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Research Article

Efficacy of Oral Pregabalin Premedication as an Adjuvant to Fentanyl in Patients Undergoing Major Surgeries under General Anesthesia: An Observational Study

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ABSTRACT

Background: Intubation and laryngoscopy may raise blood pressure and heart rate unnecessarily. To investigate the effect of Pregabalin premedication on hemodynamic responses to laryngoscopy and intubation.
Methods: A Prospective Observational study was carried out in academic year December 2013 to July 2015 on 60 ASA physical status I or II patients undergoing elective surgery under general anesthesia at tertiary care hospital. 60 patients were divided into two equal groups of 30 each who received either fentanyl (Group A) or oral Pregabalin 150 mg (Group B) 1 hour prior to surgery. Pulse rate, Systoli and diastolic blood pressure were recorded preoperative, and 0,1,3,5 and 10 minutes after induction. Confidentiality of the subject was maintained. Descriptive and inferential statistics for quantitative and categorical variables were analysed using IBM SPSS version 22.
Results: SBP, DBP, and MAP rise during laryngoscopy and during intubation in a similar way in both groups at laryngoscopy (BL) and at 1 and 3 minutes following laryngoscopy before levelling off after 10 minutes in both groups. At baseline and one minute after laryngoscopy, HR increased in both groups. At 3 min, 5 min, and 10 min following laryngoscopy, the rise was reduced in the FL group, however the differences were statistically significant, p 0.005.
Conclusion: Oral Pregabalin premedication at a dose of 150 mg one hour prior to surgery attenuates pressor response associated with laryngoscopy and endotracheal intubation.

Under general anesthesia, direct laryngoscopy and endotracheal intubation are unpleasant stimuli that can damage oropharyngeal tissues mechanically and trigger reactions in the neurological, respiratory, cardiovascular, and other physiological systems. Although temporary, bronchospasm, increased intracranial and intraocular pressure, hypertension, tachycardia, arrhythmia, and particularly hemodynamic abnormalities might be harmful to individuals with illnesses of the cardiovascular, cerebral, and endocrine systems [1].

Laryngoscopy and endotracheal intubation are essential tools in the hands of the anesthesiologist in the maintenance of airway and prevention of aspiration. In healthy individuals, transitory hypertension and tachycardia are not a cause of concern, but they can create complications in those suffering from hypertension, myocardial insufficiency, or cerebrovascular diseases [2]. Susceptible individuals develop pulmonary edema, myocardial insufficiency, and cerebrovascular accident due to this hemodynamic response [3-4].

Despite being made normotensive prior to surgery by antihypertensive medication, the hemodynamic reaction is exacerbated in hypertension individuals. [5-6]. Intraoperative myocardial infarction could develop from this reaction [7-8], acute L.V.F, [7] and intracranial

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bleed7 in individuals with end-organ decompensation. To reduce hemodynamic responses to airway instrumentation, drugs like barbiturates, alpha 2 agonists, midazolam, opioids, etc., have been used as premedication's [9]. Variability of patient response and respiratory complications were frequently observed adverse effects due to benzodiazepines. Postoperative nausea and vomiting and delayed recovery of bowel function are being noted as adverse effects of opioid analgesics that contribute to delayed discharge and recovery of activities [10]. Because of all these adverse effects a sedative drug with minimal side effects and that can be administered safely during the surgery is the need of the hour.

Currently, a multimodal regimen was made that uses non-opioid analgesics to reduce postoperative pain and anxiety [10]. A medication with analgesic, opioid-sparing, reduced opioid tolerance, anxiety-relieving, and no side effects could be a good substitute. [11].

Kovac1996 Rastogi2012Gaba mimetic drugs like Pregabalin and gabapentin have been successfully utilised by various authors [2,9-10] as oral premedication to reduce preoperative anxiety, reduce perioperative fentanyl use, and diminish pressor reaction during airway instrumentation.

Although pregabalin is not functionally connected to the inhibitory neurotransmitter Gamma Amino Butyric Acid, it is a gabapentinoid in terms of structure. Alpha 2 subunit binding of voltage-dependent calcium channel causes the synthesis of the neurotransmitter glutamate, which can operate on the central nervous system and have analgesic, anticonvulsant, and anxiolytic effects, to decrease [9].

Many studies by Rastogi et al, [2] Shirin et al, [12] Wei Chen et al, [1] were conducted using Pregabalin which showed that it could be a drug to attenuate hemodynamic response associated with direct laryngoscopy and intubation.

Pregabalin as an oral premedical is already being used in many countries. But in India, the studies showing the efficacy of Pregabalin in reducing hemodynamic response are limited. Hence, we aimed to conduct this study using 150 mg9 oral pregabalin as a premedical 1 hr before the surgery.

Aims and objectives

To study the effect of oral Pregabalin 150mg premedication for attenuation of hemodynamic response during general anesthesia and its effect on preoperative sedation and anxiety, Intraoperative hemodynamic parameters (HR, NIBP, O2 saturation effect of fentanyl top-up intraoperatively and side effects and significant adverse events postoperatively.

Methods

Source of Data:

A Prospective Observational Study was conducted after the approval of the ethical committee of the concerned tertiary care setting, and informed consent was obtained from all 100 patients undergoing elective surgeries under General anesthesia from the academic year December 2013 to July 2015. Sixty patients were selected based on inclusion criteria. Patients were recruited and divided into two groups of 30 each according to the convenience sampling method.

Methods for Collection of Data:

Sixty patients undergoing major surgical procedures were selected by convenience sampling. Informed, written consent was obtained from participants. A preset proforma was used to record the values, and confidentiality of the patients was maintained.

Inclusion criteria:

- ASA grades I and II
- Age group between 20 to 50 years

Exclusion criteria:

Patients with ASA grade III and IV

Patients with disorders of liver, renal, cardiovascular, epilepsy, and COPD patients

Pregnant and lactating women

History of any drug allergy.

Procedure:

Preanesthetic checkup and preparation: Patients were recruited in two groups of 30 each based on inclusion criteria. A detailed case history, physical examination, and routine investigations were performed.

- Random Blood Sugar,
- Blood Urea and Serum creatinine
- Electrocardiogram
- Chest X-ray

Procedure for anesthesia: The night before surgery, Tablet Ranitidine 150mg and Tablet Alprazolam 0.5mg were administered as premedication. One hour before surgery, baseline pulse rate systolic and diastolic blood pressure were recorded for both groups. RAMSAY SEDATION SCALE was used to assess preoperative sedation levels.

Group (A) received fentanyl orally with sips of water 1hour before induction

Group(B) received Pregabalin 150 milligram orally with sips of water 1hour before induction.

Into the surgery room, where monitors were attached, the initial measurements of baseline heart rate, systolic, diastolic, and mean arterial blood pressure were repeated. Inj Ranitidine 50 mg IV, Inj Ondansetron 4 mg IV, Inj Fentanyl 2 mg/kg, and Inj Midazolam 1 mg IV were used to premedicate the patients. For induction, 2 mg/kg of propofol was administered. To induce neuromuscular blockade, 0.05 mg/kg of inj. vecuronium bromide was administered.

A laryngoscopy was conducted, and an appropriate-sized cuffed endotracheal tube was used for intubation. O2 and N2O, respectively, at 33:66 In order to maintain anaesthesia, vecuronium bromide (0.05 mg/kg) was

combined with halothane (0.5%). In order to keep the systolic blood pressure and heart rate within 20% of their preoperative values, the halothane concentration and fentanyl top-up dose were both modified. Before and after induction, just after intubation, and then every 15 minutes until operation was complete, hemodynamic and respiratory parameters were continually evaluated. If the intraoperative pain relief was insufficient as indicated by a >20% increase in heart rate and mean arterial pressure, intravenous fentanyl (0.5–1 mcg/kg) was administered. Following surgery, neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV were administered to combat neuromuscular blockade. Extubation was done as part of a standard process, and the patient's reaction to the extubation's stress was noted. After transferring the patient to the recovery room, postoperative complications and postoperative pain were measured using a visual analogue scale for an hour.

Outcome variables: Duration of surgery, preoperative VAS scores, and Ramsay sedation score were considered as primary outcome variables. Changes in heart rate and systolic and diastolic blood pressure were considered as secondary outcome variables.

Statistical Methods:

Heart rate changes, blood pressure, arterial pressure, and post-op VAS score, etc. were considered as primary outcome variables. Group A (fentanyl) and Group B(Pregabalin) was considered as Primary explanatory variable. Descriptive statistics were presented as mean and standard deviation for quantitative variables and frequency and proportion for categorical variables.

Inferential statistics: Independent sample t-test (2 groups) was used to compare the mean values between study groups. Chi-square test was used to compare the categorical variables like clinical parameters, VAS scores, and other scores using IBM SPSS version 22 and P value set at < 0.05 [13].

Results

Out of 100, 60 patients included into final analysis of which Group A (fentanyl) – 30 and Group B (Pregabalin) – 30. Out of 60 subjects 40 were females. It was found that the maximum was in age group of 39-48 of which 20(66%) were in group A and 22(73.3%) in group B. (Table 1).

The baseline values of heart rate, SBP, DBP, mean AP were comparable in both the groups. At laryngoscopy and intubation systolic BP, diastolic BP and MAP rises in both groups in similar fashion at laryngoscopy (BL) and at 1 minute, 3 minutes after laryngoscopy but settled down towards baseline after 10 minutes in both groups. HR increased in both groups at basal and at 1 min after laryngoscopy. Even though increase was less in group B at 3 minutes, 5 minutes and 10 minutes and 15 minutes after laryngoscopy but the differences were statistically significant. The mean and SD of postoperative VAS score was less in group B 2.33± 0.59 which was statistically significant. The mean and SD of Ramsay sedation scores in the present study were significantly higher (p=0.001) in the group B preoperatively before induction which was 1.9 ± 0.472 and 2hours after induction 3.83 ± 0.733 (Table 2, 3 and Figure 1).

Table 1- Comparison of demographic variable between the study group in the population (N=60)

Parameters	Group A (fentanyl) (N=30)	Group B (pregabalin) (N=30)	P value
Age	43.5 ± 7.23	45.2 ± 5.84	0.32
18-28 years	3(10%)	2(6.6%)	
29-38 years	2(6.6%)	1(3.3%)	
39-48 years	20(66.6%)	22(73.3%)	0.88
49-60 years	5(16.6%)	5(16.6%)	
Sex			
Male	10(33.3%)	10(33.3%)	1
Female	20(66.6%)	20(66.6%)	
Body weight (kg)	61.56±11.27	59.13 ± 10.19	0.05
40-44kg	0(0%)	0(0%)	
45-49kg	3(10%)	3(10%)	
50-54kg	5(16.6%)	7(23.3%)	
55-59kg	10(33.3%)	11(36.6%)	
60-64kg	2(6.6%)	1(3.3%)	*
65-69kg	2(6.6%)	1(3.3%)	
70+kg	8(26.6%)	7(23.3%)	

Table 2- Comparison of clinical parameter with the study group (N=60)

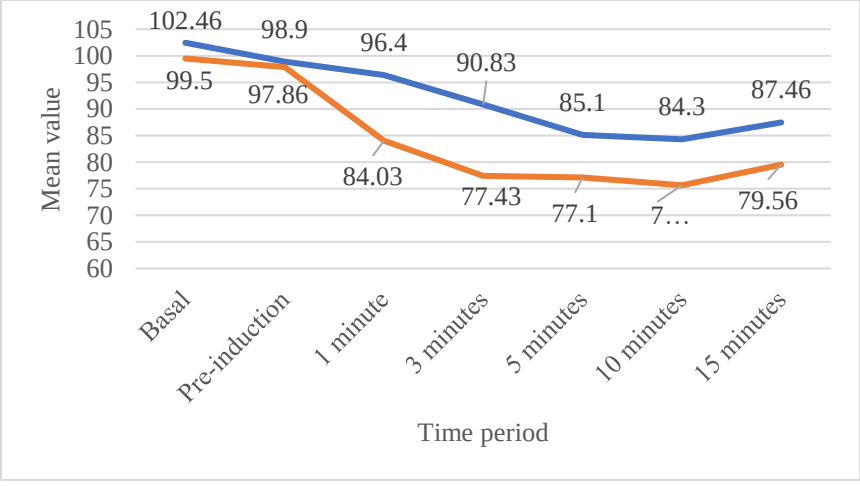
Clinical parameter	Group A(fentanyl) (N=30)	Group B(Pregabalin) (N=30)	P value
Type of surgery			
General surgeries	8(26.6%)	9(30%)	

Gynaecological surgeries	17(56.6%)	18(60%)	
Orthopedic surgeries	2(6.6%)	1(0.3%)	
Ear Nose Throat surgeries	3(10%)	2(6.6%)	0.89
Duration Of Intubation(seconds)	16.23 ± 2.215	16 ± 2.302	0.69
Postoperative VAS score	4.33 ± 0.51	2.33± 0.59	0.001
Ramsay sedation scores			
Preoperative (before induction)	1.13 ± 0.339	1.9 ± 0.472	0.001
Postoperative [2 hours]	1.33 ± 0.515	3.83 ± 0.733	0.001

Table3- Comparison of vital parameter with the study group (N=60)

Clinical parameter	Group A(fentanyl) (N=30)	GroupB (pregabalin) (N=30)	P value
Heart Rate Changes After Direct Laryngoscopy And Intubation(beats/min)			
Basal	80.76±15.896	84.13 ±10.15	0.34
Pre-induction	87.266± 16.195	85.3 ±10.33	0.58
1 min	94.96± 18.4178	92.13 ± 8.30	0.4
3 min	94.5±16.756	91.6±11.24	0.42
5 min	93.93±15.745	87.8±10.02	0.08
10 min	89.23±14.975	81.76 ±9.98	0.02
15 min	87.433±12.181	80.566±7.64	0.01
Systolic blood pressure (SBP in mmHg) changes in response to laryngoscopy and intubation			
Basal	131.76 ± 16.781	132.16 ± 10.963	0.91
Pre-Induction	132.53 ± 21.046	131.43 ± 14.39	0.81
1 min	124.83 ± 26.574	109.06 ± 15.035	0.00
3 min	116.93 ± 23.757	101.8 ± 8.178	0.00
5 min	110.23 ± 15.639	99.86 ± 11.47	0.00
10min	108.93 ± 14.393	99.6 ± 14.001	0. 01
15 min	112.1 ± 17.199	102.5 ± 12.126	0.02
Mean Diastolic Blood Pressure (DBP in mmHg) changes in response to laryngoscopy and intubation			
Basal	85.5 ± 10.092	83.26 ± 8.418	0.36
Pre-Induction	81.23 ± 14.24	80.63 ± 9.301	0.83
1 min	82.96± 21.648	71.23± 9.67	0.01
3 min	77.26 ± 17.523	64.53 ± 9.118	0.00
5 min.	72.4 ± 13.714	65.33 ± 10.067	0.02
10 min	72.50 ± 9.417	62.93 ± 9.712	0.00
15 min	75.06 ± 10.109	67.06 ± 7.987	0.00

Figure 1- Line Graph of Mean Arterial pressure between study groups (N=60)



Discussion

Sixty participants were included in the final analysis and divided into two groups Group A (fentanyl) – 30 and Group B (Pregabalin) – 30. Out of 60 subjects,40 were females. It was found that the maximum was in the age group of 39-48years, of which 20(66%) were in group A and 22(73.3%) in group B. Heart rate, systolic and diastolic blood pressure, and mean arterial pressure at baseline were similar in both groups. SBP, DBP, and MAP increased during laryngoscopy and intubation in a comparable way in both groups during laryngoscopy (BL) and at 1 and 3 minutes following laryngoscopy but then returned to baseline in both groups after 10 minutes. At baseline and one minute after laryngoscopy, HR increased in both groups. At 3 minutes, 5 minutes, and 10 minutes following laryngoscopy, the rise was reduced in the FL group, although the differences were still statistically significant (p 0.005), which shows the efficacy of Pregabalin. Tachycardia and hypertension are observed openly during laryngoscopy and intubation due to hemodynamic pressure. Hypertension may cause end-organ damage like myocardial ischemia or cerebral hemorrhage that leads to perioperative morbidity, and hence, precautionary measures should be taken to control them either through pharmacological techniques or through premedication during induction that reduces the hemodynamic pressor response to airway instrumentation [9].

Many different medications have been utilised to regulate this hemodynamic response. Recent investigations have shown that pregabalin is beneficial in reducing the pressor response after tracheal intubation. It was seen in earlier research that 150 mg of Pregabalin, taken orally an hour before surgery, was helpful in lowering the unpleasant stimuli to laryngoscopy and intubation, appropriately attenuating the hemodynamic response. [12,14-15]. In light of this, 150 mg of Pregabalin was administered in our trial one hour before to intubation, and the outcomes were examined.

In contrast to the study conducted by Sundar A S et al., the intubation time in the current study was 15.67 seconds in the pregabalin group and 16.18 seconds in the placebo group. [5] where the duration of intubation varied between 8.93 seconds and 22.42 seconds by Gupta K et al, [14] in the pregabalin group.

In the present study, the rise in heart rate at one, three and five minutes are maximum, which are in contrast with three studies by Sundar A S et al, [5] Gupta K et al, [14] Rastogi B et al, [2] which had maximum rise at the first minute. There is a fall in the systolic blood pressure in the control group in the present study and also in the study conducted by Sundar A S et al. [5] The present study, when compared to the Control group, shows a higher fall and a better trend, also seen in the study conducted by Sundar S et al, [5] which becomes important in susceptible patients. There is a fall in the diastolic blood pressure in the control group in the present study as compared to the study done by Sundar A S et al, [5] which showed a rise in the diastolic blood pressure. There is a greater fall in the diastolic blood pressure in the present study when compared to a study done by Sundar A S et al. [5] The present study does not show a rise when compared to the basal value in the placebo group, whereas the studies done by Gupta, [14] Rastogi, [2] and Sundar A S, [5] showed a rise in the mean arterial pressure.

The mean arterial pressure reduced around 12 to 20 mm hg in the present study and the study done by Sundar AS et al. [5] However, Gupta K, [14] study showed a rise in the mean arterial pressure at the 1, 3, 5 minutes. Rastogi B, [2] studied the effect of Pregabalin at two doses;75mg showed a rise in the mean arterial blood pressure, whereas the 150 mg showed a fall in the mean arterial pressure. The present study showed a 26.0% consumption of rescue analgesia (fentanyl 0.5 mcg/kg for HR or for BP≥ 20% of the baseline) in the control group as against an 8.0% consumption in the pregabalin group. The postoperative pain score, as assessed by visual analog scale one hour postoperatively, was significantly lower in the group which was given Pregabalin than the group that was given placebo in the present study.

The present study and Sundar AS et al, [5] studied the effects of Pregabalin on sedation using the Ramsay sedation score. The sedation given may only last for 6 hours as it was given an hour before the surgery, and so the elimination half-life of Pregabalin comes to 6.3 hours

Adverse effects like nausea vomiting were not observed in the present study in any of the groups. Guttuso T Jr, [16], in their study on the effect of gabapentin on chemotherapy-induced nausea in breast cancer patients, reported that postoperative nausea and vomiting is prevented by Pregabalin as it indirectly affects its opioid-sparing action or directly affects the inhibition of tachykinin activity.

Limitations:

The study was not without limitations. Stress mediators such as endogenous plasma catecholamines or cortisone were not measured. As they are the mediators of hemodynamic response, measuring their plasma levels would give greater credibility to this study and would help in understanding the exact mechanism of action of Pregabalin in attenuating hemodynamic response. The sample size was small. A bigger sample size with RCTs will give a better representation of the general population and better information on the adverse effects of Pregabalin. The interactions of Pregabalin with other drugs and anaesthetic agents have not been studied.

Conclusion

The findings of the present study concluded that there is decrease in hemodynamic response related to direct laryngoscopy and endotracheal intubation when a single dose of oral Pregabalin (150 mg) was given 60 minutes preoperatively and with better postoperative sedation and lower intraoperative requirement of rescue analgesic. Pregabalin showed no serious side effects with no significant adverse postoperative events.

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References

[1] Chen W, Huang H, Yang C, Hu X, Bao F, Jiang H. Preoperative Low-dose and High-dose Pregabalin and Cardiovascular Response to Endotracheal Intubation: A Prospective, Randomized, Single-blind, Controlled Study in China. Clin Ther. 2019; 41(1):68-77.

[2] Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: A dose response study. Indian J Anaesth. 2012;56(1):49-54.

[3] White PF, Tufanogullari B, Taylor J, Klein K. The effect of Pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg. 2009;108(4):1140-1145.

[4] Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007;104(6):1545-1556.

[5] Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive Pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth. 2012;15(1):18–25.

[6] Boerner TF, Ramanathan S. Functional anatomy of the airway. Airway management–Principles and practice, Benumof JL, ed. New York: Mosby Inc. 1996.

[7] Deem SA,Michael B, Robert FB.Physiologic and Pathophysiological Responses to Intubation. In: Carin A Hagberg,Editor.Benumof's Airway Management, 2nd Ed.USA: MosbyElsevier; 2007.

[8] Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, et al. Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II. Am J Med. 2007;120(10):871-879.

[9] Morin AM, Geldner G, Schwarz U, Kahl M, Adams HA, Wulf H, et al. Factors influencing preoperative stress response in coronary artery bypass graft patients. BMC Anesthesiol. 2004;4(1):7.

[10] Kovac AL. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. J Clin Anesth. 1996; 8(1):63-79.

[11] Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth. 1971;43(6):531-547.

[12] Parveen S, Negi DS, Kumar R, Bagwan MC. Oral Clonidine vs Oral Pregabalin Premedication to Attenuate Pressor Response to Direct Laryngoscopy in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Double-Blind Study. J Clin Diagn Res. 2016;10(9): UC21-UC25.

[13] IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

[14] Gupta K, Sharma D, Gupta PK. Oral premedication with Pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation. Saudi J Anaesth. 2011;5(2):179-184.

[15] Ghai A, Gupta M, Hooda S, Singla D, Wadhera R. A randomized controlled trial to compare Pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi J Anaesth. 2011;5(3):252-257.

[16] Guttuso TJ, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet (London, England). 2003;361(9370):1703-1705.