

Identification of Nerves Using Fluorescein Sodium NCT06054178

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1. PURPOSE OF THE STUDY

a. Brief Summary

Nerve identification during surgery remains a challenge under white light, and relies on clinical expertise. Recently, sodium fluorescein (a FDA approved compound for ophthalmic angiography) has gained traction for nerve imaging. We aim to use fluorescein to help identify nerves intraoperatively during head and neck surgery.

b. Objectives

From this study, we aim to demonstrate the feasibility of using fluorescein to identify non-pathologic nerves intraoperatively. This would open up new avenues for intraoperative fluorescence imaging, and obviate the need for expensive, proprietary nerve imaging agents (that are currently in development or early clinical trials).

c. Rationale for Research in Humans

We aim to identify nerves intraoperatively with fluorescein. Humans must be used for this study, as the kinetics in an animal model (e.g. mouse) are not comparable to that of a human. Additionally, this compound is FDA approved for use in angiography in ophthalmology and has been trialed in over a hundred patients (overseas) for pathologic nerve imaging (PMID: 36698394). Recently, a clinical trial has also been conducted in the United States for vestibular schwannoma (pathologic nerve) imaging with sodium fluorescein demonstrating safety and efficacy (PMID: 36240730). We aim to demonstrate this with non-pathologic nerves.

The typical dose used in ophthalmic angiography (FDA approved indication) is 500 mg for an adult patient (7.1 mg/kg in a 70 kg patient) - we will be utilizing a dose of approximately 0.5-3 mg/kg (less than half of currently administered doses).

Given the safety profile and immediate translatable nature of this project, human subjects will be used.

2. STUDY PROCEDURES

a. Procedures

The study is a pilot, prospective trial of patients assessing sodium fluorescein with intraoperative nerve imaging. We will be enrolling up to a total of 30 adult patients scheduled to undergo head and neck surgery within the department of Otolaryngology.

Subjects will be recruited from the Stanford Otolaryngology Clinic. Patients undergoing head and neck surgery will be eligible for the study, and will be recruited by the research physician team/PI during their pre-operative clinic visit. The PI or other member of the physician research team will review the details of the study including rationale, risks, and benefits, and if the subject is interested in participating, proceed with obtaining permission and assent, if applicable, or consent and authorization followed by the screening procedures if they or their guardian agree to participate. Approximately 20 minutes will be needed to review the regulatory documents (informed consent, HIPPA).

Sodium fluorescein (Fluorescein 10%) will be administered at a dose (0.5-1 mg/kg) intravenously by the anesthesiologist. Patient will be carefully monitored after administration to check for any adverse reactions. When facial nerves are formally visualized during surgery (as is routinely done during parotid or other head and neck surgery) - a Zeiss operating microscope (with a Yellow 560 filter), stryker endoscope with blue light, or allied vision camera (with LEDs) will be used to take images/video

of the facial nerve. There will be no violation of the sterile field. If there is poor visualization of the facial nerve, additional doses of sodium fluorescein may be administered (up to a total of 3 mg/kg) intraoperatively.

Following intraoperative imaging, will conclude the patient's participation in the research study. If deemed an inappropriate time for imaging by the attending physician surgeon, intraoperative imaging will not be pursued until deemed safe by the attending surgeon or the study terminated. This is expected to add 20 minutes to the total time of the procedure.

Following procedure conclusion, patient will also be carefully assessed in the post-operative recovery area for 1 hour to ensure there are no side effects from drug administration.

Early Withdrawal:

Subjects may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which they are entitled. Any data at the time the subject withdraws will be deleted appropriately to ensure that the data is not used in the study. All attempts will be made to prevent data at the time the subject withdraws from being analyzed or included for publication; however, no guarantee of this can be made since data may already have been published at the time the subject has withdrawn.

Data Analysis:

Photographs and videos will be collected for analysis. All patient identifiers will be removed from the photographs/videos.

b. Procedure Risks

Participation in the research study is strictly voluntary (no coercion), and all risks will be clearly outlined and explained prior to enrollment.

Sodium fluorescein is a FDA approved drug used in ophthalmic angiography, and we will be utilizing doses less than half the usual doses used for patients. Patients will be carefully screened and assessed intraoperatively/immediately post-operatively to ensure there are no side effects from drug administration.

c. Use of Audio and Video Recordings

Videos and images will be taken during the study with all patient identifiers removed. Videos and images will be shown at scientific meetings and used in a publication.

d. Alternative Procedures or Courses of Treatment

Participation as a research subject is voluntary. An alternative to participation in the study is to not enroll in the study. Subjects may withdraw at any time without altering their medical care. Enrolling in the study does not impact the patient's overall clinical treatment plan (surgery for benign head and neck indication).

e. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes, patients may continue their continued clinical therapy after conclusion of the study.

f. Study Endpoint(s)

The endpoint will be following fluorescence imaging of facial nerves after fluorescein administration. The success of visualization will be detected immediately intraoperatively.

Analysis will be completed after the first 5 patients, and if there is no benefit - the study will be prematurely closed and terminated (including on clinicaltrials.gov). If there is an obvious benefit, a total of 30 patients is expected to be recruited for this study.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Sodium fluorescein is commonly used in ophthalmology as an angiography agent to characterize retinal disease, intraocular tumors, inflammatory intraocular conditions (FDA approved for this purpose). Currently, a dose of 500 mg is administered to an adult patient (~7.1 mg/kg in a 70 kg patient) for ophthalmic angiography.

It has also been used in neurosurgery for imaging of central nervous system tumors (brain tumors) and recently been trialed in 100+ patients to image peripheral nerve schwannomas (PMID: 36698394) overseas.

In the United States, there has also recently been a clinical trial to use sodium fluorescein to image vestibular schwannomas (a tumor of the vestibular nerve, PMID 36240730). This particular study used doses between 3-5 mg/kg of sodium fluorescein given central nervous system location of the tumor. It is also used in the United States for resection of intracranial tumors (sample papers - PMID: 30738388, 32780271, 36327792).

We aim to utilize doses of 0.5-3 mg/kg given peripheral nature of the nerves (similar to doses utilized for peripheral nerve schwannomas, PMID: 36698394). This dose is less than HALF the dose utilized in ophthalmic angiography.

While prior studies have been successful in imaging pathologic nerves, no further attempts to delineate imaging of non-pathologic nerves peripherally (not ophthalmic). Based on the strong evidence from the neurosurgery/ophthalmology literature and safe profile of sodium fluorescein (given it is already FDA approved) - we formulated this study to image non-pathologic nerves. This study would obviate the need for proprietary nerve agents (which are in development with several companies), and have immediate clinical impact on patients.

b. Findings from Past Animal Experiments

Our laboratory has performed several animal experiments (not yet published) using sodium fluorescein to image the facial nerve branches. Our results demonstrate successful fluorescence of the facial nerve branches and good intraoperative identification. Our results are also comparable to a proprietary compound (PMID: 30128049) developed elsewhere, and we feel that sodium fluorescein alone provides the same efficacy in selective nerve imaging which would have immediate clinical benefit for patients.

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	LED
Manufacturer:	Thorlabs
Significant Risk? (Y/N)	N
Investigational Device 2	
Name:	Camera
Manufacturer:	Allied Vision
Significant Risk? (Y/N)	N
Investigational Device 3	
Name:	Zeiss Yellow 560
Manufacturer:	Zeiss
Significant Risk? (Y/N)	N
Investigational Device 4	
Name:	Stryker Blue Light Endoscope
Manufacturer:	Stryker
Significant Risk? (Y/N)	N

5. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

Investigational Product 1	
Name:	FLUORESCITE (fluorescein injection, USP) 10%
Dosage:	0.5-3 mg/kg
Administration Route:	Intravenous

6. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

Not Applicable

7. PARTICIPANT POPULATION

a. Planned Enrollment

I, II) 30 patients will be enrolled at Stanford Health Care in the research study.

III) Patients undergoing benign parotid surgery or head and neck surgery will be eligible for the research study. We will not recruit any patients with active head and neck cancer.

b. Age, Gender, and Ethnic Background

Ages 18 and older of all genders/ethnic backgrounds will be recruited for this study

c. Vulnerable Populations

Vulnerable subjects will not be included in this study

d. Rationale for Exclusion of Certain Populations

Children will not be included in this study, as we will first conduct a pilot study on adults

e. Stanford Populations

No participants will be laboratory personnel, employees, or students.

f. Healthy Volunteers

Healthy patients who are undergoing benign parotid surgery or head and neck surgery will be eligible for this study. Participation in this study will not impact the patient's clinical treatment course (surgery)

Involvement will be completely voluntary (no coercion), and all risks will be clearly outlined and explained prior to enrollment. Involvement will not lead to promotion or any salary compensation. Subjects/guardians may also refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which they are entitled.

g. Recruitment Details

Subjects will be recruited from the Stanford Otolaryngology Clinic. Recruitment will be performed by investigators and research physician team. Prior to recruitment, patients

will initially be approached about the study by someone they have a treating relationship with, and will need to give permission to be approached by the study team.

The PI or other member of the research team will review the details of the study including rationale, risks, and benefits, and if the subject/guardian is interested in participating, proceed with obtaining permission and assent, if applicable, or consent and authorization followed by the screening procedures, if they agree to participate.

Prospective subjects and guardians, if applicable, may take whatever time needed to consider whether to participate or not. The consent process will be documented by signature on the appropriate study form by the subject, and by the person who explained the study.

There will be no formal recruitment materials (pamphlets, flyers) used for the study. Involvement will be completely voluntary (no coercion), and all risks will be clearly outlined and explained prior to enrollment. Involvement will not lead to promotion or any salary compensation.

h. Eligibility Criteria

i. Inclusion Criteria

1. Male or female subjects
2. 18 years or older
3. Scheduled for benign parotid surgery or head and neck surgery

ii. Exclusion Criteria

1. Inability or unwillingness of a subject
2. Pregnancy
3. Vulnerable or disadvantaged population (pregnant women, decisionally impaired, homeless, employees, students)
4. Patients with severe medical condition(s) that in the view of the investigator prohibits participation in the study
5. History of adverse reaction to fluorescein.
6. History of renal failure or chronic kidney disease

i. Screening Procedures

Subjects will be recruited from the Stanford Otolaryngology Clinic. Recruitment will be performed by Investigators (attending physicians) and otolaryngology resident. The PI/research physician will identify potential subjects at their respective clinic. The PI or only the physician research team will review the details of the study including rationale, risks, and benefits, and if the subject/guardian is interested in participating, proceed with obtaining permission and assent, if applicable, or consent and authorization followed by the screening procedures, if they agree to participate.

No personal health information prior to enrollment (eg. telephone screening) will be collected. No laboratory values will be collected.

j. Participation in Multiple Protocols

Participants will be able to enrolled in more than one research study.

k. Payments to Participants

No reimbursement will be provided to the patient. Participation is strictly voluntary

l. Costs to Participants

Direct costs will not be charged to the patient.

m. Planned Duration of the Study

Direct costs will not be charged to the patient.

8. RISKS

a. Potential Risks

i. Investigational devices

The risks of the commercial camera and LED are very minimal. This is a non-implantable, non-invasive camera used for imaging. This device present no risk to participants, and will not impact clinical decision making intraoperatively. There is no violation of the sterile field.

Similarly, the Zeiss Yellow 560 system is a add-on to the existing operating room microscope (used in surgery, Zeiss Microscope). The FDA has approved this device to visualize fluorescence for intravenous fluorescein intravascularly. We will utilize this system to visualize nerves. This is a non-implantable, non-invasive system using a 560 long pass filter to visualize fluorescein fluorescence.

The stryker blue light endoscope system is a commercial device used to provide higher contrast of vascular structures on the mucosal surface. We will use this non-implantable, non-invasive system to visualize nerve fluorescence with fluorescein.

ii. Investigational drugs

No investigational drugs will be used

iii. Commercially available drugs, biologics, reagents or chemicals

Sodium fluorescein (fluorescein injection, USP 10%) will be utilized for this study. This is a commercially available drug that is FDA approved for ophthalmic angiography.

Attachment contains drug information/package insert.

We will be utilizing a dose less than HALF the dose used for ophthalmic angiography.

Sodium Fluorescein risks (please see attachments also for drug label):

Sodium fluorescein is FDA approved for ophthalmologic angiography applications. The standard dose for retinal imaging in adults is a 500 mg bolus into a peripheral vein (7.1 mg/kg in a 70 kg patient). The safety profile has been well described in the literature, with the most common reported side effects being nausea/vomiting. However, 87% of served ophthalmologists have reported this to be less than 5%. Other side effects: Urticaria at 1/82 patients, and severe adverse reactions including respiratory reaction (1/3800), cardiac (1/5300), tonic clonic seizure (1/13900). These are quite rare and estimated to occur in 1/1900 patients (PMID: 3523356).

Care will be taken to avoid extravasation of the drug into the skin during administration. Extravasation has been associated with the following per the FDA drug information sheet: Sloughing of the skin, superficial phlebitis, subcutaneous granuloma, and toxic neuritis along the median curve in the antecubital area.

iv. Procedures

Main risk to procedure involves sodium fluorescein administration (FDA approved drug). These risks will be carefully explained prior to participation.

v. Radioisotopes/radiation-producing machines

Not applicable

vi. Physical well-being

Risks of adverse reaction to sodium fluorescein injection (as noted above). Patients will be carefully screened for their exclusion criteria, and carefully instructed regarding risks of medication.

vii. Psychological well-being

Minimal to no risk to psychological well being. Strict adherence to current HIPAA guidelines will ensure no risk to confidentiality

viii. Economic well-being

No risk to economic well being. The patient will not be offered financial compensation or charged for participation.

ix. Social well-being

Minimal to no risk to social well being. Strict adherence to current HIPAA guidelines will ensure no risk to confidentiality

x. Overall evaluation of risk

Low

b. International Research Risk Procedures

Not Applicable

c. Procedures to Minimize Risk

After patients are appropriately screened and deemed eligible for the study, patient will be administered intravenous sodium fluorescein 30 minutes prior to or at induction for surgery. Doses of 0.5 mg/kg-3 mg/kg will be given in total to patients by the anesthesiologist. Patients will be very carefully monitored after drug administration, intraoperatively, and post-recovery area (immediately after surgery for 1 hour) for any complications.

Fluorescein is a FDA approved compound for angiography. Less than half the usual dose used for ophthalmic angiography will be administered to patients. Following administration, imaging will then be performed in the operating suite with an operating microscope with the fluorescein filter (Yellow 560) or allied vision camera with a LED. This process will add a total of 20 minutes to the procedure duration. There will be no violation of the sterile field. If deemed an inappropriate time of imaging by attending physician surgeon, intraoperative imaging will be not be pursued or will take place during an appropriate time deemed by attending surgeon.

Strict adherence to current HIPAA guidelines will ensure no risk to confidentiality. All digital images collected will avoid full face images, and be de-identified by research personnel.

d. Study Conclusion

Study will terminate after intraoperative imaging. Attending surgeon will determine if intraoperative imaging can safely take place during the operation. Imaging is expected to add 20 minutes to the operation. While only minimal risk, in event of adverse event, attending surgeon will be present in the operating suite and subject/guardian may call human research protections program to inquire about rights as a research subject/report research related problems.

e. Data Safety Monitoring Plan (DSMC)

- i. Data and/or events subject to review
NA
- ii. Person(s) responsible for Data and Safety Monitoring
NA
- iii. Frequency of DSMB meetings
NA
- iv. Specific triggers or stopping rules
NA
- v. DSMB Reporting
NA
- vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Y

- vii. Will a board, committee, or safety monitor be responsible for study monitoring?
(Y/N)

NA

f. Risks to Special Populations

NA

9. BENEFITS

Improved visualization of nerves intraoperatively may help with nerve identification and preservation during surgery - offering direct benefit to patients during surgery. Future patients would also have significant benefit from knowledge gained from this study.

Work performed in this study would be immediately by translatable to other disciplines for nerve preservation.

10. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.