Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation

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ABSTRACT

Background: Hemodynamic responses of laryngoscopy and laparoscopy should be attenuated by the appropriate premedication, smooth induction, and rapid intubation. The present study evaluated the clinical efficacy of oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy. **Methods:** A total of 180 healthy adult consented patients aged 35 to 52 years with American Society of Anesthesiologist (ASA) physical status I and II of both gender, who met the inclusion criteria for elective laparoscopic cholecystectomy, were randomized to receive placebo Group I, pregabalin (150 mg) Group II, or clonidine (200 μg) Group III, given 75 to 90 minutes before surgery as oral premedication. All groups were compared for preoperative sedation and anxiety level along with changes of heart rate and mean arterial pressure prior to premedication, before induction, after laryngoscopy, pneumoperitoneum, release of carbon dioxide, and extubation. Intraoperative analgesic drug requirement and any postoperative complications were also recorded. **Results:** Pregabalin and clonidine proved to have sedative and anxiolytic effects as oral premedicants and decreased the need of intraoperative analgesic drug requirement. Clonidine was superior to pregabalin for attenuation of the hemodynamic responses to laryngoscopy and laparoscopy, but it increased the incidence of intra-and postoperative bradycardia. No significant differences in the parameters of recovery were observed between the groups. None of the premedicated patient has suffered from any postoperative side effects. **Conclusion:** Oral premedication with pregabalin 150 mg or clonidine 200 μg causes sedation and anxiolysis with hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy, without prolongation of recovery time and side effects.

Key words: *Clonidine, hemodynamic response, laparoscopic cholecystectomy, laryngoscopy, pneumoperitoneum, pregabalin*

INTRODUCTION

Direct laryngoscopy and laparoscopic cholecystectomy predictably leads to tachycardia and hypertension, which are usually transient, variable, and unpredictable. Usually, these changes are well tolerated by healthy patients but may

Access this article online	
Quick Response Code:	**Website:** www.saudija.org
	DOI: 10.4103/1658-354X.82791

be fatal in patients with hypertension and coronary artery disease. Many pharmacological methods were evaluated either in premedication or during induction to attenuate the adverse hemodynamic response to laryngoscopy and laparoscopy, such as deepening the anesthesia, pretreatment with vasodilators, adrenoreceptor blockers, calcium channel blocker, and opioids, with variable results. The most recent studies were aimed to attenuate the hemodynamic response to laryngoscopy by remifentanil with different dosing regimens.

The present study was designed as prospective blind randomized controlled study to find out the efficacy of oral premedication with pregabalin or clonidine on sedation, anxiety, and changes in heart rate and mean arterial blood

pressure during laryngoscopy and laparoscopy, along with perioperative hemodynamic stability.

METHODS

Selection criteria
After approval of the Ethical Committee of Institution, 180 healthy adult consented patients aged 35 to 52 years with ASA physical status I and II of both gender (64 males, 116 females), scheduled for elective laparoscopic cholecystectomy between May 2008 and February 2010 under general anesthesia, were randomized for the present study. Patients with pre-existing cardiac disease, hypertension, asthma, and severe renal or hepatic dysfunction were excluded from the study. Other exclusion criteria included anticipated difficult intubation, patients with morbid obesity, and history of taking antihypertensive and antidepressants drugs. All patients had preanesthetic evaluation, which included history, general physical examination, systemic examination, and review of biochemical investigations before enrolment, and their basic data were recorded. The observer was totally blind about the groups or medication received by the patients.

Study drugs and randomization
All 180 enrolled patients were randomized to one of the three oral premedication treatment groups of 60 patients each. Group I received placebo, Group II received pregabalin (150 mg), and Group III received clonidine (200 µg), given with sips of water about 75 to 90 minutes before induction of general anesthesia. These doses were considered to provide adequate and comparable preoperative sedation, anxiolysis, and perioperative hemodynamic stability.

The protocol-defined primary endpoint were preoperative sedation and anxiolysis, hemodynamic responses to laryngoscopy and laparoscopy, intraoperative analgesic requirement, quality of postoperative recovery, and occurrence of premedication induced side effects.

Study procedure and measurements
Before administration of the oral premedication, each patient's baseline heart rate, mean systemic arterial blood pressure, and pulse oximetry were measured. In addition, 10 cm visual analogue scales for sedation (fully awake to extremely drowsy) and anxiety (fully calm to worst possible drowsy) were completed for each patient. All measurements were repeated before induction. If the patient was calm and asleep, anxiolysis and sedation was recorded as 10. Anesthetic and surgical techniques were standardized. The systemic mean arterial blood pressure, heart rate, pulse oximetry, $EtCO_2$, and electrocardiography (ECG) with ST segment analysis were recorded before and after induction, at 1 minute interval until 10 minutes after intubation, and 15 minutes after creation of pneumoperitoneum. Thereafter, these changes were recorded at 15 minutes intervals, followed by 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. All groups were compared for sedation and anxiety level, along with changes of heart rate and mean arterial pressure (MAP), prior to premedication, before induction, after laryngoscopy, pneumoperitoneum, release of carbon dioxide, and extubation. Intraoperative analgesic requirement and effects on postoperative recovery, nausea, vomiting, and shivering were also compared.

Anesthetic management
On arrival to operation theatre, routine monitoring of baseline vital parameters was recorded and a crystalloid intravenous infusion of 6 to 8 ml $kg^{-1}hr^{-1}$ was started. All patients were premedicated with metoclopramide (10 mg), glycopyrrolate (0.2 mg), and fentanyl (1 µg kg^{-1}). After preoxygenation for 3 minutes, anesthesia was induced with propofol 2 mg kg^{-1} or in a dose sufficient to abolish the eyelash reflex. The laryngoscopy and intubation were facilitated with rocuronium 0.8 mg kg^{-1} with minimum possible duration and were similar for all patients. Following induction, a nasogastric tube was placed. Anesthesia was maintained with minimum alveolar concentration (MAC) of 0.8% isoflurane, nitrous oxide 60% in oxygen. The patients' lungs were mechanically ventilated with minute ventilation adjusted to maintain normocapnia ($EtCO_2$ between 35 to 40 mm Hg). Supplemental neuromuscular blockade was achieved with rocuronium 0.1 mg kg^{-1} to maintain 95% relaxation.

During surgery, the peritoneal cavity was accessed with a blunt-tipped 12-mm trocar, and carbon dioxide was insufflated to create pneumoperitoneum at a rate of 2 l/min. After pneumoperitoneum, necessary change in minute ventilation was done to maintain normocapnia. Patients were positioned in a 20 degree anti-Trendelenburg position, and were rotated toward the left side to facilitate exposure of the gall bladder. The intra-abdominal pressure was maintained at 12 mm Hg throughout the laparoscopic procedure. At the end of surgery, patients were returned to supine position and residual carbon dioxide was expelled by abdominal compression. The total surgical procedure time was 75 to 90 minutes.

Intraoperatively, patients were observed for any complications like hypotension/hypertension, tachycardia/bradycardia, arrhythmias, hypercapnia, and bronchospasm. Tachycardia, hypertension, and clinically insufficient analgesia were controlled with supplementary doses of

intravenous fentanyl (0.5 µg/kg). Hypotension primarily was treated by increasing the intravenous infusion rate (15 ml/min) and additionally with vasoactive drugs. Bradycardia, defined as heart rate slower than 50 beats/min, was treated with 0.005 mg/kg i.v. atropine.

Isoflurane was discontinued after the last skin suture and residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg kg^{-1}) and glycopyrrolate (0.01 mg kg^{-1}). The extubation was performed when respiration was spontaneous and adequate.

Postoperative follow-up

Patients were transferred to postanesthesia care unit and monitored for at least 3 hours or until there were no signs of any drug-induced effects. Any hemodynamic abnormalities, need for postoperative opioid analgesic medication, and incidence of nausea and vomiting along with requirement for rescue antiemetic were also noted.

Study population size and statistical analysis

The sample size was decided in consultation with statistician, based on initial pilot observations which indicated that approximately 35 to 40 patients should be included in each group in order to ensure power 0.80 for detecting clinically meaningful attenuation of heart rate and mean arterial blood pressure by 10 to 20%. Assuming a 5% dropout rate, the final sample size was set at 180 patients.

The results obtained in the study are presented in tabulated manner and analyzed using Microsoft Excel and SPSS for windows. Hemodynamic variables were represented by mean ± S.D. Statistical significance in mean difference was done by using analysis of variance (ANOVA), student *t* and Chi square tests as appropriate. A *P* value of <0.05 was considered statistically significant.

Observation

A total of 180 patients, 60 in each group, were evaluated. All groups were comparable with respect to the demographic and operational factors. No significant differences were found between groups with respect to age, gender, weight,

time between oral premedication to anesthetic induction, duration of laryngoscopy, and surgical procedure time. Duration of anesthesia did not differ among the study groups [Table 1].

Preoperative sedation and anxiety level

The degree of sedation before premedication was comparable between the groups [Table 1]. However, they were anxious at baseline. A clear increase in sedation (>6 cm) and a moderate decrease in anxiety (2.4-3.6 cm) were observed in both premedicated groups as compared with control groups. Preoperative anxiolysis and sedation was higher in oral pregabalin group II as compared with clonidine group III (data not shown).

Cardiovascular effects

There was no significant difference in the preoperative heart rate and mean arterial blood pressure values in groups [Table 1]. Compared with control and pregabalin groups, clonidine group showed slight but statistically significant decrease in heart rate before induction. The heart rate increased significantly immediately after laryngoscopy in group I (135.6±7.26), whereas no such changes were observed in pregabalin group II and in clonidine group III. Maximum increase in heart rate from baseline was observed after 1 minute of laryngoscopy. During pneumoperitoneum, it increased by 32 beats/min in control group, while decrease in pregabalin group by 6 beat/min and clonidine group by 15 beat/min was observed. There was statistically significant attenuation of heart rate in premedicated groups (*P*<0.0001). In clonidine group, heart rate remained stabilized in comparison with group I and II [Table 2].

No significant difference was observed in the MAP before premedication in groups. Preoperative MAP changes were statistically significant in groups. After laryngoscopy, the attenuation of mean arterial blood pressure in premedicated group was statistically significant as to control group and remained stabilized during intraoperative period. The statistically significant difference was also observed in the MAP after pneumoperitoneum among groups [Table 3].

Table 1: Demographic profile, duration of laryngoscopy and laparoscopy (mean ± SD)

Demographic profile	Group I Control	Group II Pregabalin	Group III Clonidine	*P* value
Age (years)	48.46 ± 16.4	44.23 ± 15.3	43.96 ± 13.7	NS
Weight (kg)	63.6 ± 11.2	65.4 ± 12.8	65.3 ± 14.6	NS
Female/male	39/22	37/21	40/21	NS
ASA I/II	36/24	34/26	32/28	NS
Anxiety level	Anxious	Anxious	Anxious	NS
Sedation level	Awake	Awake	Awake	NS
Duration of laryngoscopy (sec)	22.08 ± 1.4	22.42 ± 0.8	23.05 ± 0.3	NS
Duration of laparoscopy (min)	79.85 ± 5.83	83.18 ± 2.52	85.56 ± 3.57	NS

Table 2: Heart rate changes after laryngoscopy in laparoscopic cholecystectomy

Heart rate	Group I	Group II	Group III	P value
Before premedication	103.56 ± 7.26	94.73 ± 1.22	96.23 ± 4.91	0.9550
Before induction	110.03 ± 2.40	89.26 ± 4.49	76.30 ± 5.22	0.0001**
After intubation	132.13 ± 3.55	90.30 ± 4.53	74.20 ± 5.47	0.0001**
15 min after pneumoperitoneum	129.66 ± 7.05	92.96 ± 4.42	76.26 ± 5.39	0.0001**
30 min after pneumoperitoneum	135.60 ± 3.05	100.3 ± 4.34	81.93 ± 5.26	0.0722
After release of CO_2	116.66 ± 4.26	89.96 ± 4.36	76.83 ± 5.82	0.7627
After extubation	118.80 ± 5.68	93.10 ± 4.49	78.70 ± 5.78	0.8322

*$P < 0.05$ is significant, **$P < 0.01$ highly significant

Table 3: Mean arterial blood pressure changes after laryngoscopy in laparoscopic cholecystectomy

MAP	Group I	Group II	Group III	P value
Before premedication	95.30 ± 2.88	93.33 ± 2.46	93.26 ± 2.64	-
Before induction	102.86 ± 3.43	93.26 ± 2.41	85.26 ± 3.27	0.0187**
After intubation	109.53 ± 4.79	96.83 ± 2.25	87.86 ± 3.09	0.0419*
15 min after pneumoperitoneum	107.5 ± 5.06	94.16 ± 2.61	85.16 ± 3.10	0.4606
30 min after pneumoperitoneum	110.43 ± 4.47	95.26 ± 2.42	88.56 ± 2.59	0.1331
After release of CO_2	100.20 ± 2.63	91.40 ± 2.51	84.83 ± 2.61	0.093
After extubation	105.96 ± 3.38	95.33 ± 2.54	87.10 ± 2.80	0.5264

*$P < 0.05$ significant, **$P < 0.01$ highly significant, MAP - Mean arterial blood pressure

Intraoperative heart rate and mean arterial blood pressure values were less and close to base levels without requirement of any other medication and remained stabilized throughout the intraoperative period in premedicated groups. In the postanesthetic care unit, heart rate and MAP remained at a lower level in premedicated group than in control group.

Anesthetic and analgesic requirements with other intraoperative interventions

Decreased amount of propofol and fentanyl was required for induction in premedicated groups as compared with control group. Three patients of clonidine group developed bradycardia (H/R <56 beats min⁻¹) 15 minutes after intubation and were treated with adequate dose of i.v. atropine. Intraoperatively, the control group was supplemented by bolus doses of fentanyl (0.5 μg/kg) when there was more than 20% increase in heart rate or mean arterial blood pressure. No analgesic supplement was needed for pregabalin and clonidine groups. Rapid intravenous infusion was needed in five patients of clonidine group to treat hypotension. None of the patients had persistent or severe hypotension, thus vasoactive drugs were not used.

Recovery and postoperative follow-up

There were no differences between the groups with respect to awakening and recovery times. They were well oriented and were able to obey commands in the postoperative care unit. Postoperative analgesic need was much less with pregabalin and clonidine group as compared with control. No significant complication has occurred after use of oral premedication with pregabalin and clonidine in our study. Postoperative nausea and vomiting were not found in any group during our study. None of the premedicated patient showed any evidence of intraoperative shivering, while 21 patients (9.5%) of control group showed shivering.

DISCUSSION

The present study evaluated the oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy. We observed the anxiolytic and sedative effects of oral premedicants without any significant respiratory depression. Hemodynamic responses of laryngoscopy and laparoscopy were attenuated by oral premedication with pregabalin and clonidine. The increase in hemodynamic values in control group may be due to inadequate sedation and analgesia. Near stable hemodynamic variables and absence of any sympatho-somatic response with oral premedication in the present study was an indication of adequate analgesia and sedation. Clonidine effectively attenuated the rise of heart rate and mean arterial blood pressure indicating inactivation of catecholamine. In our study, we have used oral premedication with pregabalin 150 mg or clonidine 200 μg and found them to be effective for perioperative hemodynamic stability. The hemodynamic results of our study were in agreement with recent results with clonidine and gabapentin. Both drugs posses several properties to make them valuable premedicants to attenuate the hemodynamic response of laryngoscopy.

Reid and Brace[1] first described the hemodynamic response to laryngoscopy and intubation, probably due to intense sympathetic discharges caused by stimulation of epipharynx and laryngopharynx.[2] Shribman *et al.*[3] reported that laryngoscopy and tracheal intubation increases arterial blood pressure, heart rate, and catecholamine levels, whereas Hassan *et al.*[4] reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure, and cerebrovascular accidents following intubation in hypertensive patients. Hypertension may affect perioperative morbidity through the extent of end organ damage.

Hemodynamic responses to laryngoscopy and laparoscopy should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage. If no specific measures are taken to prevent hemodynamic response, the heart rate can increase from 26 to 66%, depending on the method of intubation, and systemic blood pressure can increased from 36 to 45% which may be due to variation in balance sympathetic and parasympathetic outflow or receptor hypersensitivity. Anxiety, an unpleasant emotion, is another factor to adversely influence the anesthetic induction and patient recovery. These hemodynamic changes can be detrimental in elderly and hemodynamically compromised patients. More recently, Aronson and Fontes[5] found that among the various component of blood pressure, preoperative pulse pressure was independently and significantly associated with postoperative stroke, renal failure, and mortality in patients undergoing coronary artery bypass. Rise in pulse pressure as few as 10 mm Hg in both normotensive and hypertensive individual is associated with 20% or more increase risk of renal, coronary, and cerebral events. Numerous techniques have been used to reduce the incidence and severity of these hemodynamic responses.

In order to reduce the incidence and severity of the hemodynamic responses of laryngoscopy and laparoscopy, many pharmacological methods were evaluated either in the premedication or during induction, to attenuate these adverse hemodynamic responses with controversial results. Tachycardia and rhythm disturbances can be attenuated by omitting atropine as premedicant. Many studies have reviewed the impact of different drugs on hypertension following laryngoscopy. The most important were lidocaine, osmolol, sodium nitroprusside, and fentanyl. Among opioids, remifentanil (1.0 μg kg⁻¹), alfentanil (10-20 μg kg⁻¹), or fentanyl (0.5-1.0 μg kg⁻¹) were reported to have the most stable effect on hemodynamic response to laryngoscopy and tracheal intubation, but they prolonged the recovery time.[6-8] Intranasal nitroglycerine attenuated the hypertensive response to laryngoscopy and intubation, but tachycardia was observed.

The pregabalin and clonidine possesses several properties to make them valuable premedicants to attenuate the hemodynamic response of laryngoscopy and pneumoperitoneum. Pregabalin, an antiepileptic drug, is effective in controlling neuropathic component of acute nociceptive pain of surgery by inhibiting membrane voltage-gated calcium channels. It does not interact with GABA receptors. However, only few data are available in the literature regarding the effect of prebagalin on the cardiovascular system. Its analgesic, anticonvulsant, and anxiolytic activities make it useful oral premedicant. It is well absorbed after oral administration, with peak plasma concentrations occurring within 60 minutes. Clonidine activates the α_2-adrenergic receptors in the brain and spinal cord to decrease sympathetic outflow, causing sedation, analgesia, hypotension, and bradycardia without significant respiratory depression. It is well absorbed after oral administration (3-5 μg.kg⁻¹) with peak plasma concentration in 75 to 90 minute and does not require transformation into another substance prior to its action. The preoperative use decreases the intraoperative stress response by reducing the nociceptive transmission and decrease norepinephrine concentration in serum, provided hemodynamic stability.[9] Hayashi and Maze[10] and Sung *et al.*[11] reported that clonidine increases perioperative circulatory stability in patients undergoing laparoscopic cholecystectomy and potentiates parasympathetic nervous system. Laisalmi *et al.*[12] concluded that premedication with clonidine blunts the stress response to surgical stimuli and reduces the requirement of narcotic and anesthetic doses.

When assessing techniques to lessen the hemodynamic responses of laryngoscopy, the induction agents may influence the results. We induce anesthesia with propofol, which produces bradycardia. Thus, tachycardia resulting from laryngoscopy and intubation may have been attenuated by propofol in all groups. In the present study, clonidine caused intraoperative and postoperative bradycardia (HR <50 beats/min) and subsequent use of atropine, suggesting that an anticholinergic drug should be given routinely before induction of general anesthesia. Salivary and tracheobronchial mucus secretion further necessitates prophylactic administration of an antisialagogue agent. Glycopyrrolate, which does not penetrate the blood-brain barrier, was the rational choice in the present study.

The incidence of nausea and vomiting after laparoscopy has been reported to be as high as 42%, due to rapid peritoneal distension. Neurogenic pathways are also activated by traction reflexes and by splanchnic pressure and manipulation. Intravenous antiemetic such as ondansetron, often with dexamethasone, may be given preferably during surgery. Metoclopramide has also been shown to be an effective and safe antiemetic for both prevention and

treatment of postoperative nausea and vomiting.[13] In the present study, the metoclopramide was used as it acts both centrally and peripherally, speeds gastric emptying time, and increases the tone of the lower esophageal sphincter. Postoperative nausea and vomiting were not found in any group of our study.

The mechanism of shivering in patients recovering from anesthesia is poorly understood. Volatile anesthetic agents are commonly associated with altered temperature regulation. Regardless of its cause, shivering increases oxygen consumption and CO_2 production. The shivering may be abolished by a small dose of pethidine (25 mg i.v.). No patient of premedicated group showed any evidence of postoperative shivering, while 21 patients (9.5%) of control group suffered from shivering. Clonidine (1 μg/kg) may have prevented the postoperative shivering.[14] Supplemental oxygen therapy helps to prevent hypoxemia.

The procedure specific post operative pain management group[15] has provided the surgical and anesthetic management of laparoscopic cholecystectomy, following the realization that patients' outcomes can still be improved. This included adequate analgesia, which minimizes the metabolic stress and tissue damage by using small trocars, maintaining normothermia, preventing postoperative nausea and vomiting, administering adequate fluid intake, and insufflating the peritoneum with low-pressure carbon dioxide.

We studied patients up to 59 years as elderly patients take more often medications such as antidepressants, hypnotics, and antihypertensive, with increased sensitivity to drugs. The safety and effectiveness of pregabalin in pediatric patients below the age of 12 years and adolescents have not been established.

Preincisional analgesia has been shown to be more effective in control of postoperative pain by protecting the central nervous system from deleterious effects of noxious stimuli and resulting allodynia and increased pain. Within the context of an integrated approach, attempts have been recently made to introduce adjuvant with the intention to facilitate early recovery with decrease side effects related to opioids.

CONCLUSION

The pregabalin and clonidine are effective oral premedicant drugs with safe and multimodal drug profile as they cause sedation, anxiolysis, and analgesia, with successful attenuation of the deleterious hemodynamic response of laryngoscopy and laparoscopy. Both drugs have shown efficacy in decreasing the perioperative analgesic requirement. The hemodynamic stability, provided by oral premedication of pregabalin or clonidine, might enable laparoscopic cholecystectomy in obese, hypertensive, and cardiac compromised patients. As there was no postoperative respiratory depression, it may be used in asthmatic and airway compromised patients.

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