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Utilizing indocyanine green video angiography to bridge intracranial aneurysm treatment gaps in low- and middle-income countries: a mini-review

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Abstract

Intracranial aneurysms, affecting 2%–5% of the population, pose a significant challenge to neurosurgeons due to their potential to cause subarachnoid haemorrhage and high mortality rates. Intraoperative angiography is necessary for effective surgical planning and indocyanine green video angiography (ICG-VA) has emerged as a useful tool for real-time visualization of aneurysmal blood flow, aiding in better planning for potential blood flow and detection of aneurysm remnants. This mini narrative review explores the application of ICG-VA in intracranial aneurysm surgery. Compared with conventional dye-based angiography, ICG-VA is safer, more effective and more cost-effective. It can assess haemodynamic parameters, cerebral flow during temporary artery occlusion, completeness of clipping and patency of branch vessels. However, implementing ICG-VA in low- and middle-income countries presents challenges such as financial constraints, limited access to training and expertise, patient selection and consent issues. Addressing these

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obstacles requires capacity-building, training programmes for neurosurgeons and multidisciplinary teams, technology transfer, equipment donations, public–private partnerships, continued research and development, reducing conventional dye usage, reducing ICG wastage, exploring mechanisms to reuse ICG dyes and advocating for increased government funding and healthcare budgets.

Keywords

Intracranial aneurysm, low- and middle-income countries, indocyanine green video angiography, cerebrovascular neurosurgery

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Introduction

Intracranial aneurysms (IAs) are one of the most significant challenges in the domain of neurosurgery. Anatomically defined as abnormal dilatations of intracranial arteries, IAs are mostly formed either at the point of bifurcation of intracranial arteries or at the points of segmentation of arteries from the circle of Willis.[1] IAs affect approximately 2%–5% of the population, and timely diagnosis and treatment of unruptured aneurysms are crucial to minimising the impact of rupture, especially in low- and middle-income countries (LMICs).[2] Aneurysm rupture can cause subarachnoid haemorrhage (SAH), a severe and often deadly condition that accounts for 5% of all strokes.[3] The global incidence of SAH is estimated to be 6.67 per 100 000 people, with almost two-thirds of this population residing in LMICs.[4] Aneurysmal haemorrhage has a mortality rate of 50%,[5] and therefore, improving access to appropriate medical care and resources is crucial to reduce the morbidity and mortality associated with SAH caused by aneurysm rupture, particularly in LMICs where access to appropriate medical care may be limited. Recent advancements in technology, such as indocyanine green video angiography (ICG-VA), could bridge the existing gap in aneurysm surgery in developing countries.

The surgical treatment of IAs is often considered extremely arduous and requires meticulous planning and a great degree of attention to detail. Intraoperative angiography is considered an indispensable tool in this regard, with it being of paramount importance in the visualization of the blood flow to IAs, allowing for adequate surgical pre-planning.[6] To this end, the use of ICG-VA is a safe and effective tool, allowing for the real-time visualization of aneurysmal blood flow, better visualization of blood flow at aneurysm necks and adjacent vessels, and better planning for potential blood flow in the parent, branching, and perforating vessels. It also facilitates the effective detection of aneurysm remnants.[7]

Indocyanine green video angiography utilizes indocyanine green (ICG) dye, which fluoresces in the near-infrared (NIR) range, enhancing its penetration through tissues. During surgery, ICG is injected intravenously, and an NIR camera captures its fluorescence as it travels through vessels, providing dynamic information about blood flow patterns.[8] This information helps surgeons make informed decisions about aneurysm treatment, optimising outcomes. Moreover, the real-time capabilities of ICG-VA allow immediate adjustments during surgery based on the observed blood flow patterns.[9] Aneurysm surgery is an expensive procedure in LMICs and may be hindered by a lack of financial resources to support the necessary infrastructure, personnel and equipment.[10] Open surgery approaches such as aneurysm wrapping and aneurysm resection, may lead to increased mortality rates and complications, while endovascular treatment options may not always be accessible due to cost and expertise constraints.[11] Additionally, intraoperative techniques like digital subtraction angiography (DSA) can be time-consuming and entail limitations.[12]

The recent emergence of ICG-VA presents a promising solution. This imaging technique, utilizing equipment like NIR cameras and ICG dye injections, offers a simple and affordable approach. By potentially reducing the expenses associated with aneurysm surgery, ICG-VA has the potential to enhance patient accessibility in LMICs.

In this framework, the mini narrative review critically evaluates the potential impact of ICG-VA on elevating treatment outcomes for intracranial aneurysms, particularly within LMICs. The primary objective is an in-depth exploration of the application of ICG-VA in intracranial aneurysm surgery, meticulously assessing its effectiveness in enhancing patient prognoses.

Methodology

Focusing on original research studies conducted within LMICs, this analysis covers a range of study designs, including randomized controlled trials, cohort studies, case–control studies and case series. The scope includes both paediatric and adult populations, incorporating individuals with comorbidities and previous treatments in LMICs. This mini-review's core emphasis lies on full-text English articles published from LMICs, concentrating on aneurysm treatment outcomes through ICG-VA. Non-English studies or those lacking LMIC-specific data were excluded. Using pertinent keywords including 'ICG-VA aneurysm outcomes', 'indocyanine green angiography aneurysm' and 'indocyanine green angiography applications', a thorough search across databases such as PubMed→, MEDLINE→ and the Cochrane Library was conducted. Specifically, studies originating from LMICs were meticulously included in the review. Furthermore, the integration of relevant references from recent reviews on LMIC medical procedures enhances the analysis, excluding stand-alone abstracts and unpublished studies.

The application of ICG-VA for IAs in LMICs and its outcomes

Numerous recent studies have investigated the effectiveness of ICG-VA in LMICs for intracranial aneurysm surgery, yielding promising results. Using ICG-VA in conjunction with other intraoperative technologies has been demonstrated to enhance patient outcomes. For example, in a study conducted in China with 158 patients, a comprehensive approach involving the combination of somatosensory evoked potential, microvascular Doppler sonography and ICG-VA during surgery exhibited significant benefits.[13] This approach effectively reduced instances of brain tissue ischaemia.[13] Temporary occlusion of parent arteries led to reversible reductions in somatosensory evoked potentials amplitudes in 12.0% of cases, while 5.7% exhibited altered flow velocities, both of which were restored to baseline levels through clip adjustments.[13] The use of ICG-VA monitoring allowed for precise visualization of aneurysm remnants and associated changes.[13] Subsequent postoperative evaluations confirmed the successful clipping of aneurysms and ensured the maintenance of parent artery patency.[13]

Importantly, follow-up data spanning 4 months to 1.2 years demonstrated positive outcomes with minimal risk of re-haemorrhaging.[13]

Another important Chinese study demonstrated that FLOW 800, in conjunction with ICG-VA, can offer reliable semiquantitative data about the localization and flow status of major feeding arteries, which can aid in determining blood flow status after aneurysm clipping and bypass surgery.[6] Another study also highlighted the clinical value of ICG-VA in IA surgery.[9] It included 120 patients with 148 IAs and ICG-VA was performed before and after aneurysm clipping.[9] The results demonstrated that ICG-VA is a reliable and cost-effective method for real-time detection of the patency of parent, branching, perforating and residual aneurysms.[9] In addition, the use of Flow 800 also detected perforator compromise, necessitating readjustment of the clip.[9] A study conducted in Nepal also highlighted the benefits of FLOW 800, where it has the potential to predict whether patients are at risk of postoperative vasospasm following clipping of ruptured intracranial aneurysms.[14]

The utilization of ICG-VA for avoiding vascular complications during microsurgical clipping of ruptured intracranial aneurysms has also been documented in LMICs, underscoring its potentially significant role. For example, a study involving 17 Indian patients with ruptured aneurysms integrated ICG-VA into surgery.[15] Remarkably, ICG-VA influenced intraoperative decisions five times, assisting in clip adjustments, identifying compromised vessels and detecting residual filling.[15] No adverse effects associated with the use of ICG were reported.[15] The majority of patients exhibited anterior communicating artery aneurysms, followed by middle cerebral artery aneurysms, with a smaller proportion presenting internal carotid artery aneurysms.[15] The study emphasizes the significant safety and efficacy of intraoperative ICG-VA utilization during the clipping of ruptured intracranial aneurysms.[15] Notably, the study included patients with World Federation of Neurological Surgeons Grade 1 and 2 aneurysmal SAH, recognizing the potential of this technique to yield excellent outcomes, particularly in cases where precise technique is pivotal for favourable results.[15]

Similarly, Brazilian researchers investigated the outcomes of an experienced vascular neurosurgeon, concentrating on cases where aneurysms were treated with intraoperative ICG between 2009 and 2014.[16] The study encompassed the surgical clipping of 61 aneurysms in 56 patients using ICG guidance.[16] It underscores the real-time assessment of vascular structures facilitated by ICG during surgery.[16] Notably, the implementation of ICG resulted in a 3.2% rate of clip repositioning.[16] These findings underscore ICG's role as an adjunctive tool, contributing to aneurysm evaluation and treatment. The study acknowledges the vital role of a proficient vascular neurosurgeon in achieving optimal surgical outcomes and emphasizes the ongoing challenges in the seamless integration of ICG into the domain of vascular neurosurgery.[16]

Indocyanine green video angiography has also proven to be a valuable tool for assessing haemodynamic parameters and cerebral flow during temporary artery occlusion (TAO) in aneurysm surgery. For example, research has revealed that the only haemodynamic parameter change observed during TAO is an increase in blood pressure; and the duration and frequency of temporary clip usage are significant variables associated with postoperative ischemic changes.[17] The use of ICG-VA during aneurysm surgery allows the surgeon to anticipate impending ischaemia during TAO. Furthermore, the age-based analysis showed no increased risk of ischaemic complications for patients aged 50 years or older, affirming ICG's safety across age groups.[17] Surgical timing after SAH emerged as a crucial factor, with a 96-h delay linked to better outcomes and early surgery associated with higher symptomatic ischaemia rates.[17] Follow-up at an 8-month mean demonstrated a notable 84.2% of patients achieving good outcomes (modified Rankin Score 0–2) in the same study, underscoring the potential of ICG-VA to enhance safety and outcomes in intracranial aneurysm surgery.[17]

A study undertaken in India found that intraoperative ICG-VA was effective in assessing the completeness of clipping and patency of branch vessels, reducing the need for invasive postoperative angiographic imaging in selected patients.[18] Furthermore, another study also found ICG-VA to be a useful and cost-effective tool for assessing the completeness of clipping and ensuring better postoperative outcomes, replacing the need for invasive postoperative angiographic imaging in selected patients.[19] There have been recent efforts to develop handmade ICG-VA cameras for use in the operating room or laboratory for research purposes. These cameras have been tested on animal models, demonstrating the potential for use in LMICs to improve the outcome of intracranial aneurysm surgery.[20]

As much as ICG-VA has provided promising results and potential benefits in LMICs, there are still other alternative techniques that have enhanced aneurysm surgeries in LMICs. For example, a study conducted in the Department of Neurosurgery at the Sher-I-Kashmir Institute of Medical Sciences, India, has suggested that DSA may still have an advantage over ICG-VA in detecting residual aneurysm necks and reducing the risk of rupture in the future.[21] Despite this limitation, the authors pointed out that ICG-VA can be an optimal investigation for delineating vascular anatomy and confirming clip position, which can reduce mortality in LMICs where DSA facilities are limited.[21]

Overall, the current application of ICG-VA in LMICs for IA surgery is a promising avenue for improving patient outcomes and reducing the need for more invasive and expensive postoperative imaging techniques.

The need for IVG-VA expansion in various LMICs, including potential challenges and limitations

Aneurysm surgery is a complex procedure that demands specialized medical expertise from neurosurgeons, neurologists and intensive care units. However, in LMICs, accessing these specialized services poses challenges. Traditional open surgery has been the mainstay for treating intracranial aneurysms in LMICs.[22] Yet, this approach has been associated with increased patient mortality and complications.[22,23] Given the potential for incomplete clipping and subsequent rebleeding, especially in situations with compromised aneurysm localization accuracy,[23] the demand for enhanced techniques becomes imperative. In this context, the adoption of ICG-VA emerges as a promising avenue for addressing this challenge.

In a comparative study assessing periods before and after ICG-VA adoption, rebleeding incidents decreased significantly after ICG-VA implementation.[24] This reduction is attributed to the efficacy of ICG-VA in evaluating residual aneurysm filling, allowing precise clip adjustments along the aneurysm neck.[24] Additionally, open surgery in LMICs is linked to limited real-time feedback during surgery and longer operative times compared with high-income countries.[22,23] The introduction of ICG-VA addresses these limitations by providing real-time information on flow direction and intensity, aiding in evaluating artery patency during surgery.[6] Consequently, intraoperative repositioning time is reduced, leading to decreased critical ischaemia duration and a shorter overall surgical duration.[21]

While alternatives like endovascular treatment exist, they are less prevalent in LMICs due to cost and knowledge constraints.[22] Implementing ICG-VA could potentially bridge this gap, as evidenced by studies from various LMICs.[6,13,14,17] In conclusion, ICG-VA holds the promise of improving the outcomes of aneurysm surgery in resource-constrained settings. As much as ICG-VA will have major benefits in LMICs and it is vital to extend it in various LMICs, it is critical to examine the many restrictions that come with its expansion. One of the most significant limitations of ICG-VA in LMICs is the cost and availability of equipment and supplies. A surgical microscope equipped with NIR imaging technology, a light source with a wavelength covering the ICG absorption band (700–850 nm) and a video camera to record ICG dye fluorescence are all necessary for ICG-VA.[25]

These resources may be expensive and their availability may be limited in many LMICs. For instance, in many African countries, access to specialized neurosurgical equipment is often limited and most of the existing equipment is obsolete or in a state of disrepair.[26] The microscopes equipped with filters for ICG-VA during surgery are costly, making them unavailable in many healthcare centres.[27] This situation creates significant challenges for healthcare professionals who rely on ICG-VA to provide accurate and reliable information during surgery. In addition, some studies have reported that the use of ICG-VA alone may not provide sufficient information for assessing certain parameters during intracranial aneurysm surgery. For example, a study from India found that fluorescein video angiography was superior to ICG-VA in assessing perforating arteries, distal branches, and aneurysm clipping adequacy.[28] This suggests that ICG-VA may not provide a complete assessment of all parameters, and therefore, additional methods such as fluorescein video angiography may be necessary for optimal surgical outcomes.[28]

Another limitation of ICG-VA in LMICs is the limited access to training and expertise. The successful use of ICG-VA requires specialized skills and knowledge, including an understanding of the dye's pharmacology, proper injection techniques and the interpretation of the images produced in deeper operative fields, where the quality of the images can deteriorate.[25,28,29] However, many LMICs lack the resources necessary to train healthcare professionals adequately in the use of ICG-VA. There is a severe shortage of neurosurgeons and the few available specialists often lack the training and expertise necessary to perform ICG-VA adequately.[30] Challenges with patient selection and consent also limit the use of ICG-VA. In many LMICs, patients may have limited access to healthcare services and many may present with advanced disease, making them unsuitable candidates for surgery.[31] Finally, informed consent can be challenging to obtain in some settings due to language barriers, low health literacy and cultural factors, with patients being reluctant to provide consent for surgery due to their belief in traditional medicine.[32]

Future prospects for ICG-VA expansion in LMICs

To improve the use of ICG-VA in neurosurgery within LMICs, it is essential to prioritize the enhancement of capacity-building and training for neurosurgeons and multidisciplinary teams who use ICG-VA. Collaboration between high-income countries (HICs) and LMICs is necessary to achieve this goal. Successful initiatives, such as the Stanford Global

Health Neurosurgery Initiative and the Duke Global Neurosurgery and Neuroscience Group, which have improved neurosurgical training, brought significant medical resources and improved patient outcomes in China, Uganda and Jamaica, should be replicated throughout LMICs.[33] Financial constraints can be addressed through a combination of approaches, such as technology transfer, equipment donations and public–private partnerships. Additionally, the development of more affordable and cost-effective portable ICG-VA systems can help expand access to this technology in low-resource settings. Examples of such systems include the PDE-NEO system and the TIVATO system. Training programmes that incorporate e-learning and online training modules can also be more cost-effective and accessible than traditional in-person training, which can help mitigate financial barriers to acquiring new skills and knowledge. Likewise, experienced HIC neurosurgeons may improve their counterparts' skills through e-courses and telemedicine.

Looking ahead, the continued investment of resources and time into the research and development of ICG-VA and mechanisms to improve access are essential to ensuring the widespread adaptation of ICG-VA. For instance, according to a previous study, reducing the amount of conventional dye used in angiography can still result in favourable outcomes.[34] Innovative studies such as this could be instrumental in widening access to ICG-VA because they would inherently imply a reduction in cost.[34] Another avenue to be explored in the domain of cost-effectiveness is a potential reduction in ICG wastage. For example, albeit for sentinel lymph node mapping for endometrial cancer, the results of a previous study suggest that most gynaecologists use only 20%–40% of the total available ICG from the vial, resulting in significant wastage of the available ICG.[35] By reducing the sizes of ICG vials to just the amount required for the procedure, this massive wastage, amounting to as much as \$3 million for hospitals and more than \$17 million for patients per year in the US, could be conserved.[35] There is a dire need for such analyses for ICG usage in the angiography of aneurysms; simple steps like these could go a long way in making ICG-VA more affordable for LMIC settings.[35]

The widespread adoption of ICG-VA in LMICs also depends on the effective implementation of regulatory frameworks to ensure its safety and effectiveness. Primarily, they establish stringent quality control and standardization measures. These measures encompass essential aspects such as manufacturing procedures, storage requirements and quality assurance protocols. Given the potential challenges in healthcare infrastructure within LMICs, these regulations play a pivotal role in preventing the influx of substandard or counterfeit ICG products into the market.[36] Moreover, the paramount issue of patient safety becomes a focal point. Regulatory approval processes rigorously evaluate the safety profiles of medical dyes and associated devices, a facet that takes on heightened significance in LMICs. Here, limited access to medical care magnifies the potential consequences of adverse events. Within this context, a robust regulatory framework meticulously assesses potential risks, contraindications and adverse reactions tied to ICG-VA. Equipping healthcare practitioners with this critical information empowers them to make well-informed decisions that prioritize patient safety and contribute to effective medical practices.[37]

Furthermore, the incorporation of quality control mechanisms also effectively addresses the ethical considerations inherent in the process. Furthermore, these regulatory processes play an instrumental role in fostering research and innovation. Manufacturers and healthcare professionals, cognizant that their products and methodologies must meet specific standards, are incentivized to invest in the enhancement and progression of technology.[38] This impetus catalyses continuous improvements, potentially yielding adaptations that render ICG-VA more suitable and effective in addressing the distinctive healthcare challenges encountered in LMICs.

Progressing towards sustainability, local production of ICG dyes within LMICs yields a range of advantageous outcomes. Notably, it addresses the challenge of steep costs associated with importing medical supplies due to factors like transportation expenses and import duties, significantly reducing these expenses and rendering ICG-VA more financially feasible, thus enhancing its accessibility for healthcare facilities in LMICs. Moreover, a reliance on international suppliers can lead to shortages and delays, directly impacting patient care. Through local production, a steady and dependable supply of ICG dyes is assured, mitigating the risk of treatment disruptions and fortifying consistent healthcare delivery. Additionally, local production provides the avenue for tailored customization of ICG dyes to align with specific healthcare requisites and prevalent conditions in LMICs, enabling adjustments in formulations to suit local patient demographics and environmental variables, thereby optimizing the effectiveness of ICG-VA.

Establishing local production facilities serves as a catalyst for capacity building and employment generation within the region, fostering specialized skills and knowledge that extend beyond healthcare to contribute to broader economic growth and healthcare system advancement. Under the oversight of national regulatory agencies, local production adheres to stringent quality standards and safety regulations, bolstering trust in domestically produced ICG dyes. Furthermore, collaborative efforts between international experts and local producers during technology transfer not only facilitate knowledge exchange but also stimulate skill development and the establishment of best practices, further elevating the quality and impact of locally produced ICG dyes in LMICs.

In addition, better healthcare planning and prioritization, reserving ICG-VA for high-risk cases while utilizing cheaper alternatives, such as transcranial dopplers, for cases considered low-risk, could also be beneficial in the short term. By continuing investment in innovation, access to this revolutionary mechanism of diagnostic testing can be spread to areas that require it the most, ushering in a new era of health equality and equity practices.

Conclusion

The utilization of ICG-VA for IA surgery in LMICs has demonstrated promising outcomes. This cost-effective, reliable and safe modality provides real-time visualization of aneurysmal blood flow, facilitating better planning for potential blood flow patterns and aiding in the detection of aneurysm remnants. Although LMICs encounter hurdles such as limited access to training, expertise and equipment, technology transfer, partnerships and capacity-building efforts can address these issues. Furthermore, continued investment in research and development, exploring alternatives to reduce conventional dye usage and wastage, and advocating for increased healthcare funding are also critical. Enhancing accessibility to ICG-VA can improve patient outcomes, decrease mortality rates and foster equitable healthcare practices.

Author contributions

Shankhaneel Ghosh: conceptualization, methodology, writing-original draft, writing-review and editing; Wireko Andrew Awuah: supervision, writing-original draft, writing-review and editing; Hareesha Rishab Bharadwaj: writing-original draft, writing-review and editing;

Favour Tope Adebusoye: writing-original draft, writing-review and editing; Brian M. Ou Yong: writing-original draft, writing-review and editing; Jack Wellington: supervision, writing-original draft, writing-review and editing; Toufik Abdul-Rahman: writing-original draft, writing-review and editing; Denys Ovechkin: supervision.

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