**Comparing blood loss and visualization after the preoperative use of topical 0.05% Oxymetazoline versus 1:1000 epinephrine prior to endoscopic sinus surgery**

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| **Protocol Title:** | Comparing blood loss and visualization after the preoperative use of topical 0.05% Oxymetazoline versus 1:1000 epinephrine prior to endoscopic sinus surgery. |
| **Principal Investigator:** | William Yao, MD |
| **Co-Investigators:** | Martin Citardi, MD<br>Amber Luong, MD, PhD<br>Brett Jensen, MD |
| **Study Coordinator:** | N/A |
| **Population:** | Patients undergoing endoscopic sinus surgery (ESS) for CRS with or without nasal polyposis |
| **Number of Sites:** | Single site |
| **Study Duration:** | Study will continue until 50 patients are enrolled, likely 6 months to 1 year |
| **Subject Duration:** | Study intervention will only be at the time of surgery. Normal surgery post-operative visits will occur with no additional study obligations |

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**General Information**

The study will be a single center prospective randomized double blinded study to compare blood loss and visualization of the surgical field following the preoperative use of pledgets soaked in 0.05% Oxymetazoline solution or 1:1000 concentrated Epinephrine.

**Background Information**

The development of functional endoscopic sinus surgery (FESS) in the early 1970s revolutionized the treatment of sinus disease by allowing for magnified direct visualization of complex sinus anatomy. FESS has now become by far the preferred surgical treatment modality of Otolaryngologist for the treatment of chronic sinus disease.[8] The goals of FESS are to improve aeration and drainage of the paranasal sinuses by the meticulous removal of diseased air cells thereby reducing the frequency of infections.[7,8] Due to the significant vascularity of the area bleeding presents one of the primary challenges in endoscopic sinus surgery as even slight hemorrhage can cause a dramatic reduction in visibility of the surgical field which can lead to prolonged operative time and increased risk of complications.[2,3,5]

The use of several topical vasoconstrictors prior to endoscopic sinus surgery including cocaine, norepinephrine, epinephrine, phenylephrine and oxymetazoline have been described in the literature.[3,5] Historically topical cocaine was used very commonly but has fallen out of favor given the addictive potential and associated side effects of tachycardia, hypertension and enhancement of the excitatory effects of epinephrine.[3,5,6] The use of phenylephrine, a selective alpha agonist, has also been largely abandoned due to its unacceptable side effect profile including hypertensive crisis, cardiopulmonary compromise, pulmonary edema, and death. [3,5]

Due to its favorable safety profile the use of Oxymetazoline has become increasingly popular.[4,5,6] However, some authors believe the vasoconstrictive properties of oxymetazoline are inferior which could potentially lead to increased intraoperative hemorrhage. Desires for improved control of intraoperative hemorrhage and visualization has led to increased interest in the use of concentrated epinephrine prior to FESS. [4,5,9,14]

Concentrated epinephrine has been demonstrated to be safe when applied topically.[5,9] There have been reported adverse events and even deaths related to the mistaken submucosal injection of concentrated epinephrine.[5,9,13,14] This risk can be successfully mitigated with careful preparation as well as dying of the more concentrated epinephrine solution with either surgical marking pens or fluorescein strips (FULGLO; Akorn Pharmaceuticals, Lake Forest, IL) to differentiate them from local anesthetic intended for injection.[5,14] When used as intended epinephrine has been demonstrated to have an excellent safety profile.[3,5,14] To date there have been no studies directly comparing the effects of oxymetazoline and epinephrine for preoperative vasoconstriction prior to FESS.[3,11]

**Objectives**

Aim 1: Compare the Surgical field during functional endoscopic sinus surgery after the use of 0.05% Oxymetazoline or 1:1000 concentrated Epinephrine for decongestion

Hypothesis: There will be improved visualization in the concentrated epinephrine arm.

Aim 2: Compare the blood loss functional endoscopic sinus surgery after the preoperative use of 0.05% Oxymetazoline or Epinephrine

Hypothesis: There will be less bleeding in the epinephrine arm

Aim 3: Compare the surgical time to complete one sinus side during functional endoscopic sinus surgery after the preoperative use of 0.05% Oxymetazoline or Epinephrine

Hypothesis: There will be no difference in surgical time

**Study Design**

The study will be a single center prospective randomized double blinded pilot study to compare blood loss and visualization of the surgical field following the preoperative use of pledgets soaked in Oxymetazoline or Epinephrine.

The inclusion criteria will be patients undergoing bilateral endoscopic sinus surgery (ESS) in which the same sinuses and procedures on both sides are the same for CRS with or without nasal polyposis. Exclusion criteria will be pregnancy, known coagulopathy, an international normalized ratio greater than 1.3, a partial thromboplastin time greater than 50 seconds, use of non-steroidal anti-inflammatory drugs in the last 10 days (2 or more doses), use of any antiplatelet agents (eg, warfarin, clopidogrel, berlinta) poorly controlled hypertension with a

preoperative systolic blood pressure of 160mm Hg or greater or a diastolic blood pressure of 90mm Hg or greater, or having any adverse reaction to topical epinephrine or oxymetazoline.

The study will be a paired design study with one nasal cavity receiving epinephrine and the other receiving oxymetazoline. The 1:1000 epinephrine and oxymetazoline solutions both comes in a 30cc vial and each pledget will be wrung out in a similar fashion to keep volume administered similar. The side each drug will be placed on will be randomized using a block randomization scheme on the day of surgery with a block size of four. Two pledgets with the associated medication will be placed into the nasal cavity; one along the floor of the nose and another directed towards the middle meatus.

As a part of routine preoperative workup all patients receive preoperative computed tomography scans of the paranasal sinuses with a navigation protocol. These scans will be assessed using the Lund-Mackay staging system, a standardized radiological grading system used to evaluate CT scans of chronic rhinosinusitis patients. The sinonasal mucosa will also be scored by the surgeon on the day of surgery using a mucosal grading system we have used previously which was modified from a mucosal grading system originally used for grading patients with allergic fungal rhinosinusitis.[2]

The patients will be recruited from the practices of 3 fellowship trained rhinologists within our institution.

All data will be deidentified and assigned a random number. Data will be stored on a password protected file on a password protected computer.

Our primary endpoint will be to compare surgical field visualization after the use of epinephrine or Oxymetazoline using the Boezaart grading scale, an inexpensive standardized rating scale used to analyze surgical field visualization during sinus surgery. The operative field will be rated at the conclusion of the procedure by the surgeon. A representative 1 minute video will also be selected for each side. These videos will be blindly reviewed and rated by all 3 surgeons using the Boezaart scale.

Our secondary endpoint will be to compare the amount of blood loss use after the use of epinephrine or Oxymetazoline. This will be done by subtracting the amount of irrigation used from the volume collected in the suction canisters to estimate blood loss. The Neptune 2 Waste Management System (NWMS, Stryker, Kalamazoo, Michigan), a closed suction system that digitally measures the amount of fluid suctioned will be used for more accurate measuring of fluid suctioned.

Both Oxymetazoline and Epinephrine soaked pledgets are routinely used preoperatively before sinus surgery both within our institution and nationally. The choice of which is based on surgeon preference. Both have well established safety profiles. (Higgins, Korkmaz, Orlandi)

**Study Population**

The inclusion criteria will be patients undergoing endoscopic sinus surgery (ESS) for CRS with or without nasal polyposis. Exclusion criteria will be pregnancy, known coagulopathy, an international normalized ratio greater than 1.3, a partial thromboplastin time greater than 50 seconds, use of non-steroidal anti-inflammatory drugs in the last 10 days (2 or more doses), poorly controlled hypertension with a preoperative systolic blood pressure of 160mm Hg or greater or a diastolic blood pressure of 90mm Hg or greater, or having any adverse reaction to topical epinephrine or oxymetazoline.

The patients will be recruited from the practices of 3 fellowship trained rhinologists within our institution.

**Study Procedures**

As a part of routine preoperative workup all patients receive preoperative computed tomography scans of the paranasal sinuses with a navigation protocol. These scans will be assessed using the Lund-Mackay staging system, a standardized radiological grading system used to evaluate CT scans of chronic rhinosinusitis patients. The sinonasal mucosa will also be scored by the surgeon on the day of surgery using a mucosal grading system.

All patients will undergo general anesthesia using a standardized anesthesia protocol using Propofol and inhalational anesthetics. Total intravenous anesthesia will not be used. Preoperative Decadron will not be used in patients enrolled in the study.

The patients will have pledgets soaked in epinephrine 1:1,000 in one nasal cavity and pledgets soaked in oxymetazoline 0.05% to the contralateral side for topical vasoconstriction and decongestion. Both 1:1000 epinephrine and oxymetazoline solutions comes in a 30cc vial and each pledget will be wrung out in a similar fashion to keep volume administered similar. The solutions will be prepared prior to the procedure so that the surgeon will be blinded to which topical vasoconstrictor is used on each side. All topical solutions will be dyed with fluorescein strips (FULGLO; Akorn Pharmaceuticals, Lake Forest, IL) to differentiate them from local anesthetic intended for injection. Laterality of the study medication will be randomized through block randomization with a block size of four.

Following topical vasocontriction, pledgets will be removed and all patients will receive injections of 1% lidocaine with epinephrine 1:100,000 into the middle turbinate and sphenopalatine area as is routinely performed prior to sinus surgery. Complete functional endoscopic sinus surgery will then be performed as indicated using typical sinus surgery instruments. Intraoperative imaging will be recorded and deidentified for later review by blinded reviewers.
The operative field will be rated at the conclusion of the procedure by the surgeon. A representative 1 minute video from each side will later be blindly reviewed and rated by all 3 surgeons using the Boezaart scale.

There will be no additional visits or time commitments for the patients outside of routine post-operative follow up.

**Data and Safety Monitoring**

All data will be deidentified and assigned a random number. Moreover, the deidentified data will be stored on a password protected file on a password protected computer.

No adverse events are anticipated. The study should provide no additional risk to the patient.

Any potential adverse events or unanticipated problems will be monitored by the research team and reported as discovered. The research team has a pre-scheduled monthly meetings where this study will be discussed.

**Statistics**

Statistical significance will be defined as less than 0.05. For quantitative data a 2-tailed paired t-test will be used. Categorical data will be compared using the McNemar's test. For non normally distributed data a Wilcoxon rank-sum test will be used. All patients who are administered both randomized preoperative topical vasoconstrictors will be included in the study.

The blood loss of 355 ± 393mL seen in sevoflurane group from a previous study we performed in which we used oxymetazoline was used to calculate sample size.[2] With a proposed difference of 150ml of blood loss with a targeted power of 0.8 and a targeted Type 1 error rate of 5% a sample size of 50 was calculated we will plan to enroll 50 patients.

**Ethics**

No other IRB approval will be sought.

Informed consent will be obtained by one of the study investigators at the patient's preoperative visit in clinic or in the preoperative waiting area.

All data will be deindentified and assigned a random number. Data will be stored on a password protected file on a password protected computer.

**Data handling and record keeping**

All data will be deindentified and assigned a random number. Data will be stored on a password protected file on a password protected computer in the principal investigators office. All videos obtained will be de-identified and kept at the principal investigator's password protected computer in a locked office.

**Quality control and assurance**

Quality of video data and photographs will be assessed intraoperatively. A Storz representative will be available to aid with video equipment if technical difficulties were to occur.

There are no plans to have third party monitoring.

**Publication Plan**

We plan to submit the paper for publication to a high-quality ENT or Rhinology journal. Results will be available to the patients if requested.

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