Comparision Of Two Doses Of Oral Clonidine As A Premedicant For Attenuation Of Pressor Response To Laryngoscopy

Dr. Shah Hetal D , Dr. Shah Megha***

*Assistant Professor, B.JMedical College,** Consultant cardiac anesthetist Narayana Hrudayalaya Hospital, Ahmedabad , Gujarat, India

Abstract: Background: The present study compared oral clonidine 0.3mg with 0.2 mg to attenuate hemodynamic response to laryngoscopy and intubation and also to evaluate the optimal dose of oral clonidine as premedication. Methods: A prospective, randomized, double blind trial performed on 40 patients of ASA Grade I & II, scheduled for planned ENT surgeries under general anaesthesia. Patients were divided into 2 groups depending on oral clonidine dose given 90 mins prior to induction. Group A received 0.3 mg while group B received 0.2 mg clonidine. Heart rate, SBP, DBP, MAP were monitored at various time intervals e.g. before premedication, before induction, at laryngoscopy, intubation, immediately after intubation and post intubation for 30 minutes. Patients were anesthetized with sodium thiopentone (2.5%) 5-7 mg/kg followed by suxamethonium 2 mg/kg i.v. Results: We observed a significant decrease in mean HR,SBP,DBP,MAP in both the groups (clonidine 0.2 and 0.3mg) as compared to baseline and preinduction level. Tablet Clonidine 0.3 mg proved to be significantly effective in checking the rise in SBP. A highly significant ($p < 0.01$) fall in DBP was observed in Group A at 1, 3, 15, 30 mins post intubation as compared to Group B. At 3 min, 15 min and 30 min interval, highly significant ($p <0.01$) decrease in MAP observed with clonidine 0.3mg as compared to 0.2mg. In this study, no patient encounter complications like bradycardia, hypotension. Conclusions: Oral clonidine 0.3 mg premedication in adult patients 90 mins prior to induction is safe, convenient and more effective in suppressing the hemodynamic response to laryngoscopy & intubation as compared to clonidine 0.2 mg. [Shah M et al NJIRM 2013; 4(2) : 5-10]

Key Words: clonidine, premedication, pressure response, laryngoscopy

Author for correspondence: Dr. Shah Megha, Assistant Professor, B.J.Medical college, Ahmedabad, Gujarat, India. E-mail: mkshah_80@yahoo.com

Introduction: General anaesthesia with muscle relaxant using controlled ventilation involves laryngoscopy and intubation. Stimulation of supraglottic region by laryngoscopy and that of subglottic region by endotracheal tube leads to sympathoadrenal reflex due to more secretion of nor epinephrine than epinephrine[1] The response reflected as tachycardia, hypertension. However, ischemia, left ventricular failure, ventricular ectopies, heart block and intracerebral haemorrhage can also be precipitated in susceptible individuals. Various agents like intravenous or topical lidocaine, vasodilators, calcium channel blockers (CCBs), β-Blockers, α-adrenergic agonists and opioids have been used to blunt the hemodynamic response. All have potential drawbacks, which limit their application as a premedication. The use of drugs given before operation that could enhance the hypotensive action of inhalation agents without the disadvantages of intravenous vasodilators would be desirable. [2]

Clonidine, a centrally acting antihypertensive agent, reduces the sympathetic outflow via alpha 2 – adrenergic receptor activation in medulla oblongata. It also posses many properties of an ideal premedicant like analgesic, sedative , decreasing anaesthetic requirement in addition to attenuation of reflex cardiovascular response to tracheal intubation and providing hemodynamic stability during surgery. Clonidine does not alter the baroreceptor reflex or peripheral muscle sympathetic nerve activity in healthy human.

Persistent hypertension and tachycardia may be deleterious in surgeries where hypotensive anaesthesia is required or in surgeries where there is maximum chances of sympathetic stimulation like head and neck surgeries, ENT surgeries and also in patients with cardiac or cerebral diseases. This study was done in ENT patients as they differ from other patients because there are maximum chances of sympathetic stimulation in ENT surgeries. Also, they are more prone to complications like PONV. Clonidine has already proved its efficacy as an attenuating agent in various studies. [3, 4, 5] Hence, the study was aimed to evaluate safety, efficacy and to decide the optimal dose of oral clonidine as a premedication for

maximum possible attenuation with minimum side effects.

Material and Methods: The study was conducted on 40 patients of either sex, classified as American Society of Anaesthesiologists (ASA) physical status I &II scheduled for planned ENT surgeries. The study was conducted in accordance with Good Clinical Practice(GCP) guidelines. [6]Excluded were the patients with age less than 18 years; ASA status III and IV; systolic blood pressure (SBP) >160 mm Hg; diastolic blood pressure(DBP) >90 mm Hg or pulse rate <50 beats/min ; liver, renal, haematological, and left ventricular dysfunction; known hypersensitivity to the study drugs at the time of the pre-anaesthetic visit.

Premedication: Pre study evaluation considered as baseline values. All patients were kept nil per orally for 8 hours. On day of operation, vital signs were recorded. Written and informed consent was taken. Patients were divided randomly in two groups of 20 and also kept blinded to dose of clonidine they received as premedication.
Group A: Tablet clonidine 0.3 mg and
Group B: Tablet clonidine 0.2 mg given 90 min prior to induction of anaesthesia. This period of time ensures maximum plasma concentrations after oral ingestion of the drug.

Induction: Preoxygenation was done with 100% O2 for 5 minutes. Patients were induced by administrating 5-7 mg/kg thiopentone I.V. slowly over 60 seconds. Following ventilatory tests succinylcholine 2mg/kg IV was given. The patients were ventilated with 100% O2 via face mask attached to a Bain's s breathing system receiving a fresh gas blow of approximately 90ml/kg. Additional agents were not given to attenuate the stress response of laryngoscopy and intubations were done using Macintosh blade. Trachea was intubated with adequate size portex cuff tube. Pulse rate, systolic blood pressure (SBP), diastolic blood pressure(DBP), mean arterial pressure (MAP),RPP, SpO2 and ECG were measured at various time intervals e.g. before premedication, before induction, at laryngoscopy , intubation, immediately after intubation and post intubation at 1, 3, 5,15,30 mins. Anaesthesia was maintained by using O_2-N_2O (50:50) midazolam, isoflurane and non depolarising muscle relaxant Vecuronium. Fentanyl was given in 1 mcg/kg in induction and after the end of study time e.g. after half an hour of intubation, additional 2 mcg/ kg in gradual doses. Patients were monitored for complications like bradycardia (Heart rate < 60 beats/min), hypotension (SBP<90mm of Hg), arrhythmia, excessive sedation, post operative nausea and vomiting (PONV). Bradycardia was planned to treat with Inj. Atropine. Hypotension was planned to treat with I V fluids and if required Inj. Ephidrine. The perioperative analgesia was maintained with injection tramadol i.v.30 mins before extubation in both groups.

Statistical Analysis: The results were expressed as mean ± SD and analyzed using student's t- test and ANOVA. Data were computed for statistical analysis using sigma stat software (version 3.5). The difference between two groups consider significant at p <0 .05 while p <0 .01 is highly significant.

Results: In both groups, most of the patients were operated for mastoidectomy followed by nasal and thyroid surgery. In group A 12 (60%) while 11 (55%) in group B, were of ASA status I. Table-1 shows baseline characteristics of patients. Patient's baseline data were comparable. Majority of patients were between 20-29 yrs of age group. Female had predominance over males in both the groups. Basal heart rate in both groups was 70-110 beats/min. SBP in both groups were 100-150 mm Hg. All pts had basal DBP between 70-90mmHg. In both the groups, basal mean arterial pressure (MAP) was between 81-110 mmHg with equal distribution.

Effect on SBP: Decrease in SBP in both groups compared at various time intervals. After 90 mins of premedication (preinduction), a highly significant (p<0.01) mean fall in SBP (122 to 103) in group A and (123 to 111) in group B as compared to basal was observed. While comparing both the groups, significant (p <0 .05) fall in SBP was observed in Group A at preinduction and during

scopy. Premedication values were attained only after 1 min in Group A, while it took 15 mins in Group B. (Table 2)

Table-1 Baseline Characteristics

Sr No	Characteristics	Group A (mean ± S D)	Group B (mean ± S D)	p Value
1	Age	31.55	28.85	> 0.1
2	Sex (M/F)	9/11	8/12	
3	Weight	50 ± 5.9	50 ± 4.8	> 0.1
4	Heart rate	93.9 ± 11.9	95.1 ± 10.6	> 0.73
5	SBP	122 ± 13.6	123 ± 12.7	0.8
6	DBP	81 ± 7.6	78 ± 6.5	0.2

SD-Standard Deviation, SBP-Systolic Blood , Pressure(mmHg), DBP- Diastolic Blood Pressure(mmHg),

Table-2 Effect of oral clonodine 0.3mg and 0.2mg on SBP at various intervals

Event	Group A(mean ± SD) (mmHg)	Group B (mean ± SD) (mmHg)	p value
Basal	122 ± 13.6	123 ± 12.7	0.811
Preinduction	103 ± 10.9††	111.1± 11.92 †	0.03*
Scopy	109 ± 11.6	118± 11.3	0.017**
1 min	102 ± 10.1	114 ± 12	0.0014**
3 min	102 ± 10.7	118 ± 13.5	0.0001**
5 min	106 ± 12	112 ± 11.9	0.119
15 min	95.5 ± 11	108.3 ± 11.56	0.0068**
30 min	94.7 ± 10.1	106.3 ± 9.565	0.0005**

†- significant, ††-Highly significant(comparing respective group with basal), *- significant, **-Highly significant (comparing both groups)

Effect on DBP: After 90 mins of premedication (preinduction), a highly significant ($p<0.01$) fall in mean DBP (81 to66) was observed in group A while that in group B was significant (78 to75) as compared to basal. A highly significant ($p < 0.01$) decrease in DBP was observed with clonidine 0.3mg group at 1,3,15,30 mins post intubation as compared to 0.2mg. (Table-3)

Table-3 Effect of oral clonodine 0.3mg and 0.2mg on DBP

Event	Group A(mean ± SD) (mmHg)	Group B (mean ± SD) (mmHg)	p value
Basal	81 ± 7.6	78 ± 6.5	0.18
Preinduction	66 ± 16 ††	75 ± 6.1 †	0.13
Scopy	73 ± 5.5	75 ± 10	0.38
1 min	70 ± 6.7	75.5 ± 6.287	0.010**
3 min	70 ± 7.3	78 ± 6.9	0.0009**
5 min	71.5 ± 6.08	73.2 ± 5.82	0.371
15 min	65 ± 5.6	73.7 ± 6.63	0.00005**
30 min	65 ± 6.2	73.8 ± 5.064	0.00001**

†- significant, ††-Highly significant(comparing respective group with basal), *- significant, **-Highly significant(comparing both groups)

Table-4 effect of oral clonodine 0.3mg and 0.2mg on MAP

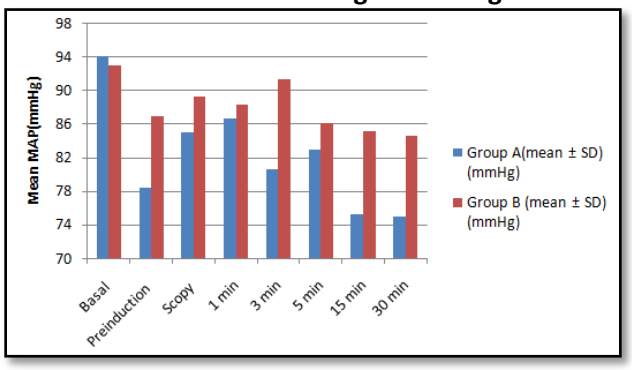
Event	Group A(mean ± SD) (mmHg)	Group B (mean ± SD) (mmHg)	p value
Basal	94.08 ± 10.24	93 ± 7.9	0.71
Preinduction	78.4± 12.4 ††	86.9 ± 7.3 † †	0.11
Scopy	85 ± 6.7	89.3 ± 8	0.07
1 min	86.67 ± 6.847	88.33 ± 7.403	0.46
3 min	80.6 ± 7.19	91.4 ± 8.37	0.00007**
5 min	82.9± 7.24	86.1 ± 6.92	0.10
15 min	75.2 ±6.76	85.2 ± 7.51	0.00006**
30 min	75 ± 6.84	84.63 ± 6	0.00002**

Table-5 effect of oral clonodine 0.3mg and 0.2mg on mean heart rate

Event	Group A(mean ± SD)	Group B (mean ± SD)	p value
Basal	93.9 ± 11.9	94.1 ± 10.6	0.737
Preinduction	82± 7.5 ††	86 ± 9.11 †	0.028
Scopy	87.1± 9.81	93 ± 10.4	0.118
1 min	83± 7.9	88.8 ± 9.96	0.047*
3 min	81 ± 7.3	96.8 ± 10	0.000001**
5 min	83.8± 8.56	88.4 ± 10.4	0.134
15 min	80 ±6.6	84.2 ± 7.4	0.06
30 min	75 ± 8.6	84.5 ± 7.1	0.00016**

Effect on MAP : From Table-4 it is evident that MAP was decreased in both groups as compared to basal. After 90 mins of premedication (preinduction), a highly significant (p<0.01) mean fall in MAP was observed in both groups as compared to basal. During laryngoscopy rise in MAP compared to pre induction values was observed but never attained basal values in both the groups. A highly significant (p <0.01) decrease in MAP observed in group A(**clonodine 0.3mg**) as compared to group B at 3 ,15 and 30 min after intubation.(Figure-1)

Figure-1
Effect of oral clonodine 0.3mg and 0.2mg on MAP



Comparision of heart rate in both the groups: Table-5 shows the comparision of mean heart rate in both groups. During laryngoscopy heart rate was much below the baseline values in group A, while in group B it touched almost the base line. After 90 mins of premedication (preinduction),a highly significant (p<0.01) fall in mean heart rate (11) was observed in group A while that in in group B was also significant (9; p<0.05) as compared to basal. Heart rate remained much below the base line values in group A during post intubation period. While in Group B it remained much near to base line till 3 mins. Group A showed highly significant (p<0.01) fall in heart rate at 3 and 30 mins post intubation as compared to group B.

Intraoperative or postoperative complication like nausea, vomiting, hypotension, sedation, and bradycardia were not detected in any group.

Discussion: This study showed that tablet Clonidine single dose is effective in controlling hemodynamic response to intubation. However, tablet Clonidine 0.3 mg proved to be significantly effective in checking the rise in SBP, DBP, MAP and HR as compared to 0.2mg at various time intervals. Different studies used clonidine 2 to 5 mcg/kg.

However, the best suitable preanesthetic dose is not well established. The effects of clonidine on sedation and hemodynamic variables are dose related and increasing the dose to more than 4 mcg/kg does not further enhance efficacy.[7] Kulka and colleague[8] blunted catecholamine release during intubation with 4mcg/kg clonidine and showed that larger clonidine doses(5 mcg/ kg oral)were not more effective. Smaller doses, however, were not sufficient to blunt the reaction to laryngoscopy. Aho et al [9] observed that rise in blood pressure and heart rate was less in both the groups (clonidine 3 mcg/kg and 4.5 mcg/kg I.M.) but 4.5 mcg/kg clonidine produced greater fall in mean arterial pressure before induction when used for suppression of haemodynamic response to pneumoperitoneum. Oral clonidine 4mcg/kg (maximum 0.2mg) premedication produced blunting of haemodynamic responses during laryngoscopy and endotracheal intubation and less sedation and same level of anxiolysis as compared to diazepam .[10]Another study by Kamran and colleagues, comparing the efficacy of oral gabapentin and clonidine 0.3mg premedication for controlling the pressor responses to laryngoscopy and tracheal intubation showed significant decrease in HR and RPP in both groups after tracheal intubation compared with those just before laryngoscopy (p < 0.05). SBP, DBP, and MAP at 1, 3, 5, 10, and 15 minutes after intubation were significantly lower compared with baseline. [11] In another study clonidine 5 mcg/kg significantly lowered MAP values in coronary bypass patients and undoubtedly contributed to isoflurane-sparing effect. [12] J. M. Marchal and colleagues done a prospective, randomized, double-blind, placebo-controlled study that showed oral clonidine 0.3mg premedication during middle ear surgery reduces bleeding, provides hemodynamic stability and also reduced isoflurane, fentanyl, and uraidil

requirements. [13]Oral clonidine 0.2mg premedication provided significant stability over hemodynamic response to intubation compared to placebo. [14] U.A. Carabine and colleagues [(3)] observed bradycardia (not required treatment) and its association with high dose, while we observed decrease in heart rate at various time intervals but no bradycardia. The reason for more effectiveness of 0.3mg over 0.2mg could be appropriate dose to act on receptors.

To best of our knowledge, no published study compared oral clonidine doses in ENT patients. So, we compared and found that a highly significant ($p < 0.01$) decrease in SBP,DBP and MAP observed with clonidine 0.3mg as compared to 0.2mg at various time interval after intubation without increasing adverse effects. Though our study is limited by small sample size, it provides a useful guide for selection of dose of clonidine. There are few limitations of our study. As this being a time frame study, we have not calculated the sample size before starting the study. Laryngoscopy and intubation is known to cause sympathetic stimulation and so release of catecholamines even in the deeper plane of anesthesia. Drugs used to attenuate this response are either sympathetic blocker, drugs decreasing catecholamines or vasodilators. Though we did not measure catecholamine levels thinking we were comparing one drug only, measuring catecholamine levels might indicate which drug produces maximum fall .Inspite of these limitations, study throws light on selection of oral clonidine dose in ENT patients.

Conclusions: It is concluded that oral clonidine 0.3 mg premedication in adult patients given 90 mins prior to induction is safe, convenient and more effective than 0.2 mg in checking the hemodynamic response to laryngoscopy and intubation without any fearful complications.

Refferences

1. Millar Forbes, F. G. Dally. Acute Hypertension during induction of anesthesia and endotracheal intubation in normotensive man. Br. J. Anaesth1970; 42 suppl7: 618-24. doi: 10.1093/bja/42.7.618
2. J. M. Marchal, A. Mez-Luque, F. Martos-crespo, F. sa´ nschezde la cuesta, M. C. MARTı´NEZ-LO´ PEZ4 and A. D. DELGADO-MARTINEZ. Clonidine decreases intraoperative bleeding in middle ear Microsurgery .Acta Anesthesiol Scand 2001; 45 :627- 33
3. U.A. Carabine, P.M.C.Wright, J. Moore. Preanesthetic medication with clonidine: A dose response study .British journal of anesthesia 1991; 67 :79-83.
4. Lemes, E.I.,F.van der fruz, P.H.Homrich, A.P.stolz, J.C.de Freitas and E.A.Fortis. Preoperative intravenous clonidine in the surgical treatment of cataract:Evaluation of the clinical benefits.Rev.bras.Anestesiol.2008,58:342-53.
5. Doak GJ , Duke PC. Oral clonidine premedication attenuates the haemodynamic effects associated with ketamine anaesthetic induction in humans. Can J Anaesth.1993; 40suppl7:612-8.
6. Good clinical practices- Guidelines for clinical trials of pharmaceutical proucts in india. New Delhi: Ministry of Health and Family Welfare, Government of India,2001.
7. Laurito C.E., Baughman V.L. Becker G.L., Cunningham F.,Pyaon B.H. and Citron G.M. *Oral* clonidine blunts the haemodynamic responses to brief but not prolonged laryngoscopy. Journal Clni Anaesth 1993; 5suppl1:54-7.
8. Kulka peter J., Tryba Michael and Zenz Micheal. Dose response effects of intravenous clonidine on stress responses during induction of anaesthesia. Anaesthesia and Analgesia. 1995;80: 263-8.
9. Aho M, Scheinin M, Lehtinen AM, et al. Intramuscularly administered dexmedetomidine attenuates haemodynamic and stress responses to gynaecologic laparoscopy. Anesth Analg 1992; 75 : 932-9.
10. Dr. Dipak L. Raval, Dr. Malini K. Mehta**.** Oral clonidine premedication for attenuation of haemodynamic response to laryngoscopy and tracheal Intubation. Indian J. Anaesth 2002; 46 suppl2 : 124-9.
11. Kamran Montazeria, Parviz Kashefia, Azim Honarmanda, Mohammadreza Safavia, Anahita Hirmanpourb. Attenuation of the pressor

response to direct laryngoscopy and tracheal Intubation: oral clonidine vs. oral gabapentin premedication.

12. Ian R. Thomson, Mark D. Peterson, and Robert J. Hudson.A Comparison of Clonidine with Conventional Preanesthetic Medication in Patients Undergoing Coronary Artery Bypass Grafting. Anesth Analg 1998;87:292-9.
13. J. M. Marchal, A. Go Mez-Luque, F. Martos-Crespo, F. Chezdela Cuesta, M. C. Martinez-Lo Pez , A. D. Delgado-Martinez. Clonidine decreases intraoperative bleeding in middle ear Microsurgery. Acta Anaesthesiol Scand 2001; 45: 627–31.
14. H.Talebi, A.Nourozi, S.Fatech, A.Mohammadzadeh. Effects of oral clonidine premedication on response to laryngoscopy and tracheal Intubation:A Clinical trial. Pakistan journal of biological sciences 2010;13(23):1146-50.

Conflict of interest: None
Funding: None