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Original Article

Premedication dilemmas, is Pregabalin the answer?

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ABSTRACT

Objective: Laryngoscopy and intubation are associated with sympathetic stimulation which can prove deleterious in patients with cardiovascular compromise; so, various methods have been tried to obtund this pressor response. In this study, we have assessed the efficacy of pregabalin in attenuating the pressor response to laryngoscopy and intubation.

Methods: This prospective randomized study included 80 patients with American Society of Anesthesiologists physical status grades I-II, in the age group of 18–60 years of age. The patients were randomized into two groups of 40 patients each. Group A received the placebo orally, 90 min prior to surgery. Group B received 150 mg of pregabalin orally, 90 min prior to surgery. These patients were assessed in terms of sedation with Ramsay sedation scale (RSS). In the operation theatre, the heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, and oxygen saturation recorded at baseline and 1, 3, 5, and 10 min after intubation. The rate pressure product (RPP) was calculated for these time intervals. In the postoperative period, patients were assessed for complications like dizziness, nausea, and blurred vision. Statistical analysis was performed using Chi-square and ANOVA tests.

Findings: The group receiving 150 mg of pregabalin as premedication was found to be adequately sedated at 1 h post-premedication with 52% patients having a RSS score of 3 compared to 4% with the same RSS score in the placebo group ($P < 0.0001$). Hemodynamics was more stable post-intubation with significant stability in the HR ($P = 0.002$) and RPP ($P = 0.004$) in the pregabalin group.

Conclusion: Pregabalin when given as a premedication provides adequate sedation and obtunds the pressor response seen with intubation.

Keywords: Laryngoscopy; Pregabalin; pressor response; Ramsay sedation scale; rate pressure product

INTRODUCTION

Laryngoscopy and tracheal intubation stimulate sympathetic responses such as tachycardia, hypertension, and arrhythmias.[1] The perturbations consist of tachycardia, increased blood pressure, and pulmonary artery pressures leading to cardiac compromise like myocardial ischemia, myocardial infarct, and cardiac dysrhythmias.[2] Adequate premedication has been shown to attenuate this pressor response. Sundar *et al.*,[3] showed that the mean systolic and diastolic pressure during different time periods after intubation were significantly lower with 150 mg of pregabalin premedication compared with placebo. Gupta *et al.*[4] also concluded that the hemodynamic pressor responses were attenuated by pregabalin with

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minimal effect on heart rate (HR). We wanted to assess pregabalin for its effect on attenuation of pressor response as well as its role in preoperative sedation and to evaluate if there were any postoperative side effects like nausea, vomiting or drowsiness.

METHODS

Approval of the Institutional Ethics Committee was sought prior to conducting this prospective double-blind randomized controlled study. Inclusion criteria consisted of patients belonging to either gender with American Society of Anesthesiologists (ASA) physical status grades I-II, aged between 18 and 60 years and scheduled for elective surgery under general anesthesia, requiring tracheal intubation. 80 patients were enrolled in the study. Individuals with hypersensitivity to pregabalin, history of seizure disorder, patients on chronic neuroleptic medications, tricyclic antidepressants or serotonin and norepinephrine reuptake inhibitors, pregnant or breastfeeding women, anticipated difficult airway, history of cardiac, pulmonary, or renal disease, allergy to any anesthetic medication, gastrointestinal disturbance, which hinders enteric absorption to oral medications and uncontrolled diabetes or hypertension were excluded from the study. After explaining about the study, a written informed consent was obtained from the patients.

The day before the surgery, a complete physical examination was carried out on all patients and the relevant investigations were asked for. The patients were kept nil orally 6 h prior to the scheduled time of surgery. The patients enrolled in this double-blinded study were randomly divided into two groups of 40 each [Figure 1]: Group A (n = 40) received a placebo orally, 90 min prior to surgery with sips of water. Group B (n = 40) received 150 mg of pregabalin with sips of water, 90 min before surgery.

In the preoperative period, routine monitoring of vital parameters was recorded and patients were preloaded with intravenous infusion of 6–8 ml/kg of crystalloids. The study drug was administered according to the randomized computer format by an anesthesiologist not involved in the study. The levels of anxiety and sedation were assessed after intake of the drug using the Ramsay sedation scale (RSS) [Table 1]. In the operation theatre, all the patients received glycopyrrolate 0.2 mg and fentanyl 1 μg/kg. Routine monitors (electrocardiogram, pulse oximeter, and noninvasive blood pressure monitoring) were attached and baseline vitals were recorded. After preoxygenation with 100% oxygen for 3 min, the patients were induced with propofol 2 mg/kg or in a dose sufficient to abolish the eyelash reflex. The patients were intubated 90 s after administering rocuronium 0.8 mg/kg. The systolic

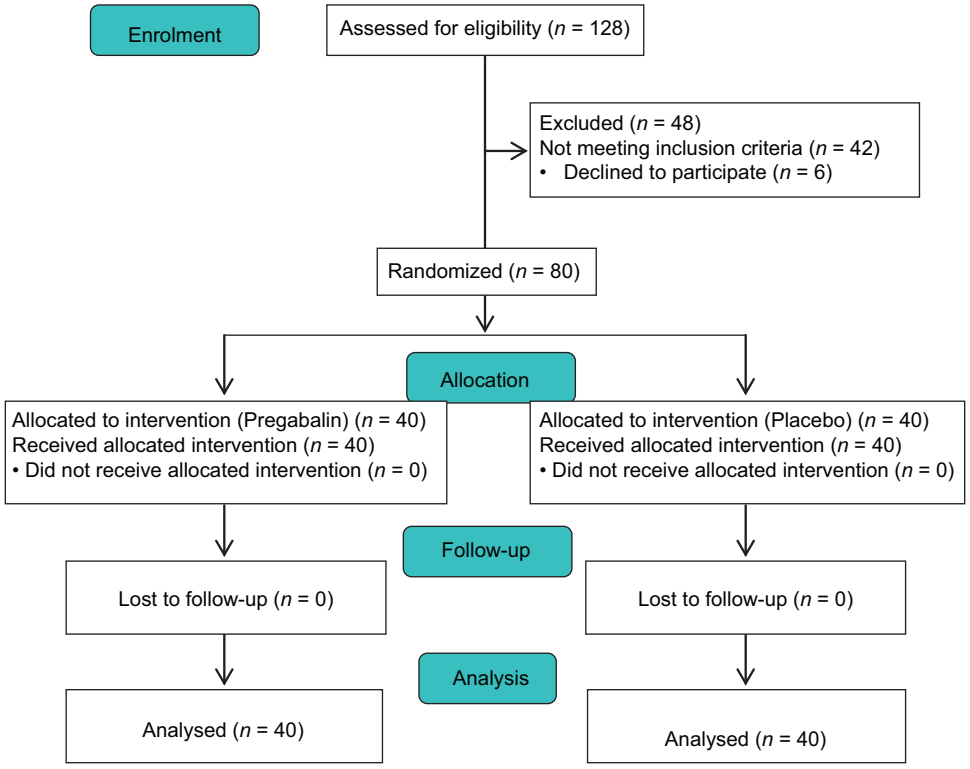

Figure 1: CONSORT diagram of the study

blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), HR, and oxygen saturation were measured at baseline (3 min before induction), just before laryngoscopy, and at 1, 3, 5, and 10 min after intubation. The rate pressure product (RPP) which is the product of HR and SBP was also calculated for the respective time intervals. Patients in whom there was a delay in intubation after laryngoscopy for more than 25 s were not included in the study. Furthermore, the patients in whom there was a delay of more than 90 min after premedication to start of the procedure, were excluded. In the postoperative period, patients were assessed for complications like dizziness, nausea, and blurred vision. At the end of the study, the observations and results were tabulated and statistically analyzed using ANOVA test, SPSS version 21 (Armonk, NY: IBM corp). The Chi-square test was used to analyze age, sex, and ASA status of the patient. The Mann–Whitney U-test was used for assessing sedation and also to know the significance in the variables of HR, SBP, DBP, MAP, and RPP.

Table 1: RSS

Level of activity	Point
Patient anxious, agitated, restless	1
Patient cooperative, oriented, and tranquil	2
Patient responding only to verbal command	3
Patient with brisk response to light glabellar tap or loud auditory stimulus	4
Patient with sluggish response to light glabellar tap or loud auditory stimulus	5
Patient with no response to light glabellar tap or loud auditory stimulus	6

RSS=Ramsay sedation scale

RESULTS

We did not find any significant differences between the two groups in terms of age, gender, and ASA grading. Premedication with pregabalin 150 mg 1 h prior to surgery was able to achieve significant levels of sedation starting 15 min after administration [Table 2]. RSS scoring was used and a RSS score of 3 was considered as adequate sedation. Accordingly, 26 patients in the pregabalin group compared to 12 patients in the placebo group were found to have a RSS of 3 after 30 min. While there was an increase in the HR seen in both groups post-intubation, but a significant difference was observed with the pregabalin group having more stable HR. This difference was significant at 1, 3, and 5 min. The HR returned to normal within 10 min in both groups. There was a significant attenuation of RPP in the pregabalin group. This was seen at 1 min and 10 min [Table 3]. There was no significant difference between the two groups in terms of MAP, SBP, and DBP.

Table 2: The sedation scores in placebo and pregabalin groups, using RSS score

Timing	RSS 2/3		
	Placebo	Pregabalin	*P*
Before premedication	40 (100)/0 (0)	40 (100)/0 (0)	-
After premedication (min)			
15	40 (100)/0 (0)	33 (82.5)/7 (17.5)	0.006
30	28 (70)/12 (30)	14 (35)/26 (65)	0.002
45	29 (72.5)/11 (27.5)	11 (27.5)/28 (70)	<0.001
60	36 (90)/4 (10)	19 (47.5)/21 (52.5)	<0.001
In operation theatre (before induction)	40 (100)/0 (0)	39 (97.5)/1 (2.5)	0.314

Data presented as number (%) of the patients. RSS=Ramsay sedation scale

Table 3: Mean HR, MAP and RPP in the study groups

Timing	Mean HR			Mean MAP			Mean RPP		
	Placebo	Pregabalin	*P*	Placebo	Pregabalin	*P*	Placebo	Pregabalin	*P*
Before premedication	84.15	86.7	0.25	94.525	93.1	0.51	10,563.725	10,571.625	0.70
Baseline (3 min before induction)	88.525	86.775	0.81	94.925	93.5	0.52	11,254.925	10,730.825	0.35
Before laryngoscopy	93.225	90.225	0.59	93.6	91.175	0.31	11,632.6	10,950.75	0.30
After laryngoscopy (min)									
1	118.025	103.025	0.002	97.775	94.925	0.28	15,410.475	12,878.4	0.004
3	109.525	97.55	0.008	91.925	89.425	0.26	13,347.55	11,424.025	0.10
5	100.025	91.9	0.03	85.65	85.625	0.99	11,466.925	10,350.925	0.08
10	92.2	86.05	0.07	83.525	84.05	0.77	10,426.15	9450.85	0.23

HR=Heart rate, MAP=Mean arterial pressure, RPP=Rate pressure product

DISCUSSION

Direct laryngoscopy and intubation can cause an increase in arterial blood pressure and HR. The hemodynamic changes stem from reflex sympathetic discharge resulting from epipharyngeal and laryngopharyngeal stimulation. This leads to increased plasma norepinephrine concentration which results in increased myocardial oxygen demand. Various drugs have been deployed including topical and intravenous lidocaine, narcotics, inhaled anesthetics, magnesium sulfate, beta adrenergic blockers, vasodilators, and alpha agonists.[5-8] The search for the perfect premedication is ever important. All the drugs being used have their own positive and negative aspects. Opioids are commonly used, but there is always a risk of respiratory depression and the route might be intravascular or intramuscular, thus making it unpleasant. There is a risk of bradycardia with alpha agonists and beta blockers. Thus, we are going to assess the efficacy and safety of using pregabalin as a premedicant.

Pregabalin is a structural analog of gamma aminobutyric acid.[9] Pregabalin has been used increasingly in recent times for the treatment of acute postoperative pain and to reduce the postoperative opioid requirements. It effectively prevents the neuropathic component of acute nociceptive pain, diabetic neuropathy, reflex sympathetic dystrophy, and postherpetic neuralgia.[10,11] It is well-absorbed orally and is well-tolerated, as it has limited side effects. There are no clinically relevant drug interactions and it undergoes negligible hepatic metabolism as it is eliminated by renal excretion. It is nonnarcotic and drug dependency does not occur. There is growing evidence, which suggests that perioperative administration of pregabalin is efficacious for allaying preoperative anxiety.[12]

In the preoperative period in our study, the patients in the pregabalin group were arousable, but adequately sedated (RSS 3) and calm compared to the placebo group. There was no respiratory depression seen in any patient. The sedative effect was seen after 15 min of pregabalin. The difference in sedation in both groups was significant throughout the preoperative group, that is, from 15 to 60 min after premedication. This is consistent with other studies, where it was demonstrated that pregabalin offered better sedation and anxiolysis when compared to placebo and clonidine.[3,13]

The patients who were given pregabalin as a premedicant were much less anxious as compared to the placebo group; this could have explained the higher HR preinduction in the placebo group. After induction and intubation there was a rise in HR and blood pressure in both groups, this was expected as a normal pressor response. This increase in HR is due to the sympathoadrenal stimulation evoked by mechanical stimulation of the upper respiratory tract caused by the stretching effects of laryngoscopy and intubation. There was an increase in HR initially for the first 1 min and then it steadily stabilized after 3 min. The steadily decreasing trend of HR after the 3rd min may be due to the decreasing concentration of circulating adrenaline and noradrenaline levels. This was observed in another study where they measured plasma concentration of adrenaline and noradrenaline before intubation and at 1, 3, and 5 min after intubation.[14] Even though there was an increase in HR in both groups, there was a significant difference between the two groups with the pregabalin group having a lower pressor response. This difference was consistently found at 1, 3, and 5 min post-intubation. Various other studies have shown attenuation of the pressor response in patients premedicated with pregabalin.[15,16]

Laryngoscopy and intubation also cause an increase in the MAP along with tachycardia. Various studies done have shown a significant attenuation of this response in individuals premedicated with pregabalin. We also studied and compared the pressor response in both groups. There was an increase in MAP at 1 min post-intubation and then it steadily decreased. There was a difference between the two groups with the pregabalin group having a lesser increase compared to placebo, but this difference was not found to be statistically significant. This finding is not consistent with other studies. This discrepancy can be attributed to the fact that there were head and neck surgeries also included which are associated with more position changes. Even though there was no significant difference between the two groups in terms of the MAP, the RPP, which is a product of HR and blood pressure showed a significant attenuation in the pregabalin group. Studying the RPP proved to be the strength of our study as RPP is a measure of the stress put on the cardiac muscle based on the number of times it needs to beat per minute (HR) and the arterial blood pressure that it is pumping against (SBP). Thus, it is a direct indication of the energy demand of the heart and thereby a good measure of the energy consumption of the heart.

We realized two limitations of our study. The sample size was small as we studied only 80 patients. Secondly we took only ASA-I and ASA-II patients, hence, the data cannot be extrapolated to ASA-III and ASA-IV patients. The beneficial effects of good premedication are more pronounced in ASA-III and ASA-IV patients, who are more vulnerable to developing cardiac complications secondary to tachycardia and hypertension.

To conclude, we have found that pregabalin when given as premedication is able to acquire adequate levels of sedation and is able to obtund the pressor responses seen with intubation. Hence, we can recommend pregabalin at a dose of 150 mg orally as a safe premedication to obtain preoperative sedation and stability of the vitals. It is an easily tolerated, effective, and inexpensive method with minimal side effects.

AUTHORS' CONTRIBUTION

Preetha Elizabeth George and Reetika Chander collected and analysed the data. Dootika Liddle and Valsamma Abraham supervised and guided the study.

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Conflicts of interest
There are no conflicts of interest.

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