Original Article

Effectiveness of Oral Clonidine & Oral Gabapentin in Attenuation of Haemodynamic Stress Response to Laparoscopic Cholecystectomy

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Abstract:

Background: *In laparoscopic surgery, Carbondioxide (CO_2) is routinely used to create pneumoperitoneum. Elevated intra-abdominal pressure, due to pneumoperitoneum, and Carbondioxide (CO_2) insufflation have adverse effects on the cardiovascular system. Plasma level of catecholamines and vasopressin are increased immediately after pneumoperitoneum. Increased catecholamine level activates the renin–angiotensin–aldosterone system, leading to characteristic hemodynamic alterations such as decreased cardiac output, elevated arterial pressure and increased systemic/pulmonary vascular resistance. Various drugs have been used to attenuate these hemodynamic responses.*

Objectives*: Purpose of this study was to evaluate the efficacy of oral Clonidine and oral Gabapentin premedication in attenuation of haemodynamic stress responses to laparoscopic cholecystectomy.*

Setting & study design: *This Placebo control study was conducted in Department of Anaesthesiology and ICU, Dhaka Medical College Hospital from 1st March 2015 to 31st August 2015. Total 60 patients with ASA grade I, II and planned for elective laparoscopic cholecystectomy were selected. Exclusion criteria were patients with history of hypersensitivity to Clonidine, Gabapentin, and patients with chronic pain, history of cardiovascular, psychiatric disease, use of psychotropic drugs, pregnancy other comorbid condition- CKD, COPD, IHD etc. Study subjects were allocated in to groups as placebo or control group (or Group P), gabapentin (300 mg) or Group G and clonidine (100 ìg) or Group C. Tested drugs were given 75 to 90 minutes before surgery as oral premedication. All groups were compared for sedation, anxiety level along with changes of haemodynamic status.*

Result*: Majority of patients (40%) belongs to age 41 to 50 yrs. Out of 60 cases 55% were male and 45% were female. Male – female ratio was 1.22:1. A clear increase in sedation and a moderate decrease in anxiety were observed in both premedicated groups as compared with control groups. Preoperative anxiolysis and sedation was higher in oral clonidine group as compared with Gabapentin group. Compared with group P, gabapentin & clonidine group showed statistically significant decrease in heart rate before induction (98, 80, 74 beat/min respectively). The heart rate increased significantly immediately after intubation in control group P, whereas no such changes were observed in group G and in group C (132, 125, 112 beat/min respectively). After laparoscopy, the attenuation of mean arterial blood pressure in premedicated group was statistically significant as to control group (Group P) and remained stabilized during intraoperative period. Study showed that premedication (Group C and G) patients were comparatively well oriented and were able to obey commands than control (Group P) in the postoperative care unit. Postoperative analgesic need was much less with gabapentin (Group G) and clonidine group (Group C) as compared with control (Group P).*

Conclusion*: The gabapentin 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 hemodynamic response of laparoscopy. Efficacy of Clonidine is superior to other also proven.*

Key words: *Laparoscopic Cholecystectomy, Haemodynamic Stress Response, Oral Clonidine, Oral Gabapentin*

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Introduction:

Laparoscopic surgery has gained popularity over open conventional surgery as it offers benefits to both patients and health care practitioners. Advantages of laparoscopic cholecystectomy are shorter hospital stay, early ambulation, smaller scar, and less compromised postoperative respiratory and gastro-intestinal functions. However, the procedure is not risk free as it is associated with significant hemodynamic changes due to creation of pneumoperitoneum, potential for systemic absorption of carbon dioxide, and reverse Trendelenberg position. Pneumoperitoneum, Trendelenberg position in 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 be fatal in patients with hypertension and coronary artery disease[1]. Various pharmacological agents like nitroglycerine, ß blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum, but they have their own disadvantages. Gabapentin (GBP) is a second generation anticonvulsant and Clonidine, a á-$_2$ adrenergic receptor agonist commonly used for maintaining haemodynamic stability, has shown promising results for attenuation of hemodynamic response associated with laparoscopic surgery. However, there is a wide difference in the dose of such drug used by various authors and there is need for further studies to determine the minimum effective and safe dose in laparoscopic surgery.

Maintenance of intraoperative haemodynamic stability, any adverse events, postoperative nausea, vomiting (PONV), and pain continue to be a major challenge in the postoperative care. Many pharmacological techniques are being used to overcome haemodynamic alteration due to CO_2 pneumoperitoneum, such as deepening the anesthesia, pretreatment with vasodilators, adrenoreceptor blockers, calcium channel blocker, and opioids, with variable results[1], but there is still lack of ideal for this purpose. Clonidine and Gabapentin has been shown to have significant effects in maintenance of haemodynamic stability and PONV. Clonidine preserves heart rate control in pneumoperitoneum and recovery periods. Oral clonidine premedication also reduces the requirement for postoperative analgesia[2]. Gabapentin effectively suppresses nausea and vomiting and controls the neuro-endocrine factors by chemical agent in laparoscopic cholecystectomy and post-operative rescue analgesic requirement[3]. This study designed for evaluation of the effects of oral clonidine and gabapentin as premedication on haemodynamic stability.

The gabapentin and clonidine possesses several properties to make them valuable premedicants to attenuate the hemodynamic response of laryngoscopy and pneumoperitoneum. Gabapentin, 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. 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. another drug Clonidine activates the á$_2$ -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 ìg.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[1]. Previous study reported that Oral pregabalin provided a moderate level of anxiolysis and minimal sedation as compared to placebo[4]. Anti-hyperalgesic drugs such as gabapentin may have a role in postoperative pain, and the combination with other antinociceptive drugs may produce synergistic analgesic effect. Study found that both gabapentin and clonidine reduce postoperative pain and total morphine consumption. Gabapentin has been also reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs[5, 6, 7].

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[8] found that among the various component of haemodynamic stability, blood pressure & pulse pressure control is independently and significantly associated with postoperative outcome. Prevention and treatment of postoperative pain and PONV continue to be a major challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient. Gabapentin is an anticonvulsant that has anti-nociceptive and anti-hyperalgesic properties. In pain models it has shown anti-hyperalgesic properties, possibly by reducing central sensitization[9]. Clonidine, a á2 adrenergic agonist, has shown clinically useful drug profile due to its sympatholytic, hypnotic, sedative, anxiolytic, analgesic and anesthetic sparing effects without respiratory depression. In recent studies clonidine has shown attenuation of the pressor responses associated with laryngoscopy by reducing norepinephrine release[10]. Therefore present study was designed as prospective blind randomized controlled study to find out the efficacy of oral premedication with gabapentin or clonidine for changes in heart rate and mean arterial blood pressure during laryngoscopy and laparoscopy, along with perioperative hemodynamic stability.

Materials & Methods:

This study was conducted to evaluate the efficacy of oral clonidine and oral Gabapentin premedication in attenuation of haemodynamic stress responses to laparoscopic cholecystectomy. Total sixty (60) patients with ASA physical status I or II and planned for laparoscopic cholecystectomy were enrolled for study. Patients were allocated into three groups according to the premedication used. The patients randomly assigned to receive either 100 µgm oral clonidine (C group, n=20), 300mg gabapentin (G group, n=20), Placebo (P group, n=20). Drug was given by an independent anesthetist in the ward therefore both the anesthesiologist and the patient was blinded to the group assignment. All patients were anesthetized with the same technique. Demographic data, vital signs were recorded. Peroperative any complication- likes bleeding, hypotension, hypertension, tachycardia, bradycardia, oxygen saturation, urinary output was recorded.

Study Procedure:

On arrival in the operation theatre all patients were canulated with 18 gauge intravenous canula and patients pulse rate systolic blood pressure, diastolic blood pressure and peripheral oxygen saturation were noted down. Patient pre-oxygenated with 100% oxygen for 5 minutes, receiving Injection. Fentanyl (1.5 ìg /kg body weight, I.V. thiopental sodium (5 mg/kg body weight was given. Endotracheal intubation was facilitated with Inj. Succinylcholine 1.5 mg/kg body weight. Anesthesia was maintained with 0.5% Halothane, 66% Nitrous Oxide in Oxygen. Controlled ventilation was maintained for all study patients. Muscle relaxation was achieved with Inj. vecuronium (0.1mg/kg body weight). Intraoperative hydration was maintained with Ringer's lactate solution. Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted about 15% reverse Trendelenberg position. Intra-abdominal pressure was not allowed to exceed 15mm Hg throughout the surgical procedure. Throughout the procedure any rise in mean arterial pressure more than 20% from baseline was treated with 50 ìg I.V. nitroglycerine. Monitoring including systolic, diastolic, mean arterial pressure, pulse rate, SpO_2 were recorded at the following points of time-prior to intubation, 2 minutes after endotracheal intubation, before pneumoperitoneum, ten minutes after pneumoperitoneum, twenty minutes after pneumoperitoneum, ten minutes after release of carbon dioxide, ten minutes after extubation. At the end of surgery residual neuromuscular blockade was reversed by appropriate dose of neostigmine and atropine intravenously. After extubation patients were transferred to recovery room. Finally, occurrence of adverse effects such as nausea, vomiting, dizziness, hallucination, and allergic reactions was recorded in the postoperative period. In case of vomiting, ondansetron 4 mg was given intravenously.

Statistical analysis:

Statistical analysis of the data was done using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) software version 22. Qualitative data such as sex, ASA physical status,

adverse effects was compared using Chi-square test. Quantitative data such as age, numeric rating scales, time to first analgesic request and total analgesic requirement in 24 h will be compared using independent t-test. $P < 0.05$ will be taken as statistically significant. All collected questionnaire checked very carefully to identify the error in the data. Data processing work consist of registration schedules, editing computerization, preparation of dummy table, analyzing and matching of data.

Result & Observation:

Total of 60 patients fulfilling inclusion/exclusion criteria were studied. Results and observations are given below:

Table I *Demographic characteristics of the patients (n=60)*

Demographic variables	Group C (n=20)	Group G (n=20)	Group P (n=20)
Age (years)			
Mean ± SD	39.4 ±4.98	41.1 ±6.31	38.85±3.96
Range	(25-60)	(20-50)	(30-60)
Sex			
Male	10(50%)	12(60%)	11(55%)
Female	10(50%)	8(40%)	9(45%)

While studying the distribution of cases by age it was found that mean age was found to 39.4 ±4.98 years in Group C, 41.1 ±6.31 years in group G & 38.85±3.96 years in group P. Unpaired student's't'-test was employed to analyze the data and data were expressed as mean ± SD. No significant differences were found between groups with respect to age (Table I).

Table II *American Society of Anesthesiologist (ASA) physical status (n=60)*

ASA status	Group C (n=20)	Group G (n=20)	Group P (n=20)
ASA I	12(60%)	15(75%)	11(55%)
ASA II	8(40%)	5(25%)	9(45%)

All patients were with ASA physical status I and II (Table II). Group C received clonidine (100 ìg), among them 12(60%) were ASA I and 8(40%) were ASA II. Group G received gabapentin (300 mg), among them 15(75%) were ASA I and 5(25%) were ASA II. Group P received placebo, among them 11(55%) were ASA I and 9(45%) were ASA II. Medication given with sips of water about 75 to 90 minutes before induction of general anesthesia. The differences was statistically not significant between two group, p-value was 0.096 ($p>0.05$).

Heart rate alteration shows in figure 1. Maximum increase in heart rate from baseline was observed after intubation. The heart rate increased significantly immediately after intubation in control group P, whereas no such changes were observed in group G and in group C (132, 125, 112 beat/min respectively). During pneumoperitoneum, it increased by 20-30 beats/min in control (P group), while decrease in gabapentin (G group) by 5-10 beat/min and clonidine (C group) by 15-20 beat/min was observed. There was statistically significant attenuation of heart rate in premedicated groups. (Figure 1)

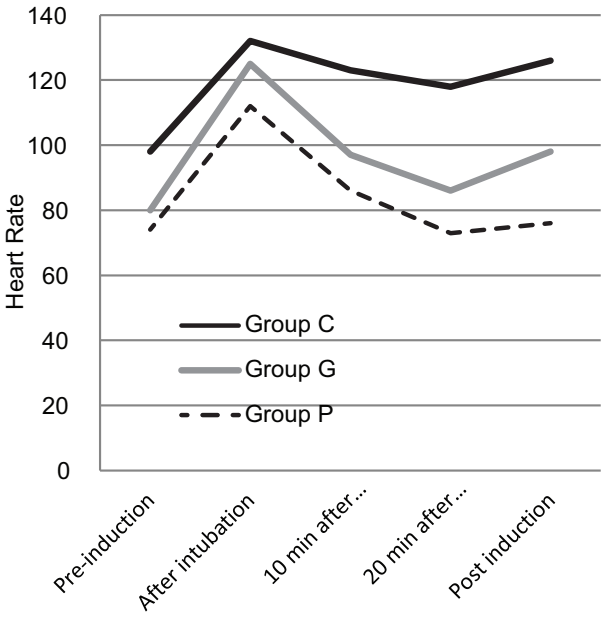

Figure 1 Heart rate alteration (n=60)

Table III
Changes of Mean arterial blood pressure (n=60)

	MBP (mmHg)		
	Group C (n=20)	Group G (n=20)	Group P (n=20)
Before induction	97.70+3.27	98.55+4.54	106.25+6.73
After intubation	98.45+3.28	99.20+4.47	109.10+12.47
10 min after pneumoperotoneum	85.05+6.39	91.85+6.03	103.oo+6.10
20 min after pneumoperotoneum	90.35+5.95	92.8+6.55	105+6.70
Post-extubation	88.15+6.59	94+5.08	102.45+5.88

The statistically significant differences were observed in the MAP at different times ($p<0.05$) pneumoperitoneum among groups (Table III).

Table IV *Evaluation of Post-operative pain and analgesic requirement (m=60)*

Variables	Group C	Group G	Group P
VAS Score			
0-3	19	16	0
4-6	1	4	2
7-10	0	0	18
Analgesic requirements			
NSAIDS	16	11	4
NSAIDS + Opids	3	5	9
Opids analgesic	1	4	7

VAS score >3 denotes moderate to severe pain. Patients in placebo and gabapentin groups experienced more pain than clonidine group during post-operative period. Postoperative analgesic need was much less with gabapentin (Group G) and clonidine group (Group C) as compared with control (Group P). Maximum number of Group C patients 16(80%) took NSAID for postoperative pain care (Table IV).

Discussion:

Total of 60 patients, 20 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 anesthesia, and surgical procedure time.

In our study, we have used oral premedication with gabapentin 300 mg or clonidine 100 ìg 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 possess several properties to make them valuable premedicants to attenuate the hemodynamic response of laparoscopy. Reid and Brace[11] first described the hemodynamic response to laryngoscopy and intubation, probably due to intense sympathetic discharges caused by stimulation of epipharynx and laryngopharynx. Shribman et al[12] reported that laryngoscopy and tracheal intubation increases arterial blood pressure, heart rate, and catecholamine levels, whereas Hassan et al.[13] 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.

In this study heart rate increased significantly immediately after intubation in control group P, whereas no such changes were observed in group G and in group C (132, 125, 112 beat/min respectively). During pneumoperitoneum, it increased by 20-30 beats/min in control (P group), while decrease in gabapentin (G group) by 5-10 beat/min and clonidine (C group) by 15-20 beat/min was observed. There was statistically significant attenuation of heart rate in premedicated groups. The heart rate decreased (125, 98, 76 beat/min respectively). In clonidine group, heart rate remained stabilized in comparison with group G and P.

Hayashi and Maze[14] and Sung et al. [15] reported that clonidine increases perioperative circulatory stability in patients undergoing laparoscopic cholecystectomy and potentiates parasympathetic nervous system. Laisalmi et al[16] concluded that premedication with clonidine blunts the stress response to surgical stimuli and reduces the requirement of narcotic and anesthetic doses.

Khan A et al reported that compared with control and pregabalin groups, clonidine group showed statistically significant decrease in heart rate before induction. Throughout anaesthesia there was statistically significant attenuation in the HR values when clonidine was compared with placebo and pregabalin. Similarly after laryngoscopy and intubation, there was statistically significant attenuation in the MAP values when clonidine was compared with placebo and pregabalin[4]. In this study no significant difference was observed in the MAP before premedication in groups. The attenuation of mean arterial blood pressure in premedicated group was statistically significant as to control group (Group P) and remained stabilized during intraoperative period.

Conclusions:

Present study concluded that oral premedication with gabapentin or clonidine provides better haemodynamic stability and analgesia in laparoscopic cholecystectomy, without prolongation of recovery time and side effects. Clonidines impersonate as superior to gabapentin for attenuation of the hemodynamic responses to laparoscopy. However, it may increase the incidence of intra-and postoperative bradycardia, but not significant. 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. therdore Clonidine or gabapentine can be used routinely.

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