

Evaluation of Intranasal Flap Perfusion by Intraoperative Indocyanine Green Fluorescence Angiography

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BACKGROUND: Vascularized intranasal flaps are the primary reconstructive option for endoscopic skull base defects. Flap vascularity may be compromised by injury to the pedicle or prior endonasal surgery. There is currently no validated technique for intraoperative evaluation of intranasal flap viability.

OBJECTIVE: To evaluate the efficacy of indocyanine green (ICG) near-infrared angiography in predicting the viability of pedicled intranasal flaps during endoscopic skull base surgery through a pilot study.

METHODS: ICG near-infrared fluorescence endoscopy was performed during endoscopic endonasal surgery for skull base tumors. Intraoperative and postoperative data were collected regarding enhancement of the flap body and pedicle. Fluorescence was rated qualitatively. Postoperatively, flap perfusion was evaluated via MRI-contrast enhancement in addition to clinical outcomes (cerebrospinal fluid leak and endoscopic flap appearance).

RESULTS: Thirty-eight patients underwent ICG fluorescence angiography. Both the body and pedicle enhanced in 20 patients (53%), while the pedicle only enhanced for 12 patients (32%), the body only for 3 (8%), and neither for 3 (8%). When both the pedicle and body enhanced with ICG, the rate of postoperative MRI contrast enhancement was 100% and the rate of flap necrosis was 0%. The sensitivity and specificity of flap pedicle ICG enhancement for predicting postoperative flap MRI enhancement were 97% and 67%, respectively. Two of 3 patients without enhancement developed flap necrosis.

CONCLUSION: ICG fluorescence angiography of intraoperative flap perfusion is feasible and correlates well with outcomes of postoperative MRI flap enhancement and flap necrosis. Additional study is needed to further refine the imaging technique and optimally characterize the clinical utility.

KEY WORDS: Skull base reconstruction, Nasoseptal flap, Fluorescence imaging, Indocyanine green, Near-infrared fluorescence, Endoscopic endonasal, Reconstructive techniques

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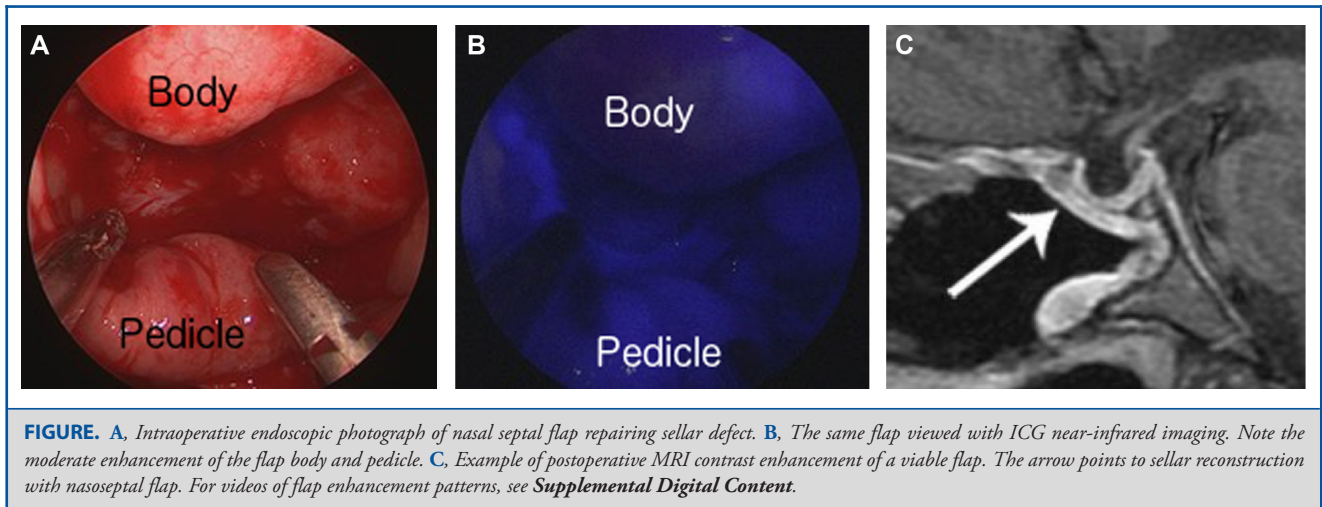
Over the last 2 decades, the nasoseptal flap (NSF) has proven to be the primary reconstructive option for endoscopic skull base defects, although multiple other intranasal and regional flaps can be utilized.^{1–3}

ABBREVIATIONS: CSF, cerebrospinal fluid; EES, endoscopic endonasal surgery; ENSF, extended nasal septal flap; ICG, indocyanine green; LNWF, lateral nasal wall flap; NPV, negative predictive value; NSF, nasoseptal flap; PPV, positive predictive value

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The flap pedicle may be compromised intraoperatively by surgical trauma or preoperatively by prior surgery that narrows the pedicle. Postoperative flap necrosis remains a primary concern for skull base surgeons because of the risk of postoperative cerebrospinal fluid (CSF) leak and meningitis. While flap failure remains a rare complication in endoscopic skull base surgery, the ramifications of such a failure can be severe with increased patient morbidity, mortality, and need for revision surgery.^{4–8} At this point, however, no validated method exists to objectively evaluate flap viability intraoperatively.

Indocyanine green (ICG) near-infrared imaging has been utilized in neurosurgery for



intraoperative angiography as well as plastic surgery for understanding tissue viability.⁹⁻¹⁵ Plastic surgeons have shown utility in predicting postoperative flap necrosis for local advancement flaps, pedicled flaps, and free-flap tissue transfers.⁹⁻¹⁷ ICG has also been used to understand pedicled flap perfusion in the head and neck region.¹⁸⁻²⁰

The objective of our pilot study was to evaluate the efficacy of ICG near-infrared endoscopy in predicting the viability of local, pedicled intranasal flaps during endoscopic endonasal surgery (EES) of the skull base.

METHODS

Institutional review board approval was obtained. All patients undergoing EES from September 2015 through December 2016 in a single, tertiary referral center were considered eligible. Patients with renal disease, liver disease, or prior allergy to iodinated contrasts or shellfish were not enrolled. Patients were also excluded if no intranasal flap was utilized for skull base reconstruction. Informed patient consent was obtained in all cases. All intranasal flaps were evaluated including the NSF, the extended nasal septal flap (ENSF) that includes nasal floor mucosa, and the lateral nasal wall flap (LNWF), also known as the inferior turbinate flap. Patients undergoing revision surgery with reutilization of prior intranasal flap reconstruction were also included.

At the time of reconstruction, the intranasal flap was positioned over the skull base defect. Traditional endoscopes were switched to ICG compatible endoscopes for near-infrared visualization (ICG Camera Head TH102, Lightsource D-Light P and Image 1S + Module H3, Karl Storz, Tuttlingen, Germany). This equipment includes a foot pedal that allows the surgeon to switch between white and near-infrared light. This endoscopic system is not yet approved by the Food and Drug Administration for EES. Under constant visualization with near-infrared light, 12.5 to 25 mg of ICG was administered intravenously (Figure). For this purpose, 25 mg of ICG was dissolved in 10 mL of sterile water (IC-Green[®], Akorn, Lake Forest, Illinois), and 5 to 10 mL was injected intravenously followed by a 10-mL saline flush. In the first several cases of the study, 25 mg was administered according to the

suggested dosage in the literature for cerebrovascular and transphenoidal microsurgery.^{2,7,8,21} Later, the dose was reduced to 12.5 mg, as this dose was equally efficacious and provided the option to administer a second injection, if necessary. The cost of injection was \$222 per 25 mg vial of ICG. The cost of ICG was partially subsidized by Karl Storz, and the ICG endoscopic system was loaned to our institution by Karl Storz.

Intraoperatively, ICG enhancement of both the flap pedicle and flap body was independently evaluated. Intraoperatively, the senior author (PG) rated the enhancement of each flap body and pedicle qualitatively as high, moderate, low, or no enhancement. Video recordings of the surgery were then secondarily evaluated by a blinded observer (AG) in the same manner. Disagreements were reviewed by a second, blinded observer (MG). Please see **Videos, Supplemental Digital Content 1-3**, for example of ICG flap enhancement patterns. For analysis purposes, high and moderate enhancement were grouped together as “positive enhancement,” whereas low and no enhancement were grouped as “no enhancement.” The time from ICG injection to flap enhancement was also recorded.

Postoperatively, MRI was obtained when clinically indicated to evaluate for completeness of resection or tumor recurrence. The primary study outcome was enhancement of the flap on postoperative MRI, as this has previously been shown to accurately predict flap necrosis.²² Patient demographics plus clinical information regarding defect location was recorded. A defect could involve multiple areas of the cranial base. Clinical outcomes such as flap necrosis on endoscopy, postoperative CSF leak, or postoperative meningitis were also recorded. The sensitivity and specificity of ICG fluorescence in the flap body and pedicle as predictive of postoperative MRI flap enhancement were independently calculated. The combined predictive value of both the flap body and pedicle was then calculated for MRI enhancement, flap necrosis, and CSF leak. Chi-square and Student’s tests were used to measure associations between intraoperative ICG flap enhancement, smoking status, diabetes, flap type, reconstruction location, and intraoperative time to ICG enhancement.

RESULTS

Thirty-eight patients underwent intraoperative evaluation of intranasal flap reconstruction using ICG near-fluorescence

TABLE 1. Clinical Characteristics.

	N	%
Age	Mean 51.8	Range 25-82
Male	18	47.4%
Flap type		
Nasal septal flap	24	63.2%
Extended septal flap	11	28.9%
Lateral nasal wall	2	5.3%
Reused flap	1	2.6%
Defect location		
Sellar only	13	34.2%
Anterior fossa	6	15.8%
Middle fossa	18	47.4%
Posterior fossa	8	21.1%
Pathology		
Chordoma	12	31.6%
Pituitary adenoma	10	26.3%
Meningioma	10	26.3%
Chondrosarcoma	2	5.3%
Craniopharyngeoma	2	5.3%
Arachnoid cyst	1	2.6%
Renal cell carcinoma	1	2.6%
Current smoker	6	15.8%
Diabetes	8	21.1%

angiography. Patient clinical characteristics are shown in Table 1. Twenty-four patients underwent NSF reconstruction followed by 11 patients, 2 patients, and 1 patient for ENSF, LNWF, and reused flaps, respectively. Thirteen patients (34%) had sellar defects only, while the remaining patients had a combination of skull base defects as seen in Table 1. Mean time to visualize fluorescence was 25 s (range 14-98 s). The postoperative MRI was obtained a median of 1.36 wk after surgery (range 0.4-55 wk).

Of the 38 flaps, both the body and pedicle displayed intraoperative ICG enhancement in 20 patients (53%). Only the pedicle displayed ICG enhancement for 12 patients (32%), while only the body did so in 3 patients (8%). Neither displayed ICG enhancement in 3 patients (8%). The relationship of intraoperative ICG enhancement of intranasal flap body and pedicle to postoperative MRI contrast enhancement, flap necrosis, or CSF leak can be seen in Table 2. The sensitivity and specificity of ICG enhancement of the flap pedicle for predicting postop MRI flap enhancement were 97% and 67%, respectively, with a positive predictive value (PPV) of 97% and negative predictive value of 67% (NPV). Similarly, the sensitivity and specificity of ICG enhancement of the flap body for predicting MRI enhancement were 70% and 100%, respectively, with a PPV of 100% and NPV of 23%. Of note, when both the flap pedicle and body displayed intraoperative ICG enhancement, the rate of postoperative MRI enhancement and flap necrosis were 100% and 0%, respectively. When examining the converse, lack of ICG enhancement was not as strong a predictor of lack of postop MRI enhancement (2 of 3

TABLE 2. ICG Enhancement of Intranasal Flap Body and Pedicle as Related to Clinical Outcomes.

Enhancement	No		Yes		P-value
	n	%	n	%	
MRI enhancement					
Body and pedicle	0	0.0	20	100.0	
Body only	0	0.0	3	100.0	
Pedicle only	1	8.3	11	91.7	
Neither	2	66.7	1	33.3	.011
Flap necrosis					
Body and pedicle	20	100.0	0	0.0	
Body only	3	100.0	0	0.0	
Pedicle only	11	91.7	1	8.3	
Neither	1	33.3	2	66.7	.011
CSF leak					
Body and pedicle	19	95.0	1	5.0	
Body only	3	100.0	0	0.0	
Pedicle only	8	66.7	4	33.3	
Neither	2	66.7	1	33.3	.908

patients) or flap necrosis (2 of 3 patients), which is reflected in specificity (67%) and negative predictive values (67%).

There was no association between intraoperative ICG enhancement and postoperative CSF leak. Six of 38 patients developed (15.8%) a CSF leak in this study, which is comparable to the overall rate of CSF leak from the institution when operating on intradural tumors (16.7%).²³ Additionally, approximately two-thirds of patients had complex defects outside the sella involving the anterior, posterior, and middle cranial fossa, which are associated with a higher rate of leak (Table 1). Additionally, only 26% of patients had pituitary adenoma, while 32% and 26% of the cohort involved chordoma and meningioma, respectively (Table 1). There was no association between time to intraoperative ICG enhancement and postoperative MRI enhancement. Additionally, no association existed between ICG enhancement and flap location, type of flap, location of reconstruction, diabetes, or smoking status.

DISCUSSION

Vascularized intranasal flaps like the NSF are the reconstructive workhorse for endoscopic skull base defects.¹⁻³ Although intranasal flap necrosis is a rare complication, the ramifications can be devastating, as CSF leak and meningitis remain primary sources of postoperative morbidity and mortality for our patients.⁴⁻⁸ A method for intraoperative evaluation of flap viability might help surgeons better understand the quality of reconstruction and mitigate postoperative sequelae associated with flap failure. Additionally, the choice of flap for reconstruction is predicated on the adequacy of the vascular pedicle. The flap pedicle may be compromised by prior endonasal surgery or intraoperative trauma (eg, drill injury). Although Doppler

ultrasonography may be useful in assessing the vessels in the pedicle, a reliable method of assessing viability would guide the selection and design of flaps.

In this proof-of-concept study, we show that intraoperative evaluation of flap perfusion with ICG near-infrared imaging is feasible and accurate at predicting postoperative MRI flap enhancement. ICG enhancement of both the flap body and pedicle was associated with a 100% rate of postoperative MRI enhancement and zero cases of flap necrosis. This result suggests that intraoperative ICG enhancement is a reliable predictor of postoperative viability. Conversely, a lack of body or pedicle ICG enhancement predicted a lack of postoperative MRI enhancement and flap necrosis, but with slightly less accuracy. These results are reflected in the strong PPVs for both the flap body and pedicle with modest NPVs.

This is the first report describing ICG near-infrared endoscopy during EES of the skull base. Numerous studies have demonstrated the ability of ICG angiography to predict local, regional, and free-flap perfusion. Not surprisingly, we are able to show a similar utility in predicting intranasal flap viability using ICG near-infrared endoscopy. While robust enhancement of both the flap body and pedicle were the most accurate in predicting flap viability, enhancement of the pedicle alone predicted postoperative MRI enhancement 92% of the time.

The exact reason that a flap can be viable with pedicle enhancement only is not known; however, the technique utilized to raise or store the flap during tumor resection may play a role. In other parts of the body, the flap is typically raised immediately prior to its inset. While this does sometimes occur when an intranasal “rescue” flap technique is used, intranasal flaps are typically harvested early in the case and stored in the nasopharynx, maxillary sinus, sphenoid sinus, or some combination.²⁴ Hours often pass between flap elevation and reconstruction, which may result in torsion of the pedicle, ischemia resulting in reperfusion injury, or venous congestion of the body. The time between flap harvest and inset was not recorded in our study, and therefore could not be analyzed at this time. Manipulation of the flap may cause temporary vasospasm that resolves in the postoperative period.

The utility of intraoperative ICG near-infrared endoscopy in predicting the postoperative success of skull base reconstruction is a clinically useful tool that may predict and help manage postoperative complications. The ability to intraoperatively assess flap viability is valuable for all cases, particularly in revision surgery when flaps are reused or when flaps include extensions that receive a random blood supply (such as the lateral nasal wall or extended nasal septal flaps). While the majority of the flaps in this study were NSF, ICG endoscopy did successfully evaluate lateral nasal wall and revision NSFs.

This study does rely on postoperative MRI to confirm flap viability. Prior study demonstrates a correlation between MRI enhancement and flap necrosis. Similarly, the physiology of MRI enhancement requires vascularity; therefore, postoperative MRI enhancement of our flaps was chosen as our primary outcome

measure of success.²² Clinically, similar results were seen for prediction of flap necrosis by intraoperative ICG near-infrared endoscopy that is corroborated by postoperative endoscopic examination in the office. Not surprisingly, postoperative CSF leak was not well predicted by ICG enhancement. This is logical because most CSF leaks are attributable to a technical error and/or poor flap positioning/sizing rather than flap necrosis.²⁵ While most leaks are not caused by necrosis, failure to inset a viable flap does increase the risk of CSF leak and meningitis. The utility of the ICG near infrared imaging is the ability to identify intraoperatively flaps that are well vascularized and at low risk of necrosis. At this point, the technology still needs refinement to improve the negative predictive value.

Limitations

This study is limited by its small sample size and the small number of necrotic flaps. Additionally, the degree of ICG enhancement cannot be objectively measured. The subjective intraoperative assessment by the senior author was reviewed by a second and third blinded observer in an attempt to ensure inter-rater reliability. Measureable, standardized procedures for objective assessment of ICG fluorescence, akin to measurement of Hounsfield units, would be preferable. Lastly, the majority of the flaps in the study were NSF, so the true efficacy of this technology with less commonly used flaps requires additional study.

CONCLUSION

Intraoperative evaluation of flap perfusion with ICG near-infrared endoscopy in EES of the skull base is feasible and accurate in predicting postoperative MRI flap enhancement and postoperative flap necrosis. When both the flap body and pedicle enhance with ICG, the likelihood of postop flap necrosis was 0%. Enhancement of the flap pedicle seems to be the most important predictor of successful reconstruction. ICG near-infrared endoscopy may prove to be a useful tool for the prevention and management of reconstructive complications.

Disclosure

Indocyanine-green costs were partially subsidized by Karl-Storz.

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Supplemental Digital Content 1. Video. Nasal septal flap reconstruction of sellar defect—Moderate ICG flap enhancement.

Supplemental Digital Content 2. Video. Nasal septal flap reconstruction of sellar defect—Enhancement of flap pedicle only.

Supplemental Digital Content 3. Video. Nasal septal flap reconstruction of sellar defect—Non-enhancing flap body and pedicle.

COMMENTS

The use of intraoperative monitoring for nasoseptal flap perfusion is likely a useful adjunct in certain cases and so this technology may be helpful.

John Schneider
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The authors present convincing evidence that the evaluation of an intranasal flap intraoperatively using indocyanine-green fluorescence angiography is a valuable tool to assess the viability of the intranasal flap. This procedure could eventually become cost effective if it prevents complications including CSF leaks requiring a return to the operating room.

The authors results are well documented and clearly presented.

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