Proposal for Intraoperative Administration of Intravenous Indocyanine Green to Evaluate Position of the Optic Canal, Position of the Internal Carotid Arteries, Tumor Vascularization, and Vessel Encasement in Endoscopic Endonasal Cranial Base Surgery.

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Objective

We intend to demonstrate the feasibility of using a nasal endoscope to perform intraoperative angiography of surgical field, with the goals to evaluate anatomical landmarks and tumor characteristics during skull base surgery and publish a technical note.

Background and Rationale

The expanded endoscopic endonasal approach (EEA) to the cranial base is increasingly being utilized to address a variety of cranial base pathologies.[1-7] The more severe complications and morbidities associated with EEA are related to vascular and cranial nerve injury. [8, 9]

The sphenoid sinus is the center and starting point for all the expanded EEA to the ventral skull base. Skull base surgeons rely on anatomical landmarks and neuro-navigation to perform a safe procedure. However, sphenoid sinus pneumatization may vary and anatomical landmarks may not be readily identifiable. In addition, surgeons may not rely exclusively on neuro-navigation since it is not always accurate and precise.

Originally FDA approved for human use in 1959, indocyanine green (ICG) is a tricarbocyanine dye with near-infrared fluorescence that has been routinely used in a variety of cerebrovascular procedures since 1972 for real-time noninvasive intraoperative angiography with a multiple-decades-long safety history.[10-14] It is administered as an intravenous bolus, typically in a dose of 25 milligrams dissolved in 10 milliliters of sterile water. It binds to large plasma proteins within 2 seconds and remains intravascular. ICG is metabolized exclusively by the liver with a plasma half-life of 150 seconds and is excreted

in bile.[15] Angiography is typically most useful approximately 45 seconds after ICG administration in distinct arterial, capillary, and venous phases.[15]

There are only a few reports in the literature describing the use of ICG and the Karl Storz nasal endoscope in EEA for benign ventral skull base lesions.[15-18] Litvack at al.[15] described the intraoperative use of ICG to successfully differentiate relatively avascular tumor from the capillary-rich normal pituitary gland as well as relatively hypervascular regions of dural invasion without complication. Hide et al. [16-17] that the real-time observation of the blood supply to the optic nerves and pituitary helps to predict the preservation of their function. Inoue et al.[18] used preoperative 3D-CT and MRI fusion models with intraoperative ICG endoscopy and concluded that the technique allowed distinct visualization of vital structures in cases where tumors had extensively infiltrated the sphenoidal sinus. Additionally, the ICG endoscope was a useful real-time monitoring tool for ETSS.

There are no other reports of ICG use in any EEA approaches to the cranial base, nor are there any reports of ICG use to characterize the tumor vascularization and its relationship to optic nerves and arteries.

The usefulness of the intraoperative ICG in cranial nerve preservation was recently studied in microscopic lateral skull base approaches.[19] The authors concluded that the course of the facial nerve can be confirmed during mastoidectomy, which reduces the possibility of iatrogenic facial nerve dysfunction. This fluorescence technique is especially helpful in establishing confidence and shortening the learning curve for beginners at mastoidectomies. We believe that the same strategy can be useful to identify the optic nerves during expanded EEA.

Proposal

Based on the positive experience of our Pilot study where ICG accurately demonstrated visualization of perfusion of the pedicled flap posterior nasal arteries and mucosal flap during endoscopic endonasal approaches, we now propose a study in which we will administer ICG during routine EEA for cranial base pathologies in which optic canal decompression, intradural tumor dissection, or dissection of tumor around the internal carotid artery will be necessary.

We anticipate needing no more than thirty-five patients to obtain the necessary information and will either seek further IRB approval or terminate this feasibility study if the necessary information cannot be obtained by the thirty-fifth patient. All surgeries will be performed in a team with Dr. Daniel Prevedello (Neurological Surgery) and either Dr. Ricardo Carrau (Otolaryngology) or Dr. Bradley Otto (Otolaryngology). We will use the Storz nasal endoscope, which is already purchased and routinely used at The Ohio State University (OSU), modified as described by Litvack *et al.*[15] to visualize the proposed real-time angiograms. These modifications include a custom xenon light source that produces both the standard white light as well as near-infrared (690-780 nm wavelength) light and a selectable near-infrared filter for the nasal endoscope, both of which will be provided by

Karl Storz free of charge. We intend to administer ICG, which is already widely used during open neurosurgical procedures, to identify anatomical landmarks (such as vascular structures leading to the optic canal and internal carotid arteries) and tumor characteristics (such as tumor vascularization, tissue differentiation, and vessel encasement) during skull base surgery at different stages of endonasal cranial base surgery and tumor dissection: before intradural dissection and during tumor dissection.

Eligibility

All adult patients selected to undergo an EEA for cranial base pathology that will require any of the following will be eligible for the study: optic canal decompression, intradural tumor dissection, dissection of tumor around the internal carotid artery.

Exclusion criteria will include patient age less than 18 years; history of sulfa, iodide, or penicillin allergy; previous anaphylactic reaction to ICG; women currently pregnant or nursing. Patients of child bearing potential are routinely screened for pregnancy before the surgery using urinary or blood beta-HCG test.

Management of Adverse Experiences

1. Adverse Events

1.1. Adverse Event Definition

An adverse event (AE) will be considered any undesirable sign, symptom or medical condition considered related to the intervention. Medical condition/diseases present before starting the intervention will be considered AEs only if they worsen after starting the study and that worsening is considered related to the study intervention. An AE is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. AEs will be recorded up to the day of the final follow-up visit, and if still present, they will be recorded as "ongoing" at the end of the study. The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits.

Risk and Benefit Assessment

Per the 2006 FDA label for ICG, the only listed risks of ICG administration are urticarial or anaphylactic reactions, which are rare. ICG contains sodium iodide, so caution is recommended in patients with a history of iodide allergy. Per this FDA label, "There are no data available describing the signs, symptoms, or laboratory findings accompanying overdosage. The LD 50 after I.V. administration ranges between 60 and 80 mg/kg in mice, 50 and 70 mg/kg in rats and 50 and 80 mg/kg in rabbits." The FDA arbitrarily suggests a maximum dose of 2mg/kg for human use, and this would be our dosage maximum. The main risk to our study population

would be a small increase in operative time under general anesthesia, which we estimate at an additional 15 minutes. Litvack *et al.* estimated that ICG angiography during their pituitary surgeries required an extra 15-20 minutes of operative time under general anesthesia, which supports our estimation.[15]

The benefits to our study will be visualization of important structures that may be encased by the tumor to avoid injury including the optic nerves, the internal carotids and minor feeding vessels. Also, determination of any residual tumor that may be left during tumor dissection helps prevent or recurrence of the tumor, which will overall decrease the morbidity of these kind of surgeries. We feel that the benefits to the study population markedly outweigh the risks.

Human Subjects

1. Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, and the rights of the participant. A copy of the consent form will be given to the subject and this fact will be documented in the subject's record.

The Principal Investigator or the Study Coordinator will be responsible for submitting any changes to the project to the IRB for approval prior to implementation of the changes. The study will also be submitted for continuing review by the IRB at periods determined by the IRB, at lease annually, for the duration of the study.

2. Subject Confidentiality

Subject data records will be identified by a study specific identification number.
All subject records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific identification number only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the sponsor, or the sponsor's designee.

3. Subjects' Rights

Subjects will have the right to withdraw from the study at any time without penalty or lose of any of their usual benefits.

Data Collection

Specifically, patient demographic/clinical information to be included in this feasibility study will include:

a. Age
b. Gender
c. Race
d. Vital Signs
e. Diagnosis
f. Duration of Disease
g. Brief Medical History
h. Description of Surgical Approach
i. Description and Images of Intraoperative Angiography

Medical imaging data to be presented will include pre- and post-operative CT and MR studies in addition to intraoperative angiography and intraoperative endoscopic images of the surgical site.

If, during the course of the procedure, the operator determines that it would be in patient's best interest to prematurely abort the procedure due to unforeseen events, it will be under the discretion of the PI to use the data from the prematurely aborted procedure. If patient has a second procedure after the first procedure was prematurely aborted, it is up to the PI discretion to re-dose patient with the ICG dye and complete the study procedures and collect study data from the second procedure. The PI may decide whether to use the data from the first procedure in this circumstance. ICG dye half-life is 3-4 minutes and does not pose a threat of overdosing.

In summary, this novel technique for performing real-time endoscopic intranasal angiography could substantially improve the safety of surgery by precisely locating the optic canal and internal carotid arteries; by providing additional information on tumor characteristics such as vascularization and vessel encasement.
This information may prompt further surgical action to avoid the complications associated with optic canal decompression, dissection near the internal carotid and tumor dissection. Presentation of this feasibility study in the literature will likely lead to wide acceptance and implementation of this technique due to the highly useful information it will yield as well as its high degree of feasibility, as institutions performing EEA procedures already possess the materials necessary to perform it.

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