

A Comparative Study on Oral Clonidine and Gabapentin for Preoperative Anxiolysis and Attenuation of Hemodynamic Response to Direct Laryngoscopy and Endotracheal Intubation.

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ABSTRACT

INTRODUCTION: Patients under going surgery experience unpleasant anxiety preoperatively that adversely influence anesthetic induction and patient recovery. Hemodynamic stability is an essential goal of any anesthetic management. The aim of this study was to compare the effects of oral Clonidine and Gabapentin in preoperative anxiolysis and attenuation of hemodynamic response to endotracheal intubation.

METHOD: This is a prospective, randomized, double blind clinical study. Sixty-six patients aged 18 to 60 years of American Society of Anesthesiologist (ASA) physical status I and II, scheduled for elective surgeries under general anesthesia with endotracheal intubation were included. Patients were randomized and given oral Gabapentin 800 mg (Group G) or Clonidine 300 mcg (Group C) or Placebo tablets (Group P) two hours prior to surgery accordingly. Study groups were compared for patient characteristics, Visual Analogue Scale (VAS) anxiety score and hemodynamic response at baseline, before intubation and after intubation at 0, 1, 3, 5 and 10 mins. Collected data were analyzed with Chi-square test and ANOVA with Post-hoc comparisons.

RESULT: VAS anxiety score was significantly decreased in group G and C as compared to Placebo ($P = <0.001$). But it was comparable between the group G and C. There was statistically significant difference in heart rate (HR) at 0, 1, 3 and 5 mins ($P = 0.023, 0.005, 0.037$ & 0.037) between group G and C. Mean arterial pressure (MAP) was statistically significant at 0 min ($P = 0.011$) and 1 min ($P = 0.036$) between group G and C whereas at 3, 5 and 10 mins it was comparable. No significant side effects of study drugs were noted.

CONCLUSION: Oral Clonidine (300 mcg) given two hours preoperatively can effectively decrease preoperative anxiety and provide good attenuation of hemodynamic response to laryngoscopy and endotracheal intubation as compare with the oral Gabapentin (800 mg) and Placebo.

KEY WORDS: Clonidine, Gabapentin, Hemodynamic response, Intubation, Laryngoscopy

INTRODUCTION

Laryngoscopy and tracheal intubation is an essential part of general anesthesia. Reid and Brace in 1940 were the first person who reported the hemodynamic responses to laryngeal and tracheal stimulation in anaesthetized person.¹ The haemodynamic changes during tracheal intubation are due to sympatho-

adrenal stimulation.² Sympatho-adrenal stimulation increases plasma concentration of catecholamines. All these lead to increase in heart rate, blood pressure, myocardial oxygen demand and dysrhythmias.³ Generally these hemodynamic changes are well tolerated in healthy individual, but may be hazardous to those with hypertension, Coronary artery disease or cerebrovascular disease.⁴

Effective attenuation of this response still remains a big challenge to the anesthesiologist. Various methods and drugs have been proposed to attenuate this response such as deepening of anesthetic plane, calcium channel blockers, beta blockers, vasodilators, opioids. But none

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of the techniques or drugs has achieved universal acceptance. Gabapentin is a structural analogue of gamma aminobutyric acid (GABA), used primarily for the treatment of seizures and neuropathic pain.⁵ It can attenuate the pressure response to the laryngoscopy and tracheal intubation.⁶ Clonidine is a direct acting alpha-2 adrenergic drug, which acts on alpha-2A adrenergic receptors in the brainstem leading to reduction in sympathetic outflow. It can also blunt catecholamine release and hemodynamic response to laryngoscopy and intubation.⁷

Ideal pre-medication would be that, which can decrease preoperative anxiety of the patients, can effectively attenuate the hemodynamic stress response to laryngoscopy and intubation and also provide post-operative analgesia. Using Gabapentin or Clonidine as pre-medication is justified as they can be easily administered, no significant side effects, easy availability with low price, both of them have sedative effect that can decrease anxiety and they can blunt the stress response. More over both drugs have anti-nociceptive effects that may be beneficial for controlling post-operating pain. Hence, this study was designed to evaluate and compare the effects of oral premedication with Clonidine and Gabapentin on preoperative anxiolysis and attenuation of hemodynamic response to laryngoscopy and tracheal intubation in normotensive patients undergoing an elective surgery.

METHOD

It was a prospective, randomized, double blind study, conducted in National Academy of Medical Sciences (NAMS), Bir Hospital from October 2013 to March 2014. Ethical approval was obtained from institutional review board before commencing the study. Sample size calculation was based on the study conducted by S. Sharma et al. using standard deviation (SD) of difference in HR at 3 minutes after laryngoscopy and intubation with the power of 90% at confidence interval of 95%, the calculated sample size was 22 patients in each group.

A total of 66 patients of American Society of Anesthesiologist physical status (ASA-PS) Grade I and II, age between 18 to 60 years who were scheduled to undergo elective surgical procedures under general anesthesia with endotracheal intubation were enrolled in the study. Patients with pre-existing co-morbid conditions like hypertension, diabetes, renal or hepatic disease, chronic obstructive pulmonary disease,

patients with sinus bradycardia, heart block, on anti-hypertensive, sedatives, hypnotics, antidepressant drugs, and patients with anticipated difficult airway, obesity, pregnancy and those who had known allergy to the study drugs were excluded from the study.

All the patients were admitted to the hospital at least a day prior to surgery. Informed written consent was taken from all patients during the pre-anesthetic checkup visit. During the pre-anesthetic checkup, all the patients were shown a VAS anxiety scale and were taught in detail about how to use a 100 mm visual analogue scale with 0 mm representing no anxiety and 100 mm being defined as extreme anxiety. Patients were kept nil per oral for six hours prior to surgery. Premedication was not given to any of them. On the day of the proposed surgery, two hours prior to surgery, baseline VAS anxiety score and baseline hemodynamic data were recorded before giving any study drugs. Patients were randomized into three groups using sealed envelope technique. Randomization was carried out by one of the trained staff who did not participate in the study process so that the researcher and the patients remained unaware of it. Group G received oral Gabapentin 800 mg (2×400 mg tablets), Group C received oral Clonidine 300 mcg (2×150 mcg tablets) and Group P received placebo (2×Vitamin tablets) with sips of water.

Before shifting the patient to operation theatre (2 hours after the administration of study drug) patients were again asked to show the level of anxiety on the VAS anxiety scale and the VAS score at that time was recorded. Side effects of the study drugs were also noted if any.

In operating room, intravenous access was gained with 18 G cannula and standard monitors were attached. Monitoring included electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure (NIBP), pulse oximetry (SpO₂) and end tidal CO₂ (ETCO₂). All patients were pre-medicated with Injection (inj.) Midazolam 0.05 mg/kg and Pethidine 0.75mg/kg Intra Venous (IV) was given for analgesia. Patients were pre-oxygenated with 100% oxygen for 3 minutes and then anesthesia was induced with inj. Propofol 2 mg/kg. Intubation was facilitated with inj. Vecuronium (0.1mg/kg). Hemodynamic variables (HR and MAP) were recorded just before intubation. Patients were manually ventilated with Oxygen and Isoflurane 1% for 3 minutes of muscle relaxant. Then direct laryngoscopy and intubation, with 7.5 mm internal diameter (ID) endotracheal tube for male and 7.0 mm ID for female,

was performed by the researcher. The duration of laryngoscopy and intubation was kept to be less than 30 seconds for all patients. Patients requiring more than 30 seconds for laryngoscopy and intubation were discarded from the study. Hemodynamic parameters (HR and MAP) were recorded at 0, 1, 3, 5 and 10 minutes after intubation by the staff who was not involved in the study. During these 10 minutes following the intubation, any of the surgical stimuli were avoided. Surgery was commenced then after and anesthesia was maintained with oxygen, Isoflurane, mechanical ventilation and maintenance dose of Vecuronium. At the end of surgery, residual neuromuscular blockade was reversed with Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01mg/kg intravenously. Extubation was done and patients were shifted to post-anesthesia care unit. Any adverse effects of study drugs were recorded and were treated as per the standard hospital protocol.

Collected data were analyzed with appropriate statistical tests using SPSS for windows, version 16. Data were expressed as mean ± standard deviation (SD) or numbers (percentages). Chi-square test was used for categorical data (Gender, ASA grade) and ANOVA with Post-hoc comparisons was used for age, weight and to compare the changes in mean hemodynamic variables among the study groups. Results were considered statistically significant if $P < 0.05$.

RESULT

The demographic profiles of patient as shown in Table 1, were comparable in age, weight, gender ratio and ASA physical status ratio among the groups.

The baseline VAS anxiety scores, recorded before the study drug administration, were comparable.

* Chi Square Test, †ANOVA

Table 2. VAS anxiety scores in the three groups (Mean±SD)

VAS anxiety score	Group G (n=22)	Group C (n=22)	Group P (n=22)	p-value*	G vs C (†)	G vs P (†)	C vs P (†)
Baseline	56.82±17.83	60.00±20.24	54.09±19.92	0.601	1.000	1.000	0.946
After 2 hours of study drug administration	40.45±13.27	33.64±11.77	58.64±14.90	<0.001	0.287	<0.001	<0.001

* ANOVA, † ANOVA with post-hoc

The baseline mean MAP was comparable among the group. There was decrease in MAP in all the

Statistically significant difference in VAS anxiety score was seen 2 hours after the administration of study drugs ($P = <0.001$). Gabapentin and Clonidine both significantly decreased the preoperative VAS anxiety score while compared each with the Placebo group, and it was statistically significant as shown in table 2 ($P = <0.001$ in both group). While the comparison between the Gabapentin and Clonidine groups shows that there is no statistically significant difference in VAS scores ($P = 0.287$).

The mean HR at baseline and after induction were comparable among the groups. HR was increased in all groups after intubation and remained elevated during first 3 minutes. Statistically significant attenuation of HR was seen in Clonidine as compared with Placebo group at all time (0,1,3,5 mins $P = <0.001$ and 10 mins $P = 0.005$). Whereas in Gabapentin group it was significant only at 0 & 1 mins ($P = 0.002$ each) after intubation as compared to Placebo group. As seen in the table 3, the comparison between Clonidine and Gabapentin showed the statistically significant difference in mean HR at 0, 1, 3 and 5 mins ($P = 0.023, 0.005, 0.037$ & 0.037).

Table 1. Demographic data of the patients

Variables	Group G (n=22)	Group C (n=22)	Group P (n=22)	P-value
Age(yrs) (mean±SD)	35.91±11.41	33.27 ± 12.03	39.55 ± 10.37	0.189 [†]
Gender (M/F)	9/13	14/8	15/7	0.146*
Weight(kg) (mean±SD)	56.77 ± 9.82	56.09 ± 8.86	55.91 ± 10.45	0.953 [†]
ASA (I/II)	20/2	21/1	20/2	1.0*

study groups following induction but it was not statistically significant. As seen in Table 4, Clonidine had significantly attenuated the MAP when compared with Placebo group at 0, 1, 3 mins ($P = <0.001$) and

5 minutes (P = 0.018). Gabapentin as compared to Placebo group had significantly attenuated MAP only at 0 min (P = <0.001) and 1 min (P = 0.004) after 1 min (P = 0.036) whereas at 3, 5 and 10 mins it was comparable.

intubation and at other time it was comparable. When Clonidine was compared with Gabapentin, mean MAP was statistically significant at 0 min (P = 0.011) and 1

Table 3. Changes in mean heart rate among three groups(Mean±SD)

Heart Rate (beats/min)	Group G (n=22)	Group C (n=22)	Group P (n=22)	p-value*	G vs C (†)	G vs P (†)	C vs P (†)
Baseline	78.77±10.87	76.59±12.07	80.82±9.52	0.440	1.000	1	0.606
Before Intubation	77.82±10.19	74.05±10.09	81.27±11.23	0.091	0.746	0.871	0.088
After Laryngoscopy & Intubation							
0 min	99.59±11.50	89.68±11.41	112.64±12.89	<0.001	0.023	0.002	<0.001
1 min	98.05±11.86	87.09±12.35	110.27±8.89	<0.001	0.005	0.002	<0.001
3 min	90.27±12.86	80.45±10.35	98.59±14.38	<0.001	0.037	0.098	<0.001
5 min	85.23±12.77	76.36±9.62	90.27±11.56	0.001	0.037	0.441	<0.001
10 min	79.91±10.23	72.05±9.56	82.77±12.56	0.005	0.058	1.000	0.005

*ANOVA, † ANOVA with post-hoc

Table 4. Changes in Mean Arterial Pressure among three groups (Mean±SD)

MAP (mmHg)	Group G (n=22)	Group C (n=22)	Group P (n=22)	p-value*	G vs C (†)	G vs P (†)	C vs P (†)
Baseline	87.36±8.53	88.77±9.86	90.32±7.01	0.521	1.000	0.766	1.000
Before Intubation	78.00±12.07	81.36±13.50	81.27±12.12	0.603	1.000	1	1.000
After Laryngoscopy & Intubation							
0 min	105.27±11.49	94.14±11.92	120.27±13.12	<0.001	0.011	<0.001	<0.001
1 min	99.64±9.19	91.82±11.66	109.77±8.99	<0.001	0.036	0.004	<0.001
3 min	88.82±10.20	82.27±12.77	97.09±10.69	<0.001	0.176	0.053	<0.001
5 min	80.55±10.15	78.36±11.04	87.18±9.58	0.016	1.000	0.108	0.018
10 min	78.05±9.83	77.45±9.26	80.82±9.46	0.461	1.000	1	0.737

*ANOVA, † ANOVA with post-hoc

During the study period, five patients (22.72%) who received Gabapentin complained of headache, dizziness and nausea. Dry mouth was found in eight patients (36.36%) in Clonidine group.

DISCUSSION

Most of the patients who are waiting for elective surgery experience unpleasant emotions called preoperative anxiety. Because of which patients may avoid planned operation and further more it adversely influence anesthetic induction and patient recovery. It has been shown that psychologically prepared patients who are less anxious before surgeries have improved postoperative clinical recovery as assessed by outcomes such as pain and analgesic use, postsurgical complications, and hospital stay. Pre-anesthetic medication forms an integral part of anesthetic management and some form of premedication is universally administered before any anesthesia to alleviate this anxiety. Although the use of pre-operative benzodiazepines is the most common practice to decrease pre-operative anxiety, they lack

a positive effect on post-operative outcome.Choice of pre-medicant is always controversial. Gabapentin and Clonidine are the drugs being extensively evaluated these days as pre-medicant.

Assessment of preoperative anxiety and evaluation of the effectiveness of interventions need a statistically valid and useful measurement tool. Various scales have been used for this purpose but the gold standard being the Spielberger State-trait Anxiety Inventory (STAI). 20 multiple-choice questions for state anxiety alone limits the use of STAI as a bedside tool for assessment. Visual Analog Scale (VAS) on the other hand allows patients to easily indicate their degree of preoperative anxiety by simply marking a point on a horizontal scale, which can easily be used in bedsides. As anesthesiologists appear to be inaccurate in assessing patient anxiety during the preoperative visit it provides a valid tool for defining the patient's anxiety level. Kindler CHet al⁸ found VAS as a useful and valid method for measuring preoperative anxiety that compares well with the state anxiety score of the STAI. Aviado⁹ also used the visual analog scale to measure preoperative anxiety in

patients with breast cancer. Based on these studies we used VAS anxiety scale as a tool for the assessment of pre-operative anxiety in this study.

Effectiveness of oral Clonidine and Gabapentin for perioperative anxiolysis has been proved in many studies. Vikash Saini et al¹⁰ studied on Clonidine and found that two hours after premedication, patients receiving Clonidine had lower anxiety score ($p < 0.01$) as compared to placebo. Similarly preoperative anxiolysis with oral Gabapentin was seen in Menigaux et al¹¹ study who found decreased preoperative anxiety, decreased pain scores, total analgesic consumption and early functional recovery after knee surgery. In their study, though they had not mentioned the baseline anxiety level, they found that the preoperative VAS anxiety score, recorded 1-2 hours after the study drug administration, in Control group was 66 ± 15 mm, while in Gabapentin group it was 28 ± 16 mm. There was statistically significant difference (p -value < 0.001) in preoperative anxiety between the groups which was similar to our study results.

We found that both Clonidine and Gabapentin had significantly decreased the preoperative VAS anxiety score as compared to Placebo. But there was no statistically significant difference among the two. In contrast to present study, Shingal SK et al¹² found statistically significant difference between Clonidine and Gabapentin. They found anxiety score and sedation score were significantly better in Clonidine as compared with Gabapentin. One of the reason might be the premedication with Alprazolam they used night prior to surgery which might have positive effect on preoperative anxiolysis.

Faheim S et al¹³ also found anxiolysis more with Clonidine (300 mcg) than Gabapentin (600 mg) and placebo. In contrast to our study, they have used a smaller dose of Gabapentin which might have affected its anxiolytic effect.

Hemodynamic stability is an integral and essential goal of any anesthetic management. Since the practice of laryngoscopy and endotracheal intubation in anesthesia, it has been found to cause remarkable changes in hemodynamic parameters. This maneuver induced marked increase in heart rate, systemic blood pressure and pulmonary arterial pressure. There has been reported that laryngoscopy and intubation cause a 40 to 50% rise in systolic blood pressure, 30% rise in diastolic blood pressure and 20% rise in HR. The rise in blood pressure is tolerated in normotensive individuals but is of greater significance in patients with coronary artery disease, vascular disorders and cerebrovascular

disorders.

Gabapentin is a structural analogue of the neurotransmitter gamma amino butyric acid (GABA). It is an adjuvant anticonvulsant drug for the treatment of refractory partial seizures. Subsequently, it was shown to be effective in treating a variety of chronic pain conditions, including post-herpetic-neuralgia. The inhibition of Calcium flux in muscle cells with a consequent inhibition of smooth muscle contraction might explain the effectiveness of Gabapentin on attenuation of the pressure response to laryngoscopy. Thus, it may act in a manner similar to calcium channel blocker.

Clonidine is a directly acting alpha-2 adrenergic receptor agonist. It acts on alpha-2A subunit of the receptors in central nervous system, stimulation of which causes reduction in the sympathetic outflow resulting into lowering of blood pressure. It is proved to be effective in treatment of patients with severe hypertensive disease. Its central sympatholytic action leads to attenuation of hemodynamic response to any nociceptive stimuli and maintains perioperative hemodynamic stability.

Montazeri et al¹⁴ compared the efficacy of oral Gabapentin 800 mg and oral Clonidine 300 mcg found that both drugs given 1 hour before operation, comparably blunted the pressor response to laryngoscopy and endotracheal intubation. Despite the dose of study drugs, the findings of our study are consistent with their study.

Sayed Mojtaba et al¹⁵ compared the effect of 900 mg Gabapentin and 200 mcg Clonidine premedication in modifying the hyperdynamic response following laryngoscopy and tracheal intubation. They found that both Clonidine and Gabapentin had effective roles in blunting the hyper dynamic responses following laryngoscopy, more so with Gabapentin. In contrast to the present study, Gabapentin was found to be better than Clonidine in their study which might be due to the difference in dose of study drugs. They had used higher dose of Gabapentin and compared with the lower dose of Clonidine as compared to the present study. Moreover the difference in induction agents might have also played some role in the study findings.

Sharma et al¹⁶ also compared 800 mg Gabapentin with 300 mcg Clonidine for the same purpose. They found that both drugs were effective in attenuation of pressure response to laryngoscopy and intubation. However, the rise in blood pressure was better attenuated by Gabapentin. In contrast to their study,

we did not find Gabapentin to be superior to Clonidine. This might have occurred due to the difference in drugs they used for induction and maintenance of anesthesia. They pre-medicated with Metoclopramide 10 minutes prior to induction while this study avoided any premedication. They used Propofol and Rocuronium for induction and 66% Nitrous oxide in oxygen with Isoflurane or Halothane for maintenance. Moreover, the inhalation agent used for maintenance of anesthesia was not same for all patients in their study as they have used either of the agents that have variable effect in the hemodynamics.

Shinghal et al¹² compare the effect of 200 mcg Clonidine and 900 mg Gabapentin and found that Clonidine provided good attenuation of hemodynamic response to laryngoscopy and intubation as compared with Gabapentin, which also fairly obtunded the hypertensive response, but not the tachycardiac response. However Faheim S et al¹³ found that hemodynamic parameters at 1, 3, 5 and 10 minutes after tracheal intubation were significantly lower in both Clonidine and Gabapentin than placebo group. Nevertheless, Gabapentin was found to be as effective as Clonidine in attenuation of pressure response to laryngoscopy and intubation.

The limitation of this study is, we could not measure the blood catecholamine level during the laryngoscopy and intubation because of unavailability of facilities. The study drugs could have been used on the basis of weight of patients.

CONCLUSION

This study concludes that oral Clonidine (300 mcg) given two hours preoperatively can effectively decrease preoperative anxiety and provide good attenuation of hemodynamic response to laryngoscopy and endotracheal intubation as compare with the oral Gabapentin (800 mg) and Placebo.

REFERENCES

1. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon the heart Surg Gynecol Obstet 1940;70:157-62.
2. Thomson IR. The hemodynamic response to intubation: a perspective. Can J Anaesth 1989;36:367-9.
3. Fassoulaki A, Melemini A, Paraskeva A, Petropoulos G. Gabapentin attenuates the pressor response to direct laryngoscopy and tracheal intubation. Br J Anaesth; 2006; 96:769-73.
4. Govindaiah MH, Suryanarayana VG, Vas P, Vlk JL, Chandra SB. Can calcium and sodium channel blockers attenuate hemodynamic responses to endotracheal intubation? Eur J Gen Med. 2008;5:198-207.
5. Steotling RK, Hiller SC. Pharmacology and Physiology in anesthetic practice. 4th ed. Lippincott Williams & Wilkins. 2006. Chapter, Antihypertensive drugs; p.338-51.
6. Memiş D, Turan A, Karamanlioğlu B, Seker S, Türe M. Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol. 2006;23(8):686-90.
7. Nishikawa T, Taguchi M, Kimura T, Taguchi N, Sato Y, Dai M. Effects of clonidine premedication upon hemodynamic changes associated with laryngoscopy and tracheal intubation. Masui 1991; 40(7): 1083..
8. Kindler CH, Harms C, Amsler F, Ihde-Schöll T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesth Analg. 2000;90(3):706-12.
9. Aviado-Langer J. Measuring preoperative anxiety in patients with breast cancer using the visual analog scale. Clin J Oncol Nurs. 2014;18(5):489-91.
10. Saini V, Anand LK, Gombar KK, Sood S, Sood R. Oral clonidine premedication in patients undergoing intraocular surgery under local anaesthesia. J Anaesthesiol Clin Pharmacol 2009;25(3):311-5.
11. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg. 2005; 100(5):1394-9.
12. Singhal SK, Kaur K, Arora P. Oral clonidine versus gabapentin as premedicant for obtunding hemodynamic response to laryngoscopy and tracheal intubation. Saud J Anaesthesiol 2014;8(2):172-5.
13. Faheim S, Hassanin M, Hafez AA. Gabapentin Versus Clonidine oral Premedication for Attenuation of pressor Response to Laryngoscopy and Endotracheal Intubation Tanta Med. Sc. J. 2008; 3(4):12-20.
14. Montazeri K, Kashefi P, Honarmand A, Safavi M, Hirmanpour A. Attenuation of the pressor response to direct laryngoscopy and tracheal intubation: Oral clonidine vs. oral gabapentin premedication. J Res Med Sci. 2011;16:377-86.
15. Marashi SM, Ghafari MH, Saliminia A et al. Attenuation of hemodynamic responses following laryngoscopy and tracheal intubation - comparative assessment of clonidine and gabapentin premedication. Mid East J Anesthesiol. 2009;20(2):233-7.
16. Sharma S, Angral R, Jamwal A, Bhanotra K. Comparative evaluation of Gabapentin, Clonidine and combination of both the drugs to attenuate the pressor response to direct laryngoscopy and intubation. The Inter J Anesthesiol. 2012;30(4). Available from: <http://ispub.com/IJA/30/4/14367>.