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A Study Protocol for Assessing the Effect of Pre-Emptive Oral Clonidine on Intraoperative Hemodynamics and Surgical Field Quality during Functional Endoscopic Sinus Surgery (FESS) under General Anesthesia

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Typically, endoscopic sinus surgery is reserved for patients with documented rhinosinusitis. The nasal mucosa is impregnated with supply of highly rich blood vessels, so excessive occurrence of bleeding during the procedure may obscure the visibility of the surgical area which might lead into complications. So to control the intraoperative blood loss, controlled hypotension during the surgery can be adopted. Clonidine, a centrally acting α_2 agonist has antihypertensive property with decreasing sympathetic outflow. Clonidine given orally judiciously prior to surgery would potentiate the inhalation agents for hypotensive action during the anaesthetic procedure without having the disadvantages of vasodilators given intravenously. This study to assess the effects of clonidine as an oral premedicant in patients who are undergoing Functional Endoscopic Sinus Surgery.

Methodology: This prospective randomized double blinded placebo controlled study will be conducted in the department of Anaesthesia, Acharya Vinoba Bhave Rural Hospital, (DMIMS)

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Jawaharlal Nehru Medical College Sawangi Wardha, within the period of time of December 2020 to November 2022. Total 60 patients will be enrolled and randomized in two groups: Group C (n= 30): Patients will be given Clonidine (200 µgm); Group P (n= 30) will be Placebo group. To shrink nasal mucosal vessels, all patients will receive nasal packing of 2% xylocaine with 1:200000 adrenaline. Then, 60 minutes after study drugs are given, patients will be shifted for procedure. Using Six-point Average Category Scale, the grading of surgical field in terms of bleeding, will be done by the operating surgeon. Qualitative data will be documented with the help of percentage table, quantitative data will be presented as mean and standard deviation, student t-test will be taken for comparison among the study groups, Chi-square test will be utilized for comparison of categorical data. SPSS (Statistical Package for Social Sciences) 20.0 version will be the Software used in the analysis and $p < 0.05$ will be considered significant statistically.
Expected Results: Oral clonidine when used as premedicant will be effective in reducing bleeding during the procedure of Functional Endoscopic Sinus Surgery.

Keywords: Functional endoscopic sinus surgery; clonidine; hemodynamic stability; surgical field; bleeding; hypotension.

1. INTRODUCTION

FESS (functional endoscopic sinus surgery) has become the cornerstone of management done surgically of the pathologies of paranasal sinuses [1].

Indications for Endoscopic Sinus Surgery: Most commonly, Endoscopic sinus surgery is performed for infectious and inflammatory sinus disease. Endoscopic sinus surgery is most commonly indicated in the following pathologies:

1. Chronic Sinusitis refractory to medical treatment
2. Recurrent Sinusitis
3. Nasal Polyposis
4. Antrochoanal Polyps
5. Sinus Mucoceles
6. Choanal Atresia Repair
7. Foreign Body Removal
8. Dacryocystorhinostomy (DCR)
9. Optic Nerve Decompression
10. Epistaxis Control
11. Orbital Decompression (eg. Graves Ophthalmopathy)
12. Cerebrospinal Fluid (CSF) Leak Closure
13. Excision of selected Tumors

Typically, endoscopic sinus surgery is reserved for patients with documented rhinosinusitis, on the basis of a thorough physical examination and a proper history, which includes CT scans if required, and in those with failed medical treatment.

Nasal polyposis may not be treated by medical therapy alone. Similarly, surgical removal is required in antrochoanal polyps as well.

1.1 Nasal Masses

Increasingly, endoscopic procedures are used to remove selected nasal masses and tumors. Removal of Inverted Papilloma by endoscopic procedure is controversial. Endoscopic procedure can be undertaken for a few lesions, wherein definitive margins and control can be acquired endoscopically; preoperative nasal endoscopy and imaging can predict this situation.

External approach should be used for more extensive lesions; either one of a Midfacial Degloving Method or a Lateral Rhinotomy Method can be used for en bloc removal of tumor. For these patients, continued research with monitoring in the long-term in this field will better outline the optimal treatment.

Cerebrospinal fluid leaks: Endoscopic procedures can be used to manage cerebrospinal fluid (CSF) leaks associated with CSF rhinorrhea. Success rates of about 78% have been reported with primary endoscopic attempts, and these success rates increase to 88% if we include revision endoscopic closures.

Because of endoscopic repair of CSF leaks, we can avoid the more extensive neuro surgical approaches done via craniotomy externally. In a few clinical settings, endo-nasal encephaloceles are treated by endoscopic approaches.

1.2 Ophthalmic Procedures

Endoscopic approaches may also be applied for ophthalmic procedures. These include the following:

1. Orbital Decompression

2. Optic Nerve Decompression for Traumatic Indirect Optic Neuropathy.
3. Endoscopic DCR

In the past, external approaches were used to perform these procedures, but with increase in clinical experience in nasal endoscopic techniques, they are now performed via endoscopic approach. These procedures should be performed only by surgeons with vast amount of training and expertise in endoscopic techniques.

1.3 Contraindications to Endoscopic Sinus Surgery

A few conditions of the sinus may not completely respond to endoscopic treatment; such conditions include complications of acute sinusitis which are intra orbital, such as frontal osteomyelitis associated with Potts puffy tumor or orbital abscess. Irrespective of availability of additional endoscopic assistance, an open approach may be preferable in these instances. A thorough review of magnetic resonance imaging (MRI) scans or CT scans done preoperatively helps guide the surgeon.

The nasal mucosa is impregnated with supply of highly rich blood vessels [2], so excessive occurrence of bleeding during the procedure may obscure the visibility of the surgical area which might lead into complications. So to control the intraoperative blood loss, controlled hypotension during the surgery can be adopted [3]. The various methods followed are as elevation of patient's head, surgery under local anaesthesia [4] along with vasoconstrictors e.g. phenylephrine, ephedrine [5,6,7], and/or general anesthesia supported by hypotensive agents [8]. Clonidine, a centrally acting α2 agonist has antihypertensive property with decreasing sympathetic outflow [9]. Clonidine given orally judiciously prior to surgery would potentiate the inhalation agents for hypotensive action during the anaesthetic procedure without having the disadvantages of vasodilators given intravenously [10].

Besides, Clonidine premedicant decreases analgesic requirement [11] and nausea, vomiting post-operatively [12].

1.4 Aim and Objectives

The aim of the present study is to analyse the effects of oral clonidine premedication in the patients undergoing Functional Endoscopic Sinus Surgery.

The objectives are to assess the efficacy of oral clonidine

- primarily,
  - as a hypotensive agent while used along with the technique of balanced anaesthesia
  - on intraoperative bleeding following a score on bleeding severity
- secondarily,
  - to maintain intra-operative haemodynamic stability with/without requirements of rescue antihypertensive drug,
  - in evaluation of any side effect and/or complication that may emerge while using clonidine.

Trial design: This is a prospective randomized control double blind study.

2. METHODOLOGY

Eligibility criteria:

- Inclusion Criteria: Patients
  - In 20 - 50 years age group
  - Weight between 40-65 kgs
  - Either gender
  - Physical status I and II of ASA
  - Selected patients for FESS.
- Exclusion Criteria: Patients'
  - Refusal to give consent
  - History of
    - Cardiovascular, pulmonary, renal, hepatic, endocrinal or neurological disease,
    - Preoperative Hypotension
    - Obesity
  - Anticipated difficult airway as per LEMON criteria
  - CVS dysfunction as sinus bradycardia/ conduction defects/ heart blocks
  - Patients taking antipsychotic drugs
  - Patients on drugs as Calcium Channel Blockers, Digitalis, β-blockers

- Allergy to study drugs
- Pregnancy, lactation

Interventions: This prospective randomized double blinded placebo controlled study will be conducted in the department of Anaesthesia, Acharya Vinoba Bhave Rural Hospital, (DMIMS) Jawaharlal Nehru Medical College Sawangi Wardha, within the period of time of December 2020 to November 2022 having taken informed written consent after proper counselling from each patient and approval of the Ethical Committee of the Institution.

Prior permission from the HOD of ENT, about the study will be sought.

60 patients selected will be randomly allocated into groups

1. Group (Clonidine, n= 30) C
2. Group (Placebo, n= 30) P

Prior to surgery, all the patients will undergo routine clinical examination and biochemistry investigation reports, electrocardiogram, X-Ray chest will be checked thoroughly before the conduct of anaesthesia.

On the day before procedure patients will be sedated with Tab. Alprazolam 0.25 mg at bedtime and will follow standard ASA fasting guidelines.
In the morning of surgery, patients will be brought to the preoperative room, monitors attached and baseline heart rate and systolic, diastolic blood pressure will be recorded prior to premedication of study drugs to the groups of patients.

Group C patients will be given oral Clonidine (200 µgm) and Group P patients will receive a placebo drug with a sip of water 60 min prior to anticipated anaesthetic induction time. In order to shrink the nasal mucosal vessels, all the patients will receive a nasal packing of 2% xylocaine with 1:200000 adrenaline. Then 60 minutes after the study drugs given, the patients will be shifted to the operating theatre.

In the operating theatre, at the pre-induction stage, pulse oximeter, leads of electrocardiography, non-invasive blood pressure monitor cuff will be attached to the patients and the values heart rate and blood pressures will be recorded. Ringers Lactate solution 15-20ml/kg will be started through an intravenous line with18G cannula.

Once pre-oxygenated with 100% oxygen for 3 minutes, inj. Fentanyl 2µgm/kg IV, inj. Glycopyrrolate 4µgm/kg IV, inj. Ondansetron 4mg/kg IV and inj. Midazolam 2 mg IV will be given and the patients will be induced with Propofol (1%) IV till the loss of verbal command (maximum upto 3mg/kg) which will be followed by 0.1mg/kg Vecuronium Bromide, the muscle relaxant through IV route, which will aid as well as facilitate laryngoscopy and intubation. Mask ventilation will be continued with 100% oxygen for 3 minutes, endotracheal intubation will be done under direct laryngoscopic vision. Maintenance of anaesthesia will be with 33% Oxygen plus 66% Nitrous oxide and sevoflurane 1.5%-2%. Inj. Vecuronium IV will be given as and when required in conventional top-up doses.

The heart rate, NIBP will be recorded on induction, then 1 min and 5 min after completion of intubation, then every 10 minutes interval for the first 30 minutes and every 20 min thereafter intraoperatively.

Any intraoperative hypertensive episode will be managed with rescue bolus doses of Propofol (10mg/bolus) so that the mean arterial blood pressure (MAP) is maintained between (60-75mmHg). Fentanyl bolus of 2 µg/kg IV will be added if unsuccessful. If still the desired target is not achieved by both the drugs, a continuous infusion of diluted concentration of nitroglycerin 100µg/ml injection will be given as 0.5-10 µg/min infusion.

Surgical field grading in terms of bleeding using Six-point Average Category Scale [13] will be done by the operating surgeon. Intraoperative bleeding will be assessed according to the scoring scale as follows:

Finding	**Score**
No bleeding	0
Slight bleeding; No suctioning of blood required	1
Slight bleeding; Occasional suctioning required. Surgical field not threatened	2
Slight bleeding; Frequent suctioning required. Surgical field threatened by bleeding a few seconds after suction was removed	3
Moderate bleeding; Frequent suctioning required. Bleeding threatened the surgical field directly after suction was removed	4

The Surgical conditions predetermined for ideal category scale of values will be 2 and 3. Incidences of untoward effects if any will be noted.

Anaesthesia will be reversed with inj. neostigmine and inj. glycopyrrolate in conventional doses. Extubation will be undertaken when stimulation while the suction catheter in the oropharynx gives a good gag reflex, movements of chest and reservoir bag give an evidence of adequate tidal volume and response to verbal commands is received.

Heart rate if comes down below 60/minute any time intraoperatively, injection Atropine will be given in titrated doses of 0.6mg IV. MAP of patients if falls below 60 mmHg infusion of IV fluids and/or inj. ephedrine 6mg IV in supplements will be tried as treatment.

2.1 Sample Size

Openepi.com. will be used for Sample size calculation. As per a previous study, assuming mean duration of surgery of 78.1 ± 14.3 min [14,15], confidence intervals at 95% (alpha error at 0.05) and power at 80%, a sample size of 28 patients will be needed to keep a minimum 15% difference in the duration of surgery between the groups. We, in each group, will include 30 patients keeping in mind for possible dropouts. A table of computer-generated random number will be the base for allocating the selected patients randomly into groups of two of 30 each. Patients in Group C will be given tab Clonidine 200 µgm, Group P patients will be given placebo both orally 60 min prior to the proposed surgery.

The tablets will be supplied in similar looking packets to avoid biasness.

2.2 Statistical Methods

Qualitative data will be documented with the help of percentage table, quantitative data will be presented as mean and standard deviation, student t-test will be taken for comparison among the study groups, Chi-square test will be utilized for comparison of categorical data. SPSS (Statistical Package for Social Sciences) 20.0 version will be the Software used in the analysis and $p < 0.05$ will be considered significant statistically.

3. EXPECTED OUTCOMES/ RESULTS

Oral clonidine premedicant, in FESS patients, will effectively reduce the bleeding during the procedure and will offer a favorable surgical outcome achieving controlled hypotension.

4. DISCUSSION

Woodcock et al. [16] in 1987, did a computer controlled study of the vapor requirements of isoflurane to assess the hypotension, the sympathoadrenal responses induced by it with clonidine premedication. They found that to maintain hypotension in the clonidine group the mean concentration of isoflurane required was 1.4% in comparison to 2.3% in the control group.

Jabalmeli et al. [13] in 2005, conducted a study with oral clonidine premedication to reduce intra-operative bleeding in 113 patients (ASA 1 and 2) undergoing FESS surgery. Oral clonidine was received by 52 patients and placebo by 61, 90 minutes prior to surgery. It was observed that clonidine not only reduced bleeding in FESS surgery but also requirements of fentanyl and hydralazine for controlling hypotension.

In 2016, Rohini V Bhat et al. [17] conducted a study on 60 ASA I or II patients randomly allocated to group C (n = 30) or group D (n = 30) following premedication with clonidine (C) versus diazepam (D) both orally, on surgical conditions in endoscopic sinus surgery and were found that higher number of patients had the surgical time, the rate of blood loss, propofol infusion rate statistically lower in the clonidine group, as compared to the diazepam group. Also there was a better surgical score (better surgical field) in the clonidine group in a higher number of patients than that of the diazepam group. Few of the studies on Clonidine use in anaesthesia were reported [18-20]. Bansal et. al. compared general anaesthesia and combined general anaesthesia with spinal anaesthesia on hemodynamic parameters [21]. Similar study on hemodynamic changes with intravenous Dexmedetomidine and intravenous Esmolol was reported by Sen et. al. [22-27].

Scope: Studies can be done to know the sedation status as well as analgesic effects of the drug clonidine in FESS surgery both intra and post operatively.

5. CONCLUSION

Conclusion will be drawn from the outcome of the study.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent will be collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval will be collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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