

A Comparative Study of Oral Clonidine versus Oral Pregabalin in Attenuating Haemodynamic Response to Laryngoscopy and Endotracheal Intubation in Elective Surgeries

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Abstract

Background: Haemodynamic changes to laryngoscopy and endotracheal intubation during elective surgeries are a major challenge to the Anaesthesiologist. Use of oral premedicants like Clonidine (200µg) and Pregabalin (150mg) can be useful. The primary objective of this study was to compare the effects of oral Clonidine (200µg) and Pregabalin (150mg) on mean arterial pressure (MAP) and heart rate (HR) during laryngoscopy. The secondary objective was to note any changes on sedation and post-operative nausea and vomiting (PONV).

Setting: The study conducted in a Tertiary Care Hospital of Kolkata, India.

Methods: Sixty adults, aged 18 to 60 years, of ASA physical status I or II, undergoing elective surgeries were randomized into 2 groups. Group C received tablet Clonidine (200µg) while group P received tablet Pregabalin (150mg), 90 minutes before the induction of general anaesthesia. Their MAP, HR were noted at different time points, and sedation scores and PONV were noted post-operatively. Statistical analysis was done using Wilcoxin test and p value < 0.05 will be considered as significant.

Results: There MAP values (during laryngoscopy, intubation, one and five minutes post-intubation) in group C were significantly lower compared to group P (p < 0.05). Similar trend was noted for heart rates (HR). The sedation scores and incidence of post-operative nausea and vomiting were significantly lower in group C compared to group P.

Conclusion: Oral Clonidine as compared to Pregabalin provides better control of mean arterial pressure and heart rate during laryngoscopy and intubation with lesser post-operative sedation and nausea/vomiting. Further large scale studies will be needed to corroborate these findings.

Keywords: Clonidine, Pregabalin, Laryngoscopy, Hemodynamic responses

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Introduction

Laryngoscopy and endotracheal intubation are an integral part of conduct of general anaesthesia. The associated hemodynamic response to laryngoscopy and intubation remain a major concern for the Anesthesiologists. This haemodynamic event is mediated by Vagus (X) and glossopharyngeal (IX) nerve which carry afferent signal from around the epiglottic region and activate the vasomotor center. [1] Direct laryngoscopy and intubation can increase the heart rate and blood pressure by 20-27% and 30-50% respectively. [2] The haemodynamic responses may be tolerated by healthy patients, but these may cause myocardial ischemia and cerebral hemorrhage in

those with a significant coronary artery or cerebrovascular diseases. [3]

Various pharmacological measures have been used to attenuate the deleterious haemodynamic effects of laryngoscopy and intubation. [4,5] Use of oral pre-medications are an area of special interest to attenuate the laryngoscopic response. But research with these oral pre-medications, specifically comparisons between different pre-medications remain limited. Clonidine is a selective alpha-2 adrenergic agonist which has sedative, anxiolytic and analgesic properties. [6] Clonidine is used as injectable, oral and in sub-arachnoid routes. Administration of oral

clonidine as a pre-medication can improve perioperative haemodynamic stability and reduce the intra-operative anaesthetic and post-operative analgesic requirements. [7] Pregabalin is structurally related to Gamma -Amino- Butyric Acid (GABA) and inhibits the synthesis of neurotransmitter glutamate. Oral pregabalin premedication cause sedation and analgesia and may have favourable cardiovascular effects. [8]

The primary objective of the present study was to compare the effects of oral Clonidine (200µg) and Pregabalin (150mg) for attenuating haemodynamic response to laryngoscopy/intubation (mean arterial pressure (MAP) and heart rate (HR) at different time intervals). The secondary objective was to compare post-operative sedation (measured by Ramsay sedation scores) and post-operative nausea and vomiting (PONV) in the two groups.

Methods

This double-blinded, randomised controlled trial was conducted from January to June 2022 in a tertiary care teaching hospital of Kolkata, West Bengal, India. The institutional ethics committee (IEC) approval was taken before beginning the study.

Sample size calculation:

The mean arterial pressure (MAP) was considered as the primary outcome variable in this study. Taking effect size of clinical interest i.e. difference in the means = $d = 9$ mm Hg, $SD = 12$ mm Hg $Z_{\alpha} = 1.96$ (corresponding to Type I error of 5% i.e.0.05) $Z_{\beta} = 0.842$ (corresponding to power of 95%) from previous studies, and using the formula $n > 2 \{ \{ Z_{\alpha} + Z_{\beta} \}^2 \times S.D.^2 / d^2$, the sample size came out to be 27.915 in each group. So, the study was started with 30 participants in each group.

Sixty patients aged 18–65 years, of both sexes, of the American Society of Anesthesiologists (ASA) physical status I and II, scheduled for elective surgeries (of expected duration less than 3 hours) under general anaesthesia were recruited. Patients with ASA Grade III and IV, having major systematic or psychiatric diseases, having anticipated difficult intubation, pregnant or lactating mothers, or patients taking clonidine or pregabalin in daily life are excluded from the study. On satisfying the inclusion and exclusion criteria, patients were informed about the study and written informed consent was obtained from all the recruited participants.

The recruited patients were randomly assigned into two groups using computer-generated random numbers. Group C received clonidine tablet (Tab. Arkamine® 0.2mg), while group P received pregabalin tablet (Tab. Pregaba® 150 mg). Allocation concealment was done using a serially numbered, opaque, sealed envelope technique. Each

patient's envelope was transferred to a dedicated nursing staff not involved in the study, who gave either clonidine or pregabalin tablets to the patients, depending on the randomization. Patients were kept nil per mouth (6 hours for solids and 2 hours for clear fluids) the tablets were given 90 minutes prior to surgery with sips of water. Envelopes containing the information about the randomization were sealed and kept with the principle investigator until the end of the study period. Patients, anaesthesiologists performing laryngoscopy and intubation, the investigator observing and recording the outcome parameters were blinded to the group allocation.

Pre-anaesthetic check-up was performed the evening before scheduled surgery. In the operating room, a standard general anaesthesia delivery protocol was followed as per the institutional norms. The standard monitors were attached and baseline MAP, HR, and sedation scores were noted. An intravenous line was secured using 18G cannula and Ringer Lactate was started at 8 ml/kg. All patients were pre-medicated with Inj. midazolam (0.05 mg/ kg) and Inj. Fentanyl at 2µg/kg was used as an analgesic. After pre-oxygenation with 100% oxygen for 3 minutes patients were induced with intravenous propofol 2mg/kg or in a dose sufficient to loss of response to verbal commands. Intravenous succinylcholine 2mg/kg was given to facilitate laryngoscopy and intubation. Oxygen saturation (SpO₂) was measured with pulse oximetry and End tidal CO₂ was measured with capnography.

The measurement of MAP and HR was taken at six time points : 1) baseline (when patient reaches the operating room) 2) during laryngoscopy/intubation, 3) Five minutes post laryngoscopy, 4) 60 minutes post laryngoscopy, 5) during extubation and 6) 60 minutes post-extubation in PACU. Degree of sedation was assessed at 1minute after arrival in operation theatre using Ramsay Sedation Scale. [9]

Anaesthesia was maintained with nitrous oxide and oxygen (60:40) and dial concentration of 0.8% Isoflurane and Inj. Atracurium .Paracetamol infusion 15mg/kg was given for analgesia. If hypertension and tachycardia occurred intraoperatively Isoflurane was increased to 1.5 %. If tachycardia and hypertension persisted beyond this dial concentration of Isoflurane, it was treated with incremental doses of Inj.Fentanyl 0.5µg/kg. And this additional Fentanyl requirement if any was recorded.

Bradycardia was considered as HR < 50 /min, and hypotension was considered as MAP < 65 mm of Hg. Bradycardia was treated with i.v atropine 10µg/kg. Hypotension was treated with fluid bolus. Isoflurane was discontinued after last skin suture (and patient were turned supine if surgery was done in prone position) and residual neuro-muscular blockade was reversed using injection .Glycopyrrolate 0.01µg/kg and Neostigmine 0.05µg/kg.

Patients were extubated when awake, warm and the protective reflexes have returned.

In the Post -Anesthesia Care Unit (PACU) patients' MAP and HR were measured 60 minutes post extubation. On arrival to PACU, sedation was assessed on Ramsay Sedation Scale in PACU at 30 minutes and 60 minutes. Post-Operative Nausea and Vomiting (PONV) was assessed on the basis of following arbitrary scale: 0 = no PONV, 1= nausea / vomiting / dry mouth / retching after 60 minutes after arrival to PACU.

Plan of Data Analysis

Categorical variables like sex, ASA physical status, post-operative nausea vomiting, were expressed as number of patients and percentage of patients and compared across the 2 groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables like age, duration of surgery, MAP, heart-rate, sedation score were expressed as Mean \pm Standard Deviation and compared across the 2 groups using Mann-Whitney U test. Intragroup deviation of continuous variable from their respective baseline values were assessed using Wilcoxon signed rank test. The statistical software SPSS version 20.0 was used for the analysis. An alpha level of 5% was taken, i.e. if any p value is less than 0.05 was considered as significant.

Results

The demographic characteristics like age, sex, and ASA physical status, duration and type of Surgery are compared between group C (receiving oral Clonidine) and group P (receiving oral Pregabalin) and no statistical significant difference was noted. (see Table 1)

Regarding the primary variables (see Table 2), a significant difference was noted between group C and group P. The baseline MAP in both the groups before administering the study drugs were almost similar with statistically insignificant difference. The MAP at all predefined intervals were lower for group C as compared to group P and this differences in MAP were statistically significant ($p < 0.05$). Similarly the baseline heart rate (HR) in both the groups prior to administering the study drugs were almost similar. However, the HR at different pre-defined intervals were significantly lower in Group C as compared to Group P.

Regarding the secondary variables (see Table 3), sedation assessed on Ramsay Sedation Score (RSS) at 1 minute after arrival in OR is nearly similar in both the groups. Also, sedation level assessed at 30 minutes and 60 minutes in PACU were significantly higher in case of Group P as compared to Group C. PONV measured at 60 minutes in PACU for group P was significantly higher than that in group C.

Table 1: Representation of Demographic variables like Age, Sex, ASA physical status, duration of surgery and Type of surgery in the group C and group P

		Group C	Group P	p Value	Significance
		Mean \pm Std. Deviation	Mean \pm Std. Deviation		
Age		32.5 \pm 9.22	37.79 \pm 8.12	0.554	No
Sex	Female	12(46.67)	13(46.67)	1.0000	No
	Male	18(53.33)	17(53.33)		
ASA	I	23(70)	24(66.67)	0.781	No
	II	7(30)	6(33.33)		
Duration of Surgery (minutes)		188 \pm 8.4	182.65 \pm 7.56	0.580	
Type of Surgery	Diagnostic Laparoscopy	1(3.33)	1(3.33)	0.935	No
	Discectomy	7(26.67)	6(16.67)		
	FESS	3(10)	4(13.33)		
	Laparoscopic Assisted Vaginal Hysterectomy	1(3.33)	0(0)		
	Common Bile Duct Exploration	1(3.33)	0(0)		
	Laparoscopic Cholecystectomy and CBD exploration	0(0)	1(3.33)		
	Laparoscopic Cystectomy	1(3.33)	3(6.67)		
	Laparoscopic Hernioplasty	4(16.67)	5(13.33)		
	Vaginal Hysterectomy	0(0)	1(3.33)		
	Mastoidectomy	3(13.33)	6(16.67)		
	Mastectomy	3(6.67)	1(6.67)		
	Open Reduction and Internal Fixation	1(6.67)	4(10)		
	Pedicle Screw Fixation	1(3.33)	2(6.67)		

Table 2: Comparison of Primary variables like Mean arterial pressure (MAP) and Heart rate (HR) between the group C and group P

	Group C	Group P	p Value	Significance
	Mean \pm Std.Deviation	Mean \pm Std.Deviation		
MAPBASE	81.53 \pm 6.66	85.43 \pm 8.55	0.053	Not Significant
MAPSCOPY	79.03 \pm 6.24	92.33 \pm 6.96	<0.001	Significant
MAP5 MIN	72.37 \pm 6.23	85.53 \pm 6.1	<0.001	Significant
MAP60 MIN	70.73 \pm 6.06	89.8 \pm 6.3	<0.001	Significant
MAPEXT	79.5 \pm 6.4	94.53 \pm 5.64	<0.001	Significant
MAP60' PACU	70.8 \pm 5.22	82.07 \pm 4.95	<0.001	Significant
HRBASE	80.37 \pm 5.4	85.32 \pm 4.11	0.210	Significant
HRSCOPY	63.2 \pm 9.21	88.1 \pm 4.37	<0.001	Significant
HR5 MIN	60.53 \pm 4.95	86.79 \pm 3.26	<0.001	Significant
HR60 MIN	57.51 \pm 5.44	73.6 \pm 3.75	<0.001	Significant
HREXT	69 \pm 5.71	84.4 \pm 4.13	<0.001	Significant
HR 10'EXT	65.5 \pm 5.3	80.23 \pm 5.16	<0.001	Significant
HR60' PACU	60.43 \pm 4.65	84.97 \pm 2.97	<0.001	Significant

Table 3: Comparison of Secondary variables like Ramsay Sedation scores (RSS) and Post-operative nausea and vomiting (PONV) in the group C and group P

		Group C	Group P	p Value	Significance
		Mean \pm Std. Deviation	Mean \pm Std. Deviation		
RSS1 MIN IN OR		2.5 \pm 0.45	2.2 \pm 0.4	0.079	Not Significant
RSS30 MIN PACU		2.91 \pm 0.26	3.63 \pm 0.5	<0.001	Significant
RSS60 MIN PACU		2.53 \pm 0.39	3 \pm 0	<0.001	Significant
PONV	NO	23(86.67)	17(50)	40(68.33)	000 Significant
	YES	6(13.33)	13(50)	20(31.67)	

Discussion

In our study oral Clonidine when compared to Pregabalin provides better control of mean arterial pressure and heart rate during laryngoscopy and intubation. Regarding the secondary variables, oral Clonidine also produced lesser post-operative sedation and nausea/vomiting.

The above study findings corroborate to some extent to previous study findings with some differences. Sharma et al, found both clonidine and gabapentin to be equally effective by oral route 2 hours before induction of anaesthesia to blunt the hemodynamic response to laryngoscopy/intubation as compared to placebo. [10] A study by Rajappa et al, found that oral Pregabalin in doses of 150 mg had a better analgesic profile than 75 mg, but with more side effects such as dizziness. They concluded that Pregabalin doses of 75 mg may be the optimal pre-emptive dose in vaginal hysterectomy. [11] Previous research found oral Pregabalin as an effective pre-medicant. Pregabalin premedication effectively reduced the consumption of all anesthetic agents during induction and maintenance of anesthesia [12] Pregabalin as premedication can enhance the recovery by decreasing anesthetic dose and postoperative pain in arthroscopic surgeries. [13] A study found oral pregabalin is an important adjuvant drug in treating postoperative pain in patients with

abdominal hysterectomy. [14] Oral clonidine is also slowly gaining a prominent place as one of the pre-medicants drug. Oral Clonidine can be used to attain controlled hypotension and lesser requirement of costly inhalational agent and other analgesic drugs with better hemodynamic stability and fewer side effects. [15] Oral clonidine premedication helped to provide perioperative hemodynamic stability, spared the use of isoflurane and reduced the requirement of postoperative analgesia.[16] A study found premedication with oral clonidine (3-3.5 mcg/kg) 90 minutes before laryngoscopy and intubation is an efficient, and inexpensive method in attenuating the haemodynamic response of laryngoscopy and intubation. [17] A systemic review found Clonidine premedication in an adequate dosage (4 μ g/kg) was likely to have a beneficial effect on postoperative pain in children. [6] A study found oral clonidine at a dose of 4 μ g.kg⁻¹ administered preoperatively is associated with a reduced incidence of postoperative vomiting in children who have undergone appendectomy. [18] But research work comparing the use of oral Pregabalin with oral Clonidine on haemodynamic response remain minimal

Pregabalin is administered orally reaches peak plasma concentrations within 1.5 hours and achieves a steady-state within 24 to 48 hours. Pregabalin

readily crosses the blood-brain barrier. Humans cannot significantly metabolize pregabalin (less than 2% metabolized) and eliminated primarily as an unchanged drug (mean elimination half-life is 6.3 hours). The FDA approved indication of Pregabalin are in treatment of neuropathic pain associated with diabetic peripheral neuropathy or spinal cord injury, neuropathic pain originating from postherpetic neuralgia, in treatment of fibromyalgia and as adjunctive therapy for partial-onset seizures in adults with epilepsy. [19]

Clonidine, an antihypertensive medication which acts on alpha-adrenergic and imidazoline receptor. It lowers blood pressure and heart rate by relaxing the arteries and increasing the blood supply to the heart. Other FDA-approved indications of clonidine are treatment of attention deficit hyperactivity disorder (ADHD) in children; management of tics commonly found with Tourette syndrome; and adjunct therapy for cancer-related pain. Clonidine has a half-life of between 6 and 20 hours. The FDA-approved indications are hypertension, treatment of attention deficit hyperactivity disorder (ADHD) in children, management of tics with Tourette syndrome, adjunct therapy for severing cancer-related pain, and use in neonatal opioid withdrawal syndrome. Dose adjustment is necessary for renal impairment, cardiovascular, bradycardia, hypotension, and severe coronary artery disease patients. Also, caution is necessary when treating patients with a history of depression, recent myocardial infarction, and syncope. [20]

Our study has some limitations. This study had been done in a single center with a limited sample size. Moreover it was conducted in ASA I-II patients with normal airway; the hemodynamic response may be exaggerated in patients with hypertension or in cases of difficult airway. Further research in such scenario is highly suggested. The invasive blood pressure monitoring would have been ideal and accurate, but it was avoided due to ethical considerations.

Conclusion

On comparison of two oral premedication drugs, oral Clonidine compared to Pregabalin provided better control of mean arterial pressure and heart rate during laryngoscopy and intubation with lesser postoperative sedation and nausea/vomiting. Further large scale studies will be required to corroborate these findings.

References

1. Lakhe G, Pradhan S, Dhakal S. Hemodynamic Response to Laryngoscopy and Intubation Using McCoy Laryngoscope: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc* 2021;59(238):554-7.
2. Safavi M, Honarmand A. Attenuation of cardiovascular responses to laryngoscopy and

- tracheal intubation-intravenous sufentanil vs pethidine. *Middle East J Anaesthesiol* 2008; 19(6):1349-59.
3. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979;51:393-7.
4. Gupta A, Mahajan HK, Sarkar A, et al. Evaluation of clonidine and lignocaine for attenuation of haemodynamic response to laryngoscopy and intubation: A randomized controlled trial. *J Clin Diagnostic Res* 2018;12(2):UC17-20.
5. Ozair E, Ali QE, Siddiqi MMH, Amir SH, Naaz S. A comparative evaluation of dexmedetomidine and fentanyl to attenuate hemodynamic response to laryngoscopy and intubation. *Asian J Med Sci* 2018;9(1):65-72.
6. Lambert P, Cyna AM, Knight N, et al. Clonidine premedication for postoperative analgesia in children. *The Cochrane database of systematic reviews*, 2014;(1). <https://doi.org/10.1002/14651858.CD009633.pub2>
7. Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. *Indian J Anaesth* 2011;55 (1):26-30.
8. Gupta K, Bansal P, Gupta PK, Singh YP. Pregabalin premedication - A new treatment option for hemodynamic stability during general anesthesia: A prospective study. *Anesth Essays Res* 2011;5(1):57-62.
9. Deol HS, Surani SR, Udeani G. Inter-rater Reliability of the Ramsay Sedation Scale for Critically-ill Intubated Patients. *Cureus* 2019; 11(10):e6021.
10. Sharma V, Fotedar K, Goel R. Comparison of Oral Clonidine and Gabapentin Premedication for Attenuation of Pressor Response to Laryngoscopy and Endotracheal Intubation. *Anesth Essays Res* 2020;14(3):412-9.
11. Rajappa GC, Vig S, Bevanaguddaiah Y, Anadaswamy TC. Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy. *Anesth Pain Med*. 2016 ;6(3):e34591.
12. Gupta P, Saxena A, Chaudhary L. Effect of Pregabalin Premedication on the Requirement of Anesthetic and Analgesic Drugs in Laparoscopic Cholecystectomy: Randomized Comparison of Two Doses. *Anesth Essays Res* 2017;11(2):330-3.
13. Ghareeb AA, Attalla HA, Ibrahim ES, Sedky AM. The effect of pregabalin premedication on anesthetic requirements and recovery time after knee arthroscopy. *Menoufia Med J* 2022 ;35:1368-73.
14. da Silva FG, Podestá MHMC, Silva TC, et al. Oral pregabalin is effective as preemptive analgesia in abdominal hysterectomy-A randomized

- controlled trial. *Clin Exp Pharmacol Physiol* 2023;50(3):256-63.
15. Chakole V, Shankar S, Kota S, et al. Efficacy of oral clonidine as premedication on intraoperative bleeding and consumption of inhalational agent in patients undergoing functional endoscopic sinus surgery. *Journal of Pharmaceutical Research International* 2021;33(47A); 511-6.
 16. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. *Acta Anaesthesiol Sin* 2000; 38(1):23-29.
 17. Priyamargavi H., Kambali M, JKJ. Effect of oral clonidine premedication on attenuating haemodynamic response to laryngoscopy and intubation during general anaesthesia. *International Journal of Basic & Clinical Pharmacology* 2023;12(3);368-74.
 18. Alizadeh R, Mireskandari SM, Azarshahin M, et al. Oral clonidine premedication reduces nausea and vomiting in children after appendectomy. *Iran J Pediatr.* 2012;22(3):399-403.
 19. Cross AL, Viswanath O, Sherman AI. Pregabalin. [Updated 2022 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2023
 20. Yasaei R, Saadabadi A. Clonidine. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.