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Pregabalin As A Premedicant To Attenuate Pressor Response In Patients Undergoing Laparoscopic Cholecystectomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

The present study was done to evaluate the ability of oral pregabalin to attenuate the pressor response to airway instrumentation in patients undergoing laparoscopic cholecystectomy under general anesthesia. Sixty-four adult patients aged between 25-55 year of either gender belonging to ASA-1 or ASA-2 physical status weighing 50-70 kg were enrolled in this study. Thirty-two patients each were randomized to group A, or group B. Patients in group A received tablet Pregabalin (150mg) and those in group B received placebo orally one hour before induction of anaesthesia. Heart rate, blood pressure, and sedation were assessed preoperatively before giving the tablets and after 30 minutes, and just before induction of anaesthesia. Intraoperative, pulse rate, mean arterial pressure, ECG in the lead II, SPO_2 and ETCO2 were monitored. All the above parameters were noted during laryngoscopy and intubation, 3 minutes after CO_2 insufflation, and then at every 10-minute interval till the end of surgery. These parameters were also recorded after extubating the patient. The Ramsay sedation scale was used to assess the sedation at the baseline, one hour after drug intake , one hour after extubation and 4 hour after surgery. Any adverse effects in the postoperative period were recorded. The result of our study shows that pre-emptive administration of oral pregabalin 150 mg significantly reduced the pressor response at the time of laryngoscopy and intubation, after CO_2 insufflation and just after extubation. We conclude that oral pregabalin premedication is effective in successful attenuation of hemodynamic pressor response to laryngoscopy, intubation and pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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INTRODUCTION

Hemodynamic pressor response to laryngoscopy and intubation results in an increased blood pressure and heart rate (Kayhan *et al.*, 2005; Morgan *et al.*, 2002). Tachycardia and hypertension cause an imbalance in myocardial oxygen demand and supply, predisposing it to ischemia, infarction and heart failure in patients with pre-existing coronary artery disease and underlying cardiac dysfunction (Ismail *et al.*, 2002).

Different techniques and pharmacological agents have been used to obtund this response. Recently studies have been carried out to evaluate the efficacy of oral pregabalin premedication on hemodynamic pressure response to airway instrumentation.

The present study was planned to evaluate the ability of pregabalin to attenuate the pressor response to airway instrumentation in patients undergoing laparoscopic cholecystectomy under general anesthesia.

MATERIALS AND METHODS

This was a prospective, randomized, double-blind, placebo-controlled study. After obtaining the Institutional Ethical Committee approval, we enrolled 64 patients undergoing laparoscopic cholecystectomy under general anesthesia. By using a computer-generated random number table, 32 patients each were allocated to group A or group, B. Written consent was obtained from all the enrolled patients. Adult patients aged between 25-55 year of either gender belonging to ASA-1 or ASA-2 physical status, weighing 50-70 kg were included in the study. The exclusion criteria were patients with anticipated difficult intubation, patients who were regularly consuming sedative; hypnotics; antidepressant drug and alcohol, pregnant and lactating females. Patients included in group A received tablet Pregabalin (150mg) and those assigned to group B received placebo orally one hour before the induction of anesthesia with sips of water. Heart rate, blood pressure, and sedation were assessed preoperatively before giving the tablets and after 30 minutes, and then again just before induction of anesthesia.

All the patients were kept nil per oral for at least 6 hours prior to surgery. Prior to induction, standard ASA monitors were attached, and intravenous access was secured. All the patients were pre oxygenated with 100% oxygen for 3 minutes. Injection Glycopyrrolate (0.2 mg), Injection Ondansetron (8 mg) and Injection Fentanyl (1.5 micrograms/kg) were given intravenously. Induction was done with injection Propofol till loss of verbal command. Injection Succinylcholine (1.5mg/kg) was administered to facilitate laryngoscopy and intubation. Heart rate (HR), and blood pressure changes were noted immediately after intubation. $ETCO_2$ was also monitored. Anesthesia was maintained with nitrous oxide (66%) and oxygen (33%) on intermittent positive pressure ventilation along with Isoflurane at the rate of 1 volume % and nondepolarizing muscle relaxant injection atracurium in intermittent dose as and when required. Minute ventilation and respiratory rate were adjusted in such a way, to keep ETCO2 at about 35 mm of Hg. At the end of the surgery, residual neuromuscular blockade was reversed by injection neostigmine 2.5 mg along with injection glycopyrrolate 0.4 mg. Oropharyngeal secretion was removed by suctioning and extubation was done after deflation of the cuff. Supplemental oxygen was given in the postoperative period.

Intraoperatively, pulse rate, systolic blood pressure, mean arterial pressure, diastolic blood pressure, ECG in the lead II, SPO_2 and ETCO2 were monitored. All the above parameters were noted during laryngoscopy and intubation, 3 minutes after CO_2 insufflation, and then at every 10-minute interval till the end of surgery. These parameters were also recorded after extubating the patient.

The Ramsay sedation scale was used to assess the sedation. Any adverse effects in the postoperative period were recorded.

Statistical Analysis

Categorical variables like gender distribution, side effects were compared across the group using a chi-square test for independence of attributes. Continuous variables, like age, weight was presented as mean $\pm$ standard deviation and compared across the two groups using unpaired t-test. The statistical analysis software SPSS version 17 was used for statistical analysis. An α level of 5% was taken, that is any p-value less than 0.05 was taken as significant.

RESULTS AND DISCUSSION

The demographic data of our study population is, as shown in Table 1. The pregabalin and the placebo groups were comparable with regards to the mean age, gender distribution and weight. The difference between the two groups was statistically, not significant.

The baseline heart rate in both the groups was almost similar and the difference was not statistically significant between the two groups (86.15 $\pm$ 6.01 vs 86.71 $\pm$ 5.78, p=0.701). Heart rate at 30 minutes and one hour after giving the premedication (pregabalin or placebo) were significantly lower in pregabalin group as compared to the placebo group (77.28 $\pm$ 5.27 vs 89.06 $\pm$ 6.87 and 74.03 $\pm$ 4.52 vs 88.31 $\pm$ 7.73, $p<0.001$). Mean heart rate one minute after intubation was significantly lower in the pregabalin group (85.62 $\pm$ 6.03 vs 105.87 $\pm$ 13.52, $p<0.001$).

During the intraoperative period as well as at the time of extubation, heart rate was found to be significantly lower in the pregabalin group compared to the placebo group as shown in Table 2 **.**

Table 1: Demographic Parameters

		Pregabalin group	Placebo group	p-Value
Age (Years)		35.25 ± 5.25	37.06 ± 6.10	0.208
Gender distribution	Male	10	9	0.784
	Female	22	23	
Weight (Kg)		56.59 ± 4.98	57.68 ± 4.61	0.366

Table 2: Comparison of heart rate (beats/minute) recordedat predefined intervals

Time Interval	Heart Rate (Mean ± SD)		p-value
	Pregabalin group	Placebo group	
Baseline	86.15 ± 6.01	86.71 ± 5.78	0.704
30 minutes after giving premedication	77.28 ± 5.37	89.06 ± 6.87	<0.001
1 hour after giving premedication	74.03 ± 4.52	88.31 ± 7.73	<0.001
1 Minute after Intubation	85.62 ± 6.03	105.87 ± 13.52	<0.001
3 Minute after CO2 Insufflation	79.43± 5.28	105.96 ± 7.82	<0.001
Intra Operative 10 Minutes	76.81 ± 5.10	98.18 ± 4.67	<0.001
Intra Operative 30 Minutes	75.09 ± 6.45	94.59 ± 5.19	<0.001
Intra Operative 60 Minutes	73.53 ± 5.19	89.21 ± 5.88	<0.001
Extubation	77.25 ± 5.94	90.50 ± 8.32	<0.001

Table 3: Comparison of mean arterial pressure (MAP)recorded at predefined intervals

Time Interval	MAP (Mean ± Std. Deviation)		p-value
	Pregabalin group	Placebo group	
Baseline	91.63 ± 5.22	91.19 ± 5.67	0.749
30 minutes after giving premedication	89.00 ± 4.04	92.44 ± 4.94	0.003
1 hour after giving premedication	88.72 ± 3.27	93.31 ± 4.90	<0.001
1 Minute after Intubation	93.72 ± 4.35	101.31 ± 3.78	<0.001
3 Minute after CO2 Insufflation	93.37 ± 3.66	99.81 ± 2.40	<0.001
Intra Operative 10 Minutes	93.38 ± 3.33	96.94 ± 2.47	<0.001
Intra Operative 30 Minutes	95.69 ± 3.45	96.56 ± 3.24	0.3
Intra Operative 60 Minutes	95.78 ± 3.03	97.47 ± 3.29	0.037
Extubation	97.44 ± 2.95	104.28 ± 3.576	<0.001

At baseline, mean arterial pressure was similar in two groups (91.63 ± 5.22 vs 91.19 ± 5.67, p=0.749). At 30 minutes and one hour after giving the premedication, MAP was significantly lower in the patients who received pregabalin as compared to those who received placebo (89.00 ± 4.04 vs 92.44 ± 4.94, p=0.003 and 88.72 ± 3.27 vs 93.31 ± 4.90, p < 0.001) .

Recorded MAP at one minute after intubation, three minutes after CO_2 insufflation and then first 10 minutes after intubation was higher in the placebo group compared to the patients who received pregabalin (101.31 ± 3.78 vs 93.72 ± 4.35; p< 0.001, 99.81 ± 2.40 vs 93.37 ± 3.66; p< 0.001, 99.94 ± 2.47 vs 93.38 ± 3.33; p < 0.001 respectively) and the difference was statistically significant.

MAP was also lower in the pregabalin group at all the time points during the intraoperative period except

Table 4: Ramsay sedation scale score 1 hour after giving premedication

Ramsay scale score	Pregabalin group	Placebo	p -value
1	4 (12.5%)	25 (78.13%)	<0.001
2	18 (56.25%)	7 (21.87%)	
3	8 (25%)	0	
4	2 (6.25%)	0	
5	0	0	
6	0	0	
Total	32 (100%)	32 (100%)	

Table 5: Ramsay sedation scale score 1 hour after surgery

Ramsay scale score	Pregabalin group	Placebo group	p-value
1	2 (6.25%)	20 (62.5%)	<0.001
2	16 (50%)	10 (31.25%)	
3	8 (25%)	2 (6.25%)	
4	6 (18.75%)	0	
5	0	0	
6	0	0	
Total	32 (100%)	32 (100%)	

Table 6: Ramsay sedation scale score 4 hours after surgery

Ramsay scale score	Pregabalin group	Placebo group	p-value
1	6 (18.75%)	11 (34.37%)	0.064
2	22 (68.75%)	21 (65.63%)	
3	4 (12.50%)	0	
4	0	0	
5	0	0	
6	0	0	
Total	32 (100%)	32 (100%)	

at 30 minutes. MAP was also significantly lower in the pregabalin group just after extubation (97.44 ± 2.95 vs 104.28 ± 3.576, p<0.001) as shown in Table 3 .

The Ramsay sedation scale scores at baseline in both the groups were similar. The Ramsay sedation scale scores one hour after giving premedication were significantly higher in patients receiving pregabalin, as shown in Table 4. The Ramsay sedation scale scores at one hour after surgery were significantly higher in the pregabalin group, as shown in Table 5. The comparison of Ramsay sedation scale score 4 hours after surgery between the two groups was statistically not significant, as shown in Table 6.

Significantly lesser number of patients required antiemetics in the pregabalin group. (9 (28.12%) vs 17 (53.12%), *p*=0.04).

Out of 32 patients in the pregabalin group, 24 (75 %) had dizziness compared to 15 (46.87%) patients in the placebo group.

The incidence of other side effects like headache, blurred vision, pruritus and abdominal distension was similar in the two groups. None of the patients in either group developed respiratory depression in the postoperative period.

Table 1 shows demographic Parameters like age , sex and weight distribution.

Table 2 shows the comparison of heart rate in the two groups. Heart rate was recorded at the baseline (before giving premedication), at 30 and 60 minutes after giving the premedication, 1 minute after intubation, 3 minutes after CO_2 insufflation, at 10, 30, and 60 minutes intraoperative and then just after extubating the patient.

Table 3 shows the comparison of mean arterial pressure (MAP) in the two groups. MAP was recorded at the baseline (before giving premedication), at 30 and 60 minutes after giving the premedication, 1 minute after intubation, 3 minutes after CO_2 insufflation, at 10, 30, and 60 minutes intraoperative and then just after extubating the patient.

Table 4 shows the Ramsay sedation scale score one hour after drug intake.

Table 5 shows the Ramsay sedation scale score one hour after surgery.

Table 6 shows the Ramsay sedation scale score 4 hours after surgery.

Laparoscopic surgeries have revolutionized general surgeries and have now become the gold standard for treatment of cholelithiasis. Laparoscopy surgery is also helpful in the staging and diagnosis of abdominal malignancy (Yeola *et al.*, 2018, 2019).Laparoscopic surgery has its own complications like significant hemodynamic changes observed during pneumoperitoneum, including a rise in heart rate, blood pressure, and an increase in systemic vascular resistance with a resultant fall in cardiac output (Guyton, 1991; Joris *et al.*, 1993).Different techniques and pharmacological agents have been used to obtund this response like Magnesium sulphate, dexmedetomidine, esmolol etc (Bhalerao *et al.*, 2017; Sen *et al.*, 2019).

In this study, we assessed the effect of Pregabalin on hemodynamic response to laryngoscopy, intubation and pneumoperitoneum, degree of sedation during pre and post-operative period.

We found that patients in the pregabalin group had significantly lower heart rate and mean arterial pressure (MAP) at the time of laryngoscopy and intubation, after CO_2 insufflation and just after extubation.

Bafna U et al. found that gabapentin 1000 mg, given 1 hour before surgery significantly attenuates the hemodynamic pressor response to laryngoscopy and intubation in normotensive patients (Bafna *et al.*, 2011). Iftikhar T et al. found that premedication with oral gabapentin decreases hemodynamic pressor response to laryngoscopy and intubation (Iftikhar *et al.*, 2011).Gupta Kumkum et al. . (Gupta *et al.*, 2011) studied the role of 150 mg oral pregabalin as premedication for attenuation of hemodynamic pressor response to laryngoscopy and intubation. They found that oral pregabalin premedication effectively leads to sedation and successful attenuation of the adverse and deleterious hemodynamic pressor response. Patients with hypertension & compromised cardiac function may benefit from intraoperative haemodynamic stability.

In the present study patients receiving pregabalin had higher Ramsay sedation scale scores as compared to the patients in the placebo group. This implies that the patients receiving pregabalin were more sedated compared to the patients receiving placebo. But, none of the patients in either group had a score of more than 4. These findings were in concordance with the findings of other similar studies conducted earlier (Gupta *et al.*, 2012; Jokela *et al.*, 2008a).

In the present study, more number of patients in the pregabalin group experienced dizziness as compared to those in the placebo group (75% vs 47%, $p<0.05$). The incidence of other side effects like headache, pruritus, blurring of vision and abdominal distension was similar in the two groups. None of the study patients developed respiratory depression in the postoperative period.

Similar to our study, Jokela R et al. . (Jokela *et al.*, 2008b) also reported a higher incidence of dizziness in patients receiving pregabalin.

CONCLUSIONS

Pregabalin as the pre-emptive medication is an effective and safe drug as it leads to sedation and haemodynamic stability in the perioperative period. A single, oral dose of 150 mg of pregabalin premedication is effective in attenuating the haemodynamic response to endotracheal intubation & pneumoperitoneum.

Limitation of the study

We need to add to the sample size to be sure about the findings.

The same applies to the incidence of complications.

Conflict of interest

Nil

Source of funding

Nil

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