Role of Intra Operative Near Infrared Indocyanine Green Videoangiography in Neurosurgery: An Initial Experience

Fluorescence angiography incorporated in microscope not only helps to identify vessels and vascular pathology but also ensures patency and adequacy of procedure like clipping of aneurysm or excision of AVM. Despite this technical advancement, cost and availability prohibits its extensive use in a developing country like ours. We here present our initial experience with intra-operative near infrared indocyanine green videoangiography (ICGA) and discuss its role in neurosurgery.

A retrospective study enrolling patients with neurovascular pathology over last 2 months was performed. Endpoints included were adequacy of procedure, complications, cost and ease of application.

IOFA was used in 15 patients, included were clipping of aneurysm (CA) (66.7%), tumor excision (TU) (13.6%), microvascular decompression (MVD) (13.3%) and arterio-venous malformation excision (AVM) (6.6%). ICGA cost Rupees 3000 extra (cost of dye) to patient but ensured adequacy of procedure (complete occlusion of aneurysm, excision of AVM, and decompression of nerve), patency of perforators, en passage vessels and veins and identify feeders without additional complications. Total procedure got prolonged by mean of 15 minutes.

ICGA is a safe, viable, useful technique to identify vascular anatomy as well as confirm adequacy of procedure without significant complications. This tool to summarize, boost surgical precision and is cost effective.

Key Words: aneurysm, avm, brain tumor, intra-operative indocyanine green videoangiography (icga), neurosurgery, tumor

Intra-operative visualization of vessels besides providing details of vascular anatomy around pathological lesions like aneurysm, arteriovenous malformation (AVM) and brain tumors helps in safe and adequate surgical procedure.

Use of near infrared (NIR) indocyanine green videoangiography (ICGA) incorporated in microscope has shown promising results. ICGA is simple and without any exposure to radiation, gives a real time status of vascular flow through aneurysm, arteriovenous malformations (AVM), tumor as well major arteries and small perforating vessels. Which are not readily visible on digital
subtraction angiography (DSA).

Despite the numerous advantages, it has been difficult to use this technology in context of Nepal due to financial constraint. To have a NIR upgrade in microscope would somewhere push the price by 2 to 3 times over a standard neurosurgical microscope. Recently we were able to get this surgical tool in our facility and have experienced a profound impact on our surgical results.

We discuss here our experience and learning curve with this surgical tool. We shall also discuss the technique and its upcoming use.

**Materials And Methods**

A retrospective study enrolling patients with neurovascular pathology operated in the unit of neurological surgery by the senior author at Kathmandu Medical College Teaching Hospital, Kathmandu over two months beginning September 2013 was performed.

Endpoints included were adequacy of procedure, complications, cost and time taken for application. Difficulties in using this technique are being discussed.

**The Dye and the principle of ICGA**

Indocyanine Green Dye (ICG) is a near infrared (NIR) fluorescent tricarbocyanine dye (molecular formula C_{43}H_{47}N_{2}NaO_{6}S_{2}). Inside vessels, ICG binds to globulins (α-lipoproteins) within seconds and remains within intravascular compartment. ICG is not metabolized in body and is entirely eliminated by liver with a plasma half-life of 3-4 minutes with only a trace detectable after 10 minutes. The recommended dose of ICG for ICGA is 0.2-0.5 mg/kg (not to exceed 5mg/kg). The locally available brand, Aurogreen is in powder form (25mg) to be mixed with 5ml of sterile water (0.5% solution).

ICG excites at 800nm light and emits fluorescence at 835 nm. After injecting into peripheral vein as a bolus, operative field is illuminated by a NIR light with a wavelength covering part of ICG absorption band. This 835 nm light is filtered away from the normal white light and detected by a special NIR CCD camera, which converts 835nm light (invisible to human eye) to white light. Real-time angiographic images, with the three distinct phases (arterial, capillary, and venous) can be observed on the video screen and recorded for further analysis during or after the surgery.

The United States Food and Drug Administration approved the use of ICG dye in 1956 for evaluation of cardio-circulatory measurements, liver function tests and ophthalmic angiography. In this study we used dye imported from India, as Aurogreen is cheaper and easily available rather than the one marketed by the company and has been shown to be equally effective without any serious issues.
Surgical Technique

We used Leica FL800 fluorescence module integrated on Leica M525 F50 microscope (Figure 1) to observe blood flow on the video monitor, which appears as black and white on NIR mode (Figure 2 & 3). This can be visualized directly through microscope eyepieces however it requires digital imaging color module (Leica DI C500 or Leica DI C700), a pricey upgrade. To change from white light to NIR mode, Leica provides a simple button found on the handgrip of the surgical microscope however it is suggested to use one xenon bulb exclusively for NIR mode for good illumination. MedXchange HDMD® recording system provides the "picture-in-picture" function, which enables re-visualization of preceding recorded tracks for easier intra-operative decision-making.

ICGA was used during dissection, prior to clip application and after clip application. It took an average of 2 minutes each. Surgical exposure was planned according to pathology using standard technique. For a good visualization, proper hemostasis and a field dry of CSF or irrigating fluid was ensured. For 360° visualization particularly during clipping of aneurysm, aneurysm sac and neck were mobilized during NIR mode and later re-evaluated on loop replay on monitor.

Results

ICGA was used in 15 patients during 2-month period, of which 27% were males. Mean age of patient was 55 years (Range 33 to 65 years). (Table 1)

All 10 patients (66.7%) who underwent clipping of aneurysm (CA) had subarachnoid hemorrhage (SAH). Two patients had Hunt and Hess (H&H) grade I, 2 grade II, 5 grade IV and 1 grade V. (Figure 3) Use of ICGA to avoid accidental clipping of perforators. (a & b) shows adequate application of clip across aneurysm arising from communicating segment of internal carotid artery (non filling of contrast in sac seen on (c)), however on further inspection, posterior communicating artery seen on (c) (shown by arrow) is not opacified on ICGA image (d). Hence clip was repositioned and finally ICGA (e & d) shows flow in the posterior communicating artery.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cases (n=15)</th>
<th>Advantage</th>
<th>Post operative complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clipping of aneurysm (CA)</td>
<td>10</td>
<td>Identify neck and sac of aneurysm (10)</td>
<td>Arterial infarct (1)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confirm adequacy of clipping (10)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Identify perforating arteries (8)</td>
<td></td>
</tr>
<tr>
<td>Excision of tumor (TU)</td>
<td>2</td>
<td>Identify feeders (1)</td>
<td>Arterial infarct (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Identify en passage artery (1)</td>
<td></td>
</tr>
<tr>
<td>Microvascular decompression (MVD)</td>
<td>2</td>
<td>Identify compressing artery (2)</td>
<td>Recurrence of symptoms (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Identify adequate decompression (2)</td>
<td></td>
</tr>
<tr>
<td>Excision of AVM</td>
<td>1</td>
<td>Identify feeders and vein (1)</td>
<td>Arterial infarct (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adequacy of nidus excision (1)</td>
<td>Residual AVM (0)</td>
</tr>
</tbody>
</table>

“*” Delayed vasospasm
* Number in brackets signify number of patients

Table 1: Use of ICGA in neurosurgical procedures
II, 5 grade IV and 1 grade V. These aneurysms were identified as anterior communicating aneurysm (ACOM) (4 patients), Middle cerebral artery (MCA) (2 patients), Distal anterior cerebral aneurysm (DACA) (2 patients) and internal carotid artery (ICA) segment (2 patients). In all patients, ICGA identified neck and sac of aneurysm with intra-operative confirmation of adequate clipping of neck as dye failed to highlight the aneurysmal sac after application of clip (Figure 2). During this maneuver in 4 cases, clips have to be reapplied and in 2, more than one clip has to be applied to occlude the neck completely. However there were perforators around neck in 8 of 10 patients that were not visible on CT angiography preoperatively and could be safely preserved. 1 patient, clip has to be re-applied as it occluded the perforator (Figure 3). Post operatively there was only 1 patient with ACOM aneurysm who due to delayed vasospasm deteriorated after day 2 following surgery and developed weakness in right foot. His CT scan revealed Left ACA territory infarct. Rest all of patients had uneventful period and had Glasgow Outcome Score of 4 at time of discharge with no postoperative focal deficits.

In 2 patients (13.3%), who underwent excision of tumor (TU), ICGA helped in diagnosing tumoral and peritumoral circulation particularly en passage feeders and later to confirm their patency after resection. It was difficult to find vessels behind the tumor as bleeding from tumor would hide the vessels even during NIR mode. In both cases we achieved gross total excision of tumors that was consequently reported as glioblastoma multiforme without any significant postoperative focal deficits. Post operatively there was no recurrence of symptoms or any focal neurological deficits.

We had 1 case that underwent excision of arteriovenous malformation excision (AVM) over occipital lobe (6.6%), a Spetzler Martin grade III associated with a high flow ACOM aneurysm. ICGA helped to identify arterial feeder and keep venous outflow from getting clipped during initial step of depriving nidus off blood supply. After excision of AVM, two weeks later his ACOM aneurysm was clipped as it failed to resolve on repeat angiography. He was discharged without deficit and presently on follow up is doing well and physically fit.

With the use of ICG there was no contrast allergy or any sign of nephropathy. ICGA cost Rupees 3000 extra (cost of dye) to patient. Procedure got prolonged by an average of 15 minutes (including time spent on analyzing images on video in loop mode).

During the course of study, we find minor problems while adjusting microscope, which subsequently improved as we gained experience. Table 2 discusses different pearls to use ICGA.

**DISCUSSION**

First used by ophthalmologists, fluorescence angiography using fluorescein was used to study retinal blood flow. It was Feindel et al, who first used this concept in intra-operative cerebral arteries. ICG is better than fluorescein as it not only emits light more intensely but also is easier to detect and has very low rates of adverse reaction. This advantage was used and first demonstrated by Raabe et al as a useful adjunct for intra-operative control of vessel patency and aneurysm occlusion during aneurysm surgery and by Woitzik et al during extracranial-intracranial bypass surgery.

<table>
<thead>
<tr>
<th>Pitfalls</th>
<th>Pearls</th>
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<tbody>
<tr>
<td>Use ICGA in all neurosurgical cases</td>
<td>Use where vascular anatomy is important</td>
</tr>
<tr>
<td>Poor visualization of vessels</td>
<td>Keep operative area dry by suction&lt;br&gt;Keep one bulb separate for NIR mode&lt;br&gt;Reduce depth of field&lt;br&gt;Keep illumination to 100%</td>
</tr>
<tr>
<td>Large volume of dye required</td>
<td>Use dye to identify anatomy and then to confirm adequacy of procedure rather than on every step of dissection</td>
</tr>
<tr>
<td>Non visualization of perforators</td>
<td>Adequate dissection of aneurysm or parent vessel to explore for perforators around aneurysm (Do not forget to look behind)</td>
</tr>
<tr>
<td>Missing daughter nidus in AVM</td>
<td>Follow each arterialized vein till they collapse after nidus excision</td>
</tr>
</tbody>
</table>

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Table 2: Pearls to use ICGA in Neurosurgery
Thapa et al.

Uses of ICGA

Recent integration of ICG video technique into a surgical microscope has obviated need to remove visible light or move microscope out of the surgical field, during the investigation and provide high-resolution NIR images based on ICG fluorescence.

For cerebrovascular surgeries, this technique has opened a new vista. Surgical clipping of aneurysm despite being effective in occluding intracranial aneurysm have a documented risk of residual aneurysm filling from 2 to 8%. It is also associated with accidental occlusion of parent, branching or perforating artery in 4 to 12% cases\(^1, 4, 8, 14, 16, 21, 23, 33\) leading to ischemic infarction which contributes to poor outcome not limited to functional, cognitive and psychological problems and even death.\(^2\) During surgical clipping, accidental occlusion of vessels (up to 22.8%) is only second to vasospasm to cause ischemic infarction after SAH secondary to aneurysm.\(^8\) De Oliveira et al reported 56% cases with perforating arteries in surgical field using ICGA, of which 30% were arising close to or from neck of aneurysm.\(^3\) Identifying these vessels and preserving them while achieving complete occlusion of neck of aneurysm is greatly helped by ICGA.

Other use is in AVM, where a complete dissection of nidus without antegrade flow in the drainer on ICGA suggests total excision. Neuronavigation however useful cannot assess flow of AVM.\(^24, 26\) Risk of residual nidus leading to re-bleed, if seen on ICGA can be avoided.\(^33\)

A major use of ICGA is in detecting patency of bypass in STA-MCA bypass that help reduce early bypass graft failure and improve surgical results.\(^37\)

ICGA have been used in brain tumor surgery to identify tumoral and peritumoral vessels and confirm their patency after resection. They can serve as an alternative to intra-operative digital subtraction angiography (DSA) or Doppler ultrasonography.\(^10, 19\)

Very few reports exist for use of ICGA in microvascular decompression for trigeminal neuralgia; however it is useful not only to identify vascular compression but also to diagnose unusual lesions like micro AVM of trigeminal root\(^12\) or developmental venous anomaly of petrous veins.\(^11\)

This technological advancement has improvised surgical precision. This can be often repeated and results are immediately available. ICGA has been found to be a simple tool for intra-operative quality control and documentation of surgical outcomes.\(^29, 30\)

Other modalities

ICGA is now being tested against intra-operative digital subtraction angiography (DSA). DSA has been used routinely\(^3, 34\) as well as in selective cases.\(^15, 27, 28\) DSA has the advantage of revealing parent vessels and branches without tissue dissection but the same time, fails to reveal arterial vessels of small diameter such as perforating vessels\(^29\) and is invasive and exposes patient to radiation. Washington et al in their study of 49 patients of aneurysm where both modalities have been used found clip adjustment rate of 4.1% with overall rate of ICGA and DSA agreement of 75.5% and discordance rate of 14.3% that required clip adjustment for aneurysmal remnants and vessel occlusion. They advised caution to use ICGA as sole mean for intra-operative evaluation of aneurysm clip application. DSA is still gold standard in selected cases like giant, complex and deep-seated aneurysm or daughter nidus in AVM.\(^36\)

Refinement in technique

Initially we used 5 ml of sterile water to dilute the dye, however as we gain experience we diluted the same in 6ml and used 2 ml boluses during each injection. We did not find any decrease in intensity or duration of illumination on this dilution.

We realized that the best way to see maximum in the field is to dissect around the lesion/ structure of interest and then try to see circumferentially around for vascular details while working in NIR mode.

Limitations

The biggest problem with ICGA is the limitation to see only those vessels that are within the microscopic field of view and superficial. Hence vessels covered by blood, lesions or brain tissue are not visible. For this reason, until unless seen circumferentially, presence of a neck remnant of a clipped aneurysm cannot be excluded if residual lesion is not seen.\(^5, 29, 30\) Compared to DSA, ICGA has much smaller area of observation\(^30\) and is also affected by calcifications, thick walled atherosclerotic vessels or by thrombosis of aneurysm.

At this moment, we suggest combining ICGA with microdoppler ultrasonography, flowmetry and intra-operative DSA to solve unanswered query related to complex cerebrovascular problems.

Cost effectiveness

As the consumable used is cheap, this technique is cost effective in delivering a safe and effective surgery. Only formidable cost is the expense of upgrade to incorporate the technology in the microscope. As patients can be discharged sooner without formidable deficits, ICGA saves lot of expense which a patient bears while staying in hospital or during rehabilitation beside the disability which come as a price due to vascular damage.
**New horizons**

Besides abovementioned uses, ICGA is being explored to detect a shunt point in a dural arteriovenous fistula and patency of dural sinus during tumor surgery. During carotid endarterectomy, it can detect location of plaque and confirm vascular patency.

A technique called as flash fluorescence has been used to identify recipient artery for bypass with distal middle cerebral artery in non-saccular aneurysm that necessitates trapping and bypass.  

ICG staining is being used to stain and demarcate brain tumor margins both in animals and humans however results are not comparable to 5-aminolevulinic acid (5-ALA) tumor fluorescence guided resection. Besides, performing ICGA after applying a temporary clip over a vein or an artery it is useful to predict a sacrificable vein or artery if a collateral flow (with drainage in case of vein and retrograde filling in case of artery) is seen.

**Conclusions**

ICGA is safe, viable and useful technique to identify vascular anatomy as well as confirm adequacy of procedure without significant complications. This tool to summarize, boost surgical precision and is cost effective and has potential of ever-increasing role in neurosurgery.

**Investment/financial Disclosure**

Authors do not have any financial interest in the subject under discussion.

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**Bibliography**


**Infrared Indocyanine Green Videoangiography**


