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Role of intravenous Clonidine hydrochloride in attenuating hemodynamic response to laryngoscopy, endotracheal intubation and pneumoperitoneum in patients undergoing elective laparoscopic cholecystectomy

Sheikh Sadat, Tasaduq Javed, Feroz Ahmad Dar* and A.Q Lone

Department of Anesthesiology and Critical Care, SKIMS Medical College & Hospital, Srinagar, J&K, India

***Correspondence Info:**
Dr. Feroz Ahmad Dar
Resident,
Department of Anesthesiology and Critical Care,
SKIMS Medical College & Hospital, Srinagar, J&K, India
E-mail: drferozhabak21@gmail.com

Abstract

Objective: To evaluate the type and extent of hemodynamic changes associated with Laryngoscopy, Endotracheal intubation and Pneumoperitoneum in patients undergoing elective laparoscopic cholecystectomy, and to study the role of intravenous Clonidine Hydrochloride in attenuating hemodynamic response in these patients.

Methods: 100 adult patients of either sex, with ASA physical status I and age 20 – 50 years were randomly allocated to receive Inj. clonidine hydrochloride 3µg/kg diluted in 10 ml Normal saline (group 1) or 10 ml Normal saline as placebo (group 2) fifteen minutes prior to induction of general anesthesia. Study parameters including heart rate, blood pressure (systolic, diastolic, mean arterial pressure) and rate pressure product were monitored and recorded at various intervals during the procedure.

Results: Inter group comparison showed a highly significant rise ($p<0.001$) in heart rate in group 2 (placebo) during various interval compared to group 1 (clonidine group). Blood pressure (systolic, diastolic, mean arterial pressure) and rate pressure product followed a similar trend like heart rate in both groups and premedication with intravenous clonidine hydrochloride (3µg/kg) definitely attenuated the rise in these hemodynamic parameters during laryngoscopy, endotracheal intubation and pneumoperitoneum**.**

Conclusions: Clonidine premedication, unless contraindicated, may be made as a routine practice to attenuate hyperdynamic response to laryngoscopy, endotracheal intubation and pneumoperitoneum, particularly in patients where such changes are undesirable (ASA III & IV).

Keywords: Clonidine, Pneumoperitoneum, Premedication

1. Introduction

The term "Laparoscopy" is a Greek word meaning, to look into the flanks achieved through the abdominal wall after creation of pneumoperitoneum [1]. The first open cholecystectomy was performed in 1882 by Carl Langenbuch [2]. Over the next several decades there were little advances in the surgical technique. Cholecystectomies were generally painful, required five to seven days of hospital stay and prolonged period before patient could return to normal activity [3]. Undoubtedly the advent of laparoscopic approach to cholecystectomy revolutionized the treatment of biliary tract disease. In 1987 Philip Mauret claimed to have performed first laparoscopic cholecystectomy at Lyon, France [4].

Laparoscopy results in multiple postoperative benefits including less surgical trauma, less pain, less pulmonary dysfunction [5], quicker recovery, and shorter hospital stay [3]. A large body of literature exists to support the safety and efficacy of laparoscopy provided that the procedures are performed quickly (an average of <20 min in the gynecologic literature), the patients are otherwise young and healthy, the procedure is done in the head down (Trendelenburg) position, relatively low insufflation pressures are used (6-10 mmHg), and the procedure is performed under light general or local anesthesia.

Although providing many benefits, laparoscopic cholecystectomy has its own short

comings [6]. The pneumoperitoneum with carbondioxide [7] and patient position associated with laparoscopic cholecystectomy induces pathophysiological changes that complicate anesthetic management. Laparoscopic Cholecystectomies can be significantly longer procedures. It is performed on patients who frequently are older and may have other underlying chronic diseases or acute illnesses. Moreover it is performed in the head-up (reverse-Trendelenburg) position, with normal insufflation pressures of 15 mmHg or more. The hemodynamic and respiratory changes associated with laparoscopy could be quite detrimental, particularly in patients having compromised cardio-respiratory reserves [8].

Hemodynamic changes[9] associated with pneumoperitoneum include; Decrease in cardiac output, Increase in arterial pressure, Increase in systemic and pulmonary vascular resistance, Diminished hepatic, splanchnic, and renal blood flow, Release of renin and aldosterone, Sympathicomimetic response (release of vasopressin, adrenaline, and noradrenalin) and Renal vasoconstriction—urinary sodium retention and temporary renal tubular dysfunction. These adverse hemodynamic changes result from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia from the absorbed carbon dioxide. In addition to these pathophysiological changes, reflex increase of vagal tone and arrhythmias can also develop.

A number of strategies have been used to blunt these adverse hemodynamic changes associated with pneumoperitoneum and make laparoscopic cholecystectomy safer for the high risk patients. These include using drugs like alpha-2 agonists (clonidine[10], dexmedetomidine[11]), beta blockers[12] and ramifentanil[13], using low pressure pneumoperitoneum[14], or alternatively not using pneumoperitoneum at all such as in abdominal wall lift (AWL) method.

Laryngoscopy and endotracheal intubation are mandatory for most patients undergoing surgery under general anesthesia. These maneuvers are invariably associated with a number of hemodynamic changes like tachycardia [15], rise in blood pressure [16], wide range of arrhythmias, and even myocardial ischemia. These reflex changes are most marked immediately after laryngoscopy and endotracheal intubation. This technique forms an integral part of anesthesiologists' contribution to perioperative patient care and at the same time provides a patent and safe airway. Irritation of larynx due to laryngoscopy leads to sympathetic stimulation causing a rise in the plasma norepinephrine level.

Keeping in view the undesirable hemodynamic changes associated with laryngoscopy endotracheal intubation and pneumoperitoneum the present study was designed to evaluate the role of intravenous clonidine to attenuate such changes in patients undergoing elective laparoscopic cholecystectomy.

2. Method

The study was conducted in a prospective randomized double blind fashion in the Department of Anesthesiology and Critical Care, Sher-I-Kashmir Institute of Medical Sciences, Srinagar. After taking permission from the hospital ethical committee and written informed consent from patients, hundred adult patients of either sex with ASA physical status I, aged between 20 to 50 years, scheduled for elective laparoscopic cholecystectomy were taken for study and allocated randomly to one of the following two groups:

Group 1 (Clonidine Group): Comprised of fifty (50) patients who received clonidine hydrochloride 3µg/kg intravenously, diluted in 10ml of saline and given slowly, fifteen minutes prior to induction of general anesthesia.

Group 2 (Control Group): Comprising of fifty (50) patients who received 10ml normal saline intravenously slowly, fifteen minutes prior to induction of general anesthesia.

The study drug was coded and prepared by person incharge of operating room, who did not reveal the nature of solution to anybody and who also maintained details about each patient in a record register confidentially. Decoding was done at the end of the study and results obtained were tabulated and subjected to statistical analysis.

On arrival in reception area intravenous cannulation was established using 18 to 20G cannula and all patients were preloaded with 500ml crystalloid over a period of fifteen minutes. In the operating room, monitors were attached as a routine and for study purpose for ECG, heart rate, non invasive blood pressure and oxygen saturation. Patients received either study drug (clonidine hydrochloride 3µg/kg intravenously diluted in 10ml of normal saline) or placebo (10ml of normal saline) intravenously 15 minutes prior to induction of general anesthesia. Inj. glycopyrrolate 0.004 mg/kg iv, Inj. Morphine 0.1mg/kg iv, Inj. ondansetron 4mg iv were given before induction. Patients were pre-oxygenated with 100% oxygen for three minutes. General anesthesia was induced with sodium thiopentone 4-6 mg/kg until loss of eye lash reflex. Endotracheal intubation was facilitated with atracurium 0.5mg/kg. Following induction of anesthesia and endotracheal intubation, nasogastric tube was inserted. Anesthesia was maintained with 33% oxygen in nitrous oxide, 0.5 to

1% halothane and atracurium 0.1mg/kg every 25 minutes. The tidal volume (V_T) and the ventilator frequency were adjusted and intermittent positive pressure ventilation (IPPV) continued by mechanical ventilator to maintain end tidal carbon dioxide between 35-45 mm Hg. Pneumoperitoneum was created by insufflation of carbon dioxide, and operation table was tilted about 15^0 reverse-Trendelenburg position. Intra abdominal pressure (IAP) was not allowed to exceed 15mmHg throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator setting (tidal volume, respiratory rate) were made to maintain normocapnia.

The study parameters including heart rate (HR beats/minute), systolic blood pressure (SBP mmHg), diastolic blood pressure (DBP mmHg), mean arterial pressure (MAP mmHg) and rate pressure product (RPP= Systolic BP x Heart rate) were monitored and recorded at the following instances during the study period:-

- Two minutes prior to administration of study drug or placebo. This served as a control parameter for each patient (T0).
- At the time of laryngoscopy and endotracheal intubation (T1).
- Five minutes after endotracheal intubation (T2).
- Immediately following creation of pneumoperitoneum (T3).
- Fifteen minutes after pneumoperitoneum (T4).
- Immediately following release of pneumoperitoneum (T5).
- Fifteen minutes after release of pneumoperitoneum (T6).

At the end of surgery residual neuromuscular block was reversed by Inj. neostigmine 50µg/kg and Inj. glycopyrrolate 15µg/kg intravenously. After extubation patients were transferred to recovery room. In the post-anesthesia care unit (PACU) they were monitored for about one hour to watch for any evidence of complications or adverse events.

2.1 The exclusion criteria from study were as follows:-

Patients with history of cardio-respiratory disease (Ischemic heart disease, hypertension, aortic stenosis, left ventricular failure, AV-conduction block, COPD, Asthma) and diabetes mellitus, Predicted difficult intubation (Mallampati class III-IV or laryngoscopic grade III-IV), prolonged laryngoscopic time (more than 30second), patients intubated after more than one attempt at laryngoscopy, Patients concomitantly taking drugs like clonidine, methyl dopa, beta blocking drugs, benzodiazepines and MAO inhibitors, Patients who develop allergy to study drug (clonidine), and Patients requiring treatment for severe hemodynamic instability following administration of study drug.

Data were entered and analyzed with the Graph Pad.com (version 5, 2010). Data were presented as median (range), mean or frequencies, as appropriate. Nominal patient's characteristics and the duration of surgery were compared using the Fisher's exact test. A Bonferroni correction was applied for multiple two-way testing. In all categories $P<0.05$ was considered statistically significant. Pulse and blood pressure were compared using Multiple comparison test (Dennett test), q value >2.740 considered statistically significant (p value<0.05).

3. Results

The two groups were comparable with respect to age (p=0.523) and sex (p = 0.531) distribution. However female patients predominated over male patients in both groups.

Baseline heart rate (Figure 1) was comparable in both the groups. However intergroup analysis revealed a highly significant (p< 0.001) rise in heart rate in group 2 (Placebo group) compared to group 1 (Clonidine group) patients at all study stages from T1 to T5 (Table1).

Figure 1: Average Heart Rates in Clonidine and Placebo Groups

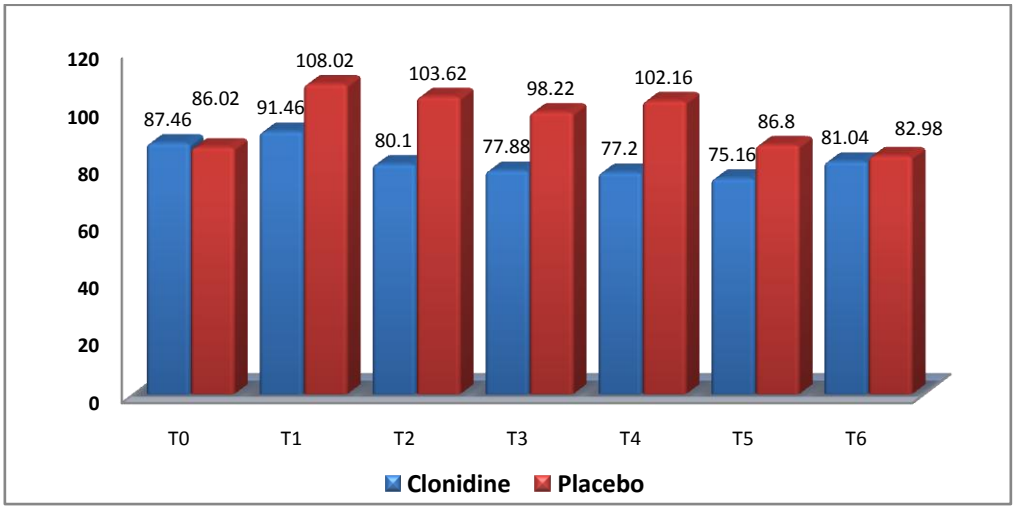


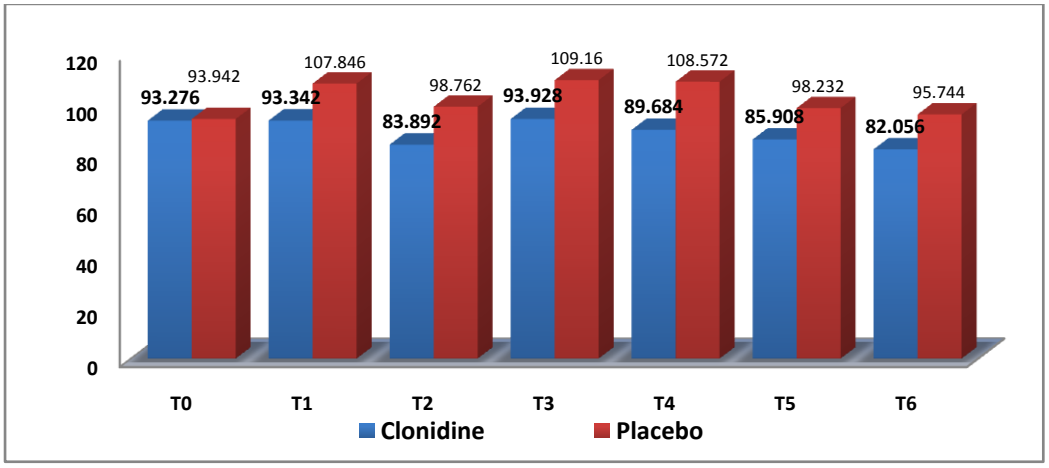
Table 1: Showing comparison of average heart rate between Group 1 (Clonidine) and Group 2 (Placebo) at different study intervals.

Study Time	Heart Rate (Beats/Minute)		P Value	Remarks
	Group 1 (Clonidine)	Group 2 (Placebo)		
T0 (Two minutes prior to administration of study drug)	87.46 ± 11.82	86.02 ±14.32	0.584	NS
T1 (At the time of laryngoscopy and intubation)	91.46 ± 11.93	108.02 ±8.68	< 0.001	HS
T2 (Five minutes after endotracheal intubation)	80.1 ± 10.25	103.62 ±7.20	< 0.001	HS
T3 (Immediately following creation of pneumoperitoneum)	77.88 ± 9.98	98.22 ± 8.39	< 0.001	HS
T4 (Fifteen minutes after pneumoperitoneum)	77.2 ± 9.66	102.16 ±7.91	< 0.001	HS
T5 (Immediately following release of pneumoperitoneum)	75.16 ± 9.70	86.8 ± 10.07	< 0.001	HS
T6 (Fifteen minutes after release of pneumoperitoneum)	81.04 ± 9.90	82.98 ± 9.21	0.3130	NS
HS= Highly Significant, NS= Not Significant				

But 15 minutes after release of the 'pneumoperitoneum (T6), the variation in heart rate was statistically insignificant. Intergroup comparison showed that baseline systolic blood pressures (T0) was comparable (p= 0.653) between the two groups. But there was a highly significant (p< 0.001) rise in systolic blood pressure in group 2 (Placebo group) compared to group 1 (clonidine group) patients at all study stages from T1 to T6. Systolic blood pressure showed an insignificant variation (p= 0.088) compared to baseline at the time of laryngoscopy and endotracheal intubation (T1), and immediately following the creation of pneumoperitoneum (T3) (p= 0.8123) in group 1 patients. However, at all other study stages there was a highly significant (p< 0.001) fall in systolic blood pressure compared to base line value. Systolic blood pressure in Group 2 patients (placebo group) showed a highly significant (p< 0.001) elevation compared to baseline (T0) at all study stages (T1- T4). However it started to return towards baseline following the release of pneumoperitoneum and was comparable to baseline value at T6 interval. Diastolic blood pressure in clonidine group showed that there was a significant (P=0.010) fall in diastolic pressure during laryngoscopy and intubation (T1). It decreased further at five minutes after endotracheal intubation (T2). However there was rise in diastolic blood pressure during creation of pneumoperitoneum (T3) but it was statistically insignificant (P=0.073) compared to base line value (T0). Thereafter there was further highly significant fall in diastolic pressures (P<0.001) till the end of the procedure (T6). In group 2 (placebo group) diastolic blood pressures showed a highly significant increase during laryngoscopy/intubation (T1) and pneumoperitoneum (T3) and remained so throughout the procedure (p< 0.001) compared to baseline values (T0). Intergroup comparison showed that baseline (T0) diastolic blood pressure was comparable (p= 0.744) between the two groups. But there was a highly significant (p< 0.001) rise in diastolic blood pressure in group 2 (Placebo group) compared to group 1 (Clonidine group) patients at all study stages from T1 to T6.

Mean arterial blood pressure (Figure 2) showed an insignificant variation (p=0.873) compared to baseline at the time of laryngoscopy and endotracheal intubation (T1), and immediately following the creation of pneumoperitoneum (T3) (p= 0.132) in group 1 patients. However, at all other study stages there was a highly significant (p< 0.001) fall in mean arterial pressure compared to base line value. Mean arterial pressure (MAP) showed a highly significant (p< 0.001) rise compared to baseline (T0) at all study stages (T1-T6) in group 2 patients (placebo group). Following release of pneumoperitoneum a drop in mean arterial pressure was seen in this group but still remained significantly elevated compared to baseline.

Figure 2: Comparison of Mean Arterial Pressures between Clonidine and Placebo Groups



Inter group analysis revealed that baseline (T0) mean arterial blood pressure was comparable between two groups (p=0.643). At all other study intervals (T1 –T6) mean arterial blood pressure remained highly significantly elevated (p< 0.001) in group 2 (Placebo group) compared to group 1 (Clonidine group) patients (Table 2).

Table 2: Showing comparison of mean arterial pressure between group 1 (Clonidine) and group 2 (Placebo), at different study intervals.

Study time	Mean Arterial Pressure (mmhg)		P Value	Remarks
	Group 1 (Clonidine)	Group 2 (Placebo)		
T0 (Two minutes prior to administration of study drug)	93.27 ± 7.77	93.94 ± 6.50	0.643	NS
T1(At the time of laryngoscopy and intubation)	93.342 ± 6.976	107.84 ± 5.24	< 0.001	HS
T2 (Five minutes after endotracheal intubation)	83.89 ± 6.92	98.76 ± 4.38	< 0.001	HS
T3 (Immediately following creation of pneumoperitoneum)	93.92 ± 6.74	109.16 ± 3.50	< 0.001	HS
T4 (Fifteen minutes after pneumoperitoneum)	89.68 ± 6.92	108.57 ± 3.29	< 0.001	HS
T5 (Immediately following release of pneumoperitoneum)	85.90 ± 6.42	98.23 ± 4.08	< 0.001	HS
T6(Fifteen minutes after release of pneumoperitoneum)	82.05 ± 5.82	95.74 ± 4.8	< 0.001	HS
HS= Highly Significant , NS= Not Significant				

In clonidine group rate pressure product showed a highly significant increase (p< 0.001) during laryngoscopy, intubation (T1). However, five minutes after laryngoscopy (T2) there was a fall in RPP compared to baseline (p < 0.001). During creation of pneumoperitoneum (T3) there was a slight rise in rate pressure product but it decreased subsequently. Thus rate pressure product was markedly lower (p< 0.001) than base line (T0) at all intervals (T2-T6) except during laryngoscopy (T1).

In Group 2 (placebo group) rate pressure product increased (p< 0.001) after laryngoscopy, intubation (T1) and remained elevated throughout the procedure. As the pneumoperitoneum was released (T5) it started to decrease and was comparable to baseline value (p= 0.713).

Inter group analysis revealed that baseline (T0) rate pressure product was comparable between two groups (p = 0.436). At all other study intervals (T1 – T6) rate pressure product remained highly significantly elevated (p< 0.001) in Group 2 (placebo group) compared to Group 1 (clonidine group).

4. Discussion

Direct laryngoscopy and pneumoperitoneum during laparoscopic surgery invariantly leads to tachycardia and hypertension [6] which is usually transient and variable. Usually, these changes are well tolerated by healthy patients but may be fatal in patients with ischaemic heart disease [10].

Pneumoperitoneum during laparoscopy produces significant hemodynamic changes, which can be detrimental, especially in elderly and thermodynamically compromised patients [10]. Pneumoperitoneum used for laparoscopic procedures is a complex pathophysiological phase. Carbon dioxide is the most commonly used agent to create pneumoperitoneum as it is colorless, non combustible, highly soluble and permeable in tissues, thus reducing the risk of gas embolism. The hemodynamic changes associated with pneumoperitoneum are the result of both increased intra-abdominal pressure and hypercarbia [7,9].

After the beginning of pneumoperitoneum, there is marked increase of vasopressin[18] levels in blood. Plasma concentrations of epinephrine, norepinephrine and renin also increase during laparoscopy[17]. To attenuate these hemodynamic responses, a wide variety of agents are being used, both during premedication and induction.

Hemodynamic responses to laryngoscopy and laparoscopy should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage[18]. 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[19], and systemic blood pressure[20] can increase from 36% to 45% which may be due to imbalance in sympathetic and parasympathetic outflow or receptor hypersensitivity. Anxiety, an unpleasant emotion, is another factor to adversely influence the anesthetic induction and patient recovery.

The safety margin of Clonidine to attenuate the hemodynomic response is ideal for its use in anesthesia. Clonidine acts as an agonist at pre-synaptic alpha-2 receptors in the nucleus tractus solitarius of the medulla oblongata [21]. Stimulation of these receptors results in the suppression of efferent sympathetic pathways and the subsequent decrease in blood pressure and vascular tone in heart, kidneys, and peripheral vasculature.

Clonidine, an imidazoline derivative is a selective alpha-2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased systemic vascular resistance and cardiac output. Clonidine has been used in various dose ranges through various routes (from 2 to 5µg /kg) in different studies [22,23].

In group 1 (clonidine group) heart rate showed a statistically significant change from baseline at various study intervals. Heart rate showed a highly significant ($p< 0.001$) rise at the time of laryngoscopy and endotracheal intubation (T1) compared to baseline value (T0) in this group. Subsequently there was a persistent and significant ($p< 0.001$) fall in heart rate compared to baseline values till immediate release of pneumoperitoneum (T5). However, fifteen minutes after release of pneumoperitoneum (T6) heart rate showed an increase compared to other intraoperative values (T1-T5), but was significantly lower ($p< 0.001$) than the base line values (T0).

In placebo group (group 2) there was a highly significant rise ($p< 0.001$) in heart rate above the base line (T0) value right from laryngoscopy (T1) upto 15 minutes after pneumoperitoneum (T1-T4). However, immediately following the release of pneumoperitoneum (T5); heart rate returned to baseline value (T0), and at 15 minutes after the release of pneumoperitoneum (T6) the rate was still below the baseline (82.98 ± 9.21 at T6 compared to 86.02 ± 14.32 at T0). However this variation was statistically insignificant ($p= 0.052$).

Inter group analysis revealed that baseline heart rate (T0) was comparable between two groups but showed a highly significant rise in placebo group during laryngoscopy and endotracheal intubation (T1), and at the time of creation of pneumoperitoneum (T3,T4) compared to the clonidine group. However, the difference in heart rates was statistically insignificant at fifteen minutes (T6) after release of pneumoperitoneum ($p= 0.313$) i.e. towards the end of procedure.

Similar results were obtained by Laisalmi M *et al*[21](2001). They found that hemodynamic responses to the onset of the pneumoperitoneum were effectively attenuated by the use of intramuscular clonidine (4.5µg/kg). They also showed an increase in heart rate lasting three hours postoperatively in the control group. With clonidine, this deleterious hemodynamic stress response was blunted. Aho M *et al*[24] (1990) used clonidine in doses of 3µg/kg and 4.5µg/kg. A significant increase in heart rate was observed at 5 and 10 minutes after induction of anesthesia, despite using a higher dose of clonidine. Our observation also showed a significant increase in heart rate in both groups at the time of laryngoscopy (T1). Similar to our study, Aho *et al*[24](1990) reported a decrease in heart rate compared to baseline in clonidine group, and persistence of increased heart rate in placebo group. Das M *et al*[31] (2007) in their study entitled "Hemodynamic changes during laparoscopic cholecystectomy: effect of clonidine premedication." found that oral clonidine effectively blunted the hemodynamic response to laryngoscopy and pneumoperitoneum.

Systolic blood pressure in group 1 patients showed an insignificant elevation at the time of laryngoscopy and endotracheal intubation (T1) and immediately following pneumoperitoneum (T3) compared to baseline. However, at other study stages i.e. T2, T4, T5 and T6 there was a highly significant ($p<0.001$) decrease in systolic blood pressure as compared to the baseline control value (T0).

In group 2 systolic blood pressure showed a highly significant ($p< 0.001$) increase during laryngoscopy and intubation (T1). Subsequently there was a fall in systolic blood pressure at T2, but still remained on higher level compared to base line. With beginning of pneumoperitoneum (T3) blood pressure again showed a highly significant increase ($p< 0.001$) and remained elevated throughout the procedure. It returned towards baseline only at the end of procedure (T6). So compared to base line value, there was a significant rise in blood pressure at all study intervals, except for 15 minutes post deflation of pneumoperitoneum (T6). Inter group analysis revealed that baseline systolic blood pressure (T0) was comparable between two groups ($p=0.653$), but showed a highly significant rise ($p<0.001$) in placebo group during laryngoscopy and intubation (T1) and at the time of pneumoperitoneum (T3) compared to clonidine group. It was observed that systolic blood pressure decreased below baseline in clonidine group at all intervals after laryngoscopy and intubation (T1) whereas systolic blood pressure in placebo group was always above the baseline reading. The difference between two groups at respective intervals was statistically significant.

Kalra *et al*[25](2011) and Tripathi *et al*[26](2011) both used two different doses of intravenous clonidine (1µg/kg, 1.5µg/kg and 1µg/kg, 2µg/kg respectively) to attenuate the hemodynamic response to laryngoscopy and pneumoperitoneum in patients undergoing laparoscopic cholecystectomy, and found a higher dose to be much better at attenuating the hemodynamic response. Kalra *et al*[25](2011) found clonidine 1.5µg/kg dose better than 1µg/kg clonidine or 50mg/kg of magnesium sulfate in attenuating stress response to laryngoscopy and pneumoperitoneum. Our study showed similar results, though we used clonidine in the doses of 3µg/kg. Aho M *et al*[24](1990) used clonidine for prevention of hemodynamic responses associated with laparoscopic surgery. They also used two different doses of clonidine (3µg/kg and 4.5µg/kg) but found a higher incidence of hypotension and bradycardia with higher dose. Diastolic blood pressure in group 1 patients showed a persistent and highly significant fall ($p<0.001$) at all study stages compared to baseline,

except at the creation of pneumoperitoneum (T3) when it revealed an insignificant rise (p=0.073).

Diastolic blood pressure analysis in placebo group showed that there was a significant rise (p<0.001) in diastolic blood pressure at all study intervals (T1-T6) compared to base line value (T0). Inter group analysis revealed that baseline diastolic blood pressure was comparable between two groups but showed a highly significant (p< 0.001) rise in placebo group during laryngoscopy and intubation (T1) and at the time of pneumoperitoneum (T2) compared to clonidine group. Diastolic blood pressure remained significantly elevated at all other intervals in placebo group when compared to clonidine group (p<0.001) at corresponding intervals. But the maximal increase in diastolic blood pressure was at the time of laryngoscopy/intubation (T1) and creation of pneumoperitoneum (T3).

Chandrashekaraiah *et al* [27](2011) observed a fall in diastolic blood pressure after clonidine premedication, as was found in our study. They found that diastolic blood pressure remained lower than baseline in clonidine group at all intervals, implying that clonidine very effectively blunted the adverse hemodynamic response associated with pneumoperitoneum, whereas in placebo group diastolic blood pressure was not effectively controlled. Our results were in harmony with Chandrashekaraiah *et al* [27](2007), although we observed an increase in diastolic blood pressure post pneumoperitoneum in clonidine group. However, it was statistically insignificant (p=0.073). Similar findings were reported by Das M *et al*[31] (2007).

Inter group analysis revealed that baseline MAP was comparable between two groups. Both groups showed an increase in MAP on laryngoscopy, but it was insignificant (p=0.873) in clonidine group, but highly significant (p<0.001) in placebo group. Again on creation of pneumoperitoneum, both groups showed a rise in MAP, but it was statistically insignificant in clonidine group, but highly significant (p<0.001) in placebo group. MAP remained significantly elevated at all other intervals in placebo group when compared to clonidine group from T1 – T6 (p<0.001).

Yu *et al* [28](2003) and Chandrashekaraiah *et al*[27](2011) used clonidine 150µg preoperatively to study the hemodynamic response to pneumoperitoneum associated with laparoscopic cholecystectomy and found it to be effective in attenuating hemodynamic response to pneumoperitoneum. Gupta K *et al*[29](2011) studied role of oral premedication with pregabalin 150mg or clonidine 200µg for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy and observed that intraoperative 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. Our results were also similar to their findings.

Inter group analysis revealed that baseline rate pressure product was comparable between two groups but showed a highly significant rise (p< 0.001) in placebo group during all study intervals compared to clonidine group.

Gobel F L *et al*[30](1978) evaluated the hemodynamic predictors of myocardial oxygen consumption and found rate pressure product as a good indicator of myocardial oxygen consumption in normotensive patients with ischemic heart disease. Intravenous clonidine premedication in our study significantly (p<0.001) lowered the rate pressure product during laryngoscopy (T1) and pneumoperitoneum (T3). Rate pressure product increase during laryngoscopy and intubation has been observed in various studies.

5. Conclusion

It is therefore suggested that clonidine premedication, unless contraindicated, may be made as a routine practice to attenuate hyperdynamic response to laryngoscopy, endotracheal intubation and pneumoperitoneum, particularly in patients where such changes are undesirable. However, further scientific work and research in this field is mandatory.

References

[1] Black TE. Anaesthesia for laparoscopic-assisted surgery. In: Healy EJ, Cohen PJ. *A practice of Anaesthesia. 6th ed. Manchester: Arnold Press.* 2000;139

[2] Beal J M. Historical perspective of gallstone disease. *Surg Gynecol Obstet.* 1984 Feb; 158(2): 181-91-96.

[3] Berggren U, Gordh T. Laparoscopic versus open cholecystectomy: Hospitalization, sick leave, analgesia and trauma responses. *British Journal of Surgery*. 1994:81(9); 1362–1365.

[4] Grzegorz S. Litynski. Mouret, Dubois, and Perissat: The Laparoscopic Breakthrough in Europe (1987-1988). *Journal of the Society of Laparoendoscopic Surgeons*. 1999; 3(2): 163–167.

[5] Williams MD, Sulentich SM, Murr PC. Laparoscopic cholecystectomy produces less postoperative restriction of pulmonary function than open cholecystectomy. *Surg Endosc* 1993; 7:489-492.

[6] Mclaughlin J G, Scheeres D E, Dean R J *et al.* The adverse hemodynamic effects of laparoscopic cholecystectomy. *Surg Endosc* 1995; 9:121-124.

[7] Talwar N, Pusuluri R, Arora MP, Pawar M *et al.* Randomized Controlled Trial of Conventional

Carbon Dioxide Pneumoperitoneum versus Gasless Technique for Laparoscopic Cholecystectomy. *JK Science* 2006:8(2):73-78.

[8] Safran D, Sgambati S, Orlando R. Laparoscopy in high-risk cardiac patients. *Surg Gynecol Obstet.* 1993; 176(6): 548-54.

[9] Joris *et al*. Hemodynamics During Laparoscopy. *Anesth Analg 1993; 76:1067-71.*

[10] Bhandari D, Tidke S. Hemodynamic changes associated with laparoscopic cholecystectomy: effect of oral clonidine premedication. *IOSR Journal of Pharmacy*, 2012:2(4): 72-77.

[11] Pekka T *et al*. The Hemodynamic and Adrenergic Effects of Perioperative Dexmedetomidine Infusion after Vascular Surgery. *Anesth Analg* 2000; 90:834–839.

[12] Koivusalo AM et al. Effects of esmolol on haemodynamic response to carbomdioxide pneumoperitoneum for laparoscopic surgery. *Acta Anaesthesiol Scand.* 1998;42(5):510-517

[13] Safavi M, and Azim H. Attenuation of cardiovascular responses to laryngoscopy and tracheal intubation - intravenous sufentanil vs pethidine. *M.E.J. Anesth.* 2008; 19 (6):1349-1360.

[14] Dexter S P L, Vucevic M *et al*. Hemodynamic consequences of high and low-pressure capnoperitoneum during laparoscopic cholecystectomy. *Surg Endosc* 1999: 13: 376–381.

[15] Kim SH, Kim YJ, Kim JR, Park KW. The Effect of Endotracheal Intabation and Extubation on the Blood Pressure and Heart Rate. *Korean J Anesthesiol*. 1981:14(4):383-395.

[16] Forbes AM, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *Br J Anaesth.* 1970; 42(7):618-24.

[17] Joris J L, Chiche J D *et al*. Hemodynamic changes induced by laparoscopy and their endocrine correlates: effects of clonidine. *J Am Coll Cardiol* 1998; 32:1389 –96.

[18] Unni VK, Johnston RA, Young HS, Mcbride RJ. Prevention of intracranial hypertension during laryngoscopy and endotracheal intubation. Use of a second dose of thiopentone. *Br J Anaesth.* 1984; 56(11):1219-23.

[19] Malde A D, Sarode V. Attenuation of the hemodynamic response to endotracheal intubation: Fentanyl Versus Lignocaine. *The Internet Journal of Anesthesiology.* 2007; 12:1.

[20] Malde A D, Sarode V. Attenuation of the hemodynamic response to endotracheal intubation: Fentanyl Versus Lignocaine. *The Internet Journal of Anesthesiology.* 2007; 12:1.

[21] M. Laisalmi, Koivusalo AM *et al*. Clonidine provides opioid-sparing effect, stable hemodynamics, and renal integrity during laparoscopic cholecystectomy. *Surg Endosc* 2001; 15: 1331–1335.

[22] Yu HP, Hseu SS *et al.* Oral clonidine premedication preserves heart rate variability for patients undergoing larparoscopic cholecystectomy. *Acta Anaesthesiol Scand.* 2003; 47(2):185-90.

[23] Kalra NK, Verma A *et al*. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. *J Anaesthesiol Clin Pharmacol.* 2011: 27(3): 344–348.

[24] Aho M *et al*. Effects of intramuscular clonidine on hemodynamic and plasma beta endorphin response to gynecological laparoscopy. *Anesthesiology* 1990; 72: 797-802.

[25] Kalra NK, Verma A *et al*. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. *J Anaesthesiol Clin Pharmacol.* 2011: 27(3): 344–348.

[26] Tripathi DC, Komal S *et al*. Hemodynamic stress response during laparoscopic cholecystectomy: Effect of two different doses of intravenous clonidine premedication. *J Anaesthesiol Clin Pharmacol.* 2011:27(4): 475–480.

[27] Chandrashekaraiah MM, Upadya M, Jayachandran SP, Wali M. Effects of clonidine premedication on hemodynamic changes during laparoscopic cholecystectomy – a randomized control study. *Applied Cardiopulmonary Pathophysiology* 15: 91-98, 2011.

[28] Yu HP, Hseu SS *et al.* Oral clonidine premedication preserves heart rate variability for patients undergoing larparoscopic cholecystectomy. *Acta Anaesthesiol Scand.* 2003; 47(2):185-90.

[29] Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation. *Saudi J Anaesth.* 2011; 5(2): 179–184.

[30] Gobel F L, Norstrom L A *et al*. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation.* 1978; 57: 549-556.

[31] Das M, Ray M, Mukherjee G. Haemodynamic changes during laparoscopic cholecystectomy: effect of clonidine premedication. *Indian Journal of Anaesthesia* 2007; 51 (3): 205-210.