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Original research article

Comparative study of oral Ivabradine and oral Metoprolol as single dose preoperative agent for maintaining hemodynamic stability in oral and maxillofacial surgeries

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Abstract

Aim: To analyse and compare the effect of Single Dose oral Ivabradine and oral metoprolol as preoperative agent in maintaining hemodynamic stability in oral and maxillofacial surgeries.

Material and methods: This prospective, double blind, randomized, comparative, hospital-based study conducted in the Department of Anesthesiology, IMS & SUM Hospital medical college on 60 patients undergoing oral and maxillofacial surgery. Patients were randomly divided into 2 groups-30 patients in each group using chit and box method i.e. Group A-Tab Ivabradine (5 mg) given orally 2 hours before induction of anesthesia and Group B-Tab Metoprolol tartrate (50 mg) given orally 2 hours before induction of anaesthesia. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure levels were recorded i.e. at baseline, just after intubation, 1, 3, 5, 10, 15, 30, 45, 60, 90 minutes and just after extubation. Blood sugar level was recorded before intubation, just after intubation, at an interval of 1 hour intraoperatively and just after extubation.

Results: After comparing both the groups, SBP values at 1min, 3min, 5min, 10min, 15min, 30min, after extubation, were statistically significant. After comparing both groups MAP values at1 min, 3 min, 5 min, 10 min, 15 min, 30 min, 45 min and after extubation were statistically significant. Mean blood glucose just after extubation *in Group A was 112.68±6.31 mg/dl, in Group B was 110.00±5.23 mg/dl.*

Conclusion: Ivabradine was found to have better control than metoprolol in controlling the HR while metoprolol have better control on SBP, DBP and MAP. Blood glucose comparison between two groups shows that there was no significant difference. Ivabradine can be recommended in cases where beta blockers are contraindicated like in bronchial asthma.

Keywords: Oral Ivabradine, oral metoprolol, hemodynamic

Introduction

Tracheal and laryngeal tissue stimulation causes increase in both sympathetic and sympathoadrenal reflex activity results in hemodynamic stress [1]. Hemodynamic stress response manifest as increased heart rate, increased blood pressure, increased myocardial oxygen demand, onset of dysrhythmias and increased blood glucose levels[2].

Oral and maxillofacial (OMF) surgeries like facial deformity and misaligned jaws, tumors and cysts of the jaw, head and neck cancer, skin cancer and trauma surgery are associated with increased risk of bleeding from both incised soft tissues and bones due to the rich blood supply. Furthermore, due to limited access, poor visibility to isolate and ligate or cauterize vessels that otherwise would have been ligated or cauterized with ease adds to the problem of bleeding during surgery that frequently obscure the operating field. Hence bloodless field is an important prerequisite in OMF surgeries[3].

Choice of premedication and anesthetic techniques may influence this neurohormonal stress

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response by modulating pathophysiological pathways[4].Metoprolol is widely used β-blocker in clinical settings, as well as in various trials by both Intravenous (IV) and oral formulations[5].Metoprolol is known to control the heart rate and preferentially acts on beta-1 adreno receptors located on cardiac muscle. However this preferential effect is not absolute, as metoprolol at higher doses also inhibits beta-2 adrenoreceptors located in vascular and bronchial smooth muscles[6].

For patients who receive calcium channel-blocker therapy, beta-blockers can be used to decrease the HR if there is no contraindication to beta-blockers. Ivabradine is the first member of a new group of drugs and is selective inhibitor of I(f) channels (funny current channels). It reduces heart rate without jeopardizing hemodynamics. Drug can be used in hypertensives as well as in normotensives, diabetics, patients with bronchial asthma where beta blockers are contraindicated.[7] Ivabradine does not negatively affect coronary circulation or ventricular function, which is particularly important in patients with myocardial ischemia. Small randomized control studies have shown superiority of Ivabradine over other drugs in controlling HR.[5]

Due to conflicting literature, the present study was planned to compare the efficacy of oral Ivabradine and oral metoprolol in maintaining hemodynamic stability in oral and maxillofacial surgeries.

Material and methods

This prospective, double blind, randomized, comparative, hospital-based study was conducted in the Department of Anesthesiology, IMS & SUM Hospital, on 60 patients undergoing oral and maxillofacial surgery after institutional Ethical committee clearance from January 2019 to March 2020. Patients of age 18-60 years planned for Oral and maxillofacial surgeries, patient with ASA CLASSI/II and who gave written and informed consent were included in this study. Patients on beta-blockers, sedative, hypnotics, anti-hypertensive drugs, having diabetes mellitus, inability to communicate with the patient due to any reason, with history of respiratory diseases like asthma, chronic obstructive pulmonary disease, history of any other systemic disease, history of chest pain, palpitations, syncope or with baseline heart rate less than 60 beats per minute, ECG abnormalities and known allergy to study medications were excluded from the study.

Patients were randomly divided into 2 groups-30 patients in each group using chit and box method i.e. Group A-Tab Ivabradine (5 mg) given orally 2 hours before induction of anesthesia and Group B-Tab Metoprolol tartrate (50 mg) given orally 2 hours before induction of anesthesia in the pre operative room . Neither the investigator nor the patient was aware, which patient is allocated into which group and were unaware of the drug being administered as it was given by a person to patient who was not involved in the study. Investigator collected data in double blind manner. Complete pre-anesthetic check-up including age, sex, residence, occupation, clinical history, family history, past history, any allergic disorder was taken and routine pre-operative investigations were done. Patients were explained about the anesthetic technique and drug being administered including side effects of the drug.

Procedure

No sedative or hypnotic drug was given to patient before surgery. Upon arrival in operation theatre monitoring of heart rate, non-Invasive Blood Pressure, Spo2, ECG were done. An intravenous access by 18G i.v. cannula was taken on the non-dominant hand and ringer lactate was started. Inj. Glycopyrrolate 0.004 mg/kg, fentanyl 2 mcg/kg and ondansetron 4 mg i.v. given as premedication. Patients were pre oxygenated with 100% oxygen for 3 mins. Induction was done with injection propofol 1.5-2 mg/kg iv and tracheal intubation done with an appropriate sized endotracheal tube was done with injection succinylcholine 2 mg/kg i.v. Maintenance of anaesthesia was done with oxygen (40%), nitrous oxide (60%), isoflurane, injection vecuronium in dose of 0.1 mg/kg i.v. followed by 0.02 mg/kg i.v. Any event of hypotension was managed with a fluid bolus of normal saline 250-300 ml and injection mephentermine 6-12 mg i.v if needed. At the end of surgery residual neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg iv and injection glycopyrrolate 0.008 mg/kg i.v. and extubation was done after return of adequate respiratory effort.

Parameters Recorded

Parameters i.e. heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure levels were recorded i.e. at baseline, just after intubation, 1, 3, 5, 10, 15, 30, 45, 60, 90 minutes and just after extubation. Blood sugar level was recorded before intubation, just after intubation, at an interval of 1 hour intraoperatively and just after extubation.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of a statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). The difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p<0.05$.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Results: 70% of total cases were male and 30% were female. Mean age in group A was 43.50±11.81 years, in group B it was 42.10±11.05 and this difference was found statistically insignificant (p=0.62). Majority of cases had age >40 years. Baseline characteristics were comparable among both the groups as p>0.05 (table 1).

Table 2 shows the SBP (mm/hg) of both the groups at different times of observation. After comparing both the groups, SBP values at 1min, 3min, 5min, 10min, 15min, 30min, after extubation, were statistically significant.

After comparing both groups DBP values at 1min, 10min, 15min, 10min, 15min, 30 min, 45 min, 60 min and after extubation were statistically significant. DBP values were statistically insignificant at baseline, just after intubation, 3min, 5 min and 90 min (Table 3).

After comparing both groups MAP values at1 min, 3 min, 5 min, 10 min, 15 min, 30 min, 45 min and after extubation were statistically significant. MAP values were statistically insignificant at baseline, just after intubation, 60 min and 90 min (Table 4).

Heart rate (HR) values were statistically insignificant at baseline, just after intubation, 1min, 3 min, 5 min, 60 min and 90 min (table 5).

Mean blood glucose before intubation in Group A was 96.07±5.54 mg/dl, in Group B was 94.38±4.84 mg/dl. On applying t test, the difference was found statistically insignificant. (p=0.87). Mean blood glucose just after intubation in Group A was 110.30±5.25 mg/dl, in Group B was 108.70±4.60 mg/dl. On applying t test, the difference was found statistically insignificant (p=0.22). Mean blood glucose 1 hour intraoperatively in Group A was 102.97±5.39 mg/dl, in Group B was 102.00±4.45 mg/dl. On applying t test, the difference was found statistically insignificant. (p=0.45). Mean blood glucose just after extubation in Group A was 112.68±6.31 mg/dl, in Group B was 110.00±5.23 mg/dl. On applying t test, the difference was found statistically insignificant as shown in graph 1.

Table 1: Gender distribution among the study subjects

Gender	Group A		Group B		Chi Square	p value
	N	%	N	%		
Male	19	63.33	23	76.67	1.27	0.26
Female	11	36.67	7	23.33		
Age Group (in years)						
21-30	5	16.67	6	20	0.87	0.62
31-40	8	26.67	7	23.33		
>40	17	56.67	17	56.67		
ASA						
Grade I	16	53.33	15	50	0.18	0.81
Grade II	14	46.67	15	50		

Table 2: Comparison of SBP (Systolic blood pressure) among the groups

Interval	Group A		Group B		t test	p value
	Mean	SD	Mean	SD		
Baseline	126.50	6.74	127.80	8.08	0.46	0.50
Just After Intubation	149.13	6.31	145.40	8.31	3.84	0.06
1 Minute	140.20	6.38	131.43	7.92	14.49	<0.01*
3 Minute	135.53	5.74	125.77	7.69	22.51	<0.01*
5 Minute	130.67	5.10	121.97	6.31	12.76	0.001*
10 Minute	124.60	7.72	109.40	6.01	33.94	<0.01*
15 Minute	117.67	8.47	103.83	5.92	18.20	<0.01*
30 Minute	112.67	9.22	99.52	6.71	16.59	<0.01*
45 Minute	102.80	7.82	95.53	4.59	5.78	0.02*
60 Minute	96.13	6.34	94.70	5.06	0.23	0.63
90 Minute	94.40	6.59	94.80	5.35	0.02	0.89
After Extubation	152.80	7.33	145.47	8.22	13.31	0.01*

*:Statistically significant

Table 3: Comparison of DBP (Systolic blood pressure) among the groups

Interval	Group A		Group B		t test	p value
	Mean	SD	Mean	SD		
Baseline	78.47	5.24	80.48	6.52	1.72	0.19
Just After Intubation	92.43	4.84	91.82	3.08	1.84	0.11
1 Minute	87	6.59	83.58	7.14	4.42	0.03*
3 Minute	82	7.33	79.13	7.77	2.16	0.14
5 Minute	79.53	6.88	75.92	8.92	3.06	0.09
10 Minute	76.07	7.40	70.86	8.01	5.97	0.02*
15 Minute	73.27	7.55	67.38	8.63	6.13	0.001*

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

30 Minute	70.40	7.36	65.92	7.78	6.02	0.008*
45 Minute	71.52	7.25	65.47	7.58	7.64	0.006*
60 Minute	72.20	6.46	66.62	7.67	6.87	0.001*
90 Minute	72.73	7.46	67.93	57.01	5.05	0.02*
After Extubation	93.90	5.27	91.60	5.69	10.88	0.002*

*: Statistically significant

Table 4: Comparison of Mean arterial pressure (MAP) among the groups

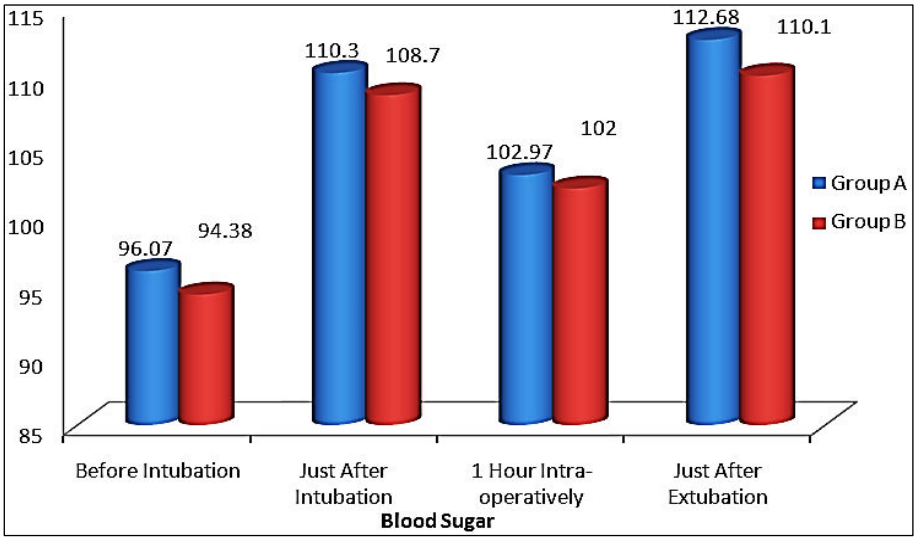
Interval	Group A		Group B		t test	p value
	Mean	SD	Mean	SD		
Baseline	94.42	5.24	95.38	6.42	1.60	0.21
Just After Intubation	111.32	4.84	110.08	3.27	1.77	0.19
1 Minute	104.73	5.11	99.52	6.91	11.04	0.002*
3 Minute	99.84	5.43	94.67	6.62	10.92	0.002*
5 Minute	96.57	5.22	91.28	7.94	9.31	0.003*
10 Minute	92.24	5.87	83.71	7.48	24.19	<0.01*
15 Minute	88.06	6.13	79.52	10.77	14.27	<0.01*
30 Minute	84.49	6.54	77.13	8.27	9.27	0.004*
45 Minute	81.51	6.12	75.84	6.98	6.92	0.011*
60 Minute	80.18	5.69	75.99	6.19	3.86	0.05
90 Minute	79.95	6.53	76.88	6.56	2.10	0.15
After Extubation	113.56	5.82	108.17	5.70	4.08	0.04*

*: Statistically significant

Table 5: Comparison of Heart rate (HR) among the groups

Interval	Group A		Group B		t test	p value
	Mean	SD	Mean	SD		
Baseline	77.6	5.71	78.54	6.79	1.18	0.47
Just After Intubation	103.23	5.53	102.97	7.29	0.03	0.87
1 Minute	93.94	4.96	92.30	7.07	1.12	0.29
3 Minute	87.72	4.69	87.28	5.60	2.02	0.16
5 Minute	81.67	7.03	83.60	6.29	1.26	0.27
10 Minute	74.13	3.93	77.73	5.26	4.34	0.04*
15 Minute	75.60	5.80	78.47	4.12	7.62	0.008*
30 Minute	73.30	4.99	77.63	5.78	6.27	0.015*
45 Minute	75.63	3.37	78.28	4.82	4.85	0.03*
60 Minute	73.70	3.72	75.46	4.13	3.30	0.07
90 Minute	75	3.46	76.48	4.29	1.99	0.16
After Extubation	103.67	5.63	107.43	5.41	4.32	0.03*

*: Statistically significant



Graph 1: Comparison of blood sugar among the groups at different intervals

Discussion: Bloodless field is an important prerequisite in oral and maxillofacial surgeries. In order to help the surgeon reduces bleeding and to improve visibility in the operative field, many anesthetists have employed induced hypotension during OMF surgeries[3].The present study was done to study and compare the effects of both the drugs in attenuation of haemodynamic responses in OMF surgeries.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

In our study, there was male dominancy among both the groups. Celik O *et al*.[8]too revealed same male dominancy. In our study statistical analysis revealed no significant difference among the two groups w.r.t. age (p=0.62). Similarly findings were revealed by study done by Ibrahim *et al*.[9]and Raghuram[10]in their study.

In our study, mean baseline Systolic blood pressure (SBP) in Group A was 126.50±6.74 while in Group B it was 127.80±8.08 and the difference was statistically insignificant. Similar insignificant difference was reported by Ibrahim *et al*.[9]and Vijay Mathur *et al*.[11]in their study while Raghuram *et al*.[10]in their study reported significant difference. In our study, after comparing both groups SBP values at 1min, 3min, 5min, 10min, 15min, 30min, after extubation SBP values were statistically significant i.e. mean SBP was more in group A as compared to group B. Similar results obtained in study conducted by Ibrahim *et al*.[9],Vijay Mathur *et al*.[11]and Raghuram *et al*.[10]. However no significant difference was reported among the groups after 60 min and 90 min of intubation in our study. This observation was different from study conducted by Vijay Mathur *et al*.[11]who revealed significant difference among the groups. Just after extubation; mean SBP in Group A was 152.80±7.33 and in Group B it was 145.47±8.22 with statistically significant difference. Similar significant difference was reported by Ibrahim *et al*.[9]and Vijay Mathur *et al*.[11]in their study.

In our study, mean baseline diastolic blood pressure (DBP) was similar among both the groups. However Raghuram *et al*.[11]in their study reported significant difference. In our study, after comparing both groups, mean DBP values at 1min, 10min, 15min, 10min, 15min, 30 min, 45 min, 60 min and after extubation were statistically significant i.e. mean DBP was more in group A as compared to group B. DBP values were statistically insignificant at baseline, just after intubation, 3min, 5 min and 90 min in our study. Similar results obtained in study conducted by Ibrahim *et al*.[9],Vijay Mathur *et al*.[11]and Raghuram *et al*.[10].However after 90 min, no significant difference between the groups was reported by Ibrahim *et al*.[9]and Vijay Mathur *et al*.[11]in their study.

In our study mean baseline heart rate (HR) in Group A was 77±5.71 while in Group B it was 78.54±6.79 with statistically insignificant difference. Similar insignificant difference was reported by Ibrahim *et al*.[9]and Vijay Mathur *et al*.[11]in their study. In contrary to this, in study conducted by Ahmed *et al*.[12],mean baseline HR in metoprolol group was 60.65±6.67 and placebo it was 72±6.49 and difference was statistically significant. (p=0.0001). Just after, 1 min, 3 min, 5 min after intubation, increase in HR was seen in both groups after intubation with statistically insignificant difference. In contrary to this, in study conducted by Ibrahim *et al*.[9],Vijay Mathur *et al*.[11]and Raghuram *et al*.[10]shows that difference in HR was statistically significant (p<0.01). After 10, 15, 30, 45 min of extubation, significant difference was observed between the groups in our study i.e. heart rate is more in group B as compared to groups A. Ibrahim *et al*.[9],Vijay Mathur *et al*.[11]and Raghuram *et al*.[10]in their study revealed similar results.

Blood sugar level just after intubation was 110.30±5.25 in Group A, while in Group B it was 108.70±4.60 with statistically insignificant difference. 1 hour intraoperatively, in Group A was 102.97±5.39 and in Group B it was102.00±4.45. Difference was statistically insignificant. Just after extubation, in group A was 112.68±6.31 and in group B it was 110.10±5.23. Difference was statistically insignificant. Results in our study were different from study conducted by Vijay Mathur *et al*.[11]in 2016 Mean blood glucose just after extubation was 115.33±7.53 in ivabradine group, 116.87±9.82 in metoprolol group and 124.97±5.81 in placebo group. Difference between two groups was statistically significant. (p<0.01) Ibrahim *et al*.[9]conducted similar study in 2015. He concluded that both drugs (ivabradine and metoprolol) didn't show any significant effect on perioperative blood glucose level.

There were no complications in our study viz. bradycardia, hypotension, bronchospasm etc. The limitations of the present study are that we did not compare different doses of ivabradine and metoprolol at different time intervals and didn't include other variables in haemodynamic stress response like catecholamines, glucagon and cortisol, blood loss.

Conclusion

We concluded that both the drugs can be used as an effective premedication, to attenuate the sympathetic response to laryngoscopy, endotracheal intubation, extubation and throughout oral and maxillofacial surgeries. However, ivabradine was found to have better control than metoprolol in controlling the HR while metoprolol have better control on SBP, DBP and MAP providing a better hypotensive effect than ivabradine. Blood glucose comparison between two groups shows that there was no significant difference. Ivabradine can be recommended in cases where beta blockers are contraindicated like in bronchial asthma.

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ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

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