Role of Oral Pregabalin as Premedication in Attenuation of Hemodynamic Responses to Laryngoscopy, Intubation, and Extubation in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Clinical Trial

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Abstract

Background and aim: Direct laryngoscopy, tracheal intubation, and extubation contribute to augmentation in heart rate and blood pressure. This can precipitate serious complications in patients with coronary artery disease, intracranial neuropathology, or reactive airways. Attenuation of hemodynamic stress response to laryngoscopy, intubation, and extubation is essential for better anesthetic outcome. The aim of this study was to evaluate the effect of oral pregabalin as premedication in attenuation of hemodynamic stress response to laryngoscopy, intubation, and extubation.

Materials and methods: This prospective randomized double-blinded placebo controlled study was conducted with 60 patients of American Society of Anesthesiologists (ASA) physical status class I/II, undergoing elective laparoscopic cholecystectomy. Patients were allocated randomly into two groups receiving either oral placebo or oral pregabalin 150 mg, 120 minutes before induction of anesthesia. Hemodynamic parameters such as heart rate, systolic, diastolic, and mean blood pressures were compared at various time points.

Results: Pregabalin showed a significant attenuation of hemodynamic stress response to laryngoscopy, tracheal intubation, and extubation compared with that of placebo. The pregabalin premedicated patients remained hemodynamically stable perioperatively without any significant side effects.

Conclusion: Pregabalin is effective in attenuating hemodynamic stress response to laryngoscopy, tracheal intubation, and extubation.

Keywords: Extubation, Hemodynamic, Intubation, Laryngoscopy, Pregabalin.

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Introduction

Laryngoscopy, tracheal intubation, and extubation are associated with various cardiovascular changes such as hypertension, tachycardia, dysrhythmias, and increased circulating catecholamines.[1] The effect although is transient, from 30 seconds after intubation to up to 10 minutes.[2] It occurs because of adrenergic response which leads to stimulation of the cardioaccelerator fibers.

Endotracheal intubation is well tolerated by normotensive patients, but even transient stimulation has been associated with increased morbidity and mortality in patients with preeclampsia, recent myocardial infarction, hypertension, and cerebrovascular pathology such as aneurysms, tumors, or raised intracranial pressure.[3,4]

Complications like dysrhythmias, intracranial bleed, myocardial ischemia, pulmonary edema, and cerebral hemorrhage can occur due to stress response during anesthetic procedures like laryngoscopy, intubation, and extubation which may increase the blood pressure by 40–50% and heart rate by 20%.[5,6]

Laparoscopy is a technique for visualization of the internal organs of abdomen or pelvis with an aid of camera using small incisions for ports which became very popular in early 1990s because less postoperative complications and pain were noted when compared with open cholecystectomy.

The pneumoperitoneum caused due to CO_2 insufflation further adds to several homeostatic alterations in acid–base balance, cardiovascular, pulmonary physiology, and stress responses.[7]

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Premedication in the form of vasodilators, adrenoreceptor blockers, calcium channel blockers, and opioids was used earlier to attenuate these responses, with variable results.[8–13]

Pregabalin, a gabapentinoid compound appears to produce an inhibitory modulation of neuronal excitability particularly in neocortex, amygdala, and hippocampus of central nervous system.[14,15]

However, there are evidences suggesting that perioperative administration is effective in attenuation of the hemodynamic

stress response to laryngoscopy intubation and extubation and preventing chronic postoperative pain, nausea, vomiting, and delirium.[16] Only limited literature is available related to the cardiovascular properties of pregabalin in patients undergoing laparoscopic surgery. Hence, this study was designed to evaluate the effect of oral pregabalin in attenuation of hemodynamic stress response during laryngoscopy, intubation, and extubation in patients undergoing laparoscopic cholecystectomy. The primary objective was to study the hemodynamic changes (heart rate, systolic, diastolic, and mean blood pressure) associated with laryngoscopy, tracheal intubation, and extubation.

MATERIALS AND METHODS

This prospective randomized double-blinded placebo controlled study was conducted after obtaining permission from the institutional ethics committee and informed consent from all the patients.

Sixty patients were randomly divided into two equal groups using a computer generated list. Group C (control group) received oral placebo in the form of oral multivitamin capsule, 120 minutes before surgery. Group P (pregabalin group) received oral pregabalin 150 mg, 120 minutes before surgery. Each patient was given either drug based on the generated list in a sealed, opaque envelope by the preoperative nurse. Both patient and investigator were unaware of the type of administered drug. Moreover, the nurse giving the drugs in the preoperative area was unaware of the study.

Inclusion criteria were patients belonging to the ASA physical status class I/II, aged 18 to 65 years and scheduled for laparoscopic cholecystectomy under general anesthesia. Exclusion criteria were patients with hypertension, diabetes, psychiatric illness, intake of sedatives, antipsychotics, and antiepileptic drugs; obesity; and drug allergy. Likewise, pregnant, lactating females, patients with anticipated difficult intubation, and those requiring more than one attempt or more than 20 seconds for laryngoscopy were excluded from the study. On day of surgery, the study drugs were given with a sip of water 120 minutes before induction of anesthesia. Continuous monitoring of the heart rate, blood pressure, and arterial oxygen saturation (SpO_2) was done in the preoperative period every 5 minutes by the nurse in charge of the preoperative room.

In the operation theater, standard 5-lead electrocardiography, noninvasive blood pressure and pulse oximetry were attached, and baseline parameters were recorded. Venous access was secured using an 18-G cannula on the dorsum of the nondominant hand. Injection midazolam 1 mg and fentanyl 1 μg/kg were given. Preoxygenation was done for 3 minutes and then proceeded for induction with propofol 2 mg/kg intravenously mixed with preservative-free lignocaine hydrochloride. Succinylcholine was used intravenously 2 mg/kg to facilitate endotracheal intubation with proper sized well-lubricated cuffed endotracheal tube. Laryngoscopy and tracheal intubation was done by the same person each time with appropriate sized, cuffed endotracheal tube. Anesthesia was maintained with inhalation of isoflurane 1 minimum alveolar concentration; nitrous oxide:oxygen 40:60. Muscle relaxation was attained with vecuronium bromide in the dose of 0.06–0.08 mg/kg intravenously as loading dose and 25% of the initial dose as maintenance doses. After completion of the surgery, neostigmine 60 μg/kg and glycopyrrolate 10 μg/kg were administered intravenously to reverse the residual neuromuscular blockade.

Hemodynamic parameters such as heart rate, systolic, diastolic, and mean blood pressures were recorded before the administration of drug (baseline), at laryngoscopy and intubation, at 1, 3, and 5 minutes after intubation, before pneumoperitoneum, 15 and 30 minutes after pneumoperitoneum, after release of CO_2, and after extubation.

In the postanesthesia care unit, the patients received the standard postoperative care including oxygen administration via face mask at 4–6 L/minute and monitoring of heart rate, noninvasive blood pressure (NIBP), respiratory rate, and SpO_2. We observed for any episodes of bradycardia, headache, nausea, vomiting, restlessness, arrhythmias, and hypotension till 24 hours postoperatively.

The primary outcome measure was to compare hemodynamic parameters at laryngoscopy, intubation, and extubation. The secondary outcomes were to evaluate the distribution of complications.

STATISTICAL ANALYSES

The sample size was calculated using the formula: ($n = [z(1 − \alpha/2)]2 \times$ SD2/d2)

where

$z(1-\alpha/2)$ = standard normal deviate for 95% confidence = 1.96

SD = standard deviation of mean arterial pressure (MAP) = 14 mm Hg

d = precision = 5%

$n = 1.962 \times 142/52$

$n = 30$

The sample size obtained was 30 patients in each group.

A statistical analysis was performed using SPSS for Windows (version 16.0, 2007; SPSS, Inc., Chicago, IL, USA). Data are expressed as mean, intragroup difference was evaluated by two-way analysis of variance, and intergroup using t test. p values of <0.05 were considered significant.

RESULTS

A total of 60 patients were enrolled in the study, and none were excluded as shown in consort chart (Flowchart 1). Demographics of both the groups were comparable in terms of age, weight, sex, duration of surgery, and ASA physical status classification (Table 1).

Systolic blood pressure was higher from baseline values in control group during laryngoscopy and intubation ($p = 0.0215$). Thereafter, this upsurge remained persistent throughout the surgery at all points of time until after extubation ($p < 0.0001$). In the pregabalin group, there was no increment, and the patients were stable at all points of time after giving the study drug (Table 2A). Similar trends were observed for diastolic and mean blood pressure (Tables 2B and 2C).

There was a significant increase in heart rate from baseline values during laryngoscopy and intubation in both the groups ($p = 0.0025$) which returned to previous values within 3 minutes in pregabalin group when compared with 5 minutes in the control group. Thereafter, the heart rate was maintained below the baseline value at all time points except after extubation in the patients receiving pregabalin. While in the control group, the rise in heart rate persisted throughout the surgery with significantly increased trend after CO_2 release ($p = 0.0328$) and after extubation ($p = 0.0017$) (Table 2D).

The comparison of SpO_2 in-between both the groups showed that the mean value of SpO_2 was slightly higher in pregabalin
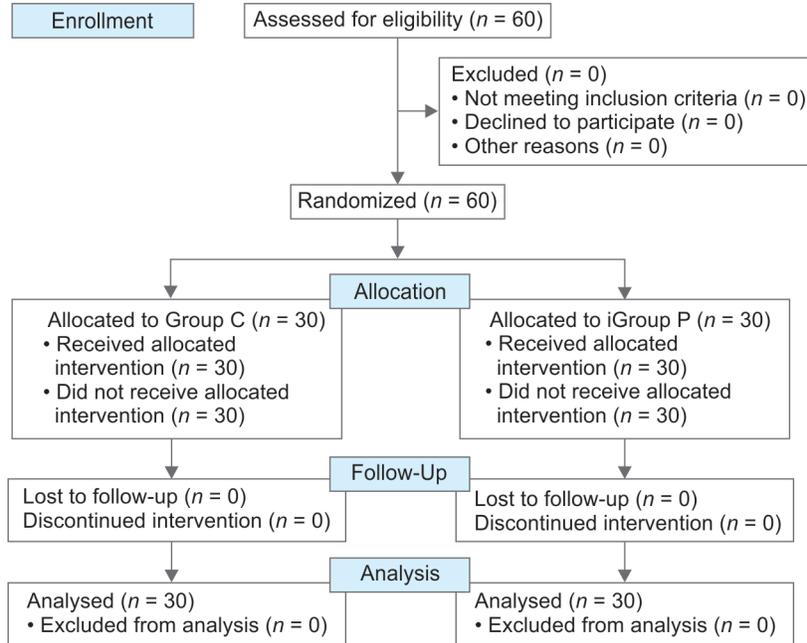
Flowchart 1: Consort flow diagram

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                    ┌──────────────┐    ┌──────────────────────────────────┐
                    │  Enrollment  │    │ Assessed for eligibility (n = 60)│
                    └──────────────┘    └──────────────────────────────────┘
                                                        │
                                        ┌───────────────────────────────────┐
                                        │ Excluded (n = 0)                  │
                                        │ • Not meeting inclusion criteria  │
                                        │   (n = 0)                         │
                                        │ • Declined to participate (n = 0) │
                                        │ • Other reasons (n = 0)           │
                                        └───────────────────────────────────┘
                                                        │
                                            ┌───────────────────────┐
                                            │ Randomized (n = 60)   │
                                            └───────────────────────┘
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	Allocation	
Allocated to Group C (n = 30) • Received allocated intervention (n = 30) • Did not receive allocated intervention (n = 30)		Allocated to iGroup P (n = 30) • Received allocated intervention (n = 30) • Did not receive allocated intervention (n = 30)
	Follow-Up	
Lost to follow-up (n = 0) Discontinued intervention (n = 0)		Lost to follow-up (n = 0) Discontinued intervention (n = 0)
	Analysis	
Analysed (n = 30) • Excluded from analysis (n = 0)		Analysed (n = 30) • Excluded from analysis (n = 0)

Table 1: Demographic data

	Mean ± SD		
Parameters	Group C (n = 30)	Group P (n = 30)	p
Age (years)	36.5 ± 12.01	34.7 ± 14.82	0.6073[#]
Sex (%)			
Male	12 (40)	12 (40)	1*
Female	18 (60)	18 (60)	
Weight (kg)	58.4 ± 6.6	60.9 ± 5.9	0.1274[#]
Duration of surgery (min)	59.6 ± 5.4	61.3 ± 5.6	0.2362[#]
ASA grade (%)			
I	13	16	0.606*
II	17	14	

*Fisher's exact test; #unpaired t test; n, number of patients; SD, standard deviation; ASA, American Society of Anesthesiologists

Table 2A: Comparison of SBP in different time intervals in-between groups

	Pregabalin group		Control group		
SBP	Mean	SD	Mean	SD	p*
Baseline	128.2	21.86	124.64	5.8	0.3922
During laryngoscopy and intubation	133.73	9.384	138.51	5.89	0.0215
1 minute	124.7	11.36	141.11	11.55	<0.0001
3 minutes	116.1	23.24	133.23	6.86	0.0003
5 minutes	117	9.137	130.7	6.87	<0.0001
Before pneumoperitoneum	114.2	8.823	128.54	9.23	<0.0001
15 minutes after pneumoperitoneum	126.7	7.597	144.21	7.02	<0.0001
30 minutes after pneumoperitoneum	124.6	6.831	140.21	8.64	<0.0001
After CO_2 release	127.9	8.501	146.34	7.21	<0.0001
After extubation	135.3	6.389	149.67	8.34	<0.0001

*Unpaired t test; SD, standard deviation; SBP, systolic blood pressure

group when compared with the control group. The difference was statistically significant at various time points (Table 2E).

In the control group, two patients had episode of nausea and vomiting; two patients reported restlessness in the immediate

Table 2B: Comparison of DBP in different time intervals in-between groups

DBP	Pregabalin group		Control group		
	Mean	SD	Mean	SD	p*
Baseline	83.47	8.046	81.88	4.53	0.3492
During laryngoscopy and intubation	86.53	8.299	91.11	4.7	0.0108
1 minute	79.43	9.008	96.54	6.11	<0.0001
3 minutes	76.13	8.153	89.28	3.8	<0.0001
5 minutes	73.8	7.631	86.54	3.44	<0.0001
Before pneumoperitoneum	73.07	8.111	84.31	5.24	
15 minutes after pneumoperitoneum	84.97	7.01	90.23	3.9	0.0007
30 minutes after pneumoperitoneum	84.3	7.34	90.01	4.9	0.0008
After CO_2 release	85.53	6.35	92.67	6.45	0.0001
After extubation	89.7	6.221	98.56	6.23	<0.0001

*Unpaired *t* test; SD, standard deviation; DBP, diastolic blood pressure

Table 2C: Comparison of MAP in different time intervals in-between groups

MAP	Pregabalin group		Control group		
	Mean	SD	Mean	SD	p*
Baseline	99.63	7.218	96.11	4.72	0.0291
During laryngoscopy and Intubation	102.23	5.469	105.28	4.5	0.0216
1 minute	94.5	9.273	111.34	7.11	<0.0001
3 minutes	90.7	8.879	103.88	4.26	<0.0001
5 minutes	88.7	7.493	101.18	4.2	<0.0001
Before pneumoperitoneum	86.73	8.004	98.34	6.34	<0.0001
15 minutes after pneumoperitoneum	98.9	6.557	103.67	5.78	0.0041
30 minutes after pneumoperitoneum	97.67	6.609	102.23	4.88	0.0035
After CO_2 release	99.83	6.012	104.9	4.34	0.0004
After extubation	104.4	5.531	112.35	5.39	<0.0001

*Unpaired *t*-test; SD, standard deviation; MAP, mean arterial pressure

Table 2D: Comparison of heart rate in different time interval in-between groups

Heart rate	Pregabalin group		Control group		
	Mean	SD	Mean	SD	p*
Baseline	87.17	8.914	85	5.77	0.2675
During laryngoscopy and intubation	95.33	8.014	88.41	8.9	0.0025
1 minute	89.8	9.622	90.88	11.66	0.697
3 minutes	86.97	11.17	87.51	8.92	0.8368
5 minutes	83.83	11.08	85.08	8.37	0.6238
Before pneumoperitoneum	82.83	9.454	85.92	10.61	0.2384
15 minutes after pneumoperitoneum	86.83	7.852	89.67	8.54	0.1851
30 minutes after pneumoperitoneum	83.7	9.763	87.45	8.23	0.1131
After CO_2 release	83.47	9.641	88.58	8.42	0.0328
After extubation	89.6	5.587	94.89	6.78	0.0017

*Unpaired *t* test; SD, standard deviation

postoperative period. In the pregabalin group, two patients had bradycardia; one patient had nausea and vomiting in the postoperative period. None of the patients had headache, arrhythmia, or hypotension (Table 3). Out of total 30 participants included in each study group, none had to be dropped off.

DISCUSSION

Airway management is one of the core skills of the anesthesiologist, via face mask ventilation, insertion of a laryngeal mask airway, endotracheal intubation by direct or indirect (video-assisted) laryngoscopy, or by use of a fiberscope. Pain relieving agents are usually administered with the concept of balanced analgesia, which involves a combination of analgesics with either synergistic or additive effects.

During laryngoscopy and intubation, there is a rise in both heart rate and blood pressure due to stimulation of sympathetic nervous system. A study conducted by Bruder et al.[6] showed that there is an average increase of 20% in heart rate and 40–50% in blood pressure from the baseline values. Similar hemodynamic

Table 2E: Comparison of SpO_2 in different time intervals in-between groups

SpO_2	Pregabalin group		Control group		
	Mean	SD	Mean	SD	p*
Baseline	99.7	0.4661	99.5	0.47	0.1012
During laryngoscopy and intubation	99.67	0.4795	99.4	0.46	0.0283
1 minute	99.8	0.4068	99.56	0.48	0.0397
3 minutes	99.63	0.4901	99.7	0.44	0.5627
5 minutes	99.7	0.4661	99.81	0.47	0.3634
Before pneumoperitoneum	99.6	0.4983	99.54	0.48	0.6337
15 minutes after pneumoperitoneum	99.67	0.4795	99.42	0.41	0.0321
30 minutes after pneumoperitoneum	99.8	0.4068	99.78	0.43	0.8593
After CO_2 release	99.73	0.4498	99.48	0.48	0.0398
After extubation	99.76	0.4498	99.49	0.49	0.0286

*Unpaired *t* test; SD, standard deviation; SpO_2, oxygen saturation

Table 3: Distribution of complications

Complications	Pregabalin group	Control group
Bradycardia	2	0
Headache	0	0
Nausea/vomiting	1	2
Restlessness	0	2
Arrhythmia	0	0
Hypotension	0	0

changes are also seen during creation of pneumoperitoneum in laparoscopic surgeries which was also showed in the study carried out by Odeberg et al.[17] and Shorrab et al.[18]

Pregabalin is a drug with analgesic, anxiolytic, and anticonvulsant property mainly used for the treatment of neuropathic pain, postherpetic neuralgia, and epilepsy. It has been used in the preoperative setup to abolish the cardiovascular stress response occurring due to laryngoscopy and tracheal intubation but with vivid doses and conflicting outcomes.[19–21]

Thus, this study was undertaken to evaluate the effect of oral pregabalin as premedication in attenuation of hemodynamic stress response to laryngoscopy, intubation, and extubation in patients undergoing laparoscopic cholecystectomy.

Saxena et al.[22] in a study to evaluate the effect of pregabalin premedication on response to laryngoscopy and intraoperative hemodynamic parameters in laparoscopic cholecystectomy observed that 150 and 300 mg pregabalin were proportionately potent in abolishing the rise in heart rate in response to laryngoscopy and intubation. Another study by Rastogi et al.[23] compared different doses of pregabalin to analyze the clinically potent and safe dose to maintain the hemodynamics during airway manipulation and observed the attenuation of MAP in the premedicated group was significant statistically, i.e., in pregabalin 75 mg group (97.80 ± 2.52 vs 110.70 ± 4.94, $p = 0.001$) and in pregabalin 150 mg group (92.06 ± 3.37 vs 110.70 ± 4.94, $p = 0.001$) to when compared with the control group, in a dose-related manner. Hence, upon these evidences, a dose of 150 mg pregabalin was selected for our study group.

We observed that pregabalin premedication provided a substantial trend of stability in all the hemodynamic parameters at all time points with negligible side effects. Our results were comparable with the observations made by Chakraborty et al.,[24]

who concluded that 150 mg of oral pregabalin safely blunts the hemodynamic response to laryngoscopy and intubation. Sundar et al.[25] conducted a study to observe the effects of pregabalin premedication on attenuation of hemodynamic stress response to tracheal intubation. They also reported opioid-sparing effect in patients undergoing coronary artery bypass graft and concluded that pregabalin premedication was effective in abolishing reflex tachycardia in response to direct laryngoscopy and tracheal intubation. Similarly, in our study, although there was a significant rise in heart rate from baseline values during laryngoscopy and intubation in both the groups ($p = 0.0025$), it returned to previous values within 3 minutes in the pregabalin group when compared to 5 minutes in the control group. Thereafter, heart rate was consistently maintained below the baseline value at all time points till after extubation in pregabalin group. These observations regarding heart rate trends were also in line with the observations reported by Singh et al.[26] They evaluated the effects of pregabalin premedication for suppressing the stress response due to laryngoscopy and tracheal intubation and found that magnitude of increase in heart rate was lower, and it was falling below the basal value at 10 minutes in the pregabalin group, but in the control group, it did not reach the baseline value even by 10 minutes following direct laryngoscopy and tracheal intubation.

Eren et al.[27] administered pregabalin to 50 patients undergoing elective spine surgery to analyze its effectiveness in abolishing the hemodynamic stress response to intubation. They found that MAP values were significantly curtailed in the pregabalin group compared with the control group (108.3 ± 6.3 vs 119.4 ± 9.8, $p = 0.0001$) during laryngoscopy and intubation even up to 10th minute. We also found that mean blood pressure was higher from baseline values in the control group when compared with the pregabalin group during laryngoscopy and intubation (105.28 ± 4.5 vs 102.23 ± 5.4, $p = 0.0215$). Furthermore in the control group, this increase persisted throughout the surgery at all points of time until after extubation ($p < 0.0001$). While in the pregabalin group, the patients were stable at all points of time after the administration of the study drug. Similar trends of stability with the pregabalin group were observed for systolic and diastolic blood pressures.

From this study, we conclude that pregabalin 150 mg seems to be an effective and safe drug to attenuate the sympathetic response to laryngoscopy, tracheal intubation, and extubation and can be useful for patients with comorbid conditions preoperatively.

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