ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11,Iss 7, Oct 2022

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

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ABSTRACT

Background: Haemdynamic pressor response to airway instrumentation is a hazardous complication of general anaesthesia along with post-operative pain. Pregabalin is a gaba pentenoid which possesses antiallodynic, anticonvulsant and antihyperalgesic properties.

Aim and Objective: The study aimed to evaluate the effects of oral preoperative pregabalin in attenuating haemodynamic response to laryngoscopy and intubation and inattenuating post-operative pain inpatients posted for elective surgery under general anaesthesia.

Methodology: This prospective randomized placebo controlled double blinded study was conducted on 50 patients of either sex by randomly allocating them in two groups (Group P & Group C).

Result: There were 68% females and 32% males in group P while in group C there were 64% females and 36% males. In the groups receiving Pregabalin, the mean age was 34.60 ± 9.71 years, while in the placebo group it was 34.60 ± 9.20 years. Patients pre-medicated with pregabalin had an attenuated hypertensive response to laryngoscopy and intubation as compared to the placebo. VAS score was lower in the 2nd hr after the surgery in the pregabalin premedicated group that the placebo group.

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Conclusion: Consequently, it can be said that pregabalin is effective in reducing post-operative pain, the hypertensive response, and has effective analgesic characteristics. It is also a relatively safe medication with few side effects.

Keywords: Oral pregabalin, Hemodynamic response, Laryngoscopy, Anaesthesia.

INTRODUCTION

Most patients awaiting elective surgery experience pre-operative anxiety.[1] Anxiety is an unpleasant emotion & may cause patients to avoid planned operation. It may also adversely influence anaesthetic induction & patient recovery.[2] The use of pre-operative benzodiazepenes is the most common practice to decrease pre-operative anxiety & produce sedation, they do not have a positive effect on post-operative outcome. [3, 4]

Laryngoscopy & intubation are associated with cardiovascular changes like hypertension, tachycardia, dysrhythmia, increased catecholamines and even myocardial ischaemia. [5] These responses may be dangerous in those with coronary artery insufficiency, vascular anomalies or intracranial disease. [6]

Gabapentin was introduced as an anti epileptic & later proved to be effective in neuropathic pain.[7] Gabapentin and Pregabalin are structural derivatives of inhibitory neuro-transmitter gamma amino-butyric acid. Pregabalin is several times more potent than Gabapentin. It selectivelybinds to alpha 2 sub unit of voltage dependent calcium channel which result in decreased synthesis of neurotransmitter glutamate. Pregabalin had been shown to be effective in varied pain etiologies like neuro-pathicpain, diabetic neuropathy, post-herpetic neuralgia reflex, Sympathetic dystrophy, acute post operative pain, and inreducing the post operative opioid requirements.

Furthermore, a growing body of evidence suggests that perioperative administration is efficacious for preoperative anxiolysis, preventing chronic postsurgical pain, postoperative nausea and vomiting, and delirium. Because patients may be anxious in the perioperative period, the anxiolytic effects of pregabalin may be beneficial.[8] Hence this prospective randomized double blind placebo controlled study was undertaken using 150 mg oral pre-gabalin as a premedicant 1hr before surgery under general anaesthesia in view of evidence based clinical practice.

MATERIALS AND METHODS

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This prospective randomized double blind placebo controlled study was conducted in Santosh Hospital associated with Santosh Medical College, Ghaziabad during the period May 2014 and July 2015. The study was undertaken after obtaining ethical committee clearance as well as after receiving informed written consent from all patients.

50 patients of ASA I & II status aged between 18-60 yrs scheduled for elective surgery under general anesthesia and satisfying the inclusion criteria were included in this study. Patients with more than 60 years of age, liver, renal, cardiovascular, respiratory or CNS disorder, Any history of drug allergy and pregnant and lactating mothers were not included in the study. The study population was randomly divided into two groups, each group containing 25 patients each:

Group P- Pregabalin 150 mg (n=25): will receive oral 150 mg of pregabalin 1hr pre-operatively

Group C-Placebo (n=25): will receive oral placebo pre-operatively.

The procedure was explained to each patient and they were given tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bed time on the previous night before surgery.

Laryngoscopy, intubation and monitoring of vitals were done by other anaesthesiologists who were blinded to the drugs used in each group. Sedation was measured using Ramsay Sedation scale at the time of drug administeration, 1 hr later and post-operatively at 2 hrs, 6 hrs, 12hrs and 24 hrs after surgery. Post-operative pain assessment was done at 2, 6, 12, 24 hr after operation using VAS (0 indicating no pain and 10 indicating worst possible pain). Post- operative follow up for 24hrs was done, side effects if any, like nausea and vomiting, dizziness, visual disturbances, headache, pain etc were treated and recorded.

The quantitative variables were expressed in terms of mean ± standarddeviation and compared across follow-ups within a group using pairedt-test/ Wilcoxon test. Qualitative variables were expressed in terms of percentages and compared between the two groups using Chi-square/ Fisher's exact test. The level of statistical significance was taken as $p \leq 0.05$ and data was analyzed by using SPSS statistical software version 17.0.

RESULTS

The following observations were made after statistical analysis of the data.

Table1: Demographic data distribution and characteristicsof the study subject.

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Demographic data distribution		Number (Percentage)	
		Group P	Group C
Age	18-30	11 (44%)	10 (40%)
	30-40	10 (40%)	11 (44%)
	> 40	4 (16%)	4 (16%)
	Mean ± SD	34.60 ± 9.71	34.60 ± 9.20
Gender	Male	8 (32%)	9 (36%)
	Female	17 (68%)	16 (64%)
Weight (kg)	Mean ± SD	60.62±9.40	60.74±9.26

The above table shows that 44 percent of the patients in the pre-gabalin group were in the age group of 18-30 years, while 40 percent of patients in the control group were in 18-30 years age group, percentage of patients in the age group of 30-40 years is 40% & 44% in pregabalin and control group respectively, while 16 percent of patients in both the groups were more than 40 years of age. Mean age in Group P was 34.60 ± 9.71 and in Group C it was 34.60±9.20. Percentage of male in pregabalin and control group were 32% & 36% respectively. The percentage of female patients were 68% & 64% in pregabalin and control group respectively. The mean weight in group P was 60.62 ± 9.40 and in Group C was 60.74 ± 9.26.

Table2: Comparison of mean heart rate, mean SBP, Mean DBP between the two groups (in beats per minute).

	Groups	Mean ± SD		Pvalue
		GroupP	GroupC	
Mean Heart Rate	BaselineHR(bpm)	82.16 ±7.41	79.52 ±7.55	0.124(NS)
	HRJustbeforeinduction	81.80 ±8.17	82.88 ±8.83	0.128(NS)
	HRJustafterintubation	97.80 ± 4.04	97.60 ±7.41	0.982(NS)
	HR2minsafterintubation	93.52 ±5.78	92.88 ±6.32	0.648(NS)
	HR5minsafterintubation	87.68 ±4.28	86.56 ±7.03	0.428(NS)
	HR10minsafterintubation	82.88 ±5.91	82.48 ±4.87	0.882(NS)
	HR15minsafterintubation	81.52 ±7.64	79.68 ±5.55	0.216(NS)
	HR20minsafterintubation	80.48 ±8.27	78.12 ±5.52	0.032(S)
Mean SBP	Baseline SBP(mm Hg)	126.88 ±11.30	125.68 ± 8.13	0.971(NS)
	SBP Just beforeinduction	126.48 ±10.90	128.16 ±9.43	0.04(S)
	SBP Just afterintubation	140.12 ±3.63	146.32 ±7.82	0.02(S)
	SBP 2 mins afterintubation	136.52 ±6.66	141.68 ±6.47	0.04(S)
	SBP 5 mins afterintubation	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)

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	SBP 15 mins afterintubation	126.88 ±7.13	128.40 ±5.77	0.03(S)
	SBP 20 mins afterintubation	125.48 ±6.27	125.84 ±5.16	0.82(NS)
Mean DBP	Baseline DBP(mm Hg)	79.76±8.08	77.60±6.48	0.71(NS)
	DBP Just beforeinduction	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 after intubation	88.84±4.79	91.04±6.00	0.04(S)
	DBP 5 mins afterintubation	85.08±4.57	85.44±6.01	0.048(S)
	DBP 10 mins after intubation	80.84±5.16	82.84±4.20	0.042(S)
	DBP 15 mins after intubation	80.72±3.95	79.72±4.01	0.03(S)
	DBP 20 mins after intubation	80.68±4.87	78.96±3.87	0.15(NS)
Mean MAP	Baseline MAP(mm Hg)	95.51±8.6	93.88±6.58	0.71(NS)
	MAP Just before induction	96±7.65	96.42±7.21	0.0482(S)
	MAP Just afterintubation	108.31±3.45	113.36±7.59	0.02(S)
	MAP 2 mins after intubation	104.49±5.42	107.80±6.16	0.03(S)
	MAP 5 mins after intubation	100.63±5.37	102.04±6.14	0.04(S)
	MAP 10 mins after intubation	97.09±5.81	98.58±3.90	0.04(S)
	MAP 15 mins after intubation	95.88±4.72	95.88±4.11	0.16(NS)
	MAP 20 mins after intubation	95.32±4.27	94.59±4.13	0.15(NS)

Table 2 shows no significant difference of HR values at the baseline between the 2 groups. The mean HR showed no significant diference in the pregabalin group & the control group just after intubation, 2 minutes after intubation, 5 minutes, 10 minutes & 15 minutes after intubation (p value= 0.98, 0.648, 0.428, 0.882, 0.21 respectively). The difference in mean SBP at 2 minutes, 5 minutes, 10minutes & 15 minutes after intubation showed lower value in pregabalin group than control group (p value= 0.04, 0.03, 0.02, 0.03 respectively). There was no significant difference in the mean SBP at 20 minutes after intubation in both the 2 groups. No significant difference was observed in DBP values at the baseline between the 2 groups, but after intubation the DBP was significantly lower in the pregabalin group than the control group (p value 0.03). The mean MAP till 10 minutes after intubation showed higher value in control group than pregabalin group. The MAP values at 15 minutes and 20minutes after intubation showed insignificant difference (p value 0.16 at 15 minutes after intubation & 0.15 at 20 minutes after intubation).

Table 3: Distribution & comparison of VAS in the groups.

TIME	GROUPS	VAS				P-VALUE
		NIL (0)	MILD (1-3)	MODERATE (4-6)	SEVERE (7-10)	
2Hour	GroupP	0(0%)	22(88%)*	3(12%)**	0(0%)	0.02(S)* 0.03(S)**
	GroupC	0(0%)	15(60%)*	10(40%)**	0(0%)	
6Hour	GroupP	0(0%)	22(88%)*	3(12%)**	0(0%)	0.68(NS)* 0.04(S)**
	Group C	0(0%)	19(76%)*	6(24%)**	0(0%)	

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12 Hour	Group P	0(0%)	25(100%)*	0(0%)**	0(0%)	0.86(NS)* 0.1 (NS)**
	Group C	0(0%)	20(80%)*	5(20%)**	0(0%)	
24 Hour	Group P	0(0%)	25(100%)*	0(0%)	0(0%)	0.89 (NS)*
	Group C	0(0%)	23(92%)*	2(8%)	0(0%)	

Table 3 shows that 88% patients had mild pain while 12% patients had moderate pain in the pregabalin group two hours after surgery while 40% patients had moderate pain & 60% had mild paininthe control group, thus suggesting that pregabalin pre-medicated patients had statistically significant lower VAS than patients in control group. While the pain score in the pregabalin and control group showed no statistically significant difference at 6hr,12 hr & 24hr post-operatively.

Table4: Analgesic consumption between the two groups.

Analgesic	**Number (Percentage)**		**p-value**
	GroupP	**GroupC**	
Notrequired	24 (96.0%)	9 (36.0%)	0.04(S)
Required	1 (4.0%)	16 (64.0%)	
Total	25 (100%)	25 (100%)	

Table 4 shows that 96% patients in the pregabalin pre-medicated group did not require analgesics in the post-operative period while 64% patients in the control group required analgesics. There is significant statistical difference between the 2 groups.

Table5: Comparison of side effects between the groups

Patientcharacteristics	**Number of Patients (%)**		**p-value**
	GroupP	**GroupC**	
Vomiting	3 (12%)	3 (12%)	1(NS)
Hypotension	1 (4%)	1 (4%)	1(NS)
Headache	3 (12%)	4 (16%)	0.96(NS)
Dizziness	3 (12%)	0 (0%)	0.03(S)

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VisualDisturbance	0 (0%)	0 (%)0	1(NS)

Table 5 shows that the number of patients who complained of vomiting was same in both groups (12% each), thus there is no significant difference in the incidence of vomiting (p-value =1). The incidence of hypotension is same in both the groups(4% each, p-value=1), while 12 % patients had complaints of headache in pregabalin premedicated group while in the control group 16% patients had vomiting (p value 0.96). None of the patients had visual disturbance in both the groups.

The patients in the pregabalin premedicated group had higher incidence of dizziness (12%), while no patient in the control group had dizziness, thus the difference was statistically significant (p-value-0.03).

DISCUSSION

Hemodynamic pressor response to airway instrumentation is a hazardous complication of general anaesthesia. Many drugs have been used to attenuate these adverse hemodynamic responses, but theadverse profile of benzodiazepines, barbiturates and opioid, along with the stress response to surgery create the need for a drug that can be used safely with limited adverse effects.

Gabamimetic drugs like gabapentin and pregabalin have been successfully used by various authors as oral premedication to attenuate pressor response during airway instrumentation, to decrease the pre-operative anxiety, to reduce perioperative fentanyl consumption & in reducing post operative pain. At present, pregabalin is available as oral preparation only. Oralbioavailability of pregabalin is > 90% (higher than gabapentin withbetter potency) and peak blood concentration of the drug is attained at1hr [9]

We studied the effect of pre-emptive oral Pregabalin 150 mg in attenuating the hemodynamic response to laryngoscopy and intubation and its effect on post-operative pain. We also assessed sedation levels produced by Pregabalin. The reason for under taking the study was to know the optimal dose of pregabalin and duration of treatment and to assess its effectiveness in the above mentioned parameters with minimal side effects. We administered this drug orally one hour before surgery. Group Preceived Pregabalin 150 mg 1hr prior to surgery and Group C received placebo 1 hr prior to surgery. The two groups were comparable with respect to their demographic variables like Age, Sex, Weight, ASA and baseline values of HR, SBP, DBP, MAP, base line sedation scores.

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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. [11] Reid et al and Hassan et al. reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebro vascular accidents following intubation in hypertensive patients.[12] These physiological changes are due to variation in the balance of sympathetic and parasympathetic outflow or receptor hypersensitivity. Specific measures should be taken to prevent these changes as hypertension may affect peri-operative morbidity through the extent of end organ damage, like myocardial ischemia or cerebral haemorrhage. [13] Aronson and Fontes stated that rise in pulse pressure as little as 10 mmHg in both normotensive and hypertensive persons is associated with a 20% or more increased risk of renal failure, coronary events and cerebral stroke. [14]

The pain assessement was done using Visual analog scale at 2 hrs, 6 hrs, 12 hrs and 24 hrs postoperatively. In the Pregabalin group 96% of the patients didn't require supplemental analgesics while the 64% of the patients in the control group required analgesics (p value=0.04). Thus it was observed that pre-gabalin had effective analgesic sparing effects.

Our observations on post-operative pain concurs to the study findings of Jakola R et al [15] who compared the effects of 75 mg pregabalin and150 mg pregabalin with placebo on 90 normotensive women undergoing laproscopic gynaecological surgery under general anaesthesia. They concluded that analgesia was better with 150 mg pregabalin group than75mg pregabalin and placebo.

Agarwal A et al [16] got similar findings in their study of preoperative oral pregabalin 150 mg on patients undergoing laproscopic cholecystectomy under general anaesthesia. The postoperative pain (static and dynamic) and patient controlled fentanyl consumption were reduced in the pregabalin group than in the placebo group ($p < 0.05$).

Several studies have reported dizziness and somnolence as the most frequently reported adverse effects of pregabalin. In our study we found that in the side effect profile 12% of the patient showed dizziness while the incidence of dizziness in the control group was0%. Kohli M et al [17] in his comparative study of 150 mg & 300 mg pregabalin also reported dizziness; incidence was higher with pregabalin 300 mg premedication (44.44%), than the group pre-medicated with pregabalin 150 mg (36.11%).

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CONCLUSION

Oral pregabalin 150 mg given 1 hr prior to surgery was associated with dizziness in 12% of the patients while none of the patients in the placebo group had complaints of dizziness. Patients pre medicated with Pregabalin had less analgesic consumption as compared to the placebo (p-value= 0.04). While no significant difference was noted in the rise of heartrate following laryngoscopy & intubation between the pregabalin group & placebo group. Thus it can be concluded that pregabalin is effective in attenuating post-operative pain, hypertensive response and has effective analgesic properties and relatively a safe drug with minimal side effects.

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