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Original Article

Anaesthesia Section

Oral Clonidine versus Ivabradine for Attenuating Stress Response in Functional Endoscopic Sinus Surgery: A Randomised Placebo-controlled Study

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ABSTRACT

Introduction: Peri-anaesthetic haemodynamic alterations, such as hypertension and tachycardia, can cause increased bleeding during Functional Endoscopic Sinus Surgery (FESS), impairing the visibility of the surgical field and resulting in scarring, adhesions, and prolonged surgery time. Various strategies involving pharmacological techniques have been used to mitigate these unfavourable reflexes. Alpha-2 agonists, such as Clonidine, are currently being employed to attenuate sympathoadrenal stimulation caused by tracheal intubation and surgery. Ivabradine is a new drug that selectively lowers Heart Rate (HR) by inhibiting cardiac funny current channels.

Aim: To compare the effects of premedication with oral Clonidine versus oral Ivabradine on attenuating haemodynamic stress response and improving the quality of the surgical field in FESS.

Materials and Methods: The present randomised, placebo-controlled, double-blind study was conducted in the Department of Anaesthesiology and Intensive care at Rajendra Hospital, Government Medical College, Patiala, Punjab, India from April 2021 to December 2022 on 90 American Soceity of Anaesthelogists (ASA) Physical status I and II adult patients (aged 18-60 years) undergoing FESS. Group A (n=30) received oral Ivabradine 5 mg, Group B (n=30) received oral Clonidine 0.2 mg, and Group C (n=30) received oral placebo tablets 2 hours before surgery. Haemodynamic parameters, including HR and Mean Arterial Pressure (MAP), quality of the intraoperative surgical field, postoperative sedation score, Visual Analogue Scale (VAS) score, time to analgesia request, blood loss, and adverse effects, were recorded. Descriptive statistics were used to calculate mean±Standard Deviation (SD) and percentage. Analysis of Variance (ANOVA), Tukey post-hoc test, Kruskal-wallis H test, and Pearson's Chi-square were applied as appropriate.

Results: The mean ages were 33.87±12.84, 35.03±12.93, and 40.9±14.46 years for Groups A, B, and C, respectively. The mean weights were 60.5±8.91, 57.83±5.66, and 57.9±5.42 kg, and the mean duration of surgery was 88.67±4.29, 88.8±4.29, and 88.03±3.93 minutes for Groups A, B, and C, respectively. There were no significant differences in terms of gender, ASA score, and type of surgery between the groups. Baseline HR and MAP were comparable among the groups. HR was significantly lower in both Groups A and B compared to Group C at all time intervals (p-value <0.001). Both drugs significantly attenuated tachycardia and hypertension in response to cardiovascular stress induced by laryngoscopy, endotracheal intubation, and extubation. However, Group B showed significantly better control of MAP throughout the intraoperative period and at extubation. The average category scale score, estimated blood loss, and postoperative VAS Score were all significantly lower in Group B than in Group A. Postoperative sedation scores were significantly higher in Group B, and the time to first rescue analgesic was longest in Group B (p<0.05). No significant side effects were observed.

Conclusion: Both Clonidine and Ivabradine effectively attenuated the haemodynamic stress response. Clonidine provided better control of MAP, resulting in reduced bleeding, improved operative field visibility, and lower postoperative analgesic requirements compared to Ivabradine.

Keywords: Haemodynamic stress, Heart rate, Laryngoscopy, Mean arterial pressure, Surgical field

INTRODUCTION

Haemodynamics fluctuations during the anaesthetic course are mostly brought on by the stress reaction during laryngoscopy, endotracheal intubation, surgical stimulation, awareness during extubation, and post anaesthesia recovery. By stimulating sympathoadrenal receptors and releasing catecholamines into the bloodstream, laryngoscopy and endotracheal intubation cause a pressor reaction characterised by an elevation in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Heart Rate (HR) [1]. This pressor response manifests within five seconds. The average rise in SBP is 25-50 mmHg, followed by a plateau at or above this peak pressure, which is sustained for 1-2 minutes. It takes about 5-10 minutes for the pressures to return to the prelaryngoscopic values [2,3].

For FESS, establishing a clear operative field is essential since the mucosa of the nose and paranasal sinuses is highly vascular and prone to bleeding. Increased bleeding due to hypertension can cause difficulty in proper field visualisation, leading to more tissue damage, scarring, postoperative adhesions, and extended surgery time. The specific objectives of anaesthesia are to maintain a stable cardiovascular and respiratory condition as well as the finest surgical field feasible throughout the procedure, during emergence from anaesthesia, and after recovery [4].

Changes in haemodynamic s due to laryngoscopy and endotracheal intubation are likely to persist during FESS. Various strategies have been applied to attenuate these unfavourable reflexes, which include deepening of general anaesthesia, topical airway anaesthesia by blocking the superior laryngeal nerve and recurrent laryngeal nerve, intravenous or transtracheal lidocaine, calcium channel blockers, beta blockers, opioids, barbiturates, benzodiazepines, and vasodilators [5].

Clonidine, an imidazole compound, is an alpha-2 adrenoreceptor agonist. It exerts a central sympatholytic effect by blocking the release of norepinephrine from both central and peripheral sympathetic nerve terminals, leading to a decrease in HR and blood pressure, thus

maintaining cardiovascular stability. In addition to its sympatholytic and antihypertensive effects, it also produces analgesia and sedation [6-8]. Previous studies have shown that premedication with oral Clonidine reduces intraoperative bleeding in FESS [9,10]. It is well absorbed orally with 100% bioavailability.

Ivabradine is the first member of a new group of drugs. It selectively inhibits the cardiac funny current channel, I(f), which modulates pacemaker activity in the sinoatrial node, providing pure HR reduction [11]. It reduces HR without altering haemodynamic s in unhealthy, compromised patients [12]. Though not fully effective, it minimises the effect of hypertension due to laryngoscopy and endotracheal intubation. These haemodynamic benefits extend during extubation and help maintain a stable haemodynamic status in the immediate postoperative period. Ivabradine is well absorbed orally from the gastrointestinal tract within 20-30 minutes, with peak plasma concentration attained by 60-90 minutes [13,14].

To date, no study has been conducted to compare the efficacy of oral Clonidine and oral Ivabradine in achieving stable haemodynamics and surgical conditions during FESS. The rationale of present study was to minimise perioperative stress response and provide a better surgical field without major haemodynamic fluctuations in patients undergoing FESS. Hence, present placebo-controlled study was conducted to evaluate the effects of oral Clonidine and oral Ivabradine on haemodynamic parameters (HR, MAP), intraoperative bleeding, amount of blood loss, postoperative sedation score, Visual Analogue Score (VAS), time to first rescue analgesic, and any adverse effects.

MATERIALS AND METHODS

The present randomised, double-blind study was conducted on 90 ASA physical status I and II adult patients (aged 18-60 years) undergoing FESS under general anaesthesia conducted in the Department of Anaesthesiology and Intensive care at Rajindra Hospital, Government Medical College, Patiala, Punjab, India from April 2021 to December 2022. The study was approved by the Institutional Ethics Committee (EC/NEW/INST/2020/997/9363 dated 15/04/21), and written informed consent was obtained from each patient. The patient and attending anaesthetist involved in the procedure were blinded to the drugs.

The primary measure of the study was to compare haemodynamic parameters, including HR and MAP, between the groups. The secondary measures included comparing the quality of the intraoperative surgical field using the category scale score, comparing postoperative sedation using the Ramsay sedation score, comparing the Visual Analogue Score (VAS), comparing the time to first rescue analgesic demand in the postoperative period, and monitoring for any adverse effects and complications.

Sample size calculation: The sample size was calculated based on a success rate of 95%, an α margin of 5%, and an error of 0.05. The calculated sample size was 25 patients in each group, but authors included 30 patients in each group to increase the power of the study. The sample size estimation was based on the observations of previous studies [13,14].

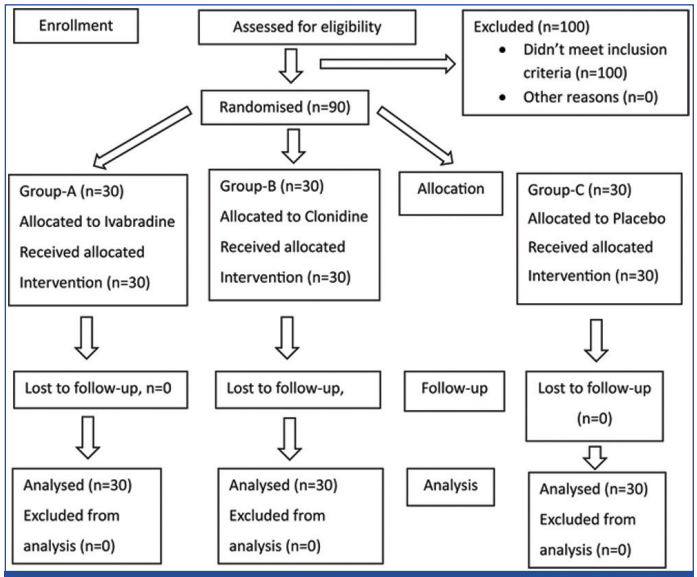
Inclusion and Exclusion criteria: All the patients aged between 18- 60 years who were undergoing FESS under general anaesthesia at study Institute and were willing to participate were included in the study.

Patients who refused to participate, had uncontrolled hypertension, diabetes mellitus, chronic respiratory, hepatic or renal problems, a history of chest pain, palpitations, syncope, baseline HR less than 60 beats per minute, ECG abnormalities, any coagulation abnormality, or were on beta-blockers, sedatives, or hypnotics were excluded from the study.

Study Procedure

During the preanaesthetic check-up, a detailed history and examination of each patient were carried out to optimise them before surgery. All relevant investigations, including complete blood count, serum electrolytes, blood urea, serum creatinine, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), viral markers, blood sugars, Bleeding Time (BT)/Clotting Time (CT), chest X-ray, and Electrocardiogram (ECG), were found to be within normal limits. Patients were familiarised with the VAS score (0- No pain, 10- worst pain) a day before surgery and were asked to grade their pain on this scale in the postoperative period.

Patients were advised to fast overnight. On the day of surgery, patients who met the inclusion criteria were randomly allocated to three groups using the closed envelope method: Group A received oral Ivabradine 5 mg [15], Group B received oral Clonidine 0.2 mg [16], and Group C received an oral placebo with sips of water two hours before surgery. The CONSORT (Consolidated Standards of Reporting Trails) diagram [Table/Fig-1] illustrates the allocation.



[Table/Fig-1]: CONSORT diagram.

Haemodynamic parameters were recorded at one hour and two hours after administering the study drugs. After confirming the fasting status and obtaining written informed consent, the patient was transferred to the operating room. Intravenous access was established using an 18 G cannula, and a Ringer lactate infusion was initiated. Baseline haemodynamic parameters {heart rate, blood pressure, Saturation of Peripheral Oxygen (SpO_2) , and $EtCO_2$} were recorded after attaching routine monitors {ECG, Non Invasive Blood Pressure (NIBP), pulse oximetry, temperature probe, capnography}.

Premedication was administered with Inj. Glycopyrrolate 0.2 mg and Inj. Butorphanol 1 mg. Following preoxygenation with 100% O_2 for three minutes, anaesthesia was induced with Inj. Propofol 2 mg/kg intravenously administered slowly, and ventilation was confirmed. Intubation was facilitated with Inj. Vecuronium 0.1 mg/kg, and laryngoscopy and tracheal intubation were performed. Anaesthesia was maintained using a mixture of 50% O_2 and 50% N_2O, titrated Isoflurane based on blood pressure, and Vecuronium 0.02 mg/kg administered every 25 minutes. Ventilation was adjusted to maintain normocapnia (End Tidal Carbon Dioxide ($EtCO_2$) 40±5 mmHg). The quality of the intraoperative endoscopic surgical field was graded using the system proposed by Fromme GA et al., and Boezaart AP et al., [17,18].

Grade Assessment:

0 - No bleeding (Cadaveric conditions)

1 - Slight bleeding; no suctioning required.

2 - Slight bleeding; occasional suctioning required.

3 - Slight bleeding; frequent suctioning required. Bleeding threatens the surgical field a few seconds after suction is removed.

4 - Moderate bleeding; frequent suctioning required, and bleeding threatens the surgical field directly after suction is removed.

5 - Severe bleeding; constant suctioning required. Bleeding appears faster than can be removed by suction. The surgical field is severely threatened, and surgery is usually not possible.

To maintain sufficient hypotension for a bloodless surgical field, the MAP was kept around 70 mmHg. Direct control of MAP was achieved by adjusting the inspired concentration of isoflurane or administering 50 mcg increments of fentanyl. Any incidence of hypotension (MAP <20%) was treated with a fluid bolus of Normal Saline (NS)-250-300 mL, and bradycardia (heart rate <50/min) was treated with atropine 0.6 mg. At the end of surgery, blood loss was estimated, and the patient was reversed with Inj. Neostigmine 0.05 mg/kg i.v. and Inj. Glycopyrrolate 0.01 mg/kg. Extubation was performed when the patient was fully awake, and haemodynamic parameters were recorded.

Heart Rate (HR) and MAP were recorded at the following time points: baseline in the morning on the day of surgery before administering the test drugs, one and two hours after giving the study drugs, immediately prior to induction, one minute and five minutes after intubation, and thereafter every 10 minutes during the intraoperative period. HR and MAP were also recorded one minute and five minutes after extubation.

The patient was transferred to the Post Anaesthesia Care Unit (PACU) and monitored for any incidence of adverse effects such as nausea, vomiting, hypotension, or bradycardia. Each adverse effect was managed appropriately. Sedation was assessed using the Ramsay sedation score, ranging from one to six, every 30 minutes for four hours.

Parameters	Group A	Group B	Group C	p-value
Mean age (years)	33.87±12.84	35.03±12.93	40.9±14.46	0.100
Gender				
Female	13 (43.33%)	8 (26.67%)	10 (33.33%)	0.397
Male	17 (56.67%)	22 (73.33%)	20 (66.67%)	
Mean weight (kg)	60.5±8.91	57.83±5.66	57.9±5.42	0.234
ASA PS				
I	19 (63.33%)	21 (70%)	27 (90%)	0.056
II	11 (36.67%)	9 (30%)	3 (10%)	
Type of surgery				
Ethmoidal polyp	17 (56.67%)	23 (83.3%)	20 (66.66%)	0.246
AC polyp	8 (26.67%)	5 (13.3%)	6 (20%)	
Mucormycosis	5 (16.6%)	2 (3.3%)	4 (13.33%)	
Duration of surgery (min)	88.67 ±4.29	88.8±4.29	88.03±3.93	0.750 F value 0.289

[Table/Fig-2]: Demographic and clinical profile of patients.
Gender and ASA Physical status- Kruskal wallis H test
Type of surgery- Chi-square test
Duration of surgery- ANOVA

STATISTICAL ANALYSIS

Descriptive statistics were conducted for all the data, and appropriate comparison tests were performed. The results were reported in terms of Mean±SD and percentages. ANOVA (Analysis of Variance, F=ANOVA value), Tukey's Post-hoc test, and Kruskal-wallis H test were utilised to determine the significance of study parameters on a continuous scale among the three groups (intergroup analysis) for metric parameters. Pearson's Chi-square test was employed for categorical scale comparisons between the groups. Statistical significance was defined as a p-value <0.05, and a p-value <0.001 was considered statistically highly significant. A p-value >0.05 indicated no statistical significance. The data were analysed using SPSS version 22.0 and Microsoft Excel. The observations are presented in tables and figures.

RESULTS

Patients in all three groups were similar with respect to demographic data, type, and duration of surgery [Table/Fig-2]. Baseline haemodynamic parameters, including HR, blood pressure, SpO_2, and $EtCO_2$, were comparable among all the groups [Table/Fig-3]. HR was significantly lower in both Group A and B compared to Group C at all time intervals, and the difference was highly significant (p<0.001). The mean HR in Group A and Group B was comparable at all time intervals, with no statistically significant difference as the p-values were >0.05 [Table/Fig-4]. ANOVA revealed highly significant variability in HR between and within the groups (F=63.358) [Table/Fig-5]. Furthermore, Tukey's post-hoc analysis showed no significant difference in HR between Group A and B (p=0.566), but there was a statistically highly significant difference in HR when Group A and B were compared with Group C (p=0.001) [Table/Fig-6].

All three groups had comparable MAP at baseline. MAP was significantly lower in Group A and B compared to Group C after one hour of administering the study drugs. The MAP in Group B was significantly lower than in Group A (p<0.05). However, at induction, the MAP in both groups was comparable, as the p-value was >0.05. After 30 minutes of intubation onwards, Group B exhibited significantly lower MAP compared to Group A (p<0.05). Between Group A and C, MAP was lower in Group A, and the difference was highly significant (p<0.001) until induction. At one minute and five minutes after intubation, there was significantly lower MAP in Group A (p<0.05). However, after 10 minutes, the difference was not significant (p>0.05) at all time intervals during the intraoperative period. At extubation, the MAP in Group A was significantly lower, with a p-value <0.05 at one minute after extubation. Compared

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
HR baseline	86.43±14.24	89.90±13.42	89.53±14.73	0.336 (0.970)	0.411 (0.829)	0.920 (0.101)	0.582 (0.544)
SBP baseline	118.93±14.02	124.97±11.39	123.37±10.64	0.073 (1.829)	0.173 (0.1379)	0.576 (0.562)	0.142 (2.000)
DBP baseline	75.97±10.07	79.13±7.18	80.20±7.77	0.166 (1.403)	0.073 (1.823)	0.583 (0.552)	0.135 (2.046)
MAP baseline	90.15±11.12	93.96±8.76	94.10±8.80	0.146 (1.473)	0.132 (1.526)	0.950 (0.063)	0.203 (1.626)
SpO_2	97.93± 0.58	97.90± 0.55	97.93± 0.52	0.820 (0.228)	1.000 (0.000)	0.810 (0.242)	0.964 (0.037)
$EtCO_2$	38.37± 0.85	38.43± 0.97	38.47± 0.94	0.778 (0.283)	0.667 (0.433)	0.893 (0.135)	0.912 (0.092)

[Table/Fig-3]: Baseline HR, SBP, DBP, MAP, SpO_2, $EtCO_2$.
Between the groups- Post-Hoc Test
Overall-ANOVA (F-value)

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
Baseline	86.43±14.24	89.90±13.42	89.53±14.73	0.336 (0.970)	0.411 (0.829)	0.920 (0.101)	0.582 (0.544)
1 hour after giving study drug	74.87±8.02	78.60±7.79	92.17±12.85	0.072 (1.830)	0.001* (6.256)	0.001* (4.945)	0.001* (25.713)

2 hours after giving study drug	74.93±8.80	78.77±8.05	93.87±12.22	0.084 (0.1.760)	0.001* (6.886)	0.001* (5.651)	0.001* (30.924)
At Induction	78.97±8.57	80.87±8.57	102.47±11.52	0.394 (0.859)	0.001* (8.963)	0.001* (8.238)	0.001* (54.841)
1 min after intubation	75.47±7.97	78.90±8.49	98.07±10.00	0.112 (1.615)	0.001* (9.681)	0.001* (8.006)	0.001* (56.678)
5 min after intubation	72.73±6.24	76.07±7.61	95.13±8.94	0.069 (1.855)	0.001* (11.259)	0.001* (8.897)	0.001* (74.414)
10 minutes	71.87±5.78	74.37±7.12	93.63±8.91	0.141 (1.493)	0.001* (11.223)	0.001* (9.253)	0.001* (78.097)
20 minutes	70.93±5.84	73.97±6.59	93.00±8.48	0.064 (1.887)	0.001* (11.740)	0.001* (9.704)	0.001* (86.141)
30 minutes	70.67±5.38	72.93±6.53	92.53±7.70	0.148 (1.467)	0.001* (12.747)	0.001* (10.627)	0.001* (99.352)
40 minutes	73.00±13.61	72.03±6.49	92.57±8.05	0.727 (0.351)	0.001* (6.777)	0.001* (10.877)	0.001* (41.343)
50 minutes	72.13±10.04	71.70±6.36	92.90±8.62	0.842 (0.22)	0.001* (8.596)	0.001* (10.841)	0.001* (61.285)
60 minutes	71.70±9.06	71.63±5.67	93.63±8.43	0.973 (0.034)	0.001* (9.708)	0.001* (11.863)	0.001* (78.115)
70 minutes	73.03±8.35	73.27±6.31	95.07±9.42	0.903 (0.122)	0.001 * (9.585)	0.001* (10.532)	0.001* (72.675)
80 minutes	75.10±7.92	75.03±6.16	96.10±9.66	0.971 (0.036)	0.001* (9.206)	0.001* (10.067)	0.001* (68.384)
90 minutes	76.43±8.59	76.03±7.00	96.57±8.80	0.844 (0.198)	0.001* (8.970)	0.001* (10.002)	0.001* (61.974)

[Table/Fig-4]: Mean Heart Rate (HR) (Beats/Min).
Between the groups- Post-Hoc Test
Overall-ANOVA (F-value)
p<0.001* Statistically highly significant

Mean Heart Rate (HR)	Sum of squares	df	Mean square	F	p-value
Between groups	7230.325	2	3615.163	63.358	0.001*
Within groups	4964.180	87	57.060		
Total	12194.505	89			

[Table/Fig-5]: ANOVA on mean Heart Rate (HR).
p<0.001* Statistically highly significant

VAR (I)	VAR (J)	Mean difference (I-J)	Std. Error	95% Confidence interval		p-value
				Lower bound	Upper bound	
Group A	Group B	-1.992	1.950	-6.643	2.659	0.566
	Group C	-19.931	1.950	-24.582	-15.280	0.001*
Group B	Group A	1.992	1.950	-2.659	6.643	0.566
	Group C	-17.939	1.950	-22.590	-13.289	0.001*
Group C	Group A	19.931	1.950	15.280	24.582	0.001*
	Group B	17.939	1.950	13.289	22.590	0.001*

[Table/Fig-6]: Tukey Post-Hoc test on mean Heart Rate (HR).
p<0.001* Statistically highly significant

to Group C, the MAP in Group B was significantly lower after one hour of administering the study drugs, and the difference was highly significant (p<0.001) at all time intervals [Table/Fig-7]. Analysis of variance revealed highly significant variability in MAP between and within the groups (F=11.136) [Table/Fig-8]. Furthermore, Tukey's post-hoc analysis showed no significant difference in MAP between Group A and B (p=0.064), but there was a statistically significant difference in MAP between Group A and C (p=0.044) and a statistically highly significant difference between Group B and C (p<0.001) [Table/Fig-9].

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
Baseline	90.15±11.12	93.96±8.76	94.10±8.80	0.146 (1.473)	0.132 (1.526)	0.950 (0.063)	0.203 (1.626)
1 hour after giving study drug	81.17±7.31	74.30±10.80	91.00±7.62	0.005* (2.886)	0.001** (5.098)	0.001** (6.922)	0.001** (27.794)
2 hours after giving study drug	81.27±7.71	74.43±13.92	90.23±7.70	0.022* (2.352)	0.001** (4.507)	0.001** (5.439)	0.001** (18.079)
At Induction	88.91±12.49	84.79±7.78	103.03±8.68	0.130 (1.535)	0.001** (5.084)	0.001** (8.575)	0.001** (28.223)
1 min after intubation	89.26±13.59	84.84±8.18	98.67±8.16	0.132 (1.526)	0.002* (3.251)	0.001** (6.555)	0.001** (14.112)
5 min after intubation	89.09±13.61	84.76±8.00	95.93±8.08	0.138 (1.503)	0.021* (2.370)	0.001 ** (5.386)	0.001** (9.094)
10 minutes	88.13±14.26	83.30±8.26	94.03±8.22	0.113 (1.607)	0.054 (1.964)	0.001** (5.046)	0.001** (7.673)
20 minutes	86.84±13.61	81.79±8.53	92.40±8.32	0.090 (1.722)	0.061 (1.909)	0.001** (4.878)	0.001** (7.748)
30 minutes	86.81±11.84	80.08±8.79	90.70±8.66	0.015* (2.499)	0.152 (1.453)	0.001** (4.713)	0.001** (8.882)
40 minutes	85.67±11.63	78.72±8.78	89.40±8.94	0.010* (2.650)	0.169 (1.394)	0.001** (4.666)	0.001** (9.036)
50 minutes	84.45±11.44	77.57±8.46	87.90±8.91	0.008* (2.751)	0.198 (1.302)	0.001** (4.606)	0.001** (8.836)
60 minutes	83.48±10.72	76.70±8.20	86.63±8.88	0.006* (2.847)	0.219 (1.242)	0.001** (4.505)	0.001** (8.891)
70 minutes	82.55±10.32	76.11±7.78	85.30±8.83	0.007* (2.784)	0.273 (1.107)	0.001** (4.276)	0.001** (8.167)
80 minutes	81.37±9.93	74.80±7.81	83.53±8.90	0.006* (2.836)	0.377(0.890)	0.001** (4.040)	0.001** (7.794)
90 minutes	80.60±9.88	74.07±8.22	82.67±9.08	0.007* (2.784)	0.403 (0.843)	0.001** (3.846)	0.001** (7.322)

[Table/Fig-7]: Mean Arterial Pressure (MAP) (mm of Hg).
Between the groups- Post-hoc test
Overall-ANOVA (F-value); p<0.05* Statistically significant; p<0.001** Statistically highly significant

Mean Arterial Pressure (MAP)	Sum of squares	df	Mean square	F	p-value
Between groups	1826.689	2	913.344	11.136	0.001*
Within groups	7135.800	87	82.021		
Total	8962.489	89			

[Table/Fig-8]: ANOVA on Mean Arterial Pressure (MAP).
p<0.001* Statistically highly significant

VAR (I)	VAR (J)	Mean difference (I-J)	Std. Error	95% Confidence interval		p-value
				Lower bound	Upper bound	
Group A	Group B	5.333	2.338	-0.242	10.909	0.064
	Group C	-5.700	2.338	-11.276	-0.124	0.044*
Group B	Group A	-5.333	2.338	-10.909	0.242	0.064
	Group C	-11.033	2.338	-16.609	-5.458	0.001**
Group C	Group A	5.700	2.338	0.124	11.276	0.044*
	Group B	11.033	2.338	5.458	16.609	0.001**

[Table/Fig-9]: Tukey Post-hoc test (Mean Arterial Pressure).
p<0.05* Statistically significant; p<0.001** Statistically highly significant

Group B had a significantly lower bleeding category score compared to Group A and C, with the difference being significant from 30 minutes onwards (p<0.05). There was no statistically significant difference noted between Group A and C [Table/Fig-10] [17,18].

Postoperative sedation score was significantly higher in Group B compared to Group A and C, with the difference being statistically significant (p<0.05) until 90 minutes. Both Group A and C showed comparable postoperative sedation scores at all time intervals (p>0.05) [Table/Fig-11].

Group B had a significantly lower postoperative VAS score compared to Group A and C, with the difference being statistically significant from 60 minutes onwards until 180 minutes in the postoperative period. Group A and C showed comparable VAS scores at all time intervals (p>0.05) [Table/Fig-12].

The time to first rescue analgesic demand was longest in Group B, with the difference being statistically significant (p<0.05) compared to both Group A and C. Additionally, Group B had a significantly lower amount of blood loss (p<0.05) compared to both Group A and C [Table/Fig-13].

There was no statistically significant difference among the three groups regarding postoperative complications, including nausea, vomiting, shivering, dry mouth, hypotension, and bradycardia (p>0.05). Bradycardia was observed only in the Ivabradine group but was statistically insignificant. No other adverse effects were noted [Table/Fig-14].

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
10 minutes	2.70±0.50	2.65±0.43	2.77±0.47	0.171 (1.387)	0.425 (0.803)	0.567 (0.576)	0.382 (0.973)
20 minutes	2.63±0.51	2.53±0.43	2.88±0.49	0.441 (0.776)	0.367 (1.620)	0.05* (1.720)	0.170 (1.80)
30 minutes	2.57±0.49	2.37±0.50	2.60±0.50	0.05* (1.558)	0.073 (1.829)	0.004* (2.58)	0.151 (1.930)
40 minutes	3.08±1.65	2.33±0.48	2.73±0.45	0.020* (2.390)	0.267 (1.120)	0.002* (3.333)	0.022* (4.014)
50 minutes	2.47±0.57	2.20±0.41	2.60±0.50	0.042* (2.082)	0.339 (0.963)	0.001** (3.406)	0.008* (5.043)
60 minutes	2.43±0.50	2.17±0.38	2.47±0.51	0.024* (2.316)	0.799 (0.255)	0.012* (2.594)	0.028* (3.714)
70 minutes	2.40±0.51	2.07±0.25	2.53±0.50	0.002* (4.506)	0.309 (1.027)	0.001** (3.264)	0.000** (9.121)
80 minutes	2.33±0.49	2.10±0.31	2.37±0.48	0.014* (2.530)	0.791 (0.266)	0.028* (2.249)	0.039* (3.373)
90 minutes	2.17±0.43	1.97±0.32	2.23±0.38	0.008* (2.725)	0.527 (0.637)	0.031* (2.209)	0.021* (4.021)

[Table/Fig-10]: Bleeding Category Score (Fromme GA and Boezaart AP scale) [17,18].
Between the groups- Post-hoc test
Overall-ANOVA (F-value)
p<0.05* Statistically significant
p<0.001** Statistically highly significant

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
M0	3.60±0.62	3.93±0.25	3.67±0.61	0.009* (2.720)	0.676 (0.421)	0.030* (2.222)	0.037* (3.421)
M30	3.47±0.51	3.87±0.35	3.60±0.50	0.001** (3.568)	0.309 (1.027)	0.019* (2.408)	0.004* (5.971)
M60	2.90±0.40	3.10±0.31	2.73±0.52	0.034* (2.169)	0.171 (1.387)	0.002* (3.327)	0.004* (5.762)
M90	2.23±0.50	2.53±0.51	2.20±0.48	0.025* (2.298)	0.795 (0.261)	0.012* (2.603)	0.021* (4.066)
M120	1.63±0.56	1.67±0.48	1.57±0.57	0.804 (0.249)	0.648 (0.459)	0.464 (0.737)	0.764 (0.271)
M150	1.53±0.51	1.60±0.50	1.50±0.51	0.610 (0.513)	0.800 (0.254)	0.445 (0.769)	0.738 (0.305)
M180	1.47±0.51	1.50±0.51	1.43±0.50	0.800 (0.254)	0.799 (0.255)	0.612 (0.510)	0.878 (0.130)
M210	1.40±0.50	1.43±0.50	1.37±0.49	0.798 (0.258)	0.795 (0.261)	0.605 (0.519)	0.874 (0.135)
M240	1.37±0.49	1.40±0.50	1.33±0.48	0.795 (0.261)	0.791 (0.266)	0.599 (0.528)	0.870 (0.139)

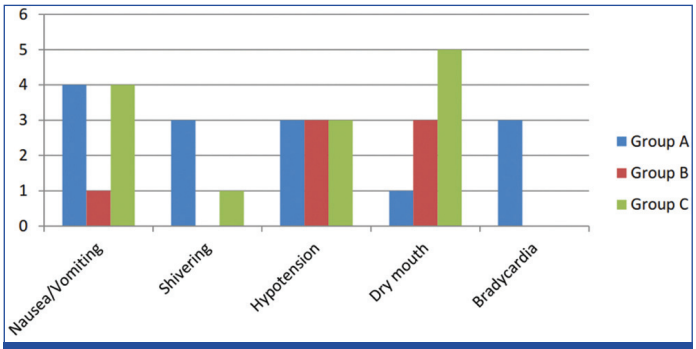
[Table/Fig-11]: Postoperative sedation score (1-6).
Between the groups- Post-hoc test
Overall-ANOVA (F-value)
p<0.05* Statistically significant
p<0.001** Statistically highly significant

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
M0	0.27±0.45	0.23±0.18	0.23±0.43	0.821 (0.313)	0.770 (0.293)	0.816 (0.343)	0.038* (3.407)
M30	0.50±0.78	0.45±0.38	0.60±0.77	0.392 (0.112)	0.618 (0.501)	0.183 (1.765)	0.036* (3.457)
M60	1.13±0.78	0.77±0.43	1.20±0.81	0.027* (2.263)	0.745 (0.327)	0.012* (2.600)	0.037* (3.413)
M90	1.17±0.46	0.83±0.46	1.20±0.48	0.007* (2.800)	0.786 (0.273)	0.004* (3.003)	0.005* (5.608)
M120	1.67±0.71	1.17±0.65	1.73±0.64	0.006* (2.847)	0.704 (0.382)	0.001** (3.409)	0.002* (6.469)
M150	1.93±0.52	1.40±0.50	1.97±0.49	0.001** (4.053)	0.799 (0.255)	0.001** (4.441)	0.001** (11.977)
M180	2.47±0.51	2.17±0.70	2.50±0.51	0.062 (1.902)	0.800 (0.254)	0.039* (4.441)	0.054 (3.019)
M210	1.90±0.99	1.83±0.87	1.93±1.01	0.784 (0.276)	0.898 (0.128)	0.684 (0.409)	0.920 (0.084)
M240	2.00±0.98	1.90±1.03	2.03±1.00	0.702 (0.385)	0.897 (0.130)	0.613 (0.509)	0.867 (0.413)

[Table/Fig-12]: Postoperative VAS score (0-10).
Between the groups- Post-hoc test
Overall-ANOVA (F-value)
p<0.05* Statistically significant
p<0.001** Statistically highly significant

Time interval	Group A (N=30)	Group B (N=30)	Group C (N=30)	Group A vs Group B	Group A vs Group C	Group B vs Group C	p-value
Time to first rescue analgesic demand	135.00±12.70	151.00±13.98	132.00±12.91	0.012* (2.609)	0.763 (0.302)	0.025* (2.303)	0.0018* (4.184)
Blood Loss	136.17±8.27	121.17±9.07	140.83±9.96	0.010* (2.678)	0.888 (0.141)	0.025* (2.305)	0.020* (4.098)

[Table/Fig-13]: Time to rescue analgesic demand and blood loss.
Between the groups- Post-hoc test
Overall-ANOVA (F-value)
p<0.05* Statistically significant



[Table/Fig-14]: Postoperative complications.

DISCUSSION

There is significant haemodynamic stress during laryngoscopy and endotracheal intubation, as both acts as mechanical stimuli that activate the sympathoadrenal axis-mediated reflex. There is a significant association between the incidence of myocardial infarction and tracheal intubation or extubation. These haemodynamic fluctuations are likely to persist in Functional Endoscopic Sinus Surgery (FESS). Various pharmacological agents have been tried to attenuate this response with varying success. Additionally, during endoscopic sinus surgery, bleeding can severely compromise an already restricted endo view, increasing the likelihood of complications when the visualisation of local anatomy is obscured. In situations of poor visibility, more tissue damage is likely to occur, which can affect the development of postoperative adhesions and the success or failure of surgery [19].

The primary finding of the present study was that both groups A and B had significantly lower Heart Rate (HR) compared to Group C at all time intervals during the surgery. Patients premedicated with either Clonidine or Ivabradine had significantly lower HR than those pretreated with placebo (p-value <0.05). There was no statistically significant difference (p>0.05) in the mean HR between Clonidine and Ivabradine at any point in time, reflecting that both Clonidine and Ivabradine are comparable in blunting the tachycardia due to any kind of surgical stress. These findings were consistent with the results of studies conducted by Raghuram CG et al., Mathur V et al., Ibrahim AN and Atallah RY, on Ivabradine; and by Singh S and Arora K, Jehangir A et al., and Rani R and Nesargi SS, on Clonidine [Table/Fig-15] [6,13-16,20].

Studies	Year	Patient number	Groups	Dose	Timings	Heart Rate (HR) (Range)	MAP (Range)	Outcome
Singh S and Arora K [6]	2011	50 (25 each group)	Group I (clonidine) Group II (vitamin c)	150 µgm po 100 mg po	90 min before induction	79.28±9.50 to 85.84±10.12 83.80±12.76 to 100.04±12.16	87.61±8.36 to 102.41±10.35 96.99±6.37 to 114.8±14.08	Group I (clonidine) has better control on Haemodynamic stress response than Group II (vitamin c)
Rani R and Nesargi SS, [20]	2015	50 (25 each group)	Group A (clonidine) Group B (Tab Ranitidine)	3 µgm/kg po 150 mg po	90 min before induction	72.68±6.30 to 92.80±9.11 82.04±9.60 to 113.96±10.20	80.39±7.09 to 98.51±8.23 90.44±5.62 to 121.46±10.09	Group A (clonidine) has better control on haemodynamic stress response than Group B (Tab Ranitidine)
Jehangir A et al., [16]	2018	100 (50 each group)	Group A (clonidine) Group B (5 mL water)	4 µgm/kg po	60 min before induction	79.65±5.95 to92.32±4.92 71.38±3.10 to 83.3±8.73	91.77±5.62 to 102.16±7.17 75.52±6.59 to 90.76±9.00	Group A (clonidine) has better control on Haemodynamic stress response than Group B (Water)
Jabalameli M et al., [9]	2005	113 GP-I 52 GP-II 61	Group I Clonidine Group II Placebo	5 µgm/kg po	90 min before operation	82±7 80±9	88±8 92±8	Group I (clonidine) has better control on Haemodynamic stress response than Group II (Placebo)

Raghuram et al., [13]	2014	50 (25 each group)	Group I Ivabradine Group II placebo	5 mg	6.00 p.m previous day and 1 hr before surgery	73.16 to 84.72 (Pulse rate) 110.84 to 119.92 (Pulse rate)	89.92 to 96.67 99.96 to 108.43	Group I (Ivabradine) has better control on Haemodynamic stress response than Group II (Placebo)
Ibrahim AN et al., [15]	2016	50 (25 each group)	Group I Ivabradine Group P Propranolol	5 mg 10 mg	Previous evening and 1 hr before induction	73.68±1.11 to 85.08.82±2.10 79.66±1.37 to 85.68±1.46	91.32±0.90 to 93.92±0.57 91.20±1.08 to 95.36±0.99	Group I (Ivabradine) has better control on Haemodynamic stress response than Group II (Propranolol)
Mathur V et al., [14]	2019	90 (30 each group)	Group I (Ivabradine) Group II (Metoprolol Group III Placebo	5 mg 50 mg	120 min before induction	66.43±7.08 to105.20±18.43 61.70±7.34 to103.40±6.89 72.57±5.99 to 125.87±6.50	66.27±3.92 to 107.33±3.91 63.93 ±4.52 to 105.73±2.82 77.97±5.36 to 114.40±3.95	Group II (Metoprolol) has better control on Haemodynamic stress response than Group I (Ivabradine) and Group III (Placebo)
Present study	2023	90 (30 each group)	Group A (Ivabradine) Group B (Clonidine) Group C (Placebo)	5 mg 0.2 mg	120 min before induction	70.67±5.38 to 86.43±14.24 71.63±5.67 to 89.90±13.42 89.53±14.73 to102.47±11.52	80.60±9.88 to 90.15±11.12 74.07±8.22 to 93.96±8.76 82.67±9.08 to 103.03±8.68	Group A (Ivabradine) and Group B (clonidine) has better control on Haemodynamic stress response than Group C (Placebo)

[Table/Fig-15]: Comparison between various studies.[6,9,13-16,20].

The baseline values of Mean Arterial Pressure (MAP) were comparable in all three groups (p>0.05). Both the Clonidine and Ivabradine groups showed lower MAP compared to the placebo group. The maximum reduction in MAP was seen in Group B (Clonidine). Compared to placebo, MAP was significantly lower with Clonidine premedication at all time intervals (p<0.001). Patients premedicated with Ivabradine showed significantly lower MAP compared to those given placebo in the preoperative period, at intubation, and at extubation. MAP between these two groups was comparable in the intraoperative period after 10 minutes post-intubation, indicating that Ivabradine successfully blunted the cardiovascular stress response. In the preoperative period, MAP in the Clonidine group was significantly lower than in the Ivabradine group. However, at induction and intubation, MAP in both groups was comparable, demonstrating that both drugs effectively attenuated the haemodynamic stress response to laryngoscopy and intubation. After 30 minutes of intubation, the Clonidine group showed significantly lower MAP than Ivabradine (p<0.05), and this difference extended until extubation. Hence, the study found that overall, better control of MAP was seen with Clonidine in the intraoperative period compared to Ivabradine.

Similar effects of oral Clonidine on MAP were shown in studies conducted by Singh S et al., Jabalameli M et al., Jehangir A et al., and Rani R and Nesargi SS, [6,9,16,20]. The finding of a decrease in MAP following premedication with oral Ivabradine was also corroborated by studies conducted by Raghuram CG et al., and Ibrahim AN and Atallah RY, [13,15]. Raghuram CG et al., found that Ivabradine 5 mg given orally was an extremely useful drug to prevent abnormal increases in heart rate but had a lesser effect on blood pressure compared to beta blockers in terms of MAP [Table/Fig-15] [6,9,13,15,16,20].

The scores of the bleeding category scale for the quality of the surgical field varied between 2-3 at most times during the intraoperative period in all three groups. A statistically significant difference was noted in Group B (Clonidine), with significantly lower scores compared to Group A and C. When comparing the category score between Group A and C, Group A (Ivabradine) showed lower scores at most time intervals compared to placebo, but there was no significant difference. Additionally, blood loss (in mL) was significantly lower in the Clonidine group compared to both the Ivabradine and control groups. The better quality of the surgical field in the Clonidine group was attributed to lower intraoperative MAP and reduced blood loss due to diminished sympathetic outflow through alpha-2 adrenoreceptor stimulation. Similar results were found in studies conducted by Jabalameli M et al., and Marchal JM et al., where they concluded that Clonidine premedication was effective in reducing bleeding in endoscopic sinus surgery compared to placebo. They also postulated that reducing MAP during general anaesthesia could minimise intraoperative bleeding [9,10].

In the present study, the postoperative sedation score was assessed using the Ramsay Sedation Score every half hour for four hours. Statistical evaluation among the groups showed that patients in the Clonidine group were more sedated but still arousable compared to patients in the other two groups, with significantly higher sedation scores until 90 minutes. Clonidine produces arousable sedation through its action on the locus coeruleus nucleus without causing respiratory depression. None of the patients in present study in the Clonidine group experienced postoperative respiratory depression. These results are consistent with the findings of a prospective randomised study on the efficacy of Clonidine in attenuating the haemodynamic response conducted by Acharya N and Routray D, where they found significantly higher sedation scores in the Clonidine group compared to the placebo group [21].

Pain intensity was assessed every half hour for four hours in the postoperative period using a 10 cm Visual Analogue Scale (VAS). Group B had significantly lower postoperative VAS scores compared to Group A and C, with the difference being statistically significant from 60 minutes onwards until 180 minutes in the postoperative period. Group A and C showed comparable VAS scores at all time intervals (p>0.05). Additionally, the time to first rescue analgesic demand was significantly longer in the Clonidine group compared to both the other groups. These results are consistent with the findings of studies conducted by Singh S and Arora K, Praveen VA and Prabhu RK, and Mikawa K et al., [6,7,8].

There was no statistically significant difference in the occurrence of postoperative complications such as nausea, vomiting, shivering, hypotension, and bradycardia among the three groups. However, the occurrence of bradycardia, although statistically insignificant, was higher in the Ivabradine group. There was no incidence of shivering in the Clonidine group.

Limitation(s)

The study has certain limitations. Firstly, the grading system used in the study was based on broad guidelines, which might have been

insensitive to subtle variations in surgical field qualities. Additionally, there could have been interobserver variability due to the involvement of different surgeons in the cases.

CONCLUSION(S)

The present study concluded that both Ivabradine and Clonidine significantly attenuated tachycardia in response to cardiovascular stress and were effective in maintaining a lower Heart Rate (HR) than placebo throughout the intraoperative period. Both drugs effectively reduced hypertension caused by haemodynamic stress from laryngoscopy and intubation. However, Clonidine demonstrated significantly better control of Mean Arterial Pressure (MAP) than Ivabradine throughout the intraoperative period and at extubation. The Clonidine group also exhibited a better quality surgical field, with significantly lower average category scale scores compared to Ivabradine. Furthermore, the Clonidine group had significantly less estimated blood loss compared to the Ivabradine group. Postoperative VAS scores were significantly lower in the Clonidine group, and the time to first rescue analgesia was significantly longer in the Clonidine group compared to the Ivabradine group. The Clonidine group also had significantly higher postoperative sedation scores compared to the Ivabradine group. Both drugs did not show any significant side effects.

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