoA, left</td>
<td>4.6</td>
<td>FL</td>
<td>None</td>
<td>120</td>
<td>Residual neck</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

F, female; AChA, anterior choroidal artery; LSO, lateral supraorbital; M, male; PCoA, posterior communicating artery; MCA, middle cerebral artery; SSO, superciliary supraorbital; FL, fron-totateral; ACoA, anterior communicating artery; IC, internal capsule.
inspected in alternating fluorescent and visible light modes with microscopic ICGA, followed by simultaneous dual modes of fluorescence and visible light with endoscopic ICGA. When an abnormal finding was identified on the second inspection with endoscopic ICGA, check-up with microscopic ICGA was repeated. When the clipping was considered incomplete in any period because of the compromise of an adjacent vessel or a remnant aneurysm, clip reposition or application of an additional clip was performed. All intraoperative procedures were recorded as videos and photos.

Perioperative Evaluation of Aneurysms and Patients
The operation was planned based on a preoperative evaluation with magnetic resonance imaging, digital subtraction angiography (DSA) with 3-dimensional reconstruction, and computed tomography (CT) angiography. All aneurysms were approached via a keyhole craniotomy, such as the superciliary supraorbital (medial supraorbital craniotomy following the skin incision along the eyebrow), lateral supraorbital (lateral supraorbital craniotomy following the skin incision behind the hairline), and frontolateral approaches (medial supraorbital craniotomy following the skin incision behind the hairline). The type of approach was determined based on the surgeon’s preference (W.-S.C.), patient’s opinion, extent of the frontal sinus, aneurysm geometry and spatial relationship of aneurysms, adjacent arteries and veins, subarachnoid space, and brain parenchyma. The most important determinant was the best corridor for clipping the aneurysm along the longitudinal axis of the parent artery. Intraoperative neurophysiologic monitoring of somatosensory and motor evoked potentials was used in all cases. Micro-Doppler was used when necessary.

With the aid of intraoperative microscopy and endoscopy as well as postoperative CT angiography or DSA, the status of clipped aneurysms was classified into 3 results: (1) “complete occlusion,” when an aneurysm is completely clipped along the ideal closure line; (2) “residual neck,” when the remnant was <1 mm in depth; and (3) “residual sac,” when the remnant was >1 mm in depth. Generally, all patients underwent CT immediately postoperatively, CT angiography at discharge, and CT 1 month postoperatively to determine the status of aneurysms and symptomatic or asymptomatic intracranial lesions. Additional CT, magnetic resonance imaging, or DSA was performed based on the status of patients and clipped aneurysms. Neurologic status was evaluated with the modified Rankin Scale preoperatively, at discharge, and 3 months after surgery.

RESULTS

Comparison of Microscopic ICGA and Endoscopic ICGA
Before the aneurysms were clipped, the orifice and trunk proper of the PCoA and AChA were possible to identify in 50% (cases 1–3, 6, and 10) and 100% of cases, respectively, with the microscope and in 100% of cases with the endoscope. Immediately after the aneurysms were clipped, the spatial relationship of the clip, aneurysm neck, parent arteries, and branching arteries could be exactly visualized in only 20% with the microscope (cases 7 and 9) and in 100% with the endoscope. After ICG administration, microscopic ICGA was able to show the branch orifice in 50% of
cases (cases 1–3, 6, and 10) and the trunk proper in 100% of cases, whereas endoscopic ICGA showed the orifice and trunk proper in 100% of cases. In a case with an AChA aneurysm (case 4), an additional clip was applied at the remnant neck after endoscopic inspection (Figure 2). In a case with a PCoA aneurysm (case 6), early faint filling of ICG into the aneurysmal sac was identified with endoscopic ICGA, but not with microscopic ICGA. Delayed ICG filling was observed with both microscopic ICGA and endoscopic ICGA, resulting in additional clip application (Figure 3). Clip repositioning was also needed in 2 cases after the identification of AChA compromise (case 8) (Figure 4) and residual sac (case 10). A comparison of microscopic ICGA and endoscopic ICGA is summarized in Table 2.

**Figure 2.** A 58-year-old woman with an unruptured right internal carotid artery (ICA)—anterior choroidal artery (AChA) aneurysm measuring approximately 4 mm (case 4). (A) The posterior communicating artery (PCoA) (thick arrow) and AChA (thin arrow) were very close to the aneurysm neck on medial view of 3-dimensional reconstructed right ICA angiography. (B) The aneurysm adhered to the right oculomotor nerve (asterisk), and orifices of the PCoA (thick arrow) and AChA (thin arrow) were identified with the microscope. (C) The retracting medial side of the ICA laterally and trunks of the PCoA and AChA (circle) were identified with the microscope. (D) After aneurysm clipping, branch orifices and the tip of the clip were not shown with the microscope. (continues)
Surgical Outcomes

Surgical outcomes are summarized in Table 1. Superciliary supraorbital, lateral supraorbital, and frontolateral keyhole approaches were used at a ratio of 1:5:4, with a median skin-to-skin operation time of 135 minutes (range, 100–280 minutes). The status of clipped aneurysms was complete occlusion in 6 cases and residual neck in 4 cases. There was no abnormal change as measured by intraoperative neurophysiologic monitoring. Postoperative complications included transient oculomotor nerve palsy in 2 cases that occurred after detaching an AChA aneurysm from the oculomotor nerve (cases 2 and 4), transient frontalis palsy and permanent anosmia in 1 case occurring after simultaneous clipping of large ACoA aneurysms (case 7), permanent frontalis palsy in 1 case (case 3), and asymptomatic infarction at the posterior limb of the internal capsule in 1 case (case 8). Asymptomatic infarction in case 8 was identified on 5-day postoperative follow-up CT angiography, although no abnormal lesion was visible on diffusion-weighted magnetic resonance imaging performed 5 hours after surgery. The possible cause of infarction is thought to be AChA compromise by the proximal migration of the clip at the aneurysm neck or AChA vasospasm, although DSA was not performed. No harm was done by the endoscopic ICGA system or ICG itself.

DISCUSSION

In this study, microscopic ICGA and endoscopic ICGA systems were compared in terms of identification of the orifice and trunk proper of the PCoA and AChA, clip position, and status of clipped aneurysms before and after clipping 10 target aneurysms located at the ICA-PCoA and ICA-AChA in 10 patients. The endoscopic ICGA system was able to identify all the components, whereas the microscopic ICGA system was able to visualize only 20% of the clip positions and 50% of the branch orifices. Based on the endoscopic ICGA findings, clips were surgically repositioned or added in 4 cases. There were no instances of brain injury by an endoscope, intraprocedural rupture, or postoperative infarction owing to the compromise of perforators and parent arteries except for 1 delayed asymptomatic infarction in the AChA territory, which was thought to result from clip slippage or vasospasm. Aneurysms were clipped more completely and safely with the aid of the dual-channel endoscopic ICGA system. A dual imaging system of visible light and fluorescence has recently been introduced for macroscopic general surgery and microscopic neurosurgery. To the best of our knowledge, our system is the first clinical application of endoscopic ICGA with a dual-channel camera, although there are a few clinical studies using endoscopic ICGA with an alternating single-channel camera for visible light and fluorescence imaging.
Microscopic ICGA systems have helped to improve surgical outcomes; however, they have some limitations.\textsuperscript{1-3,7,8} Surgeons find it difficult to see visible light and ICG fluorescent images of vascular structures beyond the straight line of microscopic view, and they detect only faint fluorescent images of deep-seated structures because of weak illumination. Endoscopic ICGA systems are very useful to visualize structures beyond the line of microscopic view, supply sufficient illumination even in deep and narrow spaces, and obtain a longer duration of ICG fluorescent imaging.\textsuperscript{1-3} Therefore, endoscopic ICGA systems can be very
helpful for aneurysms arising at the opposite side of confronting parent arteries, aneurysms harbouring multiple fine perforators on the invisible side, and aneurysms located in deep and narrow spaces. Aneurysms at the ICA-PCoA and ICA-AChA were selected in this study because they are well known to have a higher incidence of incomplete clipping and branch compromise because of
the locations and limited microscopic view. Only a few branch orifice and clip positions—less than half—were identified with microscopic ICGA even when the parent arteries were retracted or the surrounding subarachnoid space was widely dissected. However, endoscopic ICGA in this study provided all the necessary anatomic information on aneurysms, perforators, and parent arteries to plan an ideal clipping through the closure line, assess the completeness of clipping, and give an immediate chance to revise the clipping. Micromirrors have long been used to inspect hidden areas, and they are very simple to use. However, endoscopes give much better quality of imaging than mirrors, and endoscopic ICGA systems can display blood flow within vascular structures. In addition, simultaneous dual imaging of visible light and fluorescence in our system eliminates the inconvenience of switching the modes of conventional endoscopic ICGA systems between visible light and fluorescence as well as the risk of violating unseen structures when using the fluorescence mode against a dark background. The newly introduced fluorescent dye YELLOW 560 has enabled surgeons to continue to operate in fluorescent mode because the excitation and emission of fluorescein occur within the visible light spectrum. Development of new fluorescent dyes and optical devices is expected to help ensure safe and complete operations.

Important points during aneurysm clipping include the preservation of anatomic structures and blood flow within the parent arteries and perforators. Obliteration of their blood flow after clipping is common even in normal-looking vessels, especially when the vessels harbor atheroma and calcification or when the geometry of surrounding vessels changes after clipping. Flow compromise can be more common in smaller vessels such as perforators. Intraoperative physiologic monitoring is a helpful method to detect and avoid ischemia; however, it is an indirect method to identify decreases in blood flow and has a limited ability to detect ischemia outside the corticospinal tract. Intraoperative DSA is considered a gold standard for detecting incomplete clipping and unwanted occlusion of normal vessels. However, DSA is poor at detecting small perforators, is not always available in all institutes, and is invasive and time-consuming. When a critical time period of reversibility passes, flow restoration by clip repositioning may become impossible. Doppler is a safe and immediate way to check for blood flow; however, flow in the small perforators is nearly impossible to detect with Doppler. Thus, compared with other intraoperative tools, endoscopic ICGA and microscopic ICGA systems have the advantage of immediately detecting the flow in the vessels regardless of the size of the vessels. Additionally, preservation of the tolerable range of flow amount is important because of the risk of transient ischemic attack or infarction. Microscopic and endoscopic ICGA systems are limited in the quantification of flow amount. Therefore, it is recommended to check the flow and flow amount with Doppler and ICGA systems when a partial compromise of a large vessel by the clip is suspected. Flow amount in small vessels is nearly impossible to detect with any tools. Whether the flow itself exists is thought to be sufficient to predict ischemic lesions in the territories of smaller vessels such as perforators. This may be because the clip blade is larger than most perforators, meaning that perforator compromise by the clip is an all-or-nothing phenomenon similar to the flipping of a light switch. Thus, confirmation of the intact perforators and intact flow on endoscopic ICGA and microscopic ICGA systems is considered enough. Rare adverse events have been reported to occur because of clip torsion, rotation, and slippage even after intraoperative confirmation of the right clip position and the intactness of the surrounding vessels. Delayed infarction, probably by clip slippage or vasoconstriction, was also identified in 1 case of this study. Therefore, clip position and direction should be determined by considering surrounding structures and imagining the situation after brain expansion.

CONCLUSIONS

Compared with the microscopic ICGA system, our dual-channel endoscopic ICGA system provided superior detection of branch orifices and clip position. As a result, existing clips were repositioned and new clips were added based on the endoscopic findings. In addition, dual imaging of visible light and fluorescence in our system facilitated the safe and precise inspection of vascular structures and clips with the endoscope. Further advancement in neuroendoscope systems is expected in the near future.

REFERENCES


Table 2. Comparison of Microscopic and Endoscopic Indocyanine Green Angiography

<table>
<thead>
<tr>
<th>Identification of</th>
<th>Microscopic ICGA</th>
<th>Endoscopic ICGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branch orifice</td>
<td>5 (50)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Branch trunk</td>
<td>10 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Clip position</td>
<td>2 (20)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>ICG filling into</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branch orifice</td>
<td>5 (50)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Branch trunk</td>
<td>10 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Aneurysm sac</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Clip reposition or addition based on ICGA finding</td>
<td>0 (0)</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

Values are number of cases (%). ICGA, indocyanine green angiography; ICG, indocyanine green.
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