Effect of oral clonidine premedication on perioperative hemodynamic response - A randomized double blind placebo controlled study

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Abstract

Introduction: Preanesthetic medication forms an integral part of anaesthetic management. Pharmacological and non-pharmacological techniques are tried to achieve anxiolysis and better hemodynamic stability. Clonidine is alpha 2 agonist and acts on central nervous sytem. It is adminstered in various route and oral route is one of them. This study has been designed to study the effect of oral clonidine on perioperative hemodynamics.

Aims: To evaluate beneficial effects of oral clonidine in attenuating the haemodynamic responses and comparing with placebo in patients undergoing surgeries under general anaesthesia.

Settings and Design: Randomized double blind study.

Methods and Material: Two hundred patients were enrolled in this study and studied for 2 years. Randomization was carried out. Four groups, including 50 patients per group were created. Group I (Placebo) received oral tablet ranitidine 150 mg, Group II C2, C3 and C4received oral clonidine 2 µg/kg, 3µg/kg and 4µg/kg body weight respectively. Sedation, anxiolysis and hemodynamic changes were recorded.

Statistical analysis used: The statistical significance for categorical variables was determined by chi-square test. For continuous variables two sample t-test was applied. For intra group comparison paired t- test and for inter group comparison unpaired t-test was used. Results were expressed as Mean ± SD (standard deviation). A P value < 0.05 was considered statistically significant.

Results: No statistically significant differences concerning demographic data between the groups of patients computed. A significant difference observed with respect to sedation and anxiolysis between all the four groups. The HR response between clonidine (2 µg/kg, 3µg/kg and 4µg/kg) and placebo was very significant at all times ($p<0.001$) showing a favorable response towards attenuation of HR. The SBP, MAP and DBP response between clonidine and placebo is significant at all times. When compared to clonidine (2 µg/kg, 3µg/kg and 4µg/kg) group the requirement of MAC of Isoflurane in placebo group is higher.

Conclusion: Administration of oral clonidine preferably 4µg/kg, as pre-medicant results in improved perioperative haemodynamic stability and Isoflurane sparing effect.

Key Words: Anxiolysis, Clonidine, Hemodynamic response, Oral premedication.

Key Messages: Various methods are used to allay anxiety and good hemodynamic control in perioperative period. Pharmacological and non-pharmacological methods are popular. Spectrum of drugs have been tried to achieve these goals. Oral Clonidine is one of them. We studied different doses of oral clonidine and its effect during perioperative period.

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Introduction

Anxiety is emotional response to impending surgery. Premedication is important part in anaesthetic management. Reid and Bruce, Burstein and King, Harris described the haemodynamic response to laryngoscopy and intubation.[1,2] It is characterized by hypertension, tachycardia and increased circulating catecholamine levels.[3] This also causes deleterious effect to patient by increased cardiac workload. Factors affecting perioperative haemodynamic changes are premedication, anaesthetic agents, depth of anaesthesia, airway manipulation and laryngoscopy.[4]

Common methods to reduce stress response are, minimize laryngoscopy duration and or use pharmacological methods. Oral clonidine is cost-effective and is easy to administer. Different doses of oral clonidine and its effect on sympathetic response to laryngoscopy, intubation and perioperative effectiveness were studied.

Subjects and Methods

Approval by ethical committee and written informed consent from patients were obtained.

Inclusion criteria: Patients aged between 16-60 years of both sexes, ASA Grade I or II, elective surgery under General anaesthesia (GA) are included in this study.

Exclusion criteria: Unwilling patients, known neurological, endocrine, renal, cardiovascular diseases were excluded from the study.

Two hundred patients undergoing various Orthopedic, ENT, Gynecological and General surgical procedures were selected.

Method of randomization

Blocked randomization: A total 4 blocks with the size of 50 in each group, with treatment allocation of 1:1:1:1 for Group – I, Group – II C2, Group – II C3 and Group – II C4 were created by computer software. Coded envelopes used for 4 patients leading to random assignment of one subject to one group. Thus the randomization was concealed & balanced equally in all groups.

Patients in group I (Placebo) received Tab Ranitidine 150mg, 90 minutes before surgery. In oral clonidine i.e. in group II (Clonidine), C2 group received 2 µg/kg body weight of clonidine. Accordingly, patients in Group II C3 and C4 received 3µg/kg, 4 µg/kg body weight of clonidine respectively 90 min before the surgery. On the day of surgery, SBP and DBP and HR were measured before premedication and 90 minutes after. Sedation and anxiolysis scores were also recorded 90 minutes after premedication. The following scoring system was used. For sedation; asleep, drowsy and awake are considered as a score of 2, 1, 0 respectively. For anxiety; quite or comfortable, anxious and upset or worried are considered as score of 2, 1, 0 respectively.

On arrival to operation theatre, routine monitoring of preinduction vital parameters were recorded and a crystalloid intravenous infusion of 6-8ml/kg/hr. started. All patients were premedicated with Inj Fentanyl 1µg/kg. After preoxygenation, anaesthesia was induced with Inj Thiopentone 5mg/kg. The laryngoscopy and intubation were facilitated with vecuronium 0.8 mg/kg. Anaesthesia was maintained with vecuronium, Isoflurane, nitrous oxide 60% in 40% oxygen and mechanical ventilation initiated.

Patients were observed for hemodynamic changes. Clinically insufficient analgesia and depth of anesthesia were controlled with supplementary doses of fentanyl and increasing concentration of Isoflurane. Hypotension primarily treated by increasing the intravenous infusion rate (15ml/min) and titrating Isoflurane. Bradycardia was treated with Inj Glycopyrrolate (0.004mg/kg) intravenously.

Intraoperatively haemodynamics (HR, SBP, DBP and MAP) and Isoflurane concentration was recorded at induction, 1 minute after endotracheal intubation, 3,5, 10, 15 and 30 minutes after endotracheal intubation.

Isoflurane was discontinued after last skin suture, and residual neuromuscular block was reversed with Inj Neostigmine (0.05 mg/kg), Inj Glycopyrrolate (0.01mg/kg) intravenously and extubated and were transferred to post anaesthesia care unit.

Results

No significant differences noted between all the groups with respect to demographic parameters.

Sedation score: Sedation assessed on a 3 point sedation scale. In group I, sedation score of 0, 1 and 2 was seen in 45(90%), 5(10%) and no patient (0%) respectively. In Group II-C2, sedation score of 0, 1 and 2 was seen in 22(44%), 25(50%) and 3(6%) patients respectively. In Group II-C3 patients, sedation score of 0, 1 and 2 was seen in 20(40%), 26(52%) and 4(8%) respectively. In Group II-C4 patients, sedation score of 0, 1 and 2 was seen in 22(44%), 25(50%) and 3(6%) respectively.

Chi-square test showed that there is significant difference in the sedation between all four groups ($p<0.001$), but between Group II-C2, C3 and C4 there is no significant difference ($p = 0.8558$).

Anxiolysis score: Anxiolysis is assessed on a 3 point. In group I, anxiolysis score 0, 1 and 2 seen in 8(16%), 34(68%) and 8 (16%) patients respectively. In Group II-C2, anxiolysis score of 0, 1 and 2 seen in 5(10%), 15(30%) and 30(60%) patients respectively. In Group II-C3, the anxiolysis score of 0, 1 and 2 seen in 2(4%), 17(34%) and 31(62%) patients respectively. In Group II-C4 patients, the anxiolysis score 0 seen in 2(4%) and score 1 in 14(28%) patients and 34(68%) patient had a score of 2.

Chi-square test showed that there is significant difference in the anxiolysis between all four groups ($p<0.001$), but between Group II-C2, C3 and C4 there is no significant difference in the anxiolysis. ($p = 0.6307$).

Heart rate analysis: In Group I (Placebo) there is no significant change in HR noted. In Group II -C2, C3 and C4, 90 minutes after premedication there is 10.21%, 11.51% and 10.78 % decrease in HR with the mean value of 73.12, 71.62 and 71.6 from their baseline, respectively. This change is statistically significant ($P<0.0001$).

The HR was recorded after 90 minutes after premedication (Table no 1). In group I the mean HR was 77.42 ± 10.76. One minute after the laryngoscopy, HR rose to 97.12 ± 8.59 with an increase of 25.44% from pre-operative values, which is significant ($P<0.0001$). Mean heart rate (MHR) at 3 minutes was 94.68 ± 9.05 which is significantly higher ($P<0.0001$) i.e. 22.29% than pre-operative values. MHR at 5 minutes was 88.82 ± 7.58 which was significantly higher ($P<0.0001$) 14.72% than the pre-operative values. MHR at 10 minutes was 77.92 ± 5.77 and is not significantly higher (P-0.7647) than the preoperative values. MHR remained lower at 15 and 30 minutes compared to preoperative values. One minute after the laryngoscopy there was increase in MHR and remained higher at 3 minutes. MHR at 5 minutes were higher than the pre-operative values and is highly significant for group II-C2 whereas in C3 and C4 the rise in MHR was not significant. MHR at 10 minutes is not significantly higher than the pre-operative values. MHR remained significantly lower at 15 and 30 minutes compared to preoperative values. Maximum increase in HR is 14.06%, 13.18%, 11.12% in Group II-C2, C3, C4

and 25.44% in group I at 1 minute after laryngoscopy. It is statistically significant (p<0.0001) while comparing Group I with Group II-C2, Group I with Group II-C3, and Group I with Group II-C4 . The HR response between clonidine and placebo is significant at all times (p<0.001) showing a favorable response towards attenuation of HR.

Systolic blood pressure: In Group I, 90 min after premedication there was increase in SBP i.e. 1.43% with mean of 121.56 ± 12.12 from the baseline SBP 119.84 ± 11.22. This is statistically not significant (P-value 0.09).

In Group II -C2, C3 and C4, 90 minutes (Table 2) after premedication there was 5.39%, 5.82% and 5.72% decrease in SBP with mean value of 114.52 ± 10.57, 113.28 ± 10.60 and 113.56 ± 10.68 from their baseline respectively and are statistically significant. In Group I: During induction mean SBP was 121.56 ± 12.12. One minute after the laryngoscopy, the SBP rose to 143.4 ± 10.43 with an increase of 17.97 % from the pre-operative values, which is significant (P< 0.0001). Mean SBP at 3 minutes was 138.96 ± 7.99 which is significantly higher (14.13%) than pre-operative values.

Mean SBP at 5 minutes was 131.94 ± 7.72 which was significantly higher (P<0.0001), 8.43% than the pre-operative values. Mean SBP at 10 minutes was 116.54 ± 7.29 which is significantly lower (P- 0.0036) than the preoperative values. Mean SBP remained significantly lower at 15 and 30 minutes compared to preoperative values.

In group II, One minute after laryngoscopy, increase in mean SBP was 10.34 %, 8.80 % and 8.21 % respectively with mean values of 126.36 ± 8.19, 123.24 ± 11.39, and 122.88 ± 9.184, which is significant for group II C2, C3 and C4. Mean SBP at 3 minutes in group II C2 and C3 remained significantly higher than preoperative. In group II C4, mean SBP values of 115.2 ± 8.03 is not significant when compared with preoperative values. Mean SBP at 5 minutes in groups II C2, C3 and C4, were lower than pre-operative values. There is no statistically significant change in SBP at 5th minute with pre-operative values. Mean SBP remained significantly lower at 10, 15 and 30 minutes compared to its preoperative values.

Diastolic blood pressure: In Group I, 90 minutes after premedication there was significant increase in DBP i.e. 2.07 % with mean value of 78.76 ± 6.61from the baseline mean DBP 77.16 ± 6.64. (P-0.0070). In Group II -C2, C3 and C4, 90 minutes after premedication there is decrease in DBP from their baseline DBP values 77.88 ± 6.72, 78.76 ± 5.23 and 78.98 ± 6.51 respectively. Which is statistically significant (P<0.0001).

During induction (Table 3) in Group I: mean DBP was 78.76 ± 6.61. One minute after the laryngoscopy, HR rose to 92.6 ± 5.83 with an increase of 17.57% from the pre-operative values, which is significant (P<0.0001). Mean DBP at 3 minutes was 87.24 ± 5.28 which was significantly higher (P< 0.0001) by 10.77% than pre-operative values. Mean DBP at 5 minutes was 83.94 ± 5.75 which is significantly higher (P < 0.0001) by 6.58% than pre-operative values. Mean DBP at 10 minutes was 75.08 ± 4.41 which is significantly lower (P-0.0036) than preoperative values.

Group II (Clonidine): During induction of anaesthesia, the mean DBP values were 74.38 ± 6.23, 75 ± 6.69, 73.82 ± 6.05 in groups II C2, C3 and C4 respectively. One minute after the laryngoscopy, increase in mean DBP was 10.4%, 8.32%, 7.72% respectively which is highly significant for group II C2, C3 and C4. Mean DBP at 3 minutes remained higher than the preoperative values respectively. It is significant in group II C3 and highly significant in group II C2 and group II C4. Mean DBP at 5 minutes were 74.68 ± 4.40, 73.48 ± 9.14, 74.24 ± 6.05 in groups II C2, C3 and C4 respectively. There is no statistically significant change in DBP at 5th minute from pre-operative values. Mean DBP remained significantly lower at 10, 15 and 30 minutes compared to preoperative values.

Mean arterial pressure (MAP): In Group I, 90 minutes after premedication there was significant increase in MAP i.e. 2.06% with mean value of 93.96 ± 8.14 from the MAP 92.06 ± 7.98 (P-value 0.0003). In Group II -C2, C3 and C4, 90 minutes after premedication there was 5.14 %,6.07% and 6.43% decrease in MAP with mean value of 88.44 ± 7.53, 87.56 ± 7.10 and 87.82 ± 7.04 from their baseline MAP values 93.24 ± 7.74, 93.22 ± 6.35, and 93.86 ± 7.47 respectively and statistically significant (P<0.0001).

During induction (Table 4): in Group I, the MAP was 93.96 ± 8.14. One minute after the laryngoscopy, the MAP rose to 110.2 ± 7.19 with an increase of 17.27% from the pre-operative values, which was highly significant (P<0.0001). MAP at 3 minutes was 105.1 ± 5.64 which is significantly higher (P<0.0001) i.e. 11.85 % than pre-operative values. MAP at 5 minutes was 100.54 ± 5.66 which is significantly higher (P<0.0001) i.e. 6.99% than pre-operative values. MAP at 10 minutes was 89.46 ± 4.53 which is significantly lower (P-0.0036) than the preoperative values. In Group II, during induction of anaesthesia, the MAP values were 88.44 ± 7.53, 87.56 ± 7.10 and 87.82 ± 7.04ingroups II C2, C3 and C4 respectively. One minute after the laryngoscopy, increase in mean MAP was 10.37%, 8.22% and 7.76%, with mean values of 97.62 ± 7.01, 94.76 ± 8.17 and 94.64 ± 6.38 in groups II C2, C3 and C4 respectively. This is significant for group II C2, C3 and C4. Mean DBP at 3 minutes with values of 93.9 ± 4.64, 92.14 ± 11.18, 90.28 ± 5.92 in groups II C2, C3 and C4 remained higher than the preoperative values respectively, which is highly significant in group II C2, C3 and C4. MAP at 5 minutes was 88.2 ± 4.89, 86.56 ± 9.57 and 86.82 ± 6.30

in groups II C2, C3 and C4 respectively. There is no statistically significant change in MAP at 5th minute from with pre-induction values. MAP remained significantly lower at 10, 15 and 30 minutes compared to its preoperative values.

Comparison of minimum alveolar concentration (MAC) in all the groups (Table 5): The requirement of MAC of Isoflurane in group I is significantly higher when compared with Group II C2, C3 and C4.

Incidence of intraoperative bradycardia: In Group I, Group II C2, C3 and C4 it was 0%, 3 patients (6%), 6 patients (12%), 8 patients (16%) respectively. Incidence of intraoperative bradycardia in group C2 comparing with placebo group is not significant (P-0.2424). Whereas incidence of intraoperative bradycardia in groups C3 and C4 with placebo is significant (P 0.0267 and P 0.0058).Maximum incidence of intraoperative bradycardia was in C4 group i.e. 16%.

Table 1: The heart rate comparison in placebo and oral clonidine groups.

	Group 1-Placebo		Group 2-C2		Group 2-C3		Group 2-C4	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Preinduction After premedication	77.42± 10.76		73.12± 9.33		71.64 ±7.25		71.6 ± 8.78	
Post intubation								
1 min	97.12 ±8.59	<0.0001 † 25.44% †	83.4 ± 8.99	<0.0001 † 14.06% †	81.08 ± 7.86	<0.0001 † 13.18% †	79.56 ± 8.27	<0.0001 † 11.12 % †
3 min	94.68 ± 9.05	<0.0001 † 22.29 % †	81.1 ± 9.05	<0.0001 †		<0.0001 †		<0.0001 †
5 min	88.82 ± 7.58	<0.0001 † 14.72 % †	76.72 ± 8.03	0.0037 * 4.92 % *	73.56 ± 8.4	0.1098 NS 2.68%	72.9 ± 6.92	0.234 NS 1.81% NS
10 min	77.92 ± 5.77	0.76 0.64% NS	72.84 ± 7.41	0.85325 NS -0.38% NS	70.28 ± 9.48	0.3031 NS -1.9 %NS	69.8 ± 9.75	0.1251 -2.5% NS
15 min	72.32 ± 6.10	0.0033 †	68.82 ± 6.16	<0.0001 †	65.32 ± 8.21	<0.0001 †	67.18 ± 8.81	<0.0001 †
30 min	71.86 ± 5.48	0.0033 †	66.62 ± 6	<0.0001 †	63.38 ± 7.65	<0.0001 †	65.3 ± 8.3	<0.0001 †

* P<0.05 is significant, † P< 0.0001 highly significant, NS – not significant

Table 2: The systolic blood pressure comparison in placebo and oral clonidine groups.

	Group 1-Placebo		Group 2-C2		Group 2-C3		Group 2-C4	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Preinduction After premedication	121.56± 12.12		114.52± 10.57		113.28 ±10.6		113.56 ± 10.68	
Post intubation								
1 min	143.4± 10.43	<0.0001 † 17.97% †	126.36 ± 8.19	<0.000 † 10.34%	123.24 ± 11.39	<0.0001 † 8.80%	122.88 ± 9.184	<0.0001 † 8.21%
3 min	138.96 ± 7.99	<0.0001 † 14.13%	121.58 ± 6.44	<0.0001 † 6.16%	118.74± 13.43	0.0069* 4.82%	115.2± 8.03	0.1853 NS 1.44%
5 min	131.94± 7.72	<0.0001 † 3% †	113.2 ± 6.77	0.3342 NS -1.15 NS	111.2± 11.31	0.1891NS 1.84 %	110.04 ± 9.34	0.1891 NS -3.10%
10 min	116.54 ± 7.29	0.0036 † -4.13% NS	107.98 ± 8.47	<0.0001 † -5.71%	105.2 ± 11.85	0.0004 † -7.13%	105.92 ± 8.32	<0.0001 † -6.73%
15 min	117.46 ± 8.36	0.0056 † -3.37%	107.26 ± 8.36	<0.0001 † -6.34%	103.42 ± 10.58	<0.0001 † -8.70%	105.74± 9.94	<0.0001 † -6.89%
30 min	111.42 ± 8.87	<0.0001 † -8.34%	105.8 ± 8.41	<0.0001 † -7.60%	103.56 ± 9.54	<0.0001 † -8.58%	102.3 ± 8.83	<0.0001 † -9.91%

*P<0.05 is significant, † P< 0.0001 highly significant, NS – not significant

Table 3: The diastolic blood pressure comparison in placebo and oral clonidine groups.

	Group 1-Placebo		Group 2-C2		Group 2-C3		Group 2-C4	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Preinduction After premedication	78.76± 6.61		74.38± 6.23		75 ±6.69		73.82 ± 6.05	
Post intubation								
1 min	92.6± 5.83	<0.0001 † 17.57%	82.12 ± 6.42	<0.0001 † 10.4%	81.24 ± 8.41	<0.0001 † 8.32%	79.52± 6.17	<0.0001 † 7.72%
3 min	87.24 ± 5.28	<0.0001 † 10.77%	79.06 ± 4.16	<0.0001 † 6.29 %	78.34± 10.5	0.0165* 4.51%	76.84± 5.95	<0.0001 † 4.09%
5 min	83.94± 5.75	<0.0001 † 6.58%	74.68 ± 4.40	0.7037 NS -0.4%	73.48± 9.14	0.2163NS -2.02%	74.24 ±6.05	0.4306 NS 0.57 %
10 min	75.08± 4.41	<0.0001 † -4.67%	70.9 ± 5.08	<0.0001 † -4.68%	70.02 ± 8.61	0.0011* -6.64%	69.28 ± 6.80	<0.0001 † -6.15%
15 min	77.66 ± 5.19	0.18 NS -1.39%	69.28 ± 5.52	<0.0001 † -6.86%	69.02 ± 7.31	<0.0001 † -7.97%	68.06± 6.62	<0.0001 † -7.8 %
30 min	74.18 ± 5.72	<0.0001 † -5.82%	69.04 ± 6.04	<0.0001 † -7.18%	69.86± 6.28	<0.0001 † -6.85%	66.66 ± 6.88	<0.0001 † -9.7%

* P<0.05 is significant, † P< 0.0001 highly significant, NS – not significant

Table 4: The mean arterial pressure comparison in placebo and oral clonidine groups.

	Group 1-Placebo		Group 2-C2		Group 2-C3		Group 2-C4	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Preinduction After premedication	93.96± 8.14		88.44± 7.53		87.56± 7.1		87.82 ± 7.04	
post intubation								
1 min	110.2± 7.19	<0.0001 † 17.27%	97.62 ± 7.01	<0.0001 † 10.37%	94.76 ± 8.17	<0.0001 † 8.22%	94.64± 6.38	<0.0001 † 7.76%
3 min	105.1 ± 5.64	<0.0001 † 11.85%	93.9 ± 4.64	<0.0001 † 6.14%	92.14± 11.18	0.0033* 5.23%	90.28± 5.92	<0.0002 † 2.8%
5 min	100.54± 5.66	<0.0001 † 6.99%	88.2 ± 4.89	0.7037 NS -0.28%NS	86.56± 9.57	0.4129NS -1.14%NS	86.82± 6.30	0.1031NS 1.13 %
10 min	89.46± 4.53	<0.0001 † -4.58%	83.96 ± 5.99	<0.0001 † 5.07%	82.54 ± 9.37	0.0022 † 5.73%	82 ± 6.97	<0.0001 † 6.62%
15 min	91.26 ± 5.49	0.004 † 2.88%	82.6 ± 5.95	<0.0001 † 6.61%	80.52 ± 8.0	<0.0001 † 8.04%	81.38± 7.41	<0.0001 † -7.33%
30 min	87.52 ± 5.82	<0.0001 † 6.86%	81.92 ± 6.52	<0.0001 † 7.38%	81.24± 6.96	<0.0001 † 7.21%	79.18 ± 7.0	<0.0001 † -9.83%

* P<0.05 is significant, † P<0.0001 highly significant, NS – not significant

Table 5: Comparison of minimum alveolar concentration requirement of Isoflurane in all the groups.

Minimum alveolar concentration	Group 1-Placebo	Group 2-C2		Group 2-C3		Group 2-C4	
	Mean ± SD	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
At induction	0.91± 0.29	0.79 ± 0.27	0.0433*	0.73±0.29	0.0026*	0.73 ± 0.22	0.0014
1 min	1.27±0.37	0.93 ± 0.26	<0.0001 †	0.88 ± 0.29	<0.0001 †	0.79 ± 0.27	<0.0001 †
3 min	1.09 ±0.25	0.88 ± 0.19	<0.0001 †	0.85 ± 0.26	<0.0001 †	0.72 ± 0.24	<0.0001 †
5 min	0.93±0.22	0.83 ± 0.24	<0.0001 †	0.74 ± 0.19	<0.0001 †	0.66 ± 0.2	<0.0001 †
10 min	0.93±0.21	0.79 ± 0.21	<0.0001 †	0.71 ± 0.19	<0.0001 †	0.61 ± 0.17	<0.0001 †
15 min	0.86± 0.17	0.73 ± 0.2	<0.0001 †	0.62 ± 0.13	<0.0001 †	0.56 ± 0.11	<0.0001 †
30 min	0.83± 0.12	0.69 ± 0.2	<0.0001 †	0.63 ± 0.15	<0.0001 †	0.59 ± 0.17	<0.0001 †

* P<0.05 is significant, † P< 0.0001 highly significant, NS – not significant

Discussion

Earlier wine and opium were given to mitigate the terror of surgery. Since then, search for ideal premedicant has been going on. Induction of anaesthesia, laryngoscopy and intubation are associated with marked haemodynamic changes.[5,6] Mainly laryngoscopy and intubation are associated with a rise in HR, BP and arrhythmias. These haemodynamic responses are transient and short lived but may become detrimental.[4,7]

Such hemodynamic changes may be well tolerated by healthy individuals but fatal in hypertensive, coronary artery disease patients. Different modalities employed to minimize adverse hemodynamic response, like reducing laryngoscopy time to less than 15 seconds, using inhalationals,[2] topical and intravenous lidocaine,[4,8] β- lockers,[9] calcium channel blockers,[10] vasodilators,[11] opioids[12] and alpha- 2 adrenergic agonists.[13,14]

Sedation: It was assessed on a three point scale prior to induction. In group I, sedation score of 0, 1 and 2 are observed in 45(90%), 5(10%) and 0% of patients respectively. In Group II-C2 patients, the sedation score of 0 in 22(44%), score of 1 in 25(50%) and score of 2 in 3(6%) patients. In Group II-C3 patients, the sedation score of 0 in 20(40%), score of 1 in 26(52%) and score of 2 in 4(8%) patients. In Group II-C4 patients, the sedation score of 0 in 22(44%) and score of 1 in 25(50%), score of 2 in 3(6%) patients. The sedation score is found to be highly significant between the placebo and clonidine groups (p<0.001).

Raval DL et al in their study compared clonidine with placebo in 100 ASA I-II patients and showed better sedation with oral clonidine.[15] Sedative action of clonidine is by decreasing tonic activity of locus coeruleus. Hence a good sedative effect is observed in clonidine group compared to placebo group.

Anxiolysis: It was assessed on a 3 point anxiolysis scale prior to induction. In group II-C2 60%, C3 62%, and C4 68% patients were quiet with score 0.While in group I score 0 was found in 16%. The anxiolysis score is found to be highly significant between the placebo and the clonidine groups (p<0.001), whereas there is no significant changes between clonidine groups (P =0.6307). A better anxiolysis scores are seen in clonidine groups than the placebo group. Anxiolysis score is comparable with Raval et al study in which after premedication 85% of patients were comfortable and 12.5% patients were uneasy, 2.5% patients were anxious in clonidine group where as in placebo group 50% were quiet or comfortable, 30% were uneasy and 20% were anxious.[15]

Heart rate (HR): Base line HR was comparable in all four groups. In group I, 90 minutes after premedication, there is no significant change in HR (P > 0.05). In Group II -C2, C3 and C4, 90 minutes after premedication there was 10.21%, 11.51% and 10.78 % significant decrease in HR from their baseline HR respectively(P<0.001). HR, before premedication and 90 minutes after premedication were comparable between clonidine groups (P>0.05). Gupta, et al showed highly significant decrease in HR at 90 minutes after premedication in clonidine group compared to placebo.[13]

In group I one minute after the laryngoscopy, the HR increased to 25.44% from the pre-induction values, which is significant (P<0.0001). HR did not return to the preinduction value till 10 min of intubation. In group II-C2, C3 and C4 one minute after the laryngoscopy, the increase in mean HR was 14.06%, 13.18% and 11.12% and remained higher at 3 minutes In group II-C2 HR remained significantly higher than the preoperative value even at 5 min. (p-0.0037), whereas in group II-C3 and group II-C4 HR returned to

the preinduction value at 5 minutes (P>0.05). Maximum increase in HR at 1 minute after laryngoscopy is higher in placebo group while comparing with clonidine groups and is statistically highly significant (p < 0.001). These differences in HR between placebo group and clonidine groups remain statistically highly significant at all times from pre-operative values (P < 0.01).

Attenuation of maximum rise in the HR by clonidine is evident and statistically significant when compared with placebo group (p < 0.001). These results are comparable with other studies (p<0.001).[13]

The difference in the HR between Group II-C2 and C3 was not significant till 10 min after laryngoscopy (P> 0.05). While comparing Group II-C2 and C4,HR is significantly lower in Group II-C4 at 1 minute and 3 minute after laryngoscopy (P <0.05).

The differences in HR between group II-C3 and C4 remains statistically not significant at all times. Clonidine 4 µg/kg showed better dose to attenuate rise in HR while compare to clonidine 2 µg/kg.

Blood pressure: In Group I, 90 min after premedication there was no significant change in SBP, DBP, MAP from the baseline value. (P >0.05). In Group II -C2, C3 and C4, 90 minutes after premedication there was increase in SBP, DBP and MAP from their baseline BP respectively. This is statistically highly significant (P<0.01). SBP, DBP and MAP before premedication and 90 minutes after premedication were comparable between clonidine groups (P>0.05). Results are in consistent with other study.[15] In group I one minute after the laryngoscopy, SBP, DBP and MAP increased from the pre-induction values, which is significant (P<0.0001). SBP returned to the preinduction value at 10 min of intubation and as compared to the preinduction value a statistically highly significant difference in SBP was observed at the end of 1, 3 and 5 min after intubation.

In clonidine groups one minute after the laryngoscopy, there was significant increase in SBP, DBP and MAP (P<0.01), which remained significantly higher at 3 minutes in group II-C2 and C3 (P<0.01). Whereas in group II-C4 SBP not significant higher than the preinduction value. (P> 0.05) but DBP and MAP remained significantly higher (P<0.01). At 5 minutes SBP, DBP and MAP were comparable with preinduction in clonidine groups (P> 0.05).

Baseline values of BP are comparable between placebo and clonidine groups. There was maximum increase in SBP, DBP and MAP at 1 minute after laryngoscopy in placebo group and is statistically significant (p<0.01). These differences between placebo and clonidine groups remained statistically significant at all the times after intubation (P<0.01), showing a favorable response towards attenuation rise of BP with clonidine.

While comparing group II-C2 with C4, SBP was significantly lower in group II-C4 at 3 minute after laryngoscopy (P<0.01), whereas DBP and MAP were significantly lower in group II-C4 at1 and 3 minute after laryngoscopy while comparing with group II-C2 (P< 0.01).

There was no significant difference of attenuating BP response of Group C2 with C3 and C3 with C4. Clonidine 4µg/kg is better than clonidine 2 µg/kg to attenuate rise in BP.

Carabine showed that clonidine 200µg produced a significant reduction in anxiety(P<0.05), and a better quality of induction of anaesthesia when compared to 100µg.The decrease in BP and HR with clonidine 300µg were significant.[16]

Requirement of MAC of Isoflurane was significantly lower in clonidine groups compare to placebo group (P<0.05). Requirement of Isoflurane in group II C4 was significantly lower.Our findings are in concordance with Singh S et al.[14]

Incidence of bradycardia in C2 group comparing with placebo group was not significant (P-0.2424), but in groups C3 and C4 it was significant (P>0.05). Bradycardia while comparing in all the clonidine groups was not significant. (P-0.2835). Maximum incidence bradycardia was in group C4 i.e. 16%. Singh S et al in shown that 16% incidence of bradycardia with oral clonidine 150µg.[14]

Conclusion

Administration of oral clonidine preferably 4µg/kg, as a pre-medicant results in improved perioperative haemodynamic stability and Isoflurane sparing effect.

Conflict of Interest: None
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