Laser-Assisted Indocyanine Green Angiography

A Critical Appraisal

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Background: Laser-assisted indocyanine green angiography (ICG-A) has been promoted to assess perfusion of random skin, pedicled, and free flaps. Few studies address its potential limitations.

Methods: Thirty-seven patients who underwent reconstructive procedures with ICG-A were studied retrospectively to determine the correlation between clinical findings and ICG-A. Indocyanine green angiography underestimated perfusion when areas of less than or equal to 25% uptake were not debrided and remained perfused. Indocyanine green angiography overestimated perfusion when areas with greater than 25% uptake developed necrosis.

Results: Of 14 random skin flaps, ICG-A underestimated perfusion in 14% and overestimated in 14%. In 16 patients undergoing perforator flap breast reconstruction, ICG-A correlated with computed tomographic angiogram (CTA) in 85%. Indocyanine green angiography underestimated perfusion in 7% and overestimated in 7%. In 8/11 patients undergoing fasciocutaneous flaps, ICG-A aided in donor site selection. In 3/6 ALT flaps, a better unilateral blush was found that correlated with Doppler. In all 3, a dominant perforator was found. In 11 patients, there was a 9% underestimation of flap perfusion. In 3 pedicled flaps, there was a 66% underestimation and 33% overestimation of perfusion.

Conclusions: Indocyanine green angiography often confirmed our clinical/radiologic findings in abdominal perforator and fasciocutaneous flaps. It tended to underestimate perfusion in pedicle and skin flaps. When clinical examination was obvious, ICG-A rendered clear-cut findings. When clinical examination was equivocal, ICG-A tended to provide ambiguous findings, demonstrating that a distinct cutoff point does not exist for every patient or flap. Indocyanine green angiography is a promising but expensive technology that would benefit from standardization. Further research is needed before ICG-A can become a reliable tool for surgeons.

Key Words: indocyanine green angiography, mastectomy flap, fasciocutaneous flap, osteocutaneous flap, pedicled myocutaneous flap

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Indocyanine green is a contrast agent that is bound to protein in plasma. Laser-assisted indocyanine green angiography (ICG-A) is an imaging modality that provides real-time imaging of tissue perfusion using a laser to induce fluorescence of the contrast agent that is captured by camera.1-2 Indocyanine green angiography has been promoted to assess vascular perfusion of skin flaps,1-14 pedicled flaps,14-16 and free flaps.17-33 Recent studies have shown that a perfusion cutoff can predict the likelihood of flap survival.5,8-10 However, few studies have addressed the potential limitations of ICG-A.20,28 We investigated the correlation between clinical findings and ICG-A assessment of perfusion and perforator location in random skin flaps, abdominal perforator flaps, fasciocutaneous flaps, and pedicled flaps. On the basis of our experience with this technology, we also discuss the various limitations of this technology as it currently stands.

METHODS

An institutional review board–approved retrospective chart review from July 2009 to June 2012 was performed of every case in which ICG-A was performed by the senior author (E.G.H.). Thirty-seven patients were studied, and demographics such as race, flap type, indication for ICG-A were recorded. In some patients, ICG-A was used to assess more than 1 site, for example, a patient undergoing abdominal flap breast reconstruction might have ICG-A performed to assess the mastectomy flaps, identify abdominal perforators, and assess perfusion to the abdominal flap. Indocyanine green angiography findings during surgery, clinical findings during surgery, whether debridement was performed based on ICG-A, correlation between ICG-A, computed tomographic angiogram (CTA), and operative findings, whether ICG-A changed how much tissue was debrided or changed the donor site, and clinical outcome were evaluated.

Definitions

Indocyanine green angiography was considered to overestimate perfusion when tissue that looked viable by examination and ICG-A developed necrosis. Indocyanine green angiography was considered to underestimate perfusion when tissue that looked nonviable by ICG-A but viable by clinical examination was left in place and did not develop necrosis.

ICG-A for Assessment of Flap Perfusion and Perforator Location

Indocyanine green angiography was used in a number of clinical settings to gain information about tissue perfusion. Random skin flaps were assessed, usually in the setting of breast reconstruction, to determine areas requiring debridement. Perforator flaps for breast reconstruction were imaged to determine perforator location and assess flap perfusion based on different perforators or after microanastomosis to guide debridement. Flaps with a thin fasciocutaneous component (ALT/ Tibula) were imaged preoperatively to determine if the patient’s left or right side demonstrated better perfusion based on Doppler interrogation and ICG-A. Myocutaneous flaps were imaged to assess flap perfusion and guide debridement.

ICG-A Injection Protocol

UNC acquired the SPY™ device (Lifecell, Branchburg, NJ) for ICG-A in September of 2009. All but 1 patient in this study were imaged using the first generation device and software (called SPY-Q™). In most cases, 5 mL of dye was used per injection, but in some cases, 3.3 mL was used to get 3 images from one 10 mL vial of dye. Parameters for when to image tissue after injection and percentage of dye uptake considered acceptable were not established in the literature before this study, although in the last year imaging in the second minute has been suggested and more studies5,8-9 are defining absolute numbers and percentages of dye uptake associated
with tissue necrosis. For this study, we used a 25% dye uptake cutoff point in the second minute of imaging.5

ICG-A Imaging Protocol

In this study, timing of imaging depended on the indication for ICG-A. To identify perforators, imaging was performed 10 seconds after dye injection. To assess flap perfusion, imaging was usually performed for 2 minutes separated by approximately 30 seconds to save the first minute of imaging. Black and white images were reviewed, followed by the same images processed using SPY-Q™ software. We set the 100% marker in adjacent normal skin and considered tissue with less than or equal to 25% dye uptake to be nonviable according to ICG-A. When areas viewed in the first minute were less than or equal to 25% but greater than 25% in the second minute of imaging, we considered the tissue to be viable according to ICG-A. Thus, we considered the second minute of imaging to be more accurate. After mastectomy, we waited at least 20 minutes before imaging native breast skin flaps. We did not perform imaging when tumescent technique was used, as an earlier trial of the device in this setting demonstrated significant hypoperfusion consistent with epinephrine effect.

RESULTS

Random Skin Flaps

Indocyanine green angiography was used to assess random skin flaps in 14 patients. Of these patients, 12 were mastectomy flaps, 1 was penile skin after degloving for lymphedema, and 1 was neck skin after cervical lymphadenectomy. In 7 patients, areas of hypoperfusion were noted by ICG-A. In 4 cases, debridement was performed with good result and in 3 the tissue looked viable by clinical examination and was preserved. In these 3 cases, no necrosis was observed in 2 and in the other partial thickness necrosis was observed and managed conservatively. Thus, in 2 (14%) of 14 cases, ICG-A underestimated perfusion. In another 2 (14%) cases, ICG-A overestimated perfusion. All areas imaged demonstrated good dye uptake with percentages greater than 25% but full-thickness skin necrosis occurred. One was managed with debridement in clinic followed by dressing changes and the other was a case of nipple-sparing mastectomy where full-thickness necrosis occurred despite dye uptake greater than 25% (Figs. 1 and 2). At reoperation, imaging was repeated and showed uptake of approximately 30% in tissue that was nonviable by clinical examination (Fig. 3).

FIGURE 1. Overestimation of perfusion in a mastectomy skin flap. This is a left nipple-sparing mastectomy demonstrating adequate perfusion (≥30%) in the region of the left nipple areola complex. As capillary refill was present, the nipple was preserved.

FIGURE 2. Clinical evidence of left nipple necrosis developed within 48 hours. Repeat ICG-A demonstrated 30% to 35% uptake in this area. Nevertheless, debridement was performed based on clinical examination.

FIGURE 3. Nipple areolar complex (NAC) debridement. At surgery, no bleeding was noted from skin incision (arrow) and full thickness necrosis of the NAC was observed.
Perforator Flap Breast Reconstruction

Sixteen patients undergoing perforator flap breast reconstruction were imaged with ICG-A. In 13 patients, imaging was obtained immediately after dye injection to identify perforators and correlate ICG-A findings with preoperative CTA. In all but 2 cases (11/13, 85%), ICG-A correlated with CTA. In 1 case, ICG-A identified a perforator not seen on CTA. In 15 patients, flap perfusion was assessed to assist in perforator selection or to guide debridement after microanastomosis. In 4 cases, areas of hypoperfusion were noted by ICG-A. In 2, debridement was performed and no fat necrosis resulted. In 1, debridement was performed but fat necrosis developed in an area with greater than 25% dye uptake. Thus, ICG-A overestimated perfusion in 1/15 patients (7%). In 1 patient, an area with less than or equal to 25% dye uptake looked clinically viable and was not debrided with no resultant fat necrosis. Thus, ICG-A underestimated perfusion in 1/15 patients (7%).

Thin Fasciocutaneous Flaps

In 11 patients undergoing reconstruction with a thin fasciocutaneous component, ICG-A was performed. In 6 ALT flaps and 2 fibula flaps, ICG-A was used to image the patients’ left and right sides to see if images were more favorable on one side to assist in donor site selection. In 3/6 (50%) patients undergoing an ALT flap, ICG-A showed a better blush that correlated with Doppler interrogation on one side, and that side was chosen (Fig. 4). In all cases, a dominant perforator was noted in surgery that corresponded to Doppler and ICG-A. With respect to the assessment of flap perfusion, in 2 cases hypoperfusion was noted by ICG-A. In 1 case, a delayed supraclavicular artery flap was imaged and ICG-A showed hypoperfusion in the distal third. On the basis of clinical examination and prior experience with this flap, debridement was not performed and no necrosis was observed. Thus, ICG-A underestimated perfusion in 1/11 patients (9%). We did not observe any cases where ICG-A overestimated perfusion in a thin fasciocutaneous flap.

Pedicled Myocutaneous Flaps

In 3 patients undergoing pedicled myocutaneous flaps ICG-A was used to assess flap perfusion. One patient underwent pedicled TRAM flap breast reconstruction and ICG-A demonstrated hypoperfusion in areas that were then debrided. The patient, nevertheless, developed partial flap necrosis requiring debridement and thus ICG-A overestimated perfusion (33%). Two patients underwent pectoralis major flap oral cavity reconstruction and in both cases the skin island demonstrated global hypoperfusion (≤25%) by ICG-A. Clinical examination revealed expected congestion and brisk capillary refill throughout and the flaps were inset without debridement (Figs. 5 and 6). No necrosis was observed (Fig. 7) and thus ICG-A underestimated perfusion in 2/3 pedicled myocutaneous flaps (67%). On the basis of our experience in these 3 patients, we stopped using ICG-A to assess pedicled myocutaneous flaps.

Race and ICG-A

After gaining some initial experience with ICG-A, we felt it might be most beneficial in patients with darker skin, in whom clinical examination for congestion and capillary refill is less reliable. We performed ICG-A in 9 African American patients. In 2/9 (22%),
ICG-A overestimated perfusion and in another 2 (22%) ICG-A underestimated perfusion.

CONCLUSIONS

Assessment of Flap Perfusion

In most cases 32/43 (74%), ICG-A confirmed our clinical examination of flap perfusion. In 6/43 (14%), ICG-A underestimated perfusion as evidenced by areas of hypoperfusion (<25% dye uptake) that survived. In 4/43 (9%), ICG-A overestimated perfusion as evidenced by areas of normal perfusion (>25% dye uptake) that did not survive. Indocyanine green angiography performed poorly in the assessment of pedicle myocutaneous flaps. Although we hypothesized that a good indication for ICG-A might be assessment of flap perfusion in patients with dark skin, ICG-A was less reliable in these patients although our numbers are too small for meaningful statistical analysis. In 4 cases of mastectomy flap debridement and 2 cases of abdominal perforator flap debridement (6/43 = 14%), ICG-A guided the extent of resection with favorable outcome. In 1 case (2%), findings of ICG-A were ignored with resultant tissue necrosis.

Perforator Assessment

Indocyanine green angiography correlated well (85%) with CTA for localizing perforators for autologous breast reconstructions but offers no information regarding perforator anatomy proximal to the fascia. In 3/6 (50%) of patients undergoing ALT flap reconstruction, ICG-A affected the choice of donor site with favorable outcome although we do not know if choosing the other side would have resulted in a complication. Because ICG-A imaging is superficial, its use for perforator localization makes sense for thin fasciocutaneous flaps such as the ALT flap. Although some have used it to localize perforators in abdominal flap breast reconstruction, our preferred method for abdominal perforator mapping is CTA. We feel it is helpful to have knowledge of the vascular anatomy from the origin of the deep inferior epigastric vessels up to the fascia, as this can reduce operative time and give the surgeon and patient a sense of which flap type can be performed safely before surgery.

Conceptually, CTA can be seen as a technology that allows the surgeon to view the “trunks” of the vascular trees, whereas ICG-A allows a top-down view of the leaves and branches. For assessment of flap perfusion, we still feel that clinical examination is the gold standard. Indocyanine green angiography has not proven itself superior to clinical examination. A prospective randomized trial is necessary to compare clinical outcomes with use of clinical examination versus ICG-A.

Limitations of ICG-A

Indocyanine green angiography offers a snapshot of arterial perfusion with less than 1 cm depth. Patient temperature, cardiac

FIGURE 6. Pectoralis major flap inset. The pectoralis major flap demonstrates congestion after inset with brisk capillary refill. The island showed global hypoperfusion by ICGA with relative perfusion less than or equal to 25% throughout.

FIGURE 7. Late clinical result of cervical and pectoralis major flap. There was complete survival of both the cervical skin and pectoralis skin island, both areas of hypoperfusion by ICG-A.
output, volume status, blood pressure, pressor support, and the local microvascular environment can all affect superficial arterial perfusion to a flap and are certainly dynamic processes. Thus, ICG-A should not be viewed as an objective and conclusive determinant of flap perfusion but rather as an additional tool for clinical assessment.

What we found in this study was that when clinical examination was obvious, ICG-A gave us straightforward information. When clinical examination left us wanting more information, ICG-A resulted in borderline information that was difficult to interpret. In these cases, adjusting the 100% marker could shift the points of interest over or under the 25% threshold, which was unhelpful in determining whether to perform debridement of the questionable tissue.

In our opinion, CTA is superior to ICG-A for mapping perforators. We also feel that ICG-A is better for assessing flap perfusion than for mapping perforators. It is a physiological, not an anatomical study. Some surgeons may prefer to use both CTA and ICG-A. CTA, in comparison to ICG-A, is a far more established technology and therefore the additional expense of adding this imaging, which is not as well established, requires further research to prove its utility. There are many unanswered questions: How long should the surgeon wait after mastectomy before imaging? Once dye is injected, which minute of imaging is the most informative? Once images are obtained and software analysis is performed, what percentage of dye uptake is the most reliable indicator of clinically relevant hypoperfusion? It is our opinion that an animal model would greatly advance our understanding of ICG-A and allow for the development of guidelines that would improve its clinical functionality.

Venous Congestion

Although new software and clinical research may allow for the assessment of venous outflow by measuring the rate of decline of fluorescence, currently ICG-A is limited to assessing arterial perfusion. Venous insufficiency is a significant cause of flap compromise and thus ICG-A is limited in its ability to assess this aspect of flap perfusion although early animal models have indicated that the rate of fluorescent decline can be a proxy for venous compromise.20

Pedicled myocutaneous flaps are often congested immediately after flap harvest and transfer, and we found in these situations that ICG-A indicated global hypoperfusion. Such flaps often undergo microvascular remodeling in the immediate postoperative period, and ICG-A is unable to account for this process. We would have expected good dye uptake but slow dispersion with venous congestion in pedicled myocutaneous flaps, but instead we saw poor uptake. It is possible that in our cases the initial transient vascular effects from harvesting the pedicled myocutaneous flap included both arterial insufficiency as well as venous congestion. This microvascular remodeling also takes place in random flaps and to a lesser extent in microvascular free flaps, and thus it is likely that some areas of hypoperfusion on ICG-A will remain viable through microvascular remodeling, whereas others will not. Indocyanine green angiography technology cannot account for this physiological process.

Reporting Values

In the past, perfusion values were reported as absolute values. More recently, authors such as Losken and Moyer21 have reported percentages, as the absolute value is dependent on the imaging distance, skin type, and ambient light. The percentage of perfusion compares the target tissue perfusion compared with the best perfused tissue to control for these user variables, and thus has been regarded as more accurate. Although the absolute units of fluorescence are now also being used to interpret ICG-A results, the percentage of dye uptake was initially promoted as the means to interpret software analysis of ICG-A imaging. This is not completely objective, however, as the user selects where to put the “100%” marker. If one has an area of borderline perfusion (eg, 27%), then adjusting the 100% marker can tip this area below or above 25%, or whichever cutoff point is selected. In the end, it is unlikely that a singular, distinct cutoff point will exist for all flaps and patients. Rather, a range of probabilities for tissue necrosis will be predicted within a range of percentage dye uptake.

Clinical Applications

There has been an evolution of the imaging hardware and software, and the types of patients imaged with ICG-A. The first usage of ICG-A was to evaluate cardiac bypass anastomoses25–27 and angiography of retinal microcirculation.28,29 The initial clinical flap studies focused on pedicled flaps. In 2002, Holm et al28 compared the intraoperative ICG-A images of pedicled skin flaps with the clinical outcomes 1 week postoperatively in 15 pedicled skin flaps, and found that intraoperative imaging predicted regional flap-perfusion defects in all 4 cases, however, the degree of flap loss was not always accurately predicted by ICG-A. Azuma et al30 used ICG-A to preoperatively plan perforator based island flaps. They were able to locate the precise location of perforators as well as see the direction of blood flow to these flaps.

Later, authors used ICG-A for other flap types and for perioperative monitoring. Holm et al31 was the first to report on clinical free flap monitoring in 2002. Intraoperative ICG-A imaging accurately predicted the 2 complications out of 20 patients. They also used ICG-A to characterize the SIEA angiosome, and found a 0% to 100% variability, thus concluding that ICG-A is a valuable tool to assess the sufficiency of this pedicle for free tissue transfer, especially if contralateral flap zones are needed for reconstruction.32 The same group evaluated the anastomotic patency of free flaps, and showed that the most common cause of anastomatic failure was technical (12%), and that when the occlusion seen by ICG-A was ignored by the surgeon, the consequence was always flap loss or reexploration.33

Holm et al24 further refined intraoperative anastomotic imaging in a prospective trial where they demonstrated that the anastomotic transit time was a predictor of flap compromise and need for reexploration. Most recently, they showed that ICG-A had a sensitivity and specificity of 100% and 86% for correctly identifying thrombotic occlusions in 20 consecutive free flap patients.34 Mohebali et al35 used intraoperative ICG-A to validate the retrograde limb of the IMV for additional venous drainage in DIEP flaps. Newman and Samson36 in 2008 used intraoperative ICG-A assessment of perfusion in 10 consecutive free tissue transfers in 8 women undergoing microsurgical breast reconstruction. In 4 cases, ICG-A demonstrated marginal or poor flow; in 3, intraoperative adjustments were made with improvement on follow-up imaging. In the one patient in which no adjustment was made, reoperation was required for venous congestion.

Others have used ICG-A for postoperative monitoring of flaps. Krishnan11 in 2004 used ICG-A for postoperative monitoring of 9 flaps (3 of them free) and suggested that ICG-A may be too sensitive to predict outcomes related to venous congestion. This, and other studies, show that refinements in technology could broaden ICG-A utility and improve flap outcomes.

More recently, ICG-A has been used to evaluate mastectomy skin flaps. Before ICG-A, percutaneous oxygen saturation measured by spectroscopy (percutaneous oxygen saturation)30 and laser Doppler flowmetry was used to measure flap perfusion. However, these modalities have not gained popularity because of low sensitivity, complexity, and expense. Laser Doppler flowmetry has been studied in both animals and humans and proved to be an inaccurate predictor of skin flap necrosis.37

In 2004, Mayr et al10 used ICG-A to image 15 aesthetic abdominoplasty skin flaps and found that the skin flaps, especially zone 1, had poor perfusion. Losken et al12 in 2008 used flourescein...
Indocyanine green angiography has been promoted with little evidence to demonstrate its advantage over clinical examination. Specific guidelines for the timing of imaging and parameters to use when interpreting results of software image analysis have yet to be determined and are the subject of current studies.\(^5,8,9\) We currently have obtained the latest SPY\(^\text{TM}\) device with the latest SPY-Q\(^\text{TM}\) software for image analysis and the usability is greatly improved with outstanding image quality. Given the aforementioned limitations, however, we have limited the indications for using ICG-A to mastectomy flap assessment in patients with dark skin, or in patients undergoing single-stage implant reconstruction, and abdominal perforator flaps in patients with dark skin. For assessing flaps, we wait at least 20 minutes (after the mastectomy) and then assess the percentages in the second half of the second minute after dye injection. We used 5 mL of dye with the older machine after noting that 3.3 mL gave suboptimal images; 3.3 mL with the new flap is acceptable. If used for myocutaneous flaps, we would consider waiting 20 minutes after flap harvest, but this has not been studied.

Further research and refinements in hardware and software should improve results obtained with ICG-A and clarify the best indications for this promising but expensive technology.

**REFERENCES**


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