

A Comparative Study Of Oral Pregabalin And Oral Pregabalin With Intravenous Fentanyl For Attenuation Of Pressor Response To Tracheal Intubation And Laryngoscopy - A Randomised Double Blind Study

Dr.V.M.Joshi¹ , Dr.V.S.Kapurkar² , Dr. Shraddha Naik³

^{1,2,3}Associate Professor, Department of Anesthesiology, Krishna Institute of Medical Sciences, Krishna Institute of Medical Sciences Deemed to be University, Karad

Email :- drjoshivm@gmail.com

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Abstract

Cardiovascular response to air way instrumentation is a hazardous complication of general anaesthesia. It is associated with hypertension and tachycardia which is transient and often an unwanted body response. These variations are usually well tolerated in normal patients who are devoid of cardiac disorder or altered intracranial pressure. The stimulation of upper respiratory tract both during laryngoscopy and tracheal intubation leads to intense sympathetic discharge as seen by rise in catecholamine levels, hence causing the pressor response.

Haemodynamic response is exaggerated in hypertensive patients even though they may be normotensive pre-operatively by antihypertensive drugs. This response may lead to intra- perative myocardial infarction, acute left ventricular failure and intracranial bleed in patients with end organ decompensation.

Key Words: Cardiovascular, hazardous complication, anaesthesia, tachycardia, transient, disorder, haemodynamic

Introduction

Cardiovascular response to airway instrumentation is a hazardous complication of general anaesthesia. It is associated with hypertension and tachycardia which is transient and often an unwanted body response¹. These variations are usually well tolerated in normal patients who are devoid of cardiac disorder or altered intracranial pressure. The stimulation of upper respiratory tract both during laryngoscopy and tracheal intubation leads to intense sympathetic discharge as seen by rise in catecholamine levels¹, hence causing the pressor response.

Reid and Brace (1940) were the first to recognize that cardiovascular stability may be affected by intubation. Since then along with the time of King and Harris in 1950 who also came to the same conclusion as Reid that while inducing a patient, it is imperative to avoid this pressor response.

Haemodynamic response is exaggerated in hypertensive patients even though they may be normotensive pre-operatively by antihypertensive drugs. This response may lead to intra-operative myocardial infarction,

acute left ventricular failure and intracranial bleed in patients with end organ decompensation.⁵⁻⁸

Numerous medications like benzodiazepines, barbiturates, alpha 2 agonist, opioids etc have been evaluated as premedication to suppress these adverse pressor responses to airway instrumentation^{8,9}. The most common adverse effects of benzodiazepines are variability of patient's response to the drug and respiratory complications. Opioid analgesia can cause postoperative nausea and vomiting, delayed recovery of bowel function, delayed discharge and recovery of activities.^{10,11} The adverse respiratory profile of benzodiazepines, barbiturates and opioids, along with the stress response to surgery makes it essential for the need of an alternative sedative drug that has a good margin of safety.

With the above pharmacologic profile, pregabalin, like its pharmacological predecessor gabapentin, can be a good option for suppression of haemodynamic response to direct laryngoscopy and intubation.

Pregabalin has been successfully used by various authors^{12,18-24} as oral premedication to attenuate pressor response during airway instrumentation, to decrease the preoperative anxiety and perioperative opioid consumption. But most of the investigators have used opioid drug along with pregabalin. This could have biased the studies in favor of pregabalin.

Fentanyl is a synthetic phenethylpiperidine derivative, a stereospecific μ -opioid receptor agonist.²⁵ It modulates the nociceptive input and has been used at low doses to attenuate the pressor response.

There is a need to study the effectiveness of pregabalin in attenuating the haemodynamic response to laryngoscopy and intubation, in reducing the level of anxiety before anaesthesia, decreasing perioperative opioid requirement and for postoperative analgesia. Hence we have proposed to study the efficacy of oral pregabalin when given alone as premedication and when given in combination with pre-induction intravenous fentanyl.

Aim: To study a comparison between pressor response to laryngoscopy and endotracheal intubation with oral pregabalin premedication alone and oral pregabalin as premedication and pre-induction intravenous fentanyl at pre-specified doses.

Objectives:

- i. To study the levels of anxiety and sedation preoperatively
- ii. To study the response of intubation, induction and laryngoscopy on the haemodynamic
- iii. To study the analgesic requirement post-operatively for the first 24 hours

Review of Previous Studies on Haemodynamic Response

Laryngoscopy and tracheal intubation provoke a transient but marked sympathetic response, manifesting as tachycardia and hypertension. In 1940, Reid and Brace first described haemodynamic response to laryngoscopy and intubation. These facts were further confirmed by various investigators and were interpreted as a result of reflex sympathoadrenal response.³ A study was done to examine changes in plasma catecholamines during intubation to determine if an increase occurred, and if one specific catecholamine might predominate. Significant increase in mean arterial pressure and plasma noradrenaline were noted. The increase in arterial pressures were associated with increase in noradrenaline concentration. Adrenaline and dopamine concentration did not change significantly following intubation. The result suggested a predominant sympathetic response during intubation and a need for prophylaxis in patients at risk.

The haemodynamic response to laryngoscopy and tracheal intubation may not be of much significance in an otherwise normal individual, but in susceptible patients particularly those with systemic hypertension, coronary artery disease, cerebrovascular disease or intracranial aneurysms, even these transient changes can result in potentially deleterious effect like left ventricular failure, pulmonary edema, myocardial ischemia, ventricular dysrhythmias and cerebral haemorrhage.²⁻⁷

In 1960, Wycoff²⁷ studied the changes in blood pressure after the administration of suxamethonium during endotracheal intubation and the effects of regional and topical oropharyngeal and laryngeal anaesthesia on changes in the heart rate and blood pressure. The blood pressure was raised in all the cases after scoline but returned to normal within 1 minute. There was also a transient rise in blood pressure after laryngoscopy and intubation which returned to normal within 4 minutes in all patients. In patients in whom surface anaesthesia was applied, laryngoscopy and endotracheal intubation caused a lesser degree of rise in blood pressure than in

others.

Ward and Allen (1965) compared the pressor response to laryngoscopy under halothane anaesthesia with and without topical laryngeal anaesthesia.²⁸ Topical anaesthesia was achieved by transtracheal injection of lignocaine which prevented the increase in heart rate and hypertension associated with intubation in 5 out of 7 patients. But the drawback was the occurrence of heart rate changes following transtracheal injection and endotracheal intubation under halothane anaesthesia.

However, many other authors thought that, the very process of laryngoscopy needed for spraying would produce undesirable haemodynamic responses. To prevent this, lignocaine was administered intravenously few minutes before intubation to attenuate laryngoscopic reactions.³⁰

Studies on the Analgesic Effect of Pregabalin Postoperatively

Bornemann-Cimenti et al.⁵¹ conducted a study on “Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy”. Patients undergoing elective transperitoneal nephrectomy received 300 mg pregabalin or placebo 1 hour before anaesthesia. After operation, patients received piritramide via a patient-controlled analgesia device. Pain levels and side-effects were documented. The area of hyperalgesia for punctuate mechanical stimuli around the incision was measured 48 hours after the operation with a hand-held von Frey filament. Mechanical pain threshold was tested before and 48 hours after surgery with von Frey filaments with increasing diameters. The study has shown that preoperative administration of 300 mg pregabalin in patients undergoing transperitoneal nephrectomy reduces postoperative opioid consumption and decreases the area of mechanical hyperalgesia.

Pesonen et al.⁵² conducted a study on “Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial”. Seventy patients, aged ≥ 75 years, were randomized to receive either 150 mg of pregabalin before operation and 75 mg of pregabalin twice daily for 5 postoperative days or placebo. Pain intensity was measured with the Verbal Rating Scale (VRS). When pain intensity was ≥ 2 on the VRS, patients received oxycodone either IV (0.05 mg/kg) or orally (0.10–0.15 mg/kg). Postoperative confusion was measured with the Confusion Assessment Method for the intensive care unit (CAM-ICU). Postoperative pain was assessed by a telephone interview 1 and 3 months after operation. The administration of pregabalin reduced postoperative opioid consumption after cardiac surgery, reduced the incidence of confusion on the first postoperative day and increased time to extubation when compared with placebo. Three months after operation, patients in the pregabalin group experienced less pain during movement.

Preoperative Sedation - Assessment by Ramsay Sedation Scale

Ramsay sedation scale is a contrivance which is used to appraise sedation in a patient. Agitation is most often described as excessive restlessness which is characterized by non-purposeful mental and physical activity due to internal tension and anxiety.^(58,59,60)

In general, clinicians assess for agitation as they subjectively observe the patient's physical activity, nonverbal behavior, and verbalizations. Consequently, findings of agitation may vary among clinicians due, at least in part, to confusion about the definition of agitation. To minimize this variation, experts have developed scales to assess agitation; most also include measures of sedation. The most commonly used scales are the Ramsay Sedation Scale⁶¹ the Riker Sedation-Agitation Scale (SAS), and the Richmond Agitation Sedation Scale (RASS). Each of these scales evaluates the degree of agitation at one point in time and describes patient behavior.⁶²

A straight forward, and valid self-report measure is crucial, given the need to minimize patient burden and given the poor relationship between patient-generated and clinician-generated anxiety ratings.

This simple scale was named after Dr. Michael A.E. Ramsay an anaesthesiologist. He became president of the Baylor Research Institute. He used althesin or alphaxalone-alphadone sedative to determine the different level of sedation in a patient. In this scale 6 levels are used to represent different levels of sedation. First level represent the least amount of sedation and sixth the most. 1) Awake and anxious, agitated, or restless; 2) Awake, cooperative, accepting ventilation, oriented, tranquil; 3) Awake; responds only to commands; 4) Asleep; brisk response to light glabellar tap or loud noise; 5) Asleep; sluggish response to light glabellar tap or loud noise

stimulus but does not respond to painful stimulus; 6) Asleep; no response to light glabellar tap or loud noise. This scale is widely used by doctors, nurses, anaesthesiologists to find out the effect of treatment and administration of optimal dosage to the patient. The disadvantage of this scale is that, it purely depends upon the patient response.

Material And Methods

Source of data : A prospective, randomized, double blind, clinical study titled “Comparison Of Oral Pregabalin Versus Oral Pregabalin And Intravenous Fentanyl For Attenuation Of Pressor Response To Laryngoscopy And Tracheal Intubation -A Prospective Randomized Double Blind Clinical Study” was conducted after approval of ethical committee and informed consent on 60 patients, undergoing elective surgeries under General anaesthesia at Krishna Hospital and Medical Research Centre, Karad, from the academic year December 2017 and July 2019.

Design of the study: A Prospective randomized double blind clinical study

Inclusion criteria: i) ASA physical status I and II; ii) Age 20 to 50 years; iii) BMI 18-25; iv) Elective surgeries under general anaesthesia

Exclusion criteria: i) Patients with respiratory, cardiovascular or cerebrovascular disorders, hepatic and renal dysfunction; ii) Pregnancy; iii) Patients physically dependent on narcotics; iv) Patients with hypertension, diabetes mellitus, pheochromocytoma, patients on pregabalin, β -blockers, antidepressants, anxiolytics, anticonvulsant or antipsychotics; v) Predicted difficult airway; vi) Patients allergic to opioids or pregabalin

Statistical Analysis:

- Descriptive and inferential statistical analysis was carried out in the present study.
- The Microsoft Excel 2007 and SPSS 20 version software packages were used for data entry and analysis.
- The categorical factors were represented by the number and frequency (%) of cases.
- The continuous variables were represented by measures of central frequency (like mean, median, mode) and deviation (SD and range) wherever appropriate.
- Statistical Analysis were done by Unpaired student's t-test, Fisher's exact test, Friedman's test, and General Linear Model for repeated measure.
- P-value <0.05 was considered as statistically significant.

Discussion

The cardiovascular response during laryngoscopy and intubation, occurs in the form of tachycardia and hypertension, frequently. Shribman et al.⁵⁶ reported that blood pressures and catecholamine levels increase with laryngoscopy alone or with airway instrumentation and intubation will increase heart rate significantly. Reid et al¹ and Hassan et al.⁷⁰ reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accidents following airway instrumentation in hypertensive individuals. These physiological changes are due to variation in the balance of sympathetic and parasympathetic outflow or receptor hypersensitivity. Specific measures should be taken to prevent these haemodynamic response as hypertension may affect perioperative morbidity leading to end organ damage, like myocardial ischemia or cerebral haemorrhage. Aronson and Fontes⁷¹ quoted that increase in pulse pressure as little as 10 mmHg in both normotensive and hypertensive person is associated with a 20% or more increase in risk of renal failure, coronary events and cerebral stroke.

Observation and Result

Our study primarily evaluates oral pregabalin as premedication in comparison with pregabalin combined with intravenous fentanyl as premedication for preoperative sedative effect and for suppression of cardiovascular response to laryngoscopy and tracheal intubation in ASA physical status I and II patients undergoing elective surgery under general anaesthesia. Our objective was to define whether pregabalin alone was efficacious in blunting the haemodynamic response to laryngoscopy and intubation alone or when given along with

intravenous opioid (fentanyl 2 μ g/kg) in a double blind prospective randomized controlled study. The study population consisted of 60 patients divided into two groups with 30 patients in each group. Group P (pregabalin group) consisted of 30 patients who were given oral pregabalin 150 mg as premedication 60 min before intubation and Group PF (pregabalin and fentanyl group) consisted of 30 patients who were given oral pregabalin 150 mg, 60 min before surgery and intravenous fentanyl (2 μ g/kg) 5 min before induction, to blunt the haemodynamic response to laryngoscopy and intubation.

Cardiovascular Effects: i) Variations in Heart Rate

The present study showed that there was significant increase in HR in Group P when compared to Group PF immediately after laryngoscopy and intubation and 1 min after intubation when we applied GLM for repeated measure. When we considered the number of patients who had $\geq 20\%$ increase in heart rate the number was significantly higher in Group P at the time of intubation but subsequently the two groups showed similar parallel trend. Pregabalin in combination with fentanyl is superior in suppressing the rate response to laryngoscopy and intubation. Nonetheless, we can say that pregabalin group had only transient increase in heart rate at the time of intubation.

Rastogi et al.¹⁴, in their study have opined that in comparison to placebo, oral pregabalin 150 mg suppressed heart rate response. However they have used glycopyrrolate, midazolam, butorphanol also for premedication which could have influenced their findings. Moreover, the statistical analysis that they have resorted to may not be robust, since they have used different levels of measurements as independent and have not taken into consideration, the number of patients with $\geq 20\%$ increase in heart rate. Our statistical analysis is more robust. Gupta et al.¹⁷ compared oral pregabalin 150 mg versus placebo for haemodynamic response to laryngoscopy and intubation. In their study, there was significant rise in heart rate in both groups but there was less increase in pregabalin group as compared to control group. They used midazolam in addition for premedication which could influence the study finding regarding heart rate response. We did not use midazolam.

In another study of Salman et al.¹⁸, sixty patients allocated into two groups who received oral pregabalin 150 mg and placebo, showed no difference in heart rate at anytime between the two groups. The finding of this study was similar to our study.

Channaiah et al.⁴⁶ compared placebo and IV 2 μ g/kg fentanyl and noted that there was statistically significant decrease in heart rate during intubation in fentanyl group which is similar to our study.

ii) Variation in Blood Pressure

The present study showed significant increase in SBP in Group P when compared to Group PF immediately after intubation and 1 min after intubation. There was also significant increase in DBP and MAP immediately after intubation, 1 min and 3 min after intubation in Group P when compared to Group PF.

When we considered the number of patients in both the groups having $\geq 20\%$ increase in MAP from baseline, the difference was significant in group P when compared to group PF ($P = 0.000$, Friedman's test). Hence pregabalin alone could not control pressure response to laryngoscopy and tracheal intubation but could do so only when combined with intravenous fentanyl.

Rastogi et al.¹⁴, in their study also used midazolam and butorphanol along with pregabalin and came to a conclusion that oral pregabalin 150 mg reduces pressure response to airway instrumentation. The use of midazolam and opioid might have enhanced the effect of pregabalin. Hence their study results agree with our findings.

In contrast to our study findings, Eren et al.¹⁹ concluded that pregabalin given alone suppresses pressure response. This is in contrast to our findings that pregabalin along with fentanyl is effective in attenuating pressure response in comparison to pregabalin alone.

Channaiah et al.⁴⁶ compared placebo and IV 2 μ g/kg fentanyl and noted that there was statistically significant decrease in SBP, DBP and MAP during intubation which echoes in comparison to our study.

In study done by Hosalli et al.⁴⁷, blood pressure response was completely abolished by a bolus dose of fentanyl 5 μ g/kg in comparison with fentanyl 3 μ g/kg following laryngoscopy and intubation. In our study, the blood pressure response was suppressed in Group PF where in 2 μ g/kg fentanyl along with pregabalin was used. Even though we used lower dose, the pressure response could be suppressed which demonstrates that effect of fentanyl was augmented by pregabalin. As the study results show, pregabalin has an opioid sparing effect in

suppressing pressor response to laryngoscopy and intubation.

Conclusion

- 150mg of pregabalin was administered an hour before induction of anaesthesia as a single oral dose and it caused adequate sedation
- A transient increase in heart rate was observed at the time of intubation but it could not generate a pressure response to endotracheal intubation and laryngoscopy. Pregabalin and intravenous fentanyl effectively suppressed the rate and pressure response.

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