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Effect of oral premedication with ivabradine on surgical field and intraoperative bleeding during functional endoscopic sinus surgeries: A prospective, randomized, and placebo-controlled study

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ABSTRACT

Background: Ivabradine is an effective drug to prevent abnormal increase in heart rate (HR). **Aims and Objectives**: The aims of this study were to determine if a pre-operative oral dose of ivabradine (2.5 mg) reduces intraoperative bleeding during functional endoscopic sinus surgery (FESS) and improves visualization of operative field. **Materials and Methods**: A prospective, randomized, and placebo-controlled study was carried out in 30 patients of ASA grade I and II, aged between 18 and 60 years undergoing FESS surgeries. The patients were randomly allocated into two groups. Group I – received 2.5 mg of tablet ivabradine and Group P – received a placebo (vitamin tablet) 1 h before surgery. Blood loss and hemodynamic parameters (HR, systolic, diastolic, and mean blood pressure) were assessed perioperatively. Surgical field was graded by operating surgeon using Fromme – Boezaart score (FBS) at the end of procedure. Post-operative monitoring for any complications was also done. **Results**: Mean final blood loss in Group I was 165.73 ± 43.48 mL and in Group P was 246.25 ± 30.76 mL. There was a significant difference in mean final blood loss (mL) between two groups with $P < 0.001$. In Group I – 13.33% had FBS 1 and 86.67% had FBS 2, whereas in Group P – 6.67% had FBS 2, 86.67% had FBS 3, and 6.67% had FBS 4. Thus, Group I had lower FBS scores than Group P and was statistically significant. **Conclusion**: Pre-operative oral ivabradine helps in reducing intraoperative bleeding in FESS surgery and provides good surgical field compared to placebo.

Key words: Blood loss; Functional endoscopic sinus surgery; Hypotensive anesthesia; Ivabradine; Surgical field

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INTRODUCTION

Functional endoscopic sinus surgery (FESS) is an established surgical treatment of sinusitis and nasal polyps; yet, the success of this procedure depends on visual clarity of the surgical field, through the endoscope.[1]

FESS gives the advantage of good illumination and clear vision with minimally invasive surgery and thereby it is possible to achieve consistently good results.[2]

Operative field visibility is a major factor for FESS outcome and is related to the amount of intraoperative bleeding, which interferes with field visibility and could be a prime obstacle for success of FESS and may result in many complications.[2,3]

Various interventions are performed with general anesthesia for FESS, aiming at reducing intraoperative bleeding and improving visibility of surgical field.

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Hypotensive anesthesia is a renowned modality used for control and reduction of bleeding during surgery. The state of "hypotension" is achieved by reducing the peripheral vascular resistance, reducing the heart rate (HR) per minute, and by inter coordinating these two effects.[2]

Most frequently, peripheral vasodilators, β-blockers, and volatile anesthetics are used to cause induced hypotension.[2] Various agents such as magnesium sulfate, vasodilators (sodium nitroprusside), nitroglycerine, high doses of potent inhaled anesthetics and beta-adrenergic antagonist, and alpha agonists (dexmedetomidine) have been used to achieve controlled hypotension.[4]

Some disadvantages have been reported of these techniques including delayed recovery from inhaled anesthetics, resistance to vasodilators, tachyphylaxis, and cyanide toxicity for nitroprusside.[4] In our study, we intended to use ivabradine as it has a profound effect in controlling HR which is one of the modalities to decrease intraoperative bleeding and provide blood less surgical field. Ivabradine is a distinctive drug, classified as a cardiotonic agent. It is a highly selective inhibitor of "If" channels (Funny current or funny channels or pacemaker current). "If" blockade results in a decrease in the slope of spontaneous depolarization, leading to an increase in the time interval between successive action potentials in the SA node, thus decreasing the HR.[5]

Ivabradine decreases the HR without any inordinate change in hemodynamics of unhealthy, compromised patients. The drug can be used both in hypertensive and normotensive patients. It has no significant negative inotropic effect like a beta-blocker and can be even used in patients with bronchial asthma, where beta-blockers are contra-indicated.

Ivabradine reduces the HR without causing a precipitous fall in blood pressure and it conserves myocardial oxygen reserve and also reduces myocardium oxygen demand. Hence, in every aspect, ivabradine is an ideal drug to be used during general anesthesia procedures in view of its multiple benefits on the myocardium.[5]

Although ivabradine is commonly used in critical care setup to reduce HR, its use intraoperatively during surgeries has not been explored sufficiently except for its effect to attenuate hemodynamic response during laryngoscopy and intubation.

Hence, this study explores newer aspect of ivabradine by evaluating its effects on surgical field and control of intraoperative bleeding to provide a blood less field during FESS (due to its effects on HR) and prevent complications associated with it.

Aims and objectives

The pimary objective of this study was to determine if a pre-operative oral dose of ivabradine (2.5mg) would reduce bleeding during FESS and improve visualization of the operative field.

The secondary objectives were to compare hemodynamic parameters between the groups and to assess for any complications.

MATERIALS AND METHODS

After obtaining the Institutional Ethical Committee approval, a comparative clinical study was carried out at Rajarajeswari Medical College and Hospital, Kambipura, Bangalore. For sample size calculation, the published data of Jacob et al.,[1] were consulted to get an idea of population variance. We assumed that a minimum difference in mean blood loss of 100 ml between two groups would be clinically significant. Allowing 5% alpha error (95% Confidence level) and setting the power of the study at 95%, the sample size of 13 was obtained for each group. With 10% non-response value, sample size of 13+1.3=15 cases was included in each group.

Informed written consent was taken from all the patients after explaining the procedure and associated risk. Thirty adult patients of ASA grade I and II, aged between 18 and 60 years scheduled for elective FESS under general anesthesia were included in the study.

Patients with cardiovascular diseases, HR <70 bpm, ECG abnormalities, pregnant, breastfeeding women, any coagulative disorders, hepatic or renal impairment, patients on any anti-hypertensive medications, and any known allergy to drug were excluded from our study.

All the patients were subjected to detailed preanesthetic evaluation. Routine investigations and specific investigations were done as per patient's clinical condition.

Patients were randomly divided into two groups of 15 each using computer-generated simple random numbers and group allocation was done with sealed envelope method, on previous day of surgery.

Group I – patients received ivabradine tablet 2.5 mg orally, 1 h before surgery (FESS).

Group P – patients received a placebo (vitamin tablet) orally, 1 h before surgery. Patients were kept nil per oral for 8 h and were given Inj. Ranitidine 50 mg IV and Inj. Ondansetron 4 mg IV on the morning of surgery.

Patient's baseline HR, blood pressure, and pre-operative hemoglobin were recorded before administration of the study drug by principal investigator.

Oxymetazoline nasal drops were applied to serve the purpose of nasal decongestion and saline soaked ribbon gauze packing of nostrils was done in pre-operative room for 15 min in both the groups.

In both the groups, on arrival of the patient to the operation theater, pulse oximeter, non-invasive blood pressure, and ECG leads were attached. Anesthesia was administered by an anesthetist not involved in the study. Hemodynamic parameters such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation were recorded. A crystalline intravenous infusion of 6–8 ml/kg was started. All patients were premedicated with IV midazolam 0.01 mg/kg and 2 mcg/kg of IV fentanyl.

After preoxygenation with 100% oxygen for 5 min, the patient was induced with inj. propofol 2 mg/kg till the loss of verbal commands. Neuromuscular blockade was achieved by injection vecuronium 0.1 mg/kg to aid in laryngoscopy and intubation. Anesthesia was maintained with isoflurane (0.5–1 MAC), with 50 % N_2O in oxygen and intermittent doses of vecuronium 1 mg. The patients were mechanically ventilated to maintain the normocapnia ($ETCO_2$ between 35 and 40 mmHg).

Immediately, after tracheal intubation, throat packing with ribbon gauze was done and the head of the operation table was elevated to 30 degree. HR, SBP, DBP, and MAP were non- invasively recorded before induction of anesthesia and was monitored every 5 min, but was expressed collectively every 15 min until the end of surgery. Intravenous paracetamol 15 mg/kg was given at end of surgery for post-operative analgesia. Surgical field was scored at the end of procedure by operating surgeons who was blinded to study drug using Fromme-Boezaart score. All the patients were followed up in PACU for 12 h and their HR and blood pressure were recorded by an independent observer not involved the study. Any incidence of adverse effects of ivabradine was looked for in the post-operative period. Post-operative hemoglobin level was also assessed on POD-1.

Operative field bleeding and subsequently its visibility were graded using a six-point scale:

Fromme-Boezaart scale[1]

- 0 = no bleeding
- 1 = slight bleeding not requiring suction evacuation
- 2 = slight bleeding requiring occasional suction
- 3 = slight bleeding requiring frequent suction evacuation, bleeding threatens surgical field for a few seconds after suction is removed
- 4 = moderate bleeding requiring frequent suction evacuation; bleeding threatens surgical field directly after suction is removed; and
- 5 = severe bleeding and constant suctioning is required, bleeding appears faster than can be removed by suction, and surgical field is severely threatened and surgery is hardly possible or impossible at all.

Total amount of bleeding was calculated by subtracting the saline used for wash during surgery from the total amount of blood collected in clean dry suction container and by also counting the number of cotton strips used during surgery. A fully soaked cotton strip was estimated to contain 5 mL of blood and a partially soaked one as containing 2.5 mL.

Statistical analysis

Data were entered into Microsoft Excel data sheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Independent t-test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables.

Graphical representation of data

Microsoft Excel and MS word were used to obtain various types of graphs such as bar diagram and line diagram.

P-value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software

Microsoft Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA), was used to analyze data.

RESULTS

In our study, 30 patients with ASA grade I/II were enrolled into two groups (Group I and Group P) with 15 in each. Demographic profile of the study participants is shown in Table 1. Both the groups had no statistically significant difference with respect to age, gender, and body mass index (BMI) with P=0.923, 0.713, and 0.769, respectively.

Mean HR was compared between two groups prior and post-intubation and every 15 min until 2 h, then every 2nd hourly thereafter as illustrated in Figure 1. There was

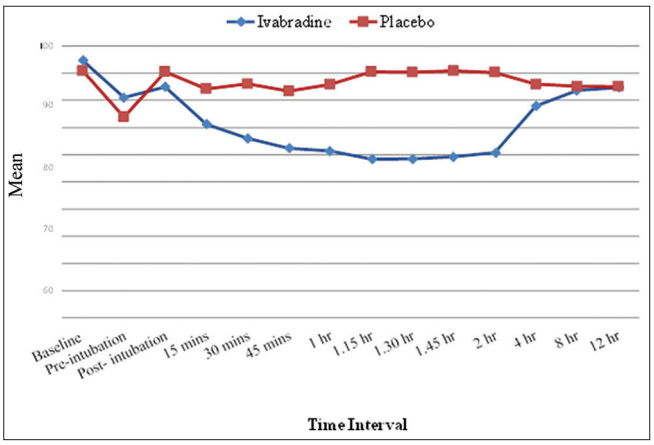

Figure 1: Line diagram showing mean heart rate comparison between two groups at different periods of follow-up

a significant difference in mean HR between two groups at post-intubation and from 15 min to 4 h with significant P<0.05. Group I patients mean HR was less variable from their baseline values compared to group P, thereby providing a controlled surgical field. At other intervals (8th and 12th h), there was no significant difference noticed.

Mean final blood loss (ml) in Group I was 165.73±43.48 and in Group P was 246.25±30.76. There was a statistically significant difference between two groups, as shown in Table 2, with P<0.001 indicating that intraoperative bleeding was comparatively less in patient who received ivabradine preoperatively.

Fromme-Boezaart score (FBS) to assess surgical field based on surgeon scrutiny showed that in Group I 13.33% had FBS 1 and 86.67% had FBS 2.

In Group P, 6.67% had FBS 2, 86.67% had FBS 3, and 6.67% had FBS 4.

There was a significant difference in Fromme-Boezaart scale distribution between two groups (P≤0.01) with better visualization and surgical field obtained in Group I (Table 3).

DISCUSSION

FESS involves intricate technique which needs a clean and blood-less field for better visibility. In FESS surgeries, general anesthesia is often preferred over topical anesthesia as it produces a static surgical field, effective airway protection, adequate analgesia, patient comfort, and the provision for controlled hypotension. The use of hypotensive anesthesia, further, reduces bleeding and thus improves the field during surgery. To attain clear visibility

Table 1: Demographic profile in the groups

Demographic variables	Group I	Group P	P-value
Age (years)	36	36.4	0.923
Gender (F/M)	6/9	7/8	0.713
BMI	22.64	22.88	0.769

Table 2: Mean final blood loss at the end of the surgery (mL) comparison between two groups

Parameter	Group				P-value
	Ivabradine [I]		Placebo [P]		
	Mean	SD	Mean	SD	
Final blood loss (mL)	165.73	43.48	246.25	30.76	<0.001*

Table 3: FBS distribution between two groups

Parameters	Ivabradine [I]	Placebo[P]	P-value
FBS 1	2 (13.3)	0	<0.001*
FBS 2	13 (86.7)	1 (6.7)	
FBS 3	0	13 (86.6)	
FBS 4	0	1 (6.7)	

FBS: Fromme-Boezaart Score, data are presented as number of patients and proportions, Chi-square test applied, χ^2=26.286, df=3, *P*≤0.001*

in the surgical field, various pharmacological methods such as opioids, beta-blockers, alpha 2 agonist, and arterial vasodilators have been used priorly. These methods decrease intraoperative bleeding by either reducing blood pressure or HR or combination of both. Hence, the surgical field visibility depends on the type of anesthesia, blood pressure, and HR.

Numerous studies on controlled hypotension in FESS have been done which used wide array of pharmacological agents.[2,3,6-10] No prior studies using ivabradine have been conducted, hence making this a novel concept to be inspected on.

Ivabradine 5 mg is the initial dose being prescribed in cardiac patients. If bradycardia occurred with this dose, it would be titrated down to 2.5 mg accordingly. We used a dose of 2.5 mg in our study, anticipating any profound bradycardia which might be induced by synergistic effects of anesthetic agents used along with ivabradine and thereby avoiding it.

The demographic parameters such as age, gender, and BMI were comparable in both the groups with no statistical significance (P>0.05; Table 1).

In this study, we evaluated ivabradine's primary action on HR. By reducing HR, the diastolic period increases and

leads to lowering of venous pressure thereby reducing venous oozing.[1]

We found that ivabradine significantly reduced intraoperative bleeding compared to a placebo (P<0.001) with mean blood loss being lower in patients who received ivabradine 1 h before surgery (mean blood loss in Group I=165.73±43.48 mL and Group P=246.25±30.76 mL; Table 2). Controlled surgical field was provided with ivabradine with no extreme changes in hemodynamic parameters such as HR and blood pressure. Reduction in HR induced by the drug generally peaked within 1 h of starting the procedure and was maintained throughout surgery (Figure 1). The capillary oozing at the surgical site was much reduced due to this effect and it improved field visibility markedly.

The surgical field was graded by the operating surgeon at the end of procedure using the Fromme-Boezaart score.[1] We found that patients in ivabradine group were given lower scores like 1 and 2, whereas, in placebo group, maximum patients received score of 3 (Table 3). This showed that ivabradine gave a satisfactory field to surgeon by minimizing bleeding and reducing the frequency of suctioning.

Jacob et al.,[1] studied the effect of pre-operative dose of bisoprolol (2.5 mg) on surgical field during FESS. They found that bisoprolol reduced bleeding and provided good visibility of operating field owing to its effect on blood pressure and HR as well.

Zaky and Saleh[2] compared the adequacy and outcome of controlled hypotensive anesthesia using remifentanil and magnesium sulfate during FESS. They found that remifentanil was superior to magnesium sulfate in reducing intra-operating bleeding and thereby improved field visibility.

All these studies[2-4,6,8,9] used varied group of drugs for achieving controlled hypotension. There is no research conducted using ivabradine for hypotensive anesthesia, and hence, our study evaluates this new concept without being braced on by previous studies.

The hemodynamic parameters (HR, SBP, DBP, and MAP) were maintained throughout surgery and provided a stable field for operation.

The use of ivabradine furnished another benefit of attenuation of laryngoscopic and intubation response in this study (Figure 1). There was no significant hemodynamic fluctuation before and after intubation. This aspect of ivabradine has been explored in some recent studies and excellent results have been obtained.[5,11-13]

The dose of ivabradine (2.5 mg) used in our study gave a controlled field and did not cause any sudden drop-in HR. Adrenaline and isoprenaline were kept ready to antagonize any profound bradycardia, but none were used making this dose of ivabradine safe to administer.

Few complications have been reported with ivabradine such as blurred vision, dizziness, and light headedness, but these are not common and occur in rarity. No complications were found during intraoperative and post-operative period in our study with dose of 2.5 mg.

Newer studies are being conducted assessing the effect of ivabradine on blood pressure and other pleiotropic effects.[14] With its ability to provide perioperative hemodynamic stabilization in non-cardiac surgery,[15] hence, it, further, adds a strong basis to our study.

Thus, oral premedication with ivabradine has helped significantly in reducing intraoperative bleeding during FESS surgery and improved field visibility compared to a placebo.

Limitations of the study

1. The effect of ivabradine on surgical field was not studied in FESS procedures involving extensive nature of disease (extensive polyposis and malignancy).
2. Sample size is small, and further, studies are recommended with larger study group to evaluate this concept.

CONCLUSION

This prospective, randomized, and double-blinded placebo-controlled study found that oral premedication with tablet ivabradine helped in reducing intraoperative bleeding and improved visibility of surgical field compared to placebo in FESS surgery with stable hemodynamics throughout the surgery.

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SMJI- Contributions to conception or design of work, literature review, interpretation of result and preparation of manuscript; **SK**- Literature review, data collection, statistical analysis and interpretation and preparation of manuscript; **SrK**- Analysis and drafting data, interpretation of results, revision of manuscript.

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