Section: Anaesthesia

Original Research Article

EFFECT OF ORAL PREGABALIN AS PREMEDICATION ON LARYNGOSCOPY RESPONSE: A RANDOMIZED PLACEBO CONTROLLED TRIAL

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ABSTRACT

Background: Pregabalin is a novel drug that exhibits analgesic, anticonvulsant, and anxiolytic properties by decreasing the levels of neurotransmitters such as glutamate, noradrenaline, serotonin, dopamine, and substance P. Hence, the present study was undertaken to determine the role of oral pregabalin as premedication on attenuation of stress response to laryngoscopy.

Materials and Methods: The present study was conducted among 100 patients who underwent elective surgery under general anaesthesia. Patients were randomly assigned in two groups of 50 each. Group P patients were administered oral pregabalin at a dosage of 150 mg, while group C patients were given oral placebo in the form of oral multivitamin tablet. The study recorded heart rate (bpm) and non-invasive measurements of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and mean arterial pressure (MAP) (mmHg) at various time points. A significance level of $P < 0.05$ was used to determine statistical significance. The analysis was conducted using the SPSS statistical tool version 20.0 (IBM in Armonk, NY).

Results: Heart Rate increased significantly after laryngoscopy and tracheal intubation in all groups ($P<0.05$). However, the increase in heart rate was significantly lower in pregabalin group compared to the placebo group ($P<0.05$). Systolic blood pressure was higher from baseline values in control group during laryngoscopy ($p = <0.05$). Thereafter, this upsurge remained persistent throughout the surgery at all points of time till 10 minutes after laryngoscopy ($p <0.05$). In the pregabalin group, there was no increment, and the patients were stable at all points of time after giving the study drug with similar trend observed for diastolic and mean blood pressure.

Conclusion: Pregabalin effectively reduces the physiological stress response to laryngoscopy.

Keywords: Haemodynamic Stress Response; Laryngoscopy; Pregabalin.

INTRODUCTION

The majority of patients who undergo elective surgery commonly experience preoperative anxiety. Anxiety exerts an impact on the subjective views of patients, and preoperative anxiety is correlated with an elevated amount of postoperative pain.[1]

Direct laryngoscopy and tracheal intubation predictably lead to haemodynamic stress response characterized by increased heart rate (tachycardia) and elevated blood pressure (hypertension). The plasma concentration of catecholamines rises, which can lead to cardiac ischemia and cerebral hemorrhage.[2] The impact, however temporary, lasts from 30 seconds after intubation to a maximum of 10 minutes. The occurrence is a result of the adrenergic response, which stimulates the cardioaccelerator fibers. Normotensive patients generally tolerate it well, but even temporary stimulation has been linked to higher rates of illness and death in patients with conditions such as preeclampsia, recent heart attack, high blood pressure, and cerebrovascular disorders

like aneurysms, tumors, or elevated intracranial pressure.[3]

While preoperative benzodiazepines are commonly used to reduce preoperative anxiety, they do not yield a favorable impact on the postoperative outcome.[1] Premedication in the form of vasodilators, adrenoreceptor blockers, calcium channel blockers and opioids were used earlier to attenuate these responses, with variable results.[2]

Pregabalin is a novel drug introduced for its epileptic action. It is a molecule belonging to the gabapentinoid class, has been observed to exert an inhibitory effect on the excitability of neurons, specifically in the neocortex, amygdala, and hippocampus of the central nervous system. Pregabalin targets the alpha2–delta (α2–δ) protein as site of action. This protein serves as an auxiliary subunit of voltage-gated calcium channels. Pregabalin exerts a subtle effect on the release of several neurotransmitters at the synapse by binding to α2–δ subunits.[4] It exhibits analgesic, anticonvulsant, and anxiolytic properties by decreasing the levels of neurotransmitters such as glutamate, noradrenaline, serotonin, dopamine, and substance P.5 Hence, the present study was undertaken to determine the role of oral pregabalin as premedication on attenuation of stress response to laryngoscopy.

MATERIAL AND METHODS

The present randomized double-blind placebo-controlled study was conducted among 100 patients who underwent elective surgery was conducted in the Department of Anesthesia, Maharaja Agrasen Medical College, Agroha, Hisar, Haryana. Ethical clearance was obtained from the Institutional Ethics Committee. The study included patients of any gender, with ASA physical status classification I and II, aged between 18 and 60 years, who were scheduled to undergo surgery under general anesthesia. The study excluded patients who had ASA physical status classification III and IV, anticipated difficult intubation, intubation exceeding 30 seconds, multiple intubations attempt during laryngoscopy, severe renal or hepatic disease, allergies, chronic hypertension, ischemic heart disease, left ventricular failure, major cardiac disorders, patients on β- blockers or vasodilators, allergic to any anaesthetic medication, and obesity.

Patients were randomly assigned in two groups of 50 each using computerized random allocation. Following a comprehensive preanesthetic assessment and after obtaining informed consent from the patients, patients were administered medications in the preoperative area 60 minutes prior to surgery. Group P was administered oral pregabalin at a dosage of 150 mg, while group C was given oral placebo in the form of oral multivitamin tablet.

Upon arriving the operation room, an 18G intravenous (IV) cannula was placed into a peripheral vein, and Ringer's lactate solution was initiated at a rate of 6 mL per kilogram of body weight. All groups were subjected to a standardized anesthetic procedure. Following a 3-minute period of preoxygenation, anesthesia was initiated using intravenous thiopentone at a dosage of 5 mg per kilogram. Intravenous succinylcholine was administered at a dosage of 1.5 mg per kilogram to aid in the process of endotracheal intubation. The duration of laryngoscopy and intubation was restricted to less than 15 seconds for all patients. The anesthetist, who was blinded to drug administered in each group, conducted the monitoring of vital parameters. The study recorded the heart rate (bpm) and non-invasive measurements of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and mean arterial pressure (MAP) (mmHg) at various time points. These time points included baseline vital parameters, before induction, during induction, after laryngoscopy and intubation, and at 2, 4, 6, 8, and 10 minutes after intubation. After performing endotracheal intubation, a nasogastric tube (14 F) was inserted.

Patients were mechanically ventilated and maintained with a gas-mixture of nitrous oxide and oxygen (2:1) with isoflurane. Neuromuscular paralysis was induced by administering vecuronium at a dosage of 0.08–0.12 mg/kg. Analgesia during surgery was achieved by administering 1–1.5 µg/kg of fentanyl. Neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg were administered intravenously to reverse the residual neuromuscular blockade at the end of the surgery. The patients were extubated after adequate respiration and after following verbal commands. Inj. Diclofenac sodium 1.5mg/kg i.v and injection Paracetamol 15mg/kg were administered after extubation for post-operative analgesia.

At the end of the study, the findings were given as the mean value (mean ± SD). The quantitative data (mean ± SD) between the groups was statistically analyzed using the Student's "t" test. The Chi-square test was used to perform statistical analysis on the qualitative data between the groups. A significance level of $P < 0.05$ was used to determine statistical significance. The analysis was conducted using the SPSS statistical tool version 20.0 (IBM in Armonk, NY).

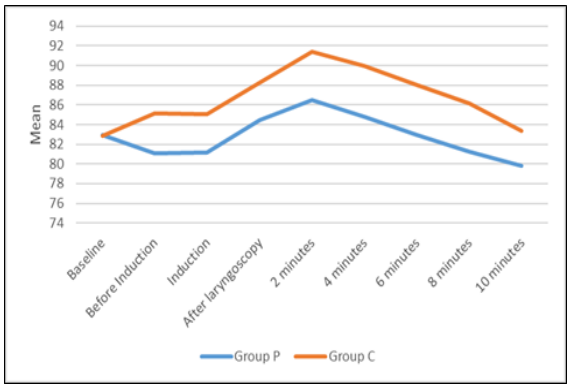
RESULTS

A total of 100 patients were enrolled in the study, with 50 in each group. The mean age in group P (oral pregabalin) 38.48±11.11 and in control group was 38.78±10.34 (table 1). 52% females in group P and 50% in control group with remaining male patients in each group (group 2). Similar distribution was found with ASA grading and there were no

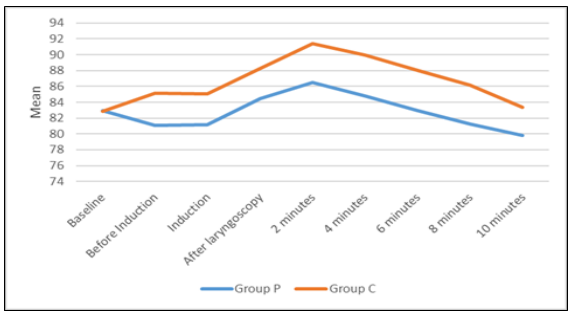
significant differences in age, ASA physical status, mean weight wise among the groups (P>0.05).

HR increased significantly after laryngoscopy and tracheal intubation in all groups (P<0.05). However, the increase in HR was significantly lower in pregabalin group compared to the placebo group (P<0.05). The maximum attenuation was observed at 2 minutes was 86.50±8.48 after laryngoscopy in pregabalin group and was 91.38±7.89 in control group to baseline of 82.96±9.58 and 82.86±8.54 respectively and differences was statistically significant (table 5 and graph 1).

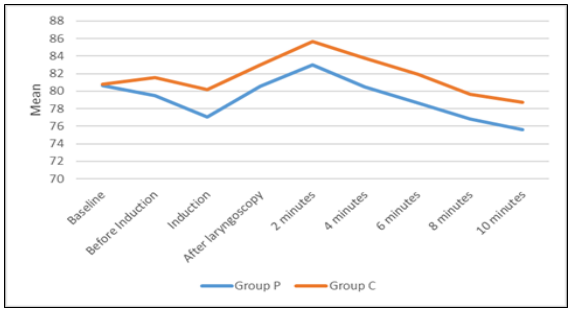
Systolic blood pressure was higher from baseline values in control group during laryngoscopy (p = <0.05). Thereafter, this upsurge remained persistent throughout the surgery at all points of time till 10 minutes after laryngoscopy (p <0.05). In the pregabalin group, there was no increment, and the patients were stable at all points of time after giving the study drug (table 6, graph 2). Similar trends were observed for diastolic (table 7, graph 3) and mean blood pressure (table 8, graph 4).



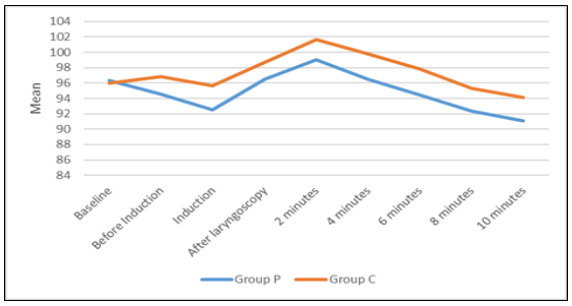
Graph 1: Comparison of mean HR of subjects in the two groups at different time intervals



Graph 2: Comparison of mean SBP of subjects in the two groups at different time intervals



Graph 3. Comparison of mean DBP of subjects in the two groups at different time intervals



Graph 4: Comparison of mean MAP of subjects in the two groups at different time intervals

Table 1: Age group-wise distribution of subjects in the two groups

Age Group (Years)	Group P		Group C	
	Frequency	Percent	Frequency	Percent
21-30	2	4.0	0	0.0
31-40	14	28.0	15	30.0
41-50	12	24.0	11	22.0
51-60	12	24.0	16	32.0
>60	10	20.0	8	16.0
Mean±SD	38.48±11.11		38.78±10.34	
Total	50	100.0	50	100.0

Table 2: Gender-wise distribution of subjects in the two groups

	Group P		Group C	
	Frequency	Percent	Frequency	Percent
Female	26	52.0	25	50.0
Male	24	48.0	25	50.0

Table 3: ASA Grading distribution of subjects in the two groups

Grade	Group P		Group C	
	Frequency	Percent	Frequency	Percent
1	46	92.0	46	92.0
2	4	8.0	4	8.0

Table 4: Comparison of mean weight of subjects in the two groups

	Mean	Std. Deviation	t value	p value
Group P	65.40	9.57	0.043	0.966
Group C	65.32	9.19		

Table 5: Comparison of mean HR of subjects in the two groups at different time intervals

Time point	Group P		Group C		t value	p value
	Mean	Std. Deviation	Mean	Std. Deviation		
Baseline	82.96	9.58	82.86	8.54	.055	.956
Before Induction	81.06	9.16	85.10	8.22	-2.322	.022*
Induction	81.18	8.93	85.04	8.00	-2.276	.025*
After laryngoscopy	84.44	8.27	88.24	7.92	-2.346	.021*
2 minutes	86.50	8.48	91.38	7.89	-2.980	.004*
4 minutes	84.80	8.88	89.96	8.22	-3.014	.003*
6 minutes	82.92	8.64	88.04	8.30	-3.023	.003*
8 minutes	81.28	8.10	86.18	8.33	-2.981	.004*
10 minutes	79.80	7.23	83.36	8.45	-2.263	.026*

*Statistically significant

Table 6: Comparison of mean SBP of subjects in the two groups at different time intervals

Time point	Group P		Group C		t value	p value
	Mean	Std. Deviation	Mean	Std. Deviation		
Baseline	127.82	8.12	126.30	4.90	1.134	.260
Before Induction	124.76	7.60	127.44	4.65	-2.128	.036*
Induction	123.48	7.27	126.72	5.02	-2.593	.011*
After laryngoscopy	128.28	6.52	130.24	4.86	-1.704	.092
2 minutes	131.04	6.17	133.76	4.35	-2.547	.013*
4 minutes	128.56	5.79	131.82	4.05	-3.260	.002*
6 minutes	125.92	5.73	129.58	4.27	-3.622	<0.01*
8 minutes	123.32	5.63	126.78	4.01	-3.539	.001*
10 minutes	122.12	4.91	125.08	4.34	-3.193	.002*

*Statistically significant

Table 7: Comparison of mean DBP of subjects in the two groups at different time intervals

Time point	Group P		Group C		t value	p value
	Mean	Std. Deviation	Mean	Std. Deviation		
Baseline	80.62	5.80	80.82	5.22	-.181	.857
Before Induction	79.48	5.31	81.58	5.68	-1.911	.059
Induction	77.02	5.49	80.16	6.01	-2.727	.008*
After laryngoscopy	80.58	4.88	82.98	5.74	-2.252	.027*
2 minutes	82.98	4.26	85.66	5.48	-2.728	.008*
4 minutes	80.52	4.27	83.78	5.03	-3.494	.001*
6 minutes	78.68	4.70	81.96	4.95	-3.397	.001*
8 minutes	76.84	4.36	79.64	4.91	-3.016	.003*
10 minutes	75.58	4.81	78.70	4.54	-3.336	.001*

*Statistically significant

Table 8: Comparison of mean MAP of subjects in the two groups at different time intervals

Time point	Group P		Group C		t value	p value
	Mean	Std. Deviation	Mean	Std. Deviation		
Baseline	96.35	6.05	95.98	4.58	.348	.729
Before Induction	94.57	5.57	96.87	4.86	-2.193	.031*
Induction	92.51	5.56	95.68	5.34	-2.911	.004*
After laryngoscopy	96.48	5.01	98.73	5.11	-2.227	.028*
2 minutes	99.00	4.43	101.69	4.83	-2.906	.005*
4 minutes	96.53	4.31	99.79	4.25	-3.807	<0.01*
6 minutes	94.43	4.43	97.81	4.24	-3.896	<0.01*
8 minutes	92.33	4.24	95.35	4.17	-3.588	.001*
10 minutes	91.09	4.31	94.16	4.02	-3.682	<0.01*

*Statistically significant

DISCUSSION

The present study evaluated the efficacy of pregabalin as oral premedication on attenuation of stress response to laryngoscopy. Laryngoscopy contributes significantly to hemodynamic changes. Few studies.[6,7] reported that laryngoscopy may cause different hemodynamic responses usually in the form of tachycardia and hypertension. Another study reported higher incidences of myocardial ischemia, cardiac arrhythmias, acute left ventricular failure and cerebrovascular accidents after intubation in hypertensive patients.8There is an increase in plasma concentration of catecholamines

which leads to the adverse conditions viz myocardial ischemia and cerebral haemorrhage. Pregabalin is a congener of gabapentin, an antiepileptic drug, acts by inhibiting membrane voltage-gated calcium channels in the central nervous system. It does not interact with GABA receptors. It has analgesic, anticonvulsant, and anxiolytic properties. It is effective in controlling neuropathic pain.[9]

This study aimed to assess the impact of oral pregabalin as a premedication in reducing the hemodynamic stress response to laryngoscopy in patients undergoing elective surgery and found that administering pregabalin as a premedication resulted in a significant and consistent improvement in all hemodynamic parameters at all-time points, with minimal occurrence of adverse effects.

The pregabalin possesses several properties to attenuate the hemodynamic response of laryngoscopy and pneumoperitoneum. Pregabalin, an antiepileptic drug, is effective in controlling neuropathic component of acute nociceptive pain of surgery by inhibiting membrane voltage-gated calcium channels. It does not interact with GABA receptors. However, only few data are available in the literature regarding the effect of pregabalin on the cardiovascular system. Its analgesic, anticonvulsant, and anxiolytic activities make it useful oral premedication. It is well absorbed after oral administration, with peak plasma concentrations occurring within 60 minutes.[10]

Our study is in concordance with other studies. In the study by Singh D et al,1 before and 60 min after administration of similar dose of oral pregabalin as our study, anxiety VAS was measured. The heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were measured before, 60 min after drug administration, and 2, 4, 6, 8, and 10 min after intubation. Pregabalin reduced VAS as well as laryngoscopy and intubation stress response as compared to placebo during preinduction. Patients premedicated with pregabalin were hemodynamically stable and reported no adverse effects.

In another similar study conducted by Rastogi et al,[11] different doses of pregabalin were compared to determine the optimal dose for maintaining stable hemodynamics during airway manipulation. The study found that the premedicated group experienced a significant decrease in mean arterial pressure (MAP) compared to the control group. Specifically, the pregabalin 75 mg group had a MAP of 97.80 ± 2.52 compared to 110.70 ± 4.94 in the control group ($p = 0.001$), and the pregabalin 150 mg group had a MAP of 92.06 ± 3.37 compared to 110.70 ± 4.94 in the control group ($p = 0.001$). These results suggest a dose-dependent relationship. In a study conducted by Saxena A et al,[12] the impact of pregabalin premedication on the response to laryngoscopy and intraoperative hemodynamic parameters in laparoscopic cholecystectomy was studied and both 150 mg and 300 mg doses of pregabalin were reported to be equally effective in preventing the increase in heart rate that occurs during laryngoscopy and intubation.

Another study in consistent to our results, Gupta K et al,[10] reported that oral premedication with pregabalin 150 mg causes sedation and anxiolysis with hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy, without prolongation of recovery time and side effects. Similarly, another study by Chakraborty R et al,[13] found that 150 mg oral pregabalin safely reduces laryngoscopy and intubation hemodynamic response. Therefore, based on this, a dosage of 150 mg of pregabalin was chosen for our study group.

Chen W et al,[14] reported that pregabalin (150 or 300 mg) was associated with reduced blood pressure fluctuations after intubation, but with no significant differences between the 2 dose groups. Pregabalin was associated with an inhibitory effect on heart rate fluctuations and reduced hemodynamic complications after intubation, in a dose-dependent manner, but no effect on the required perioperative opioid dosage was found. Both doses were effective in reducing preoperative anxiety, but visual analog scale pain scores at 1 hour after surgery were reduced only in limb and spine as well as abdominal surgeries. Eren G et al,[15] gave pregabalin to a cohort of 50 patients who were undergoing elective spine surgery in order to assess its efficacy in eliminating the hemodynamic stress response to intubation. The study revealed that the mean arterial pressure (MAP) values were considerably reduced in the pregabalin group compared to the control group (108.3 ± 6.3 vs 119.4 ± 9.8, $p = 0.0001$) during laryngoscopy and intubation, even up to the 10th minute.

Sundar AS et al,[16] evaluated how pregabalin premedication affects the reduction of the hemodynamic stress response to tracheal intubation. In addition, they observed a reduction in the need of opioids in patients who underwent coronary artery bypass graft surgery. They concluded that administering pregabalin before the procedure effectively eliminated the occurrence of reflex tachycardia in response to direct laryngoscopy and tracheal intubation. Parveen S et al,[17] found that oral pregabalin 150 mg was effective in blunting haemodynamic stress response to laryngoscopy and tracheal intubation and also compared the effects with clonidine reporting post-operative analgesia was better in pregabalin group as compared to clonidine group. Both the drugs cause sedation, but it was more with the use of pregabalin. Similarly, Waikar C et al,[18] also found that pregabalin 150 mg attenuated blood pressure response fairly well. Raichurkar A et al,[19] studied the effect of 150 mg oral pregabalin and 200 µg oral clonidine for attenuation of orotracheal response. And found that pregabalin significantly reduces the response more than clonidine group.

The patients in the pregabalin group were stable at all-time points following the administration of the

study medicine. Comparable patterns of stability in systolic and diastolic blood pressures were noted in the pregabalin group.

CONCLUSION

To conclude, based on the present study that pregabalin 150 mg appears to be a reliable medication for reducing the sympathetic reaction to laryngoscopy.

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