The University of Texas Medical Branch

Title: Comparison of blood loss and intraoperative visibility between Labetalol and Esmolol: A randomized controlled trial

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1. Introduction and Purpose

Bleeding during endoscopic sinus surgery (ESS) affects the ability of the surgeon to identify key structures such as the skull base, orbit, nerves and major vessels. Rhinologists have examined multiple ways to decrease intraoperative bleeding as well as improve endoscopic visibility.

This study hypothesizes that intraoperative blood pressure control with esmolol decreases blood loss and improves operative visibility during ESS as compared to labetalol. The effect will be objectively studied by comparing estimated blood loss and intraoperative visibility utilizing validated intraoperative bleeding/ visibility scores. In addition, patients will be stratified in accordance to their severity of their disease according to their Lund Mackay scores based on their CT scan findings that are routinely obtained prior to surgery.

The short half-life and the ability of continuous infusion of esmolol provides a tighter control of intraoperative blood pressure. Additionally, its selective beta blockade avoids antagonizing the effect of the topical epinephrine vasoconstrictor that is used intraoperatively during ESS.

If the study demonstrated a significant difference between the groups, it would potentially affect our selection of beta blockers during ESS. The potential benefits include providing safe, complete surgery and potentially decreasing cost. The complications that could potentially arise from poor intraoperative visibility include CSF leak and orbital injuries that could lead to lead to blindness.

2. Background

During ESS, bleeding from the mucosal surfaces often interferes with visualization of the anatomy and increases the small risks of serious complications such as injuring the skull base leading to a cerebrospinal fluid leak or an injury to the eye. Additionally, the bleeding interferes with visualization during the procedure and a reduction of the bleeding would result in greater ease and thoroughness of the sinus surgery.

Historically, several ways have been used to decrease intraoperative bleeding. Controlled hypotension (keeping the mean arterial pressure between 50 and 60) has been used using either the anesthetic agents alone or using either sodium nitroprusside or esmolol drips [1-3].The use of these medications increases the risk of serious side effects such as cyanide toxicity and myocardial depression. Recent studies have shown that controlled hypotension is associated with increased morbidity and mortality. The latter was found to be in the range of 20 to 60 deaths in 100,000 patients mainly as a consequence of ischemic organ failure [4]. There is also good evidence that decreasing the MAP below 70 can even increase intraoperative bleeding due to local arteriolar vasodilatation which results from decreased blood flow to the tissues, increased local carbon dioxide concentration and decreased pH.

[3,5].Another mechanism that can explain this is an increase in cardiac output during controlled hypotension resulting from reflex tachycardia specially with the use of a pure vasodilator like sodium nitroprusside [6].

There are multiple factors which contribute to blood loss during surgery, including, but not limited to surgical and anesthetic technique. At the University of Texas Medical Branch, the endoscopic surgical technique is fairly uniform and comparable to practices throughout the world. Most of the endoscopic sinus surgery is performed under general anesthesia. There is a suggestion among ENT physicians and anesthesiologist that different blood pressure medications affect intraoperative visibility and possibly lead to less intraoperative blood loss. It is also thought that intraoperative topical decongestants (specifically epinephrine) work by binding to alpha receptors. Labetalol, which is an alpha and beta blocker, may interfere with the effect of this topical decongestant. [7-9] The goal of this investigation is to formally evaluate this notion utilizing two very commonly used blood pressure medications: Labetalol and esmolol. This study does not use any medications that are not routinely used during endoscopic sinus surgery at the University of Texas Medical Branch.

3. Concise Summary of Project:

Subjects who are scheduled for routine endoscopic sinus surgery will be recruited (n=40). The subjects in this prospective study will be randomized to either receive labetalol or esmolol. Current standard of care in preventing hypertension during sinus surgery due to stimulation and injection and application of sympathetic agents includes, narcotic administration, increasing volatile agent (Sevoflurane), esmolol, labetalol and other agents (hydralazine, nicardipine and nitroprusside). It is not known the impact these anti-hypertensive agents have on blood loss or blood in surgical field.
Intraoperatively, topical epinephrine pledgets will be used for decongestion similar to what is done routinely in endoscopic sinus surgery.
Intraoperative visibility will be scored utilizing two validated endoscopic visbility scores. In addition, at the end of surgery the estimated blood loss will be calculated by subtracting the amount of irritagation used during surgery from the amount of blood in the suction canisters.
In addition, the surgical video will be recorded and the intraoperative visibility will also be recorded by an independent observer.
In addition to the demographics and our primary outcome, secondary outcomes will be collected including duration of anesthesia, duration of surgery, final CO2, postoperative bleeding, visit to the ED following discharge, need for medical attention following discharge, surgeon satisfaction on a likert scale (1-10), need for surgical re-intervention, and pain score after surgery, as well as time spent in recovery, use of anti-emetics postop, and nurses notes on as regards to pain and recovery.

Subjects may be excluded from the study if the anesthesiologist deemed it necessary that the protocol drug can not be used on the patient for any reason. Otherwise, it is expected that the surgeries will be routinely performed and the study outcome

variables do not interfere with the routine.

4. Study Procedures:

This will be a prospective randomized study comprising subjects (n=40) over 18 years of age scheduled for ESS. The inclusion criteria will be male or female patients with ASA physical status 1 (normal otherwise healthy patient) or 2 (patient with mild systemic disease) and patients who have chronic sinusitis with or without nasal polyps. Exclusion criteria include: pregnancy, asthma, obstructive pulmonary diseases, sinus bradycardia and severe bradycardia, sick sinus syndrome, heart failure, end-stage renal disease, stroke, diabetes mellitus, preoperative use of nonsteroidal anti-inflammatory medications (NSAIDS) or aspirin (ASA) within the last week, and a body mass index (BMI) greater than 40. Additionally, any patient that the anesthesiologist deems unfit for randomization will also be excluded.

We will randomize the patients in blocks of 4 to determine the impact of a specific study drug (either esmolol (n=20) or labetalol (n=20) along with sevoflurane to control blood pressure on bleeding. The patients will be classified according to their Lund Mackay scores, which will be obtained from their routine CT scan performed prior to their surgery.

Written informed consent will be obtained. On arrival to the operating room, all the patients will be monitored as per usual anesthesia routine. Patients in both groups will be induced using 1-2 mg midazolam PRN anxiety, 1-3 mcg/kg fentanyl, 20-40 mg lidocaine, 1-2 mg/kg propofol, and 0.05-0.1 mg/kg vecuronium. Thereafter, maintenance with general anesthesia will receive 1-2% of sevoflurane (end expired). Both groups may receive fentanyl throughout the case at the discretion of the anesthesiologist. The dose of fentanyl is not to exceed 5 mcg/kg. The patient's mean arterial blood pressure (MAP) will be maintained at 70-80 mm Hg (80 for hypertensive patients) by first adjusting the sevoflurane concentration within their range (between 1-2 percent for the sevoflurane. If sevoflurane is maximized (Fe sevo >2%) and the target MAP is not achieved, then the patients will receive either esmolol or labetalol (study drug will be blinded for surgeon).

The surgical procedure will not be altered. All patients will be placed supine with 6 degrees head up the entire procedure. Local vasoconstriction will be performed first with bilateral endonasal application of oxymetazoline soaked pledgets for 2 minutes. This is followed by placing topical epinephrine pledgets (1:1000) throughout the duration of the case. Our primary Outcome measures will include 1) intraoperative visibility utilizing two validated bleeding scores (Wormald and Boezart score) intraoperative visibility (1 minute, and every 20 minutes thereafter) 2) estimated blood loss at the of end of surgery which will be calculated by subtracting the amount of irrigation used from the total blood in the suction canisters.
Blood loss will be evaluated by the blinded rhinologist (MRC) and an independent observer who will review the un-identified endoscopic surgical videos.

In addition to the demographics and our primary outcome, secondary outcomes will be collected including duration of anesthesia, duration of surgery, final CO2, postoperative bleeding, visit to the ED following discharge, need for medical attention following discharge, need for surgical re-intervention, Bispectral index (**BIS**) monitoring intraoperatively (taped on patient forehead), surgeon satisfaction score on likert scale (1-10), and pain score after surgery, as well as time spent in recovery, use of anti-emetics postop, and nurses notes on as regards to pain and recovery. All the medications used in this study are used as part of the standard of care when patients develop high intraoperative blood pressure as a result of the usuage of the topical decongestants.

Blood pressure control medications:
Labetalol is a mixed adrenergic receptor antagonist (beta 1> alpha 1 blocker). If randomized, the anesthesiology investigator will obtain 3 bottles of labetalol (100 mg in 10 mL). Per protocol, aliquots of 10-30 mg of labetalol will be administered SIVP if MAP > 80 and sevoflurane [2%]. Initial dose will be 20 mg (within 2 min), followed by infusion of 0.25-0.5 µg/min. Maximum dose = 300 mg for case duration. If maximum dose is acheived, other agents per discretion of the anesthesiologist will be administered.

Esmolol is a specific beta adrenergic antagonist (beta 1>> beta 2). If randomized, the anesthesiology investigator will obtain a 2500 mg in 20 mL vial. Esmolol will be diluted in 250 mL 0.9% NaCl to achieve a concentration of 10 mg/mL. Per protocol, an infusion of esmolol at a rate of 0.1 mg/kg/min if MAP > 80 and sevoflurane [2%]. The dose can be titrated up to 0.3 mg/kg/min. If after 30 min, the esmolol dose is >0.3 mg/kg/min other agents per discretion of the anesthesiologist will be administered.

5. Sub-Study Procedures:
   N/A

6. Criteria for Inclusion of Subjects

   The inclusion criteria will be male or female patients with ASA physical status 1 (normal otherwise healthy patient) or 2 (patient with mild systemic disease) and patients who have chronic sinusitis with or without nasal polyps and who are scheduled for a routine ESS.

7. Criteria for Exclusion of Subjects

   Exclusion criteria include: pregnancy, asthma, obstructive pulmonary diseases, sinus bradycardia and severe bradycardia, sick sinus syndrome, heart failure, end-stage renal disease, stroke, diabetes mellitus, preoperative use of nonsteroidal anti-inflammatory medications (NSAIDS) or aspirin (ASA) within the last week, and a body mass index (BMI) greater than 40. Subjects may be excluded from the study if the

anesthesiologist deemed it necessary that the protocol drug cannot be used on the patient for any reason. Otherwise, it is expected that the surgeries will be routinely performed and the study outcome variables do not interfere with the routine.

8. Sources of Research Material

Intraoperatively, a bleeding score will be used (validated questionnaire) based on the visibility. In addition, at the end of the surgery, the estimated blood loss will be calculated. All other secondary outcomes will be collected following the completion of surgery. These will be obtained from the medical record (duration of anesthesia, duration of surgery, final CO2, Bispectral index (**BIS**) monitoring, postoperative bleeding, visit to the ED following discharge, need for medical attention following discharge, need for surgical re-intervention, and pain score after surgery, as well as time spent in recovery, use of anti-emetics postop, and nurses notes on as regards to pain and recovery).

9. Recruitment Method and Consenting Process:

The informed consent for the study will be obtained either in the preoperative clinic visit or on the day of the surgery in the pre-operative holding area. Informed consent for the study will be separate from the surgical consent. The name of the attending surgeon will be written on the study consent together with the name of the attending anesthesiologist. The informed consent will then be included in the patients' charts.

10. Potential Risks:

The risks and benefits of the study will be discussed with the patient on obtaining written informed consent. Consent for surgery and anesthesia will be done as usual. The study adds no risks above those associated with risks of surgery and risk of anesthesia. Neither anesthetic technique used here breaches the standard of care nor is the surgical technique not altered. There is no clear evidence of any difference in between the two groups in the literature in regards to their effect on recovery time or their gastrointestinal side effects (nausea and vomiting).

11. Subject Safety and Data Monitoring

Monitoring of the patients will abide by the standards set forth by the American Society of Anesthesiology. Additionally, the standard surgical procedures will be applied in this study.

Any adverse event will be reported immediately to the IRB and FDA if it was drug related. Given that the medications used in this study are used routinely by anesthesiologists, the reported adverse event will unlikely be related to the study itself.

12. Procedures to Maintain Confidentiality

As a patient enters the study, the investigator will assign that patient to the next sequential study code number available. All data and subject information will be stored in the investigator's laboratory in locked file cabinets or on a secure computer. Access to the data will be restricted to the investigators, nurses, and technicians involved in this project.

13. Potential Benefits

The main benefit is that if there is a difference between the groups then they will have less blood loss. The choice of medication for blood pressure control intraoperatively will likely be implemented should the results demonstrate any difference between the groups. In the event that there was no difference between the groups, then the medications can continue to be used without the concern of impaired visibility to the endoscopic surgeon.

The study adds no risks above those associated with risks of surgery and risk of anesthesia. Neither anesthetic technique used here breaches a standard of care nor is the surgical technique altered. There is no clear evidence of any difference in between the two groups in the literature in regards to their effect on recovery time or their gastrointestinal side effects (nausea and vomiting).

14. Biostatistics

Accurate power analysis cannot be done since there is a lot of controversy in the older studies. For this reason, our number of patients (N=40) to be included in the study was inferred based on the estimated difference in the mean of blood loss between the groups as being 110 ml and an estimated standard deviation of the mean between the two groups to be 150 and 200 respectively.

If the results of the two groups stratified didn't show a normal distribution, then they will be compared using the Wilcoxon rank sum test with P value significant ≤0.05. If the results were normally distributed, then a student t -test will be used with P value significant ≤ 0.05.

15. Bibliography:

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