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Research Article

Evaluation of Oral Pregabalin Premedication for Attenuation of Haemodynamic Response during Tracheal Intubation in Adult Patients with Controlled Hypertension For Elective Surgery

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ABSTRACT

Background: The laryngoscopy and tracheal intubation is a noxious stimuli resulting in transient but marked sympathetic response. This response is exaggerated in patients with hypertension. This study evaluated the role of oral pregabalin premedication in attenuation of haemodynamic response during tracheal intubation in adult patients with controlled hypertension posted for elective surgery.

Methods: A prospective double blinded randomized study was carried out in a total of 60 adult patients (aged 18-65 years, either gender) with controlled hypertension after being randomized into two groups with 30 patients in each. Prior to induction, Group PL received Placebo (multivitamin) and Group PB received pregabalin 75mg tablet 1 hour. The anaesthesia technique was standardized as per department protocols. Both groups were evaluated for pre-operative sedation, haemodynamic changes after premedication, before and after induction, after the laryngoscopy and tracheal intubation and post-operative side effects.

Results: There was attenuation of haemodynamic responses without significant side effects with pregabalin. Statistically significant increase in post intubation systolic, diastolic and mean blood pressure was seen in group PL as compared to group PB. In both groups, a reduction in heart rate was observed and was statistically significant 1 minute after intubation in group PB. Pre-operative sedation levels were higher in PB group in comparison to PL group. No post-operative side effects observed in both the groups.

Conclusion: In controlled hypertensive patients, oral pregabalin 75 mg attenuated the haemodynamic responses to laryngoscopy and tracheal intubation. It produced effective pre-operative sedation without any post-operative side effects.

Introduction

Laryngoscopy and tracheal intubation induces a transient increase in autonomic response. The force and duration of laryngoscopy primarily determines the magnitude of cardiovascular response [1]. Usually these changes are transient without deleterious consequences in healthy individuals, but can be fatal in high risk populations such as patient with hypertension, cerebrovascular disease, intracranial aneurysm, coronary artery disease, valvular heart disease, leading to cardiac

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arrhythmias, left ventricular failure, myocardial ischemia and cerebral haemorrhage [2].

Marked cardiovascular changes occur during laryngoscopy and intubation leading to 40-50% increase in blood pressure and 20% increase in heart rate [3]. Hypertensive patients have exaggerated sympathetic overactivity, increase in catecholamines concentration as well as increased sensitivity of peripheral vasculature to the circulating catecholamine leading to exaggerated hemodynamic response.

For safely conducting anaesthesia, the haemodynamic responses during laryngoscopy and tracheal intubation should be supressed to maintain balance between the myocardial oxygen supply and demand. Various studies have evaluated the role of pharmacological measures such as adrenergic agonist [4-5], adrenoreceptor blockers [6], opioids [7-8], vasodilators, anticonvulsant (gabapentin) [9-10] in attenuation of haemodynamic stress response with variable results and also emphasized on its associated adverse effects like hypotension, bradycardia and respiratory depression post operatively.

Pregabalin, a congener of gabapentin [(S)-3 aminomethyl-5- methylhexanoic acid], is an antiepileptic drug with anticonvulsant, anxiolytic, analgesic properties and effective in preventing neuropathic component of acute nociceptive pain of surgery [11-12]. Pregabalin is an ideal drug to blunt both heart rate and blood pressure response associated with airway instrumentation [13-14]. Very few studies regarding pregabalin use for attenuation of hemodynamic responses following laryngoscopy and intubation in controlled hypertensive patients are present in literature till date [15]. Thus, the study was designed to evaluate role of oral pregabalin premedication on haemdynamic response during airway instrumentation.

Methods

This prospective double blinded randomized clinical study to evaluate haemodynamic responses to laryngoscopy and tracheal intubation was carried out in 60 adult patients with controlled hypertension (BP<140/90 mmHg, controlled with less than 2 antihypertensive drugs) undergoing elective surgeries under general anaesthesia in a tertiary care centre after approval from Institutional Ethical Committee. It was registered at ctri.nic.in (Clinical Trials Registry - India CTRI Reference No. 2018/09/15585, date of registration-05/09/2018) before patients enrollment.

All adult controlled hypertensive patients (BP<140/90 mmHg on less than 2 antihypertensive drugs), aged 18 - 65 years, either gender with American Society of Anaesthesiologist (ASA) Physical Status grade II were included for the study (Figure 1, Consort Diagram).

Patients with cardiac disease (ejection fraction of less than 45%), chronic obstructive pulmonary disease, impaired kidney, liver, endocrine or neurological function, patient with morbid obesity, pregnancy, anticipated difficult airway, having history of allergic reaction to the study drugs, major surgery exceeding >4 hours with major fluid shift as well as difficult intubation with intubation time exceeding more than 20 seconds were excluded from this study.

After obtaining informed written consent, patients were randomly allocated into one of the two groups using computer generated random allocation chart.

Group PL (n=30) were given multivitamin tablet (Placebo)

Group PB (n=30) were given pregabalin (75mg oral tablet)

Anesthetic Technique

A thorough pre anaesthetic evaluation was carried out. The consented patients were kept fasting after midnight and tablet pantoprazole 40mg and tablet alprazolam 0.25mg were given on the night before surgery as per our institutional protocol. On the morning of surgery baseline vitals including heart rate, mean arterial pressure (MAP) and sedation level (according to Modified Ramsay Score) were noted before premedication. The patients received a tablet placebo (multivitamin) or tablet pregabalin 75mg with a sip of water, 1 hour prior to surgery, according to the group allocated.

After shifting the patient to operating table, all ASA II standard monitors [oxygen saturation (spO2), electrocardiography (ECG), Noninvasive blood pressure, end tidal carbon dioxide (EtCO2)] were connected and baseline parameters were recorded. The pre-operative level of sedation was assessed using Modified Ramsay sedation scale: 0: - Paralysed and unable to evaluate. 1: - Awake. 2: -Lightly sedated. 3: -Moderately sedated, follows simple commands. 4: -Deeply sedated, responds to non-painful stimuli. 5: -Deeply sedated, responds to painful stimuli. 6: -Deeply sedated, unresponsive to painful stimuli. Intravenous (i.v.) access was secured with 18 gauge cannula. All the parameters were recorded by anesthesiologist blinded for the study group.

After preoxygenation with 100% O2 for 3 minutes, induction was started with i.v. fentanyl 2mcg/Kg over 30 seconds followed by etomidate 0.2mg/Kg over 45 seconds (titrated to response) and vecuronium 0.12mg/Kg after check ventilation. The patient's ventilation was assisted for 3 minutes with O2:N2O(50/50) with isoflurane (targeted MAC of 1%). Lignocaine 1.5 mg/kg body weight was given 90 seconds before intubation and trachea was intubated using proper sized cuff endotracheal tube which was performed by experienced anaesthetist blinded for the study. Haemodynamic parameters [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure(MAP), SPO2 and ECG for cardiac arrhythmias) were noted before induction, before intubation and at the following specified times (1,3,5,7,9 minutes after intubation and before the start of surgical procedure).

All patients were mechanically ventilated using volume controlled mode of ventilation with 6-8mL/Kg tidal

volume and respiratory rate adjusted with EtCO2 monitoring with targeted value of 30-40 mm of Hg. Anaesthesia depth was maintained with O2:N2O (50/50) and isoflurane. Vecuronium and fentanyl were supplemented as per requirement intra-operatively.

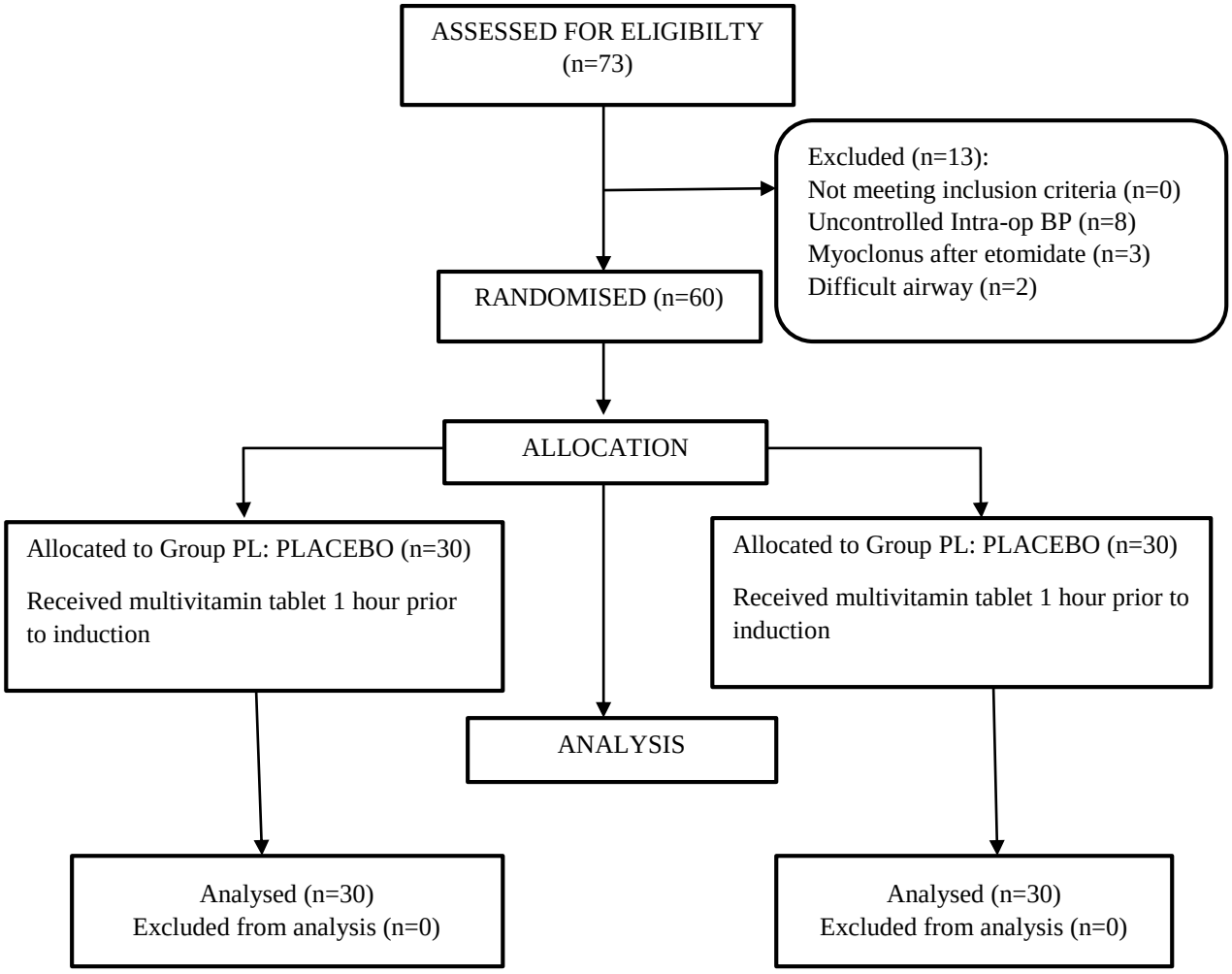

Figure 1- Consort Diagram

Intraoperatively, HR, SBP, DBP, MAP, ECG, spO2 and EtCO2 were monitored and recorded at every 5 min interval. At the end of surgery, neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and glycopyrrolate (0.01 mg/kg) and trachea was extubated following standard extubation criteria.

Post-operatively, all patients in the recovery room were monitored for SBP, DBP, MAP, HR, spO2 and for complications like vomiting, hypotension, hypertension, sedation etc continuously upto 6 hours postoperatively and necessary intervention was taken as required.

Hypertension and hypotension was defined when variations more than 20% from baseline in an upward or downward direction respectively. Hypotension, bradycardia was treated with intravenous fluid and inj. Atropine as when required and recorded.

Outcomes Measured:

The primary outcome was assessed by evaluating the efficacy of pregabalin on attenuation of haemodynamic responses (HR, SBP, DBP, MAP) during laryngoscopic endotracheal intubation at different points of time (baseline, before induction, before intubation and 1,3,5,7,9 minutes post intubation) in controlled hypertensive patients and secondary outcome were assessed by effect of pregabalin on sedation score (Ramsay sedation score) and side effects like vomiting.

Sample Size

According to previous study [19] taking mean difference in hemodynamic response between placebo group and oral pregabalin group as 11± 15, with 80% power of study and 5% level of significance, minimum required sample size were 30 patients in each study group. Hence, total sample size taken was 60 (30 patients per group).

Formula used for comparing mean of two groups

$$N >= 2(\text{Standard Deviation})2 * (Z\alpha + Z\beta)2 \quad (\text{Mean Difference})2$$

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data were tested by Kolmogorov- Smirnov test. If the normality is rejected, then non parametric test were used.

Statistical tests were applied as follows

1.Quantitative variables were compared using unpaired t-test/mann-whitney test (when the data sets were not normally distributed) between the two groups and paired t-test/ wilcoxon signed rank test within the groups across follow-ups.

2.Chi-Square test /fisher's exact test was used for qualitative variables

• A p value of <0.05 were considered statistically significant.

Results

The demographic parameters (age, gender and weight) were similar in the two groups with no significant statistical significance as depicted in (Table 1).

A declining trend in systolic blood pressure was seen with respect to time from baseline to before intubation in both the groups. As depicted in (Table 2), at time interval of 1, 3, 5 and 7 minutes post intubation SBP in group placebo(PL) was significantly higher as compared to group pregabalin(PB) with p value 0.0001, 0.005, 0.004 and 0.021 respectively. At 9 minutes after intubation SBP was comparable between the groups with no significant difference between them. (P value=0.981).

As shown in (Table 3), before induction, mean value of diastolic blood pressure in group placebo (PL) was slightly lower as compared to group pregabalin (PB) and before intubation mean value of DBP in group placebo (PL) was slightly higher as compared to group pregabalin (PB), but no significant difference; before induction 79.37 ± 10.6mm Hg vs83.43 ± 10.12mm Hg and before intubation 76.93 ± 12.66mm Hg vs 75.8 ± 12.31mm Hg in group placebo (PL) and group pregabalin (PB) respectively.

At 1,3,5,7 and 9 minutes after intubation, DBP in group placebo (PL) was significantly higher as compared to group pregabalin (PB) with p value <.0001, .001, .016, .045 and .014 respectively.

Before induction and before intubation, mean value of mean arterial pressure in group placebo(PL) was slightly lower as compared to group pregabalin(PB), but the difference was not significant; before induction 97.37 ± 12.04mm Hg vs101.97 ± 8.87mm Hg and before intubation 93.33 ± 13.33mm Hg vs94.43 ± 13.16mm Hg in group placebo(PL) and group pregabalin(PB) respectively.

At 1,3,5, and 7 minutes after intubation, MAP in group placebo (PL) was significantly higher in comparison to group pregabalin (PB) with p value =0.0001, 0.001, 0.006, and 0.026 respectively. At 9 minutes after intubation mean arterial pressure was comparable between the groups with no statistically significant difference between them (P value=.068) as shown in (Table 4).

After 1 of administration of placebo/ pregabalin, sedation level of all the patients was 1 (awake) in group placebo (PL) whereas 33.33% of patients in group pregabalin (PB) had sedation level 2 (lightly sedated) as depicted in (Figure 3). Mean value of sedation level in group PL was 1 ± 0 and in group PB was 1.33 ± 0.48. It was evident that sedation level was significantly higher in group pregabalin (PB) in comparison of placebo. (P=0.008).

There was no episode of vomiting reported in both groups post operatively.

Reduction in heart rate was observed in both groups at each time interval when compared to baseline. At each time period, percentage reduction in heart rate in pregabalin (PB) was more as compared to placebo (PL) but the difference was not statistically significant except at 1 minute after intubation (p=0.031) as depicted in (Figure 2).

Table 1- Demographic characteristics

Demographic Profile	Group PL (n=30)	Group PB (n=30)	P value
AGE in years (Mean ± Standard Deviation)	44.73 ± 11.47	46.5 ± 14.98	0.074
SEX RATIO (Male: Female)	16 : 14	10 : 20	0.226
WEIGHT in Kg (Mean ± Standard Deviation)	59 ± 11.17	63.8 ± 13.09	0.129

Table 2- Comparison of systolic blood pressure (mm Hg) between groups

Systolic blood pressure (mmHg)	GROUP PL (n=30)		GROUP PB (n=30)		P value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Baseline	135.53 ±14.41	133.5 (127-144)	142.53 ± 14.05	139 (134-150)	0.062
Before induction	133.3 ±18.08	132.5 (125-146)	139.33 ± 10.56	140 (130-148)	0.120
Before intubation	126.17 ±18.64	128 (117-134)	131.73 ± 18.31	135 (128-138)	0.248
1 minute after intubation	141.2 ±18.84	140 (132-153)	123.97 ± 12.79	123.5 (117-128)	0.0001
3 minute after intubation	129.63 ±20.55	130.5 (123-139)	116.57 ± 13.1	115 (106-123)	0.005

5 minute after intubation	120.67 ±16.36	121.5 (111-130)	109.8 ± 11.72	107.5 (104 - 116)	0.004
7 minute after intubation	111.23 ±13.71	108.5 (102-121)	103.83 ± 10.13	103 (98- 109)	0.021
9 minute after intubation	103.53 ±11.22	102 (95-111)	103.47 ± 10.74	104 (98 - 109)	0.981

Table 3- Comparison of diastolic blood pressure (mm Hg) between groups

Diastolic blood pressure (mmHg)	GROUP PL (n=30)		GROUP PB (n=30)		P value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Baseline	82.83 ± 8.57	83 (76- 89)	85.3 ± 8.06	86 (80- 90)	0.256
Before induction	79.37 ± 10.6	78.5 (72-86)	83.43 ±10.12	83.5 (78-89)	0.134
Before intubation	76.93 ± 12.66	79.5 (68-86)	75.8 ±12.31	79 (69-83)	0.727
1 minute after intubation	86.5 ± 13.13	86 (79- 94)	73.2 ± 9.6	71 (68-80)	<.0001
3 minute after intubation	82.9 ± 16.49	82 (76- 93)	70.5 ± 9.25	68.5 (66-78)	0.001
5 minute after intubation	74.97 ± 13.19	72 (67- 82)	67.57 ±9.69	66 (60-76)	0.016
7 minute after intubation	71 ± 12.34	70 (64- 76)	65.37 ±8.65	65 (59-72)	0.045
9 minute after intubation	70.13 ± 11.4	69 (63- 76)	63.47 ±8.75	65 (57-71)	0.014

Table 4- Comparison of mean arterial pressure (mm Hg) between groups

Mean blood pressure (mmHg)	GROUP PL (n=30)		GROUP PB (n=30)		P value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Baseline	100.43 ± 8.11	99.5 (97- 105)	104.4 ± 8.16	103.5 (100 - 108)	0.064
Before induction	97.37 ± 12.04	97.5 (91 - 104)	101.97 ± 8.87	101 (97 - 108)	0.097
Before intubation	93.33 ± 13.33	97 (85 - 103)	94.43 ± 1316	98 (89 - 102)	0.749
1 minute after intubation	104.77 ± 13.85	106 (100 - 111)	90.1 ± 9.5	89 (86 - 97)	<.0001
3 minute after intubation	98.57 ± 16.39	98.5 (92 107)	85.77 ± 9.75	84.5 (79 - 94)	0.001
5 minute after intubation	90.23 ± 13.63	87.5 (85 - 98)	81.63 ± 9.54	80.5 (75 - 89)	0.006
7 minute after intubation	84.4 ± 12.15	84.5 (78 - 91)	78.2 ± 8.65	78 (72 - 86)	0.026
9 minute after intubation	81.27 ± 9.7	83 (73 - 87)	76.8 ± 8.87	78 (71 - 83)	0.068

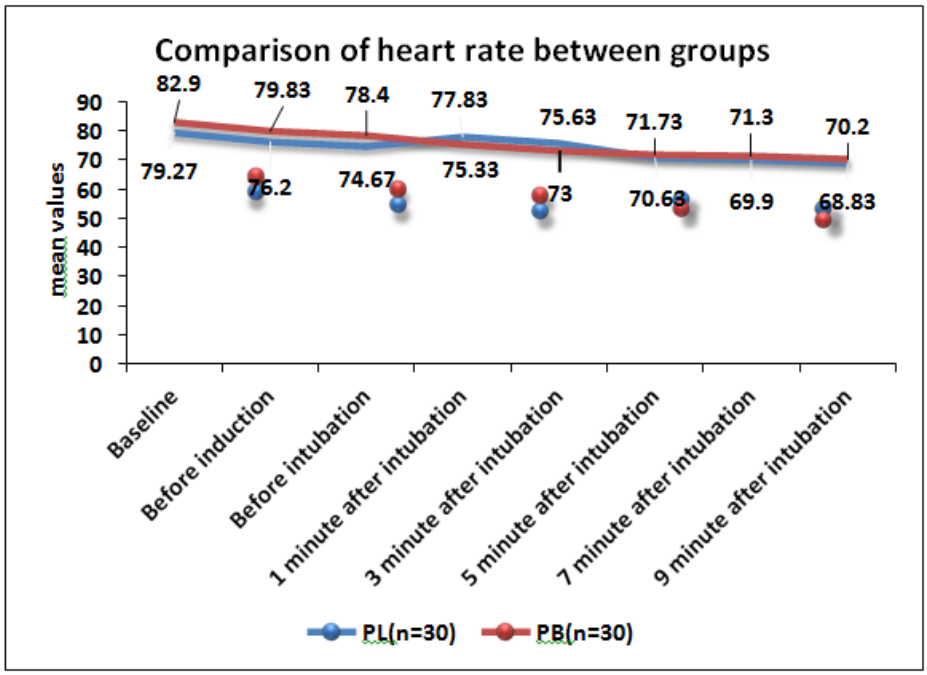

Figure 2- Comparison of heart rate between groups

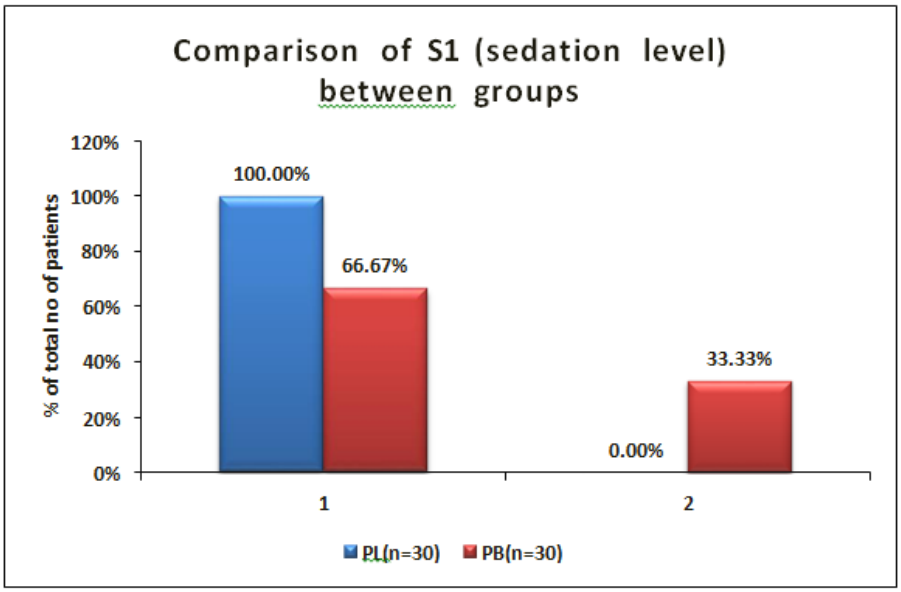

Figure 3- Comparison of sedation level between groups

Discussion

Airway instrumentation (laryngoscopy and endotracheal intubation), a potent noxious stimuli gives rise to transient but marked sympathetic response (increase in heart rate, blood pressure, myocardial oxygen demand, arrhythmias, increased circulatory catecholamines). These type of responses may prove fatal in patients with underlying co-morbidities as supported by studies published by Saha et.al, Prys-Roberts et.al. [2-3].

In our study, patients of both groups were similar in terms of demographic data- Age, Sex, Weight and the mean baseline heart rate was comparable in both the groups (79.27± 11.99 vs 82.9±15.91) as depicted in (Figure 2). There was fall in heart rate in both the groups, the fall was more in PB group but was comparable to PL group except at 1 minute post intubation which showed statistically significant difference (p =0.31). The heart rate in PB group continued to fall from baseline to before induction, before intubation, at 1, 3, 5, 7, 9 minutes post intubation which was statistically significant (<0.05).

The result of our study was similar to comparative study conducted by Singh G et.al using oral pregabalin 150 mg with placebo and found a statistically significant drop in heart rate from baseline at 1 minute post intubation in pregablin group compared to placebo group (p = 0.0217). [13] Sunder et al also similarly observed that heart rate was lower in 150 mg pregabalin group given 1 hour prior to induction than that of control group [16]. However, study conducted by Bhawna et.al and Bhandari et.al did not show any significant effect of pregabalin in attenuation of heart rate response [15,17].

In our study, the mean baseline systolic blood pressure was comparable in both the groups (135.53±14.41 vs 142.53±14.05). The fall in SBP before induction, before intubation and 9 minutes after intubation were comparable in both the groups with a p value>0.05. Fall in SBP at 1, 3, 5 and 7 minutes post intubation was statistically significant in PB group compared to PL group with p value being <0.05 at 1,3,5,7 minutes respectively. However, at 9 minutes of post intubation the fall in SBP was comparable between the groups (p value>0.981). Fall in systolic blood pressure in PB group was statistically significant at all point of time i.e starting from pre intubation to 9 minutes post intubation (131.73±18.31) vs (103.47±10.74) as compared to baseline (p value<.05).

Dhanya PR et.al also in their prospective randomized study found that systolic blood pressure at 1, 3, and 5 min post intubation was significantly lower with 150 mg pregablin group (p value<.05) compared to placebo group which is in accordance with our present study [18].

In our study, the mean baseline diastolic blood pressure was comparable in both the groups (82.83±8.57 vs 85.3±8.06). The fall in DBP before induction and before intubation were comparable in both groups (p value>.05). Fall in diastolic blood pressure was more in PB group as compared to PL group at 1, 3,5,7,9 minutes after intubation with p value <0.05 which were statistically significant.

Fall in diastolic blood pressure in PB group statistically significant from before intubation to 9 mins (75.8±12.31) vs (63.47±8.75) as compared to baseline (<0.05). Dhanya PR et.al reported a highly significant fall in DBP with pregabalin group at 1 min post intubation (p value<0.000)

compared to contol group, however there was no statistical significane at 3,5,10 minutes (p value>.05) unlike our findings.

In our study, the mean baseline mean arterial blood pressure was comparable between two groups (100.43±8.11 vs 104.4±8.16). The fall in MAP before induction, before intubation and at 5, 7, 9 minutes post intubation were comparable in both the groups (p value>.05) however statistically significant fall in MAP was more in PB group at 1, 3 min post intubation as compared to PL group with P value at 1 min and 3 min being <0.05. Fall in mean arterial blood pressure in PB group was statistically significant starting from pre intubation to 9 minutes post intubation (94.43±13.16 vs 76.8±8.87) as compared to baseline which was similar to study conducted by Singh G et.al who also reported a significant fall in MAP at 1, 3, 5,10 min post intubation in pregabalin group compared to placebo group with P value <0.05 [13]. Gupta et al also in their prospective randomized controlled study found significant attenuation of mean arterial blood pressure with 150 mg oral pregabalin with (p value<.007) compared to control group [14].

However, Meena et.al did not find any significant attenuation of mean arterial blood pressure or heart rate with 75 mg oral pregabalin compared to 150mg oral pregabalin [19].

None of the patients had persistent or severe fall in BP, thus vasoactive drugs were not required.

Khan AA et.al also in their study found that oral clonidine 300 microgram given 120 minutes prior to induction significantly decreased mean arterial blood pressure with p value (<.05) in comparison to oral pregabalin 75 mg, revealing safety of oral pregabalin 75mg dose compared to 300 microgram as a causative agent for hypotension [20].

The mean value of sedation level in the current study was significantly higher in PB group as compared to PL (1±0 vs1.33±0.48). Similar findings were observed in many studies like study conducted by Bhawna et.al who also found significantly higher sedation with 150 mg pregabalin [15]. Paul F.white also reported increased perioperative sedation in dose related manner with oral pregabalin with increasing doses [21]. Gupta et.al also in their studies commented that pregablin 150 mg produces more preoperative anxiolysis and sedation compared to clonidine 200 microgram [22].

We conclude that 75 mg oral pregabalin premedication is safer and suitable alternative for attenuation of hemodynamic pressor response to laryngoscopy and tracheal intubation in controlled hypertensive patients compared to its placebo counterpart.

Conclusion

Pregabalin is an effective drug resulting in sedation and attenuation of pressor response upon airway instrumentation.

A single, oral pregabalin 75mg dose attenuated haemodynamic responses (systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate) to laryngoscopic tracheal intubation in hypertensive patients. It produces effective preoperative sedation making patient comfortable after one hour of premedication and it does not produce any postoperative nausea and vomiting.

Limitations

1. The study was a single centre prospective randomized control study. A multi-centric study with larger sample size would have been more informative.
2. Perioperative measurement of stress hormones like endogenous plasma catecholamines or cortisol values were not measured in our study.
3. Perioperative analgesic consumption was not commended in our study.

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