Evaluation of the efficacy of pre-operative oral pregabalin in attenuating haemodynamic response to laryngoscopy and intubation and on post-operative pain in patients undergoing elective surgery under general anaesthesia

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Abstract

Objective: Haemodynamic response to airway instrumentation is a hazardous complication of general anaesthesia. We evaluated the efficacy of preoperative 150 mg of oral pregabalin in attenuating haemodynamic response to laryngoscopy and endotracheal intubation as well as its efficacy in post-operative analgesia.

Methods: In this randomized double blind placebo controlled study 50 patients between 18-60 years, ASA grade I & II, of both genders were randomly divided into two groups of 25 patients. Group P received oral pregabalin 150 mg & Group C received placebo, 1hour prior to surgery. Anaesthesia technique was standardized and both groups were assessed for haemodynamic changes during laryngoscopy and postoperatively for level of sedation and pain. Statistical analysis was done using SPSS 17.

Results: There was significantly less increase in systolic, diastolic and mean blood pressure in group p following intubation when compared to group c (p= 0.02, 0.03, 0.02 respectively). Preoperative & post-operative sedation scores were relatively higher after pregabalin premedication. Group p also had reduced analgesic consumption as compared to group c (p=0.04).

Conclusion: This study shows that premedication with 150 mg of oral pregabalin safely attenuates haemodynamic responses to laryngoscopy & intubation & decreases post-operative pain with acceptable levels of sedation.

Keywords: Haemodynamic response, Pregabalin, laryngoscopy, Intubation, Sedation, Analgesia

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Introduction

Laryngoscopy & intubation are associated with cardiovascular changes like hypertension, tachycardia, dysrhythmia and even myocardial ischaemia.[1] These responses may be dangerous in individuals with coronary artery insufficiency, vascular anomalies or intracranial disease.[2] Techniques proposed to attenuate these responses like deepening the plane of anaesthesia, pretreatment with nitroglycerin, beta blockers, calcium channel blockers, opioidsare associated with variable response.[3-6] Managing postoperative pain and associated anxiety again calls for treatment with multimodal regimens.[7]

Pregabalin is a gamma amino butyric acid(GABA) analogue, pharmacologically active S-enantiomer of 3-aminomethyl-5-methylhexanoic acid. Pregabalin is structurally related to inhibitory neurotransmitter GABA but it is not functionally related to it. It selectively binds to alpha 2 subunit of voltage dependent calcium channel which result in decreased synthesis of neurotransmitter glutamate & produces an inhibitory modulation of neuronal excitability particularly in areas of CNS(neocortex, amygdala and hippocampus) resulting in analgesic, anticonvulsant and anxiolytic activity.[8] Pregabalin is absorbed rapidly through oral route and peak plasma concentration is attained within one hour. Average bioavailability exceeds 90% and the elimination half-life is 5.5-6.7 hours. It undergoes renal excretion and 98% of the absorbed dose is excreted unchanged in the urine.

Several techniques have been proposed fot attenuating haemodynamic response to airway instrumentation, all of which are associated variable response and unwanted side-effects. We have conducted this study because a growing body of evidence suggests that peri-operative administeration of gabapentinoids is efficacious for pre-operative anxiolysis, preventing chronic post- surgical pain, post-operative nausea and vomiting and acceptable side effects.[9]

The present study was designed as a randomized double blind placebo controlled study to evaluate the effects of single premedication dose of oral pregabalin 150 mg in attenuating haemodynamic response to laryngoscopy & endotracheal intubation along with effects on post-operative analgesia &sedation.

Methods

After obtaining ethical committee clearance, fifty consented patients between 18-60 years, belonging to American Society of Anaesthesiologist (ASA) class I and II scheduled for superficial surgeries under general anaesthesia which did not require extensive

manipulation were included in the study. The exclusion criteria were pregnant and lactating females, patients posted for emergency surgeries, drug/alcohol abuse, obese patients, patients with liver, renal, cardiovascular, respiratory or central nervous system disorder, patients on antipsychotics and NASAIDs and history of drug allergy.

After obtaining necessary pre-anaesthetic clearance, all the patients were given tablet alprazolam 0.25 mg and tablet ranitidine 150 mg orally on the night before surgery. They were kept nil orally from midnight. On the day of surgery, the patients were randomly selected via opaque sealed envelope to receive either 150 mg pregabalin (group p) or placebo (group c)1 hour prior to the surgery. The study variables were recorded by another anaesthetist who was unaware of the nature of the drug administered and was in charge of the case. Hence both the patient and the concerned anaesthetist were blind to the nature of the drug.

An intravenous line with 18-gauge cannula was secured. Patient's basal pulse rate, blood pressure & sedation score by Ramsay sedation scale were recorded when the drug was administered. In the operation theater, all patients were premedicated with injection glycopyrrolate 0.2 mg, injection tramadol 2mg/kg and injection ondansetron 4mg intravenously after attaching the monitors. After pre-oxygenation, anaesthesia was induced with injection thiopentone sodium 5mg/kg till the loss of eye-lash reflex. After bag and mask ventilation, injection vecuronium 0.1 mg/kg was given. Patient was intubated with appropriate sized tube. Laryngoscopy & intubation time was kept minimum (15sec). If more than 3 attempts of laryngoscopy were done, the patient was dropped out of the study. Anaesthesia was maintained with N_2O:O_2, isoflourane and vecuronium. At the end of surgery, residual neuromuscular blockade was reversed using injection neostigmine 0.05mg/kg, injection glycopyrrolate 0.005mg/kg and the patient was extubated. Injection Diclofenac 75 mg was given intravenously at the time of skin closure and post-operatively twelve hourly. If patient still complained of pain, injection tramadol 100mg intravenous was given.

Pulse rate, systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP) were recorded before and after the induction of anaesthesia, just after intubation and 2 mins, 5 mins, 10 mins, 15 mins and 20 mins after intubation respectively. Sedation was measured using Ramsay Sedation scale(RSS) at the time of drug administration, 1 hour later and post-operatively at 2 hours, 6 hours, 12hours and 24 hours. (RSS: 1. Awake; anxious, agitated, or restless; 2. Awake; co-operative, oriented, tranquil; 3. Awake; responding only to commands; 4. Asleep; brisk response to light glabellar tap or loud noise; 5. Asleep; sluggish response to light glabellar tap or loud noise stimulus but doesn't respond to painful stimulus; 6. Asleep; no response to light glabellar tap or loud noise).

Post-operative pain assessment was done at 2, 6, 12, 24 hours after operation using ten-point Visual analogue scale (VAS), with 0 indication no pain and 10 indicating worst possible pain. VAS scores were kept at 3 or less than 3.

Statistical analysis was done using SPSS 17. Continuous variables were expressed as mean±sd. Continuous variables were evaluated by t test or Mann Whitney U test. Categorical variables were assessed using Chi-squared test or Fisher Exact test. P less than 0.05 was taken as significant.

Results

The patients in pregabalin group (group p) and placebo group (group c) were comparable with respect to demographic data.

Table 1: Demographic Profile

	Group P	**Group C**
Age (mean±SD)	34.60±9.71	34.60±9.20
Male: Female	8:17	9:16
Weight (kg) (Mean±SD)	60.62±9.40	60.74±9.26

The mean heart rate comparisons showed no significant difference in the pregabalin group & the control group at all the studied intervals except at 20 minutes after intubation (group p=80.48$\pm$8.27, group c= 78.12$\pm$5.52) (p = 0.032). However, mean heart rate just after intubation increased by 18.9 % from baseline in the group p, while it increased by 22.7% in group c. Subsequently the heart rate increase showed statistically significant rise from the baseline in both the groups. This increase became insignificant at 10 minutes in group p, while it was 15 minutes in group c(Table 2).

Table 2: Comparison of percentage difference of heart rate values from the baseline in two groups(bpm)

Variables (HR)	P Group Baseline- 82.16 ± 7.41				C Group Baseline-79.52 ± 7.55			
	Value	Difference	% Difference	P value	Value	Difference	% Difference	P value
Just before induction	81.80±8.17	-0.36±0.76	0.43%	0.925 (NS)	82.88±8.83	3.36±1.28	4.22%	0.04 (S)
Just after intubation	97.80±4.04	15.64±3.37	18.98%	0.01(S)	97.60±7.41	18.08±0.14	22.73%	0.001 (S)
2 mins later	93.52±5.78	11.36±1.63	13.75%	0.03(S)	92.88±6.32	13.36±1.23	16.80%	0.02 (S)
5 mins later	87.68±4.28	5.52±3.13	6.71%	0.042 (S)	86.56±7.03	7.04±0.52	8.85%	0.03 (S)
10 mins later	82.88±5.91	0.72±1.50	0.87%	0.182 (NS)	82.48±4.87	2.96±2.68	3.72%	0.03 (S)
15 mins later	81.52±7.64	-0.64±0.23	0.77 %	0.82(NS)	79.68±5.55	0.16±2.00	0.20%	0.92 (NS)
20 mins later	80.48±8.27	-1.68±0.86	2.04%	0.012 (S)	78.12±5.52	-1.14±2.03	1.43%	0.049 (S)

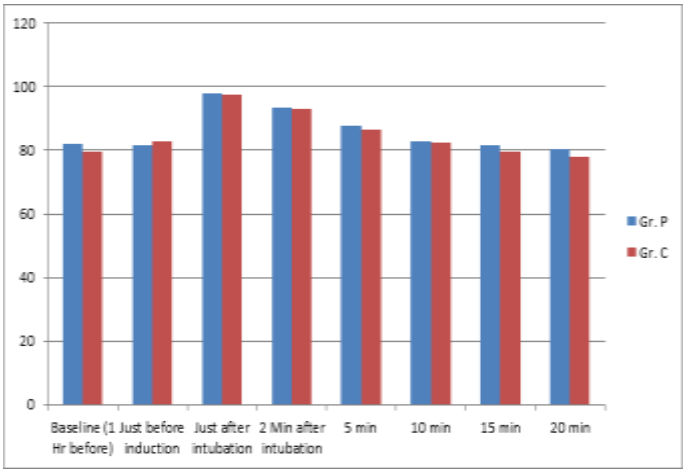

Fig. 1: Changes in the mean heart rate between the two groups

After intubation the systolic blood pressure (SBP) was significantly lower in the group p than the group c for rest of the studied intervals (Table 3). In group p just after intubation the SBP increased by 10% above the baseline. Subsequently it started settling down and by 15 minutes it reached baseline. In the group c just after intubation the SBP increased by 16.4% above the baseline. The SBP also started settling down but continued to be statistically higher than the baseline till 20 minutes after intubation(Table 4).

Table 3: Comparison of mean systolic blood pressure between two groups (mm Hg)

Groups	Group P	Group C	P value
Baseline SBP	126.88±11.30	125.68 ± 8.13	0.971(NS)
SBP Just before induction	126.48±10.90	128.16±9.43	0.04(S)
SBP Just after intubation	140.12±3.63	146.32±7.82	0.02(S)
SBP 2 mins later	136.52±6.66	141.68±6.47	0.04(S)
SBP 5 mins later	132.12±7.29	135.44±6.86	0.03(S)
SBP 10 mins after intubation	128.36±8.00	131.68±4.30	0.02(S)
SBP 15 mins later	126.88±7.13	128.40±5.77	0.03(S)
SBP 20 mins later	125.48±6.27	125.84±5.16	0.82(NS)

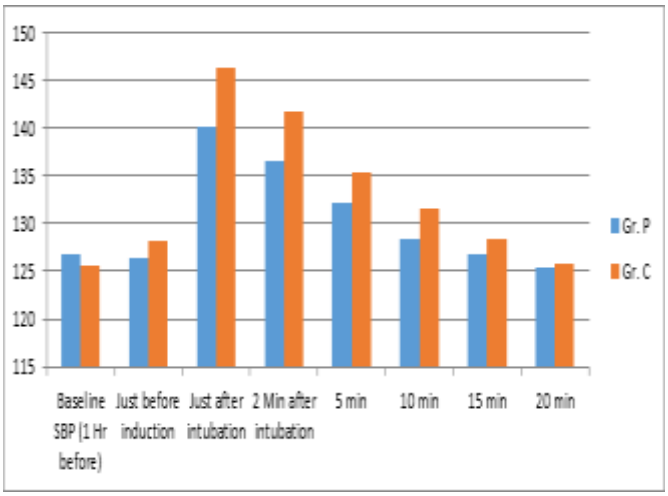

Fig. 2: Changes in the Systolic Blood Pressure between the two groups (mm Hg)

Table 4: Comparison of the percentage difference of systolic blood pressure from baseline in two groups(mm Hg)

Variables (SBP)	P Group Baseline-126.88±11.30				C Group Baseline-125.68±8.13			
	Value	Difference	% Difference	P value	Value	Difference	% Difference	P value
Just before induction	126.48±10.90	0.40±0.40	0.31%	0.98 (NS)	128.16±9.43	2.48+1.30	1.97%	0.048 (S)
Just after intubation	140.12±3.63	13.24±7.67	10.43%	0.03 (S)	146.32±7.82	20.64+0.31	16.42%	0.001 (S)
2 mins later	136.52±6.66	9.64±4.94	7.59%	0.03 (S)	141.68±6.47	16+1.66	12.73%	0.001 (S)
5 mins later	132.12±7.29	5.24±4.01	4.13%	0.04 (S)	135.44±6.86	9.76+1.27	7.76%	0.02 (S)
10 mins later	128.36±8.00	1.48±3.30	1.16%	0.048 (S)	131.68±4.30	6+3.83	4.77%	0.03 (S)
15 mins later	126.88±7.13	0±4.17	0	1(NS)	128.40±5.77	2.72+2.36	2.16%	0.04 (S)
20 mins later	125.48±6.27	-1.40+5.03	1.10%	0.01 (S)	125.84±5.16	0.16+2.97	0.12%	0.97 (NS)

There was no significant difference in diastolic blood pressure (DBP) values at the baseline between the two groups, but after intubation the DBP was significantly lower in the group p than in group c and it remained so for rest of the studied intervals (Table 5). Just after intubation, the DBP showed a 16.6% rise above the baseline in the group p, while it was 24.8% in group c. There was significant rise in blood pressure in both the groups, but this percentage difference from the baseline was less in group p as compared to the group c(Table 6).

Table 5: Comparison of mean diastolic blood pressure in two groups (mm Hg)

Groups	Group P	Group C	P value
Baseline DBP	79.76±8.08	77.60+6.48	0.71(NS)
DBP Just before induction	80.88±6.98	80.64+6.72	0.08(NS)
DBP Just after intubation	93.04±4.36	96.92±7.78	0.03(S)
DBP 2 mins later	88.84±4.79	91.04±6.00	0.04(S)
DBP 5 mins later	85.08±4.57	85.44±6.01	0.048(S)
DBP 10 mins later	80.84±5.16	82.84±4.20	0.042(S)
DBP 15 mins later	80.72±3.95	79.72±4.01	0.03(S)
DBP 20 mins later	80.68±4.87	78.96±3.87	0.15(NS)

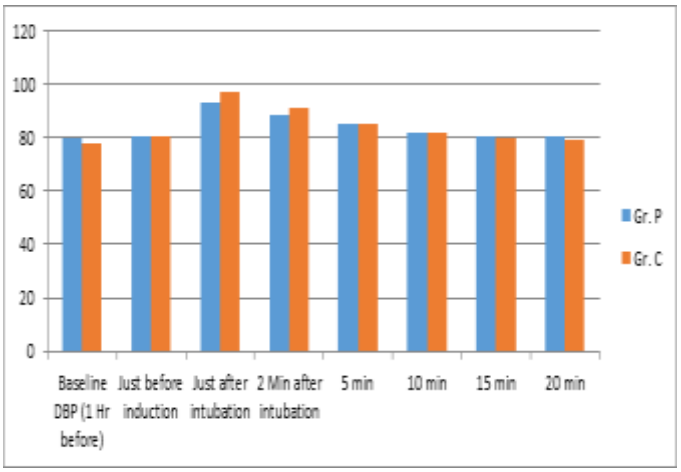

Fig. 3: Changes in the mean Diastolic Blood Pressure between the two groups (mm Hg)

Table 6: Comparison of percentage difference of diastolic blood pressure from baseline in two groups (mm Hg)

Variables (DBP)	P Group Baseline-79.76±8.08				C Group Baseline-77.60+6.48			
	Value	Difference	% Difference	P value	Value	Difference	% Difference	P value
Just before induction	80.88±6.98	1.12±1.10	1.40%	0.18 (NS)	80.64+6.72	3.04±0.24	3.92%	0.89 (NS)
Just after intubation	93.04±4.36	13.28±3.72	16.65%	0.001 (S)	96.92±7.78	19.32±1.30	24.89%	0.001 (S)
2 mins later	88.84±4.79	9.08±3.29	11.38%	0.002 (S)	91.04±6.00	13.44±0.48	17.32%	0.001 (S)
5 mins later	85.08±4.57	5.32±3.51	6.67%	0.003(S)	85.44±6.01	7.84±0.47	10.10%	0.002(S)
10 mins later	80.84±5.16	3.08±2.92	2.90%	0.003 (S)	82.84±4.20	5.24±2.28	6.46%	0.002 (S)
15 mins later	80.72±3.95	0.96±4.13	1.20%	0.046 (S)	79.72±4.01	2.12±2.47	2.73%	0.048 (S)
20 mins later	80.68±4.87	0.92±3.21	1.15%	0.04 (S)	78.96±3.87	1.36±2.61	1.75%	0.04 (S)

After intubation the mean arterial blood pressure (MAP) was statistically lower in the group p than in group c. This difference persisted till 10minutes following intubation (Table 7). In group p just after intubation the MAP represented a rise of 13.4% above the baseline, while it was 20.7% in group c. By 20 minutes it settled down in group p, while it continued to be elevated in group c(Table 8).

Table 7: Comparison of mean arterial blood pressure in two groups (mmHg)

Groups	Group P	Group C	P value
Baseline MAP	95.51±8.60	93.88±6.58	0.71(NS)
MAP Just before induction	96.00+7.65	96.42±7.21	0.0482(S)
MAP Just after intubation	108.31+3.45	113.36±7.59	0.02(S)
MAP 2 mins later	104.49+5.42	107.80±6.16	0.03(S)
MAP 5 mins later	100.63+5.37	102.04±6.14	0.04(S)
MAP 10 mins later	97.09+5.81	98.58±3.90	0.04(S)
MAP 15 mins later	95.88+4.72	95.88±4.11	0.16(NS)
MAP 20 mins later	95.32+4.27	94.59±4.13	0.15(NS)

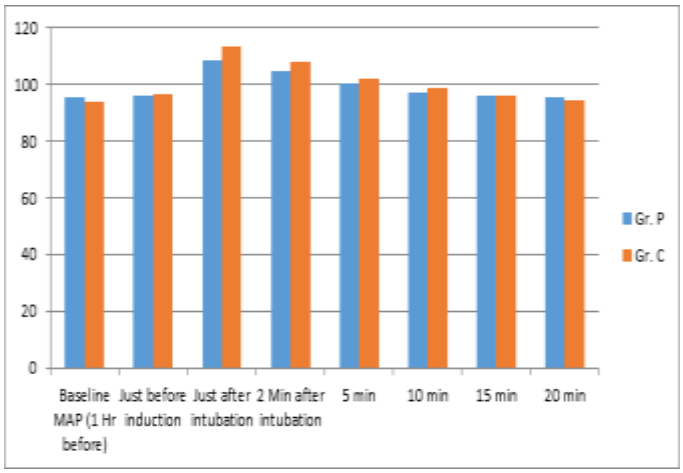

Fig. 4: Changes in the Mean Arterial pressure between the two groups (mm Hg)

Table 8: Comparison of percentage difference of mean arterial blood pressure from baseline in two groups (mm Hg)

Variables (MAP)	P Group Baseline- 95.51±8.60				C Group Baseline-93.88±6.58			
	Value	Difference	% Difference	P value	Value	Difference	% Difference	P value
Just before induction	96.00+7.65	0.49+0.95	0.51%	0.046 (S)	96.42±7.21	2.54+0.63	2.70%	0.02(S)
Just after intubation	108.31+3.45	12.80+5.15	13.40%	0.01 (S)	113.36±7.59	19.48+1.01	20.75%	0.01 (S)
2 mins later	104.49+5.42	8.98+3.18	9.40%	0.02 (S)	107.80±6.16	13.92+0.42	14.82%	0.01 (S)
5 mins later	100.63+5.37	5.12+3.23	5.36%	0.02 (S)	102.04±6.14	8.16+0.44	8.69%	0.02 (S)
10 mins later	97.09+5.81	1.58+2.79	1.65%	0.05 (S)	98.58±3.90	4.70+2.68	5%	0.05 (S)
15 mins later	95.88+4.72	0.37+3.88	0.38%	0.044 (S)	95.88±4.11	2+2.47	2.13%	0.04 (S)
20 mins later	95.32+4.27	0.19+4.33	0.19%	0.15 (NS)	94.59±4.13	0.71+2.45	0.75%	0.042 (S)

Sedation scores were higher in group p as compared to group c (Fig. 1). Postoperative visual analog scales (VAS) were lower in group p. Rescue analgesic was required by 4% of the patients in group p, while it as required by 34% of the patients in group c (p= 0.04)

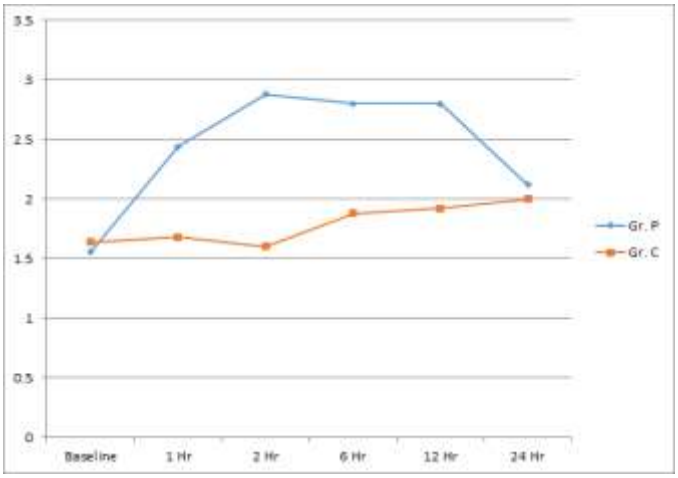

Fig. 5: Trend table showing mean sedation score in the two groups

Discussion

The haemodynamic pressor response during laryngoscopy and intubation occurs frequently.[10] Shribman et al. reported that laryngoscopy increases the blood pressure and catecholamine levels, while intubation significantly increases heart rate which could lead to dangerous sequelae.[11] Though various agents have been used to prevent these pressure responses, but still the search for ideal agent continues.[12-15] The present study shows that pregabalin effectively reduces the hemodynamic responses to intubation and laryngoscopy.

Our study concurs with the study conducted by Rastogi et al who found that 150 mg of pregabalin successfully attenuated the haemodynamic response to airway instrumentation.[16]

Another study conducted by Sundar et al comparing the efficacy of pregabalin in attenuating the pressor response to airway instrumentation in patients undergoing off-pump coronary artery by-pass surgery (OPCAB)concluded that pregabalin 150 mg given 1-hour prior, suppressed the reflex haemodynamic response to laryngoscopy and intubation.[17]

However, unlike other studies our study did not note any significant difference in the heart rate between the two groups following intubation. The probable reason could be the dose and type of different premedication and induction agents used in other studies.

Our study also confers to the study done by Chaudhary et al who did a comparative study between pregabalin and clonidine. They observed that pregabalin was equally efficacious in stabilizing the haemodynamics during laryngoscopy. However, pregabalin premedication was associated with higher mean heart rate values after intubation as compared to the clonidine group.[18]

Raichurkar A et al conducted a comparative study of 200µg clonidine and 150mg pregabalin given 90 minutes before surgery and noted that pregabalin was better in attenuating hypertensive response to airway instrumentation while heart rate was better attenuated by clonidine premedication.[19]

Kumkum Gupta et al conducted a comparative study between pregabalin 150 mg and clonidine 200 mcg premedication and found that both drugs attenuated hemodynamic response, but attenuation was superior in clonidine premedicated group.[20]

Our study reveals that pregabalin produces sedation and hence reduces the anxiety, as assessed by Ramsay sedation scores. Preoperative anxiety is an important problem because it not only changes the drug dosages needed for induction, maintenance and recovery of anaesthesia, but it also affects the physiological condition of the patient. Stress releases hormones like cortisol, catecholamines which increase negative nitrogen balance & catabolism and ultimately delay wound repair and weaken immune system.[21]

Our study concurs with the studies done by Ghai et al who observed that sedation scores were more in the pregabalin premedicated group than after gapapentin premedication.[22]

Yucel et al and Aggarwal et alnoted that pregabalin premedication result in higher sedation scores as compared to the placebo group.[23,24]

Kohli M et al observed higher sedation scores in Pregabalin premedicated groups than the control group.[25] O Mathiesen et al also found that pregabalin premedication caused increased sedation along with reduced analgesic consumption in the post-operative period.[26]

Our study observed that pregabalin had analgesic sparing effects. Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. Transmission of nociceptive stimuli from the periphery to the central nervous system (CNS) results in neuroendocrine stress response involving hypothalamic pituitary adrenocortical and sympathoadrenal interactions.The attenuation of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications. The same findings were supported by another study who found that preoperative oral pregabalin 150 mg reduces pain following laparoscopic cholecystectomyand reduces patient controlled fentanyl consumption.[24] Our findings are further supported byJakola et al who found that analgesia was better with 150 mg pregabalin than with 75 mg pregabalin and placebo.[27]

Sagit M el al found that a single preoperative oral dose pregabalin 75 or 150 mg is an effective method for reducing postoperative pain and total analgesic consumption.[28]

Pregablin effectively attenuates heamodynamic stress responses to intubation, with adequate sedation and analgesia when compared to placebo, but its comparison with other drugs with similar effects need to be evaluated to exert its supremacy.

Conclusion

We conclude that premedication with 150 mg of oral pregabalin one hour before surgery can be safely used to attenuate haemodynamic response to laryngoscopy & intubation along with decreasing post-operative pain and analgesic consumption with acceptable levels of sedation.

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