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Original Article

Use of Low Dose Pregabalin for Attenuation of Hemodynamic Response to Laryngoscopy and Intubation in Treated Hypertensive Patients

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ABSTRACT

Introduction: Laryngoscopy and tracheal intubation are two powerful noxious stimuli that can be potentially deleterious specially in hypertensive patients. This study evaluated the efficacy of low dose oral pregabalin used as a premedication for attenuation of this marked sympathetic response of airway instrumentation.

Materials and Methods: This was a double blind randomised study done at a tertiary level referral hospital. The trial was registered as UMIN-000037103 (https://www.umin.ac.jp/ctr/). Patients were randomly assigned into two groups. Placebo arm received multivitamin capsule and treatment arm received Cap. Pregabalin (75 mg), 60 minutes before the induction of general anesthesia. The level of preoperative sedation was assessed with the Ramsay Sedation Scale. Heart rate, systolic, diastolic and mean arterial blood pressure were monitored and recorded before and during induction, during laryngoscopy and 1, 3 and 5 minutes of intubation.

Results: A total of 50 patients, 25 in each arm were enrolled. The baseline characteristics were comparable. SBP was significantly lower in the Pregabalin group than in Placebo at all the periods of recording, however, DBP and MAP decreased significantly during, after 1 and 3 minutes of laryngoscopy (p=0.001). Sedation was significantly better in the Pregabalin group with 86% in RSS 3 compared to 80% of a placebo arm in RSS2 (P <0.001).

Conclusions: Premedication with a single oral dose of Pregabalin (75 mg) is effective for sedation and attenuation of hemodynamic response to direct laryngoscopy and endotracheal intubation in controlled hypertensive patients without any side effects.

Keywords: Induction; Premedication Pressure response

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INTRODUCTION

Laryngoscopy and tracheal intubation comprise two essential portions of general anesthesia. Handling of upper respiratory tract leads to a noxious stimuli that bring a powerful sympathetic hemodynamic response exhibiting as increase in heart rate, blood pressure and arrhythmias which are usually transient but variable and unpredictable.[1] Pressor response to laryngoscopy and intubation starts within five seconds of laryngoscopy, reaches a peak in 1–2 min, and returns to baseline within five minutes.[2] These responses may be detrimental to the patients especially suffering from hypertension, coronary artery or cerebrovascular

diseases leading to serious perioperative complications.[3,4]

Various pharmacological approaches have been evaluated either as premedication or during induction to attenuate the adverse hemodynamic response and the search for a deal drug or technique is still ongoing.[5] Pregabalin, a gabapentinoid, has anxiolytic, sedative, antiallodynic, antihyperalgesic, antinociceptive and antisecretory properties.[6] It is absorbed and tolerated well after oral administration, with limited side effects.

There are various studies regarding the use of pregabalin for attenuation of pressor response during laryngoscopy and intubation in normotensive patients.[7,8] However only a few trials have evaluated hemodynamic pressor response among controlled hypertensive patients. The inhibitory effects of pregabalin on membrane voltage-gated calcium channels can be the reason for its response to laryngoscopy and intubation. When given orally, pregabalin reaches its peak level in plasma within one hour.[6] The aim of the study was to evaluate the response of preemptive pregabalin in attenuating the hemodynamic response to laryngoscopy and intubation in treated hypertensive patients.

MATERIALS AND METHODS

This was a hospital based prospective, randomized, double-blind, comparative, interventional study. The study was conducted in the department of Anaesthesiology of Shree Birendra Hospital, Katmandu from March 2019 to June 2019. Ethical approval was taken from the institutional review board and the trial was registered in UMIN database as UMIN-000037103 (https://www.umin.ac.jp/ctr/). The hospital administration had the authority to stop the study should any unwanted serious adverse events occur. After written informed consent, patients with controlled hypertension under antihypertensives between 30 and 70 years of age with ASA physical status II were randomized. All underwent a thorough pre-anesthetic assessment. The exclusion criteria included unwilling patients, patients with ASA grade III or higher, pre-existing cardiac disease, asthma, and severe renal or hepatic dysfunction, anticipated difficult intubation, patients with morbid obesity and those taking antidepressant drugs.

It was calculated that a total of 50 patients (25 in each arm) would be required for the analysis with an alpha error at 0.05 and the power of study at 80%. Randomization was done by closed envelope technique. The observer was totally blinded about the groups or medication received by the study population. Patients were randomized into two arms, treatment arm and placebo arm.

All the patients were pre-medicated with Tab Diazepam 5 mg a night before surgery. On arrival at the pre-operative room, baseline vital parameters were recorded. Treatment arm received Pregabalin (75 mg) and placebo arm received matching multivitamin capsule 60 minutes before induction of general anesthesia. Group allocations and administration of study drugs were done by a trained anesthetic assistant who was unaware of the study protocol and was not involved in the study.

On arrival at the operation theatre, a crystalloid intravenous infusion of 6-8ml kg-1hr-1 was started. Monitors were attached and heart rate and systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure(MAP) before induction was recorded. The preoperative level of sedation was assessed by the Ramsay sedation scale[9] The Ramsay sedation score (1 to 6) was assessed one hour after administering the drug. A score of three or more suggested that adequate sedation had been obtained. Inj midazolam 0.04 mg /kg and inj Fentany l1.5ug/kg were given. After preoxygenation for 3 minutes, anesthesia was induced with titrating the dose of Inj. Propofol to abolish the eyelash reflex. The laryngoscopy and intubation were facilitated with Inj Vecuronium 0.1mg kg-1 after careful check ventilation. Intubation was done after 3 minutes with an appropriate size endotracheal tube by the consultant anesthesiologist. Anesthesia was maintained with 100% oxygen and 1 to 1.5% Isoflurane and was adjusted to maintain SBP and heart rate within 20% of preoperative values. Inj Vecuronium (0.001mg/kg) was repeated as per requirement. Intraoperatively, the heart rate, MAP, electrocardiography, pulse oximeter (SpO2) and EtCO2 levels were continuously monitored and recorded before and during induction, during laryngoscopy and 1, 3 and 5 min after intubation.

Patients were be observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm, and were managed accordingly. Patients were transferred to a post-operative ward and were monitored for at least four hours or until there were no signs of any drug- effects such as nausea, dizziness, respiratory inadequacy or hemodynamic instability. Other side effects were noted if any and treated accordingly.

We used intention-to-treat analysis for all efficacy analyses, analyzing all participants who underwent randomization. The reporting of the study was done as per the consort guidelines (fig. 1). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as numbers and frequencies. Categorical variables were compared using the $\chi 2$ test and continuous variables with independent t-test. A P value of <0.05 was considered significant. All statistical analyses were performed using the SPSS 20.0 statistical package.

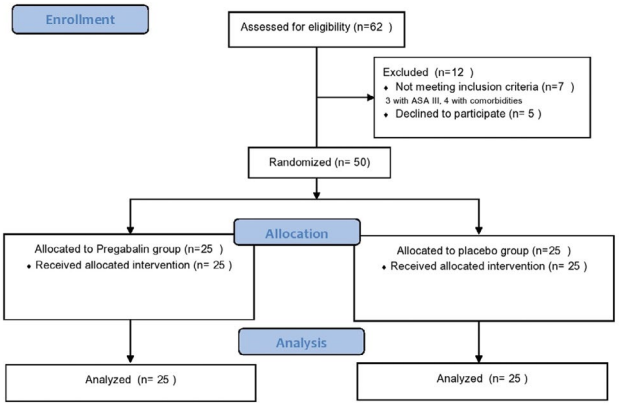

Figure 1: Flow chart of the participants in the study

RESULTS

A total of 62 patients were assessed for the elligibility and finally, 50 patients were included in the study with 25 in each arm (fig. 1). The study period was of four months and the study was terminated after the fulfillment of sample size. The patients in both groups were comparable with respect to baseline characteristics (Table 1).

Table 1: Baseline characteristics of the study population

Variables		Pregabalin n=25	Placebo n=25
Gender	Male	16(64%)	12(48%)
	Female	9 (36%)	13(52%)
Age (Mean±SD)		51.48± 9.53	52.97± 8.13
Weight (Mean±SD)		57.96±8.96	60.56±3.25
No of antihypertensive drugs	1	15(60%)	12 (48%)
	≥ 2 drugs	10 (40%)	13 (52%)
ASA grading	2	25(100%)	25(100%)
Heart rate, beats/min, (Mean±SD)		73.36±5.97	71.60±7.58
SBP mm Hg (Mean±SD)		123.52±12.68	122.52±8.53
DBP (Mean±SD)		78.64±5.94	78.76±3.33
MAP (Mean±SD)		90.28±6.55	87.80±4.36

There was a significant decrease in heart rate in the pregabalin group after medication before induction ($p<0.05$), but no significant difference in change of heart rate could be seen during induction, laryngoscopy and 1 minute after the laryngoscopy. Significant attenuation in heart rate after 3 minutes ($p<0.01$) and 5 minutes ($p<0.01$) of laryngoscopy was recorded as compared to the placebo (Table 2).

Table 2: Comparison of Heart rate (Mean) in two groups

Heart rate		Pregabalin	Placebo	p value
Baseline		73.36±5.97	71.60± 7.58	(>0.05)
Before Induction		82.92± 6.78	87.32± 5.23	(<0.05)
Induction		78.40± 3.86	79.52± 4.85	(>0.05)
During Laryngoscopy		92.76± 7.84	98.80±15.88	(>0.05)
After laryngoscopy	1 minute	90.92±7.74	96.68±11.61	(>0.05)
	3 minutes	83.28± 4.29	88.28± 7.85	(<0.01)
	5 minutes	78.40± 4.30	82.24± 4.50	(<0.01)

SBP was significantly lower in the Pregabalin group than in placebo in all the recording ($P=0.001$). SBP increased more on placebo group than that of the premedicated group after 1 minute, 3 minutes and 5 minutes of laryngoscopy and were statistically significant; $p<0.05$(Table 3).

Table 3: Comparison of Systolic Blood Pressure (Mean) in two groups

Heart rate		Pregabalin	Placebo	p value
Baseline		123.52±12.68	122.52 ± 8.53	>0.05
Before Induction		136.40± 9.94	145.76 ± 9.58	<0.05
Induction		105.40± 11.80	98.84 ± 7.58	<0.05
During Laryngoscopy		141.36± 8.93	150.88 ± 10.49	<0.05
After laryngoscopy	1 minute	147.84± 8.31	154.84 ± 11.80	<0.05
	3 minutes	120.82± 8.81	130.48 ± 10.52	<0.05
	5 minutes	120.08± 5.58	128.24 ± 16.36	<0.05

Changes in DBP after premedication were statistically significant in two groups. We found that after premedication diastolic blood pressure was better controlled in pregabalin arm compared to placebo before induction, during and after 1, 3 and 5 minutes of laryngoscopy. No change of DBP was seen during induction and after 5 minutes of laryngoscopy (Table 4).

Table 4: Comparison of Diastolic Blood Pressure (Mean) in two groups

Diastolic Blood pressure		Pregabalin	Placebo	p-value
Baseline		78.64± 5.94	78.36±3.33	>0.05
Before Induction		85.60± 5.07	89.96±5.39	<0.05
Induction		71.60± 9.81	69.64± 13.39	>0.05
During Laryngoscopy		89.48± 5.55	100.48± 18.48	<0.05
After laryngoscopy	1 minute	87.76± 7.33	97.56± 14.41	<0.05
	3 minutes	82.80± 8.66	89.36± 7.86	<0.05
	5 minutes	79.56± 5.96	81.60± 10.49	>0.05

A significant decrease in mean arterial pressure was observed in the Pregabalin group at all periods of observation expect during induction and after 5 minutes of laryngoscopy which was not statistically significant (Table 5).

Table 5: Comparison of Mean Arterial Pressure

Diastolic Blood pressure		Pregabalin	Placebo	p-value
Baseline		90.28± 6.55	87.80±4.36	>0.05
Before Induction		100.20± 7.04	107.60± 12.03	<0.05
Induction		80.00± 14.24	74.60± 10.98	>0.05
During Laryngoscopy		111.24± 9.49	120.60± 11.26	<0.05
After laryngoscopy	1 minute	110.16± 4.22	120.08± 21.89	<0.05
	3 minutes	91.68± 4.34	98.40± 9.23	<0.05
	5 minutes	86.64± 4.20	89.26± 7.14	>0.05

With respect to sedation scores in our study, the pre-operative sedation score of the Pregabalin group was found to be higher as compared to that of the Placebo group. The result showed that a majority of patients, 86% in placebo arm fell in RSS 2, 14% in RSS 1 and none in RSS 3. However, in the pregabalin group, 80% of the patients fell in RSS 3 ($P<0.001$). No patient in the study developed delayed recovery, nausea, vomiting, dizziness or any other significant adverse events.

DISCUSSION

The present study evaluated the efficacy of oral premedication with low dose pregabalin on controlled hypertensive patients for hemodynamic stability during laryngoscopy and intubation. Laryngoscopy and endotracheal intubation contribute significantly to hemodynamic changes. Shribman et al[10] and Bucx et al[11] reported that laryngoscopy and more specifically endotracheal intubation may cause different hemodynamic responses usually in the form of tachycardia and hypertension. There is an increase in plasma concentration of catecholamines which leads to the adverse conditions viz myocardial ischemia and cerebral haemorrhage.[12,13] Hassan et al[14] reported higher incidences of myocardial ischemia, cardiac arrhythmias, acute left ventricular failure and cerebrovascular accidents after intubation in hypertensive patients.

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. Effect of pregabalin on attenuating stress response to laryngoscopy and

tracheal intubation was evaluated previously in a few studies[7,8] It was found to be very useful and effective premedication to blunt hemodynamic stress response to laryngoscopy and tracheal intubation without much side effects in all those studies.

A comparison of the preoperative RSS between the arms in our study after one hour of premedication showed that a majority of patients (86%) in placebo arm fell in RSS 2 and 14% in RSS 1. However, in the pregabalin arm, 80% of the patients fell in RSS 3. Sedation was hence significantly better in the Pregabalin group. Our results were in agreement with the results of Rajappa et al[15] who studied the efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. They found that patients receiving either 75mg or 150 mg of pregabalin were adequately sedated (RSS>3) one hour after administration. Previous studies have reported more dizziness with the use of pregabalin.[15,16] None of our patients complained dizziness which could be due to the lower dose of pregabalin used.

In our study, there was a significant difference in heart rate between pregabalin and placebo arm before induction but not during and after the laryngoscopy. An initial increase in heart rate was present in both the groups, however it reduced faster in the pregabalin group compared to placebo when measured at 3 and 5 minutes. The results were consistent with the study by Meena et al[17] and El-Hussiny H et al[18] where the rise of heart rate was of shorter duration in the pregabalin group. In the study done by Rastogi et al[7], there was a significant rise in heart rate post-intubation in the pregabalin group. It may be because of the use of butorphanol instead of potent analgesic fentanyl which was used in our study.

Attenuation in SBP with pregabalin premedication was greater than DBP. SBP decreased significantly during all periods of recording in pregabalin arm whereas DBP and MAP reduced before induction, during and after 1 and 3 minutes of laryngoscopy. The haemodynamic results of our study were in agreement with the other studies.[8,18,19] A similar observation was also found by Eren et al[20] on cardiovascular response to tracheal intubation with and without pregabalin premedication. Gupta K et al[21], however, showed an initial rise in the mean arterial after premedication but it was significantly attenuated after induction and laryngoscopy in the pregabalin group. The exact mechanism of attenuation of pressure response to laryngoscopy and intubation by pregabalin is unclear. Memis et al[22] theorized that it is possibly due to the inhibition of calcium efflux from muscle cells with consequent inhibition of smooth muscle relaxation.

We evaluated only a single oral dose of pregabalin in our study. Larger sample-size with varying doses of pregabalin can be studied in future studies. Another limitation in our study is that we did not correlate the duration of hypertension, types of hypertensive medications like the use of beta blockers, or presence of associated conditions like diabetes which could have a confounding effect on the hemodynamic response in our patients.

CONCLUSIONS

Premedication with a single oral dose of pregabalin (75 mg) is effective for sedation and attenuation of hemodynamic response to direct laryngoscopy and endotracheal intubation in controlled hypertensive patients without any side effect.

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