DOI: 10.14260/jemds/2015/808

ORIGINAL ARTICLE

ORAL CLONIDINE PREMEDICATION: A COMPARATIVE STUDY WITH A PLACEBO IN ATTENUATING HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

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HOW TO CITE THIS ARTICLE:
Gurudatta K. N, Ashwini S. "Oral Clonidine Premedication: A Comparative Study with a Placebo in Attenuating Hemodynamic Responses to Laryngoscopy and Intubation". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 32, April 20; Page: 5523-5532, DOI: 10.14260/jemds/2015/808

ABSTRACT: BACKGROUND: Sympathetic response associated with laryngoscopy and endotracheal intubation is a potential cause for a number of complications especially in patients with cardiovascular compromise. The aim of our study was to evaluate and study the efficiency of oral Clonidine premedication in this respect as compared with a placebo. **METHODS:** 100 surgical patients of either sex of physical status ASA I/II were randomly divided into two groups. Group I, who received oral Clonidine tablet 0. 003mg (3µg) /kg 90 minutes before surgery and group II, who received oral Ranitidine tablet 150mg 90 minutes before surgery. Basal parameters like HR, SBP, DBP were measured before premedication and for 90 minutes after; scoring was done for sedation, anxiolysis and antisialogogue effects 90 minutes after premedication. **RESULT:** Oral Clonidine showed statistically significant attenuation of haemodynamic responses to laryngoscopy and intubation and in addition it was found to have good sedative, anxiolytic effect as comared with placebo. **CONCLUSION:** we conclude that oral Clonidine premedication with dose of 3µg/kg is highly effective in attenuating hemodynamic response to laryngoscopy and intubation.

KEYWORDS: Responses, Laryngoscopy, Intubation, Clonidine, Ranitidine, Premedication.

INTRODUCTION: The frequent occurrence of hemodynamic responses to laryngoscopy and endotracheal intubation has attracted the attention of anesthesiologists since 1940's. Ensuing tachycardia, rise in blood pressure, sometimes dysrhythmias that occur during intubation are potentially harmful especially in patients with cardiac problems and raised intracranial pressure. In hypertensive patients, the cardiovascular responses to laryngoscopy and intubation are exaggerated due to the narrow arterial lumen, blunted baro reflex responses and increased sympathetic activity.[1]

Most studies have been conducted to attenuate this response. The search for effective attenuation of these responses include IV or topical lignocaine,[2] vasodilators[3] like NTG, adrenergic blockers, narcotics[4] and inhaled anesthetics,[5] using deeper plane of anesthesia, calcium channel blockers, opioids etc.,

METHODS: The study was conducted after approval from the hospital ethical committee. After an informed written consent, 100 adult patients of either sex and of physical status ASA I/II who were scheduled for various elective surgeries (General Surgery, Ortho, ENT) were selected for the study.

Inclusion Criteria Age: 18 to 55years, ASA physical statues: I/II.

Exclusion Criteria: 1) Emergency surgeries 2) ASA physical status III or more 3) patients with Neurological and endocrine abnormalities 4) Patients with renal impairment and hepatic diseases 5) Patients with valvular heart disease; hypertension IHD;

100 cases were divided into two groups with 50 cases in each group.

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Group I: All patients in this group received oral Clonidine 3 µg/kg 90 minutes before surgery.

Group II: All the patients in this group received oral Ranitidine 150mg, 90 minutes before surgery.

On the day of surgery systolic blood pressure (SBP) , diastolic blood pressure (DBP) ; heart rate and respiratory rate were measured before premedication and for 90 minutes after. Scoring was done for sedation, anxiolysis and antisialogogue effects 90 minutes after premeditation. Other unwanted effects like hypotension, bradycardia and vomiting were evaluated.

The following scoring system was used.

Degree of sedation	Score
Asleep	3
Moderately drowsy (drowsy but arousable)	2
Mildly drowsy (awake but un-communicative)	1
Awake and talkative	0
Sedation score (4 point scale)	

Degree of anxiety	Score
Quite or comfortable	0
Uneasy	1
Anxious or worried	2
Very upset/worried	3
Frightened or terrified	4
Anxiety score (5 point scale)	

Degree of Dryness	Score
Dry mouth	2
Moist	1
Wet	0
Antisialogogue effect score (3 point scale)	

Antisialogogue effect was scored by checking drying of mouth with a blotting paper by blotting the tongue and inner aspect of check for 30 seconds each. After the above assessment an 18g intravenous cannula was inserted and infusion of lactated ringer solution was given throught the study. Patients were connected to the Multi Para Monitor to know the non-invasive Blood Pressure. (NIBP), ECG in lead II, SP02 before induction.

Anaesthesia Technique: All the patients were pre oxygenated with 100% oxygen for 5 minutes before induction. Anaesthesia was induced with injection.

Thiopentone sodium 2.5% dose being 4-5 mg/kg which was administered slowly till the loss of eyelash reflex. Injection Succinylcholine was administered at a dose of 1.5mg/kg. i. v. Laryngoscopy was done with standard Macintosh blade. Intubation was done with appropriate sized disposable high volume, low pressure cuffed endotracheal tube.

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The patients were maintained with Nitrous oxide and Oxygen and injection Vecuronium (0. 1mg/kg stat) incremental doses of which was given every 20 minutes. SBP, DBP, & HR were monitored during induction and at 1, 5, 10, 15 and 30 minutes, after intubation. A sedative was not given routinely and was given only if deemed necessary on the basis of haemodynamic criteria. At the end of surgery, reversal was done with Inj. Neostigmine 0. 05mg/kg and inj. Glycopyrolate 0. 01mg/kg. Extubation done and patients were shifted to recovery ward for further observations.

The data were statistically analyzed. Pair wise comparison between the groups was done by repeated measure of ANOVA test, Bonferroni test and followed by students unpaired't' test. For all the tests, a 'p' value of ≤ 0. 05 were considered significant. Chi-square test was also used.

Particulars	**Group I**	**Group II**	
Age (y)	39.04±12.07	40.26±12.5	p>0.05 NS
Sex (M/F)	29/21	28/22	x2=0.0815 p>0.05 N.S
Weight (Kg)	53.2±7	59.9±6.9	p>0.05 N.S.

Table 1: Demographic Profile

NS: Non-significant

Sedation Score	**Group I (Clonidine)**		**Group II (placebo)**	
	N	%	N	%
0	20	40	45	90
1	18	36	5	10
2	12	24	0	0
3	0	0	0	0
Total	**50**	**100**	**50**	**100**

Table 2: Sedation score

In group I, sedation score of 0 (fully awake) was seen in 20 (40%) patients; score 1 in 18 (36%) patients, score 2 was seen in 12 (24%) patients and no patients had a score of 3. In group II patients sedation score "0"s was seen is 45 (90%) patients and score 1 in 5 (10%) patients. No patient had a score of 2 and 3. There was a significant difference in sedation between the two groups (p<0.001).

Anxiety Score	**Group I (Clonidine)**		**Group II (placebo)**	
	N	**%**	**N**	**%**
0 (quiet/comfortable)	32	64	0	0
1	18	36	7	14
2	0	0	26	52
3	0	0	12	24
4 (Frightened/terrified)	0	0	5	10
Total	**50**	**100**	**50**	**100**

Table 3: Anxiety score

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Anxiolysis was assessed on a 5 point Anxiety score. In group I, score 'o' was seen in 32 (64%) patients and a score of 1was seen in 18 (32%) patients. There were no cases in score range of 2, 3 and 4. In group II no. patients showed 0 score and score of 1was observed in 7 (14%) patients, Score of 2 in 26 patients (52%) , score of 3 in 12 patients (24%) and score of 4 in 5 patients (10%).

The anxiolysis was found to be highly significant between the two groups (p<0.001). The group I (Clonidine) showed better score than the group II.

Antisialogogue	Group I (Clonidine)		Group II (placebo)	
	N	%	N	%
0 (wet mouth)	3	6	27	54
1	20	40	23	46
2 (dry mouth)	27	54	0	0
Total	**50**	**100**	**50**	**100**

Table 4: Anti-sialogogue effect score

In group I, Antisialogogue effect score 'o' was seen in 3 patients (6%) , score 1 in 20 patients (4o%) and score 2 in 27 (54%) patients. In group II, antisialogogue score 'o' was seen in 27 patients (54%) score 1 in 23 patients (46%) and no patient had a score of 2. There was a significant difference in the antisialogogue effect between the two groups. P (<0. 001).

	Group I (Clonidine)	Group II (placebo)
Minimum	150	175
Maximum	350	350
Mean	216. 5	250
Std. deviation	38. 0	40. 72

Table 5: Dosage of Thiopentone in mg

From the above data it is clear that oral Clonidine premeditated group required less dosage for induction when compared to the placebo group.

Time of assessment	Group I (Clonidine)	Group II (Placebo)	Within the group changes from Pre-op value in Group I (%)	Within the Group changes from Pre-op value in group II	Group I V/s Group II.pValue
pre-op	73.0 ± 4.5	78.4±8.1			
Induction	73.1 ± 4.5	78.8±8.2	0.1 (0.17%)	0.08	>0.05 NS
1 m	89.8 ± 7.2	108.0±9.8	16.8 (24%)	29.3	<0.001
3 m	84.5 ± 7.1	105.5±10.1	11.5 (165%)	26.8	<0.001
5 m	81.6 ± 6.4	101.2±8.5	8.6 (12%)	22.5	<0.001
10 m	78.6 ± 6.9	97.8±7.3	5.6 (5.6%)	19.4	<0.001
15 m	76.2 ± 6.5	93.3±7.8	3.2 (4.5%)	14.9	<0.001
30 m	74.8 ± 6.0	82.7±7.4	1.8 (4.5%)	4.3	<0.05

Table 6: Within the group and between the group comparison of changes in Mean Heart Rate, presented as HR ±SD

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Analysis of HR: Group I (Clonidine) - The preoperative mean HR with standard deviation in this group was 73.0 ± 4.5. At 1 minute from the onset of laryngoscopy, a 24% increase in mean HR was observed with values of 89.8 ± 7.2 and remained high. Subsequently a decreasing trend in HR was noted starting from 3 minutes to 30 minutes after laryngoscopy. The HR at the end of 30 minutes was 74.8 ± 6.0, which was not significantly higher than the preoperative values. In group II, the mean HR was 78.4 ±8.1. At 1 minute from the onset of laryngoscopy the HR rose to 108.0 ± 9.8 with an increase of 37.7% from the pre-operative value. At 3 minutes HR was found to be 105.5 ±10.1.Subsequently a decreasing trend in HR was noted from 3 to 30 minutes after laryngoscopy. The Heart rate at 30 minutes was 82.7 ± 7.4, which was significantly higher than the pre-operative values. The difference in HR between (group I Clonidine) and Group II (Placebo) remained highly significant at all times of assessment (P<0.001) except at 30 minutes when it was just significant (P<0.05) .Premedication with Clonidine showed favorable responses towards attenuation of HR.

Time of Assessment	Group I	Group II	within the group changes from pre-operative value in Group I		within the group changes from pre-operative in group II		Group I V/s Group II P. Value
Pre -op	116.5±13.6	119.5±13.6		%			
Induction	115 ± 8.5	120.8±12.3	1.5	-1.29%	1.28	1.05%	p>0.05
1 m	130.8±8.1	154.1±9.9	14.32	12.30%	34.60	28.94%	p<0.001
3 m	126.9±8.2	149.6±8.8	10.36	8.90%	30.16	25.22%	p<0.001
5 m	123.6±8.3	143.8±8.4	7.12	6.13%	24.36	20.37%	p<0.001
10 m	119.8±8.7	137.5±8.7	3.36	2.90%	18.00	15.05%	p<0.001
15 m	117.5±8.7	130.6±9.5	0.6	0.53%	11.08	9.25%	p<0.001
30 m	115.6±8.6	119.0±12.8	0.64	-0.53%	0.44	0.35%	p>0.05

Table 7: Systolic Blood pressure presented as Mean ± SD's in mm Hg

Analysis of systolic Blood Pressure: In Group I (Clonidine) the mean preoperative systolic blood pressure was 116.5±8.7. At 1 minute following laryngoscopy a 12.3% increase in SBP was noted with a mean value of 130.8±8.1. SBP remained 126.9±8.2 at 3 minutes after laryngoscopy. There was a subsequent gradual fall in SBP and at 30 minutes SBP was just below the baseline with a mean value of 115.9±8.6. In Group II (Placebo) preoperative blood pressure was 119.5±13.6. There was a 28.9% increase in SBP following one minute after laryngoscopy with a mean value of 154.1±8.8. At 3 minutes SBP was found to be 149.6±8.8 SBP then decreased and at the end of 30 minutes. It was 119.0±12.8 (0.35% above the baseline) Clonidine group showed a better attenuation of Systolic Blood response compared to the Placebo group.

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Time of Assessment	Group I	Group II	within the group changes from the pre-operative value in Group I		within the group changes from the pre-operative value in group II		Group I V/s Group II p Value
Pre -op	80.4±7.4	80.9±7.3	-	-			P>0.05
Induction	80.6±7.7	82.2±7.4	0.2	0.3%	1.3	1.6%	P<0.001
1 m	89.3±6.0	98.8±5.1	8.9	11.09%	17.9	22.12%	P<0.001
3 m	87.0±6.0	94.5±4.9	6.6	8.16%	15.6	19.28%	P<0.001
5 m	83.9±6.3	91.4±5.9	3.5	4.4%	10.5	12.97%	P<0.001
10 m	82.2±6.3	88.5±5.2	1.8	2.2%	7.6	9.39%	P<0.001
15 m	80.4±7.0	86.2±5.9	0.0	0.05%	5.3	6.55%	P<0.001
30 m	80.2±7.0	84.4±6.4	0.2	0.2%	4.4	5.43%	P<0.05

Table 8: DBP in mm Hg ± SD

Analysis of DBP: Rise in the DBP in the Placebo group at laryngoscopy and intubation was significant. DBP at 1 minute of laryngoscopy showed an increase of 22.12%. While the corresponding increase in the Clonidine group was 11.09%. Attenuation of DBP by Clonidine as compared to Placebo was highly significant until 15 minutes (P<0.001) and at 30 minutes it was statistically significant. (p<0.05)

DISCUSSION: It is well documented that laryngoscopy and endotracheal intubation following induction of anesthesia is commonly associated with hemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngo- pharyngeal stimulation.[6] The more common responses to airway manipulation are hypertension and tachycardia mediated by cardio accelerator nerves and sympathetic chain ganglion.[7] This response includes wide spread release of norepinephrine from the adrenergic nerve terminals and epinephrine from adrenal medulla.[8]

Hypertensive response to the endotrachial intubation partly results from the activation of renin- angiotensin system, which is innervated by beta adrenergic nerve terminals. This increased sympatho-adrenal activity may frequently result in hypertension, tachycardia and arrhythmias.[9] The average increase in BP by 40-50% and 20% increase in heart rate have been observed. This increase in BP and Heart rate are usually transitory, variable and unpredictable. Transitory hypertension and tacdrycardia are probably of no consequence in healthy individuals.[10]

But either or both may be hazardous to those with pre-ecclampsia, myocardial insufficiency or cerebrovascular diseases.[11] This sympatho adrenal responses to laryngoscopy results in an increased cardiac work load which in turn may culminate in preoperative myocardial ischemia and acute heart failure in susceptible individuals. This response is undesirable in any patient with heart disease and HBP. Various agents have been used to attenuate hypertensive response including topical lignocaine sprays, deeper plane of anesthesia by inhalational agents, narcotics like fentanyl, sufentanil, Magnesium sulphate, calcium channel blockers[12] Vasodilators like SNP & NTP. There is increasing evidence that control of heart rate and blood pressure response to endotracheal intubation is essential to prevent adverse cardiovascular outcomes.[13,14]

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Heart rate is a major determinant of myocardial oxygen consumption and tachycardia is poorly tolerated in patients with coronary artery diseases. Studies show that incidence of myocardial ischemia is high when intra operative heart rate exceeds 110/minutes.[15] Clonidine hydrochloride is an imidazole derivative. It is a centrally acting adrenergic agonist that lowers blood pressure by decreasing basal sympathetic nervous system activity. It is rapidly absorbed from G. I tract.

The onset of action is within 30-60 minutes with peak effect occurring 2-4 hours after oral administration. Peak plasma levels occur at 90 minutes and the plasma half-life is 6-15 hours.[16] Clonidine is metabolized mainly by the liver. Approximately 40 to 60% of an oral dose is excreted unchanged in the urine within 24 hours. It is thought to act by selective stimulation of post synaptic adrenergic receptors in the central nervous system, more specifically the nucleus tracus solitarius of medulla oblongata and hence the reduction in catecholamine levels. This causes inhibition of basal efferent sympathetic vasoconstrictor effects on the peripheral and renal vasculature.[17]

The decrease in heart rate during Clonidine therapy reflects vagal stimulation or S. A node inhibition. Stimulation of inhibitory sympathetic nerves results in increased vagal tone. In addition Clonidine has presynaptic agonist activity. This may inhibit neurotransmitter release and contribute to the decrease in circulating norepinephrine concentration, found during Clonidine therapy. Its side effects are dry mouth and sedation. Clonidine has been used a premedicant drug.[18] It reduces anesthetic requirement, improves hemodynamic stability especially during laryngoscopy and intubation and also potentiates post-operative analgesic regimens.

Sedation: Sedation was assessed on a four point scale prior to induction of anesthesia. In Clonidine group, 'O' score (awake) was seen in 20 patients (40%) and score 1 was seen in 18 patients (36%), and 12 patients (24%) had a score of 2 (moderately drowsy). In Placebo group (oral ranitidine) sedation score of '0' was seen in 45 (90%) patients and score of 1 in 5 patients (10%) Raval DL et al[19] in their study showed sedation score of 'o' in 42.5%; score 1 in 49.5%, score of 2 in 5% and a score of 3 (asleep) in 3% patients in the Clonidine group. This study by Raval et al showed better sedation with oral Clonidine in comparison to Placebo which produced less sedation. The sedative action of Clonidine may be due to decreased tonic activity of locus coeruleus.

Anxiolysis: Anxiolysis is one of the requirements of a good premedicant. Scoring was assessed on a 5 point Anxiety scale prior to induction of anesthesia. In Clonidine group 32 patients (64%) were comfortable (score 0) and 18 patients (36%) had a score of 1 (uneasy) and no cases were observed with a score of 2, 3, 4. In the placebo group, no patients were observed with a score of 0; 7 patients (14%) were of score 1; 26 patients (52%) had a score of 2, 12 patients (24%) had a score of 3 and 5 patients (10%) were with a score of 4. The anxlolysis was found to be highly significant in the clonidine group. This was comparable with study by Raval DL et al,[19] in which after Clonidine premedication 85% of patients were comfortable and 12.5% of patients were uneasy and 2. 5% patients were anxious whereas in the placebo group 50% were comfortable, 30% were uneasy and 20% were anxious. Anxlolysis caused by Clonidine is elicited at central alpha-2 adrenoceptors. Hence it can be considered as an anesthetic adjuvant.

Antisialogogue Effect: Clonidine premedication is accompanied by a substantial degree of dryness of mouth. This is due to the effect of drug on presynaptic alpha adrenoceptors in the brain stem as well as on parasympathetic nerves which supply the salivary glands.

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In our study Clonidine group showed a score of 0 (wet mouth) in 6% patients, score of 1 in 40% patients and score 2 (dry mouth) in 54% patients. Placebo group showed a score of 0 in 54% patients; score of 1 in 46% patients Raval DL et al[19] showed better antisialogogue effect of 80% with a score 2 (dry mouth) in Clonidine group compared to only 30% in Placebo group.

Dosage of Thiopentone: Clonidine has been found to reduce the inducing dose of Thiopentone and the MAC values of inhalation anesthetics. In our study Clonidine produced a significant reduction in the inducing dose of Thiopentone with a mean dose of SD of 216.5±38.0 mg as compared to placebo groupwith a mean Thiopentone dose of 250±40.72mg. Similar findings were observed by carobine U. A, Wright PMC; Moore J who observed a reduction in the sleep dose of Methohexitone after Clonidine premedication.[20]

Heart Rate: The increase in mean HR at 1 minute of laryngoscopy was 24% in Clonidine group while it was 37.7% in placebo group. It reached a value which was clinically less significant by the end of 30 minutes in Clonidine group while HR remained on a higher range in the placebo group. Attenuation of HR response to laryngoscopy was statistically highly significant in Clonidine group when compared with placebo group.

A similar finding was found in a study done by Roy s et al.[21]

SBP: The maximum increase of SBP at 1 minute after laryngoscopy was by 12.3% in Clonidine group, while the rise was by 28.9% in the placebo group. The attenuation of SBP response to laryngoscopy and intubation by Clonidine was statistically significant ($p<0.001$).

Study by Pouttu J et al[22] showed similar results.

DBP: Maximal rise in DBP was 11. 09% in Clonidine group and it was 22.13% in Placebo group ($p<0.001$).

None of the patients in the Clonidine group had bradycardia and hypotension.

CONCLUSION: Oral Clonidine proved to be a good agent for the attenuation of haemodynamic responses to laryngoscopy and intubation. Anxyolysis and sedation induced by Clonidine is better compound to placebo.

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DOI: 10.14260/jemds/2015/808

ORIGINAL ARTICLE

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FINANCIAL OR OTHER COMPETING INTERESTS: None

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Date of Submission: 23/03/2015.
Date of Peer Review: 24/03/2015.
Date of Acceptance: 08/04/2015.
Date of Publishing: 20/04/2015.