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A Comparative Analysis of Perioperative Hemodynamic Stability with Dexmedetomidine and Clonidine Infusions in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Background: *The present study has been conducted to compare the beneficial effect of the two alpha 2 agonists Clonidine and Dexmedetomidine in maintaining the perioperative hemodynamic parameters during laparoscopic cholecystectomy.* ***Methods:*** *The present Double-Blind Randomized Control Trial was conducted in the Department of Anesthesiology, Prathima Institute of Medical Sciences, Naganoor, Karimnagar under general anesthesia. A total of n=45 patients randomly allocated in three groups, Group I (Placebo group), Group II (Clonidine Group) and Group III (Dexmedetomidine Group) of n=15 patients each, undergoing elective laparoscopic cholecystectomy, under general anesthesia were studied. The patients received preloaded and coded study drugs as infusion Normal Saline, Clonidine 4µg/kg/hr and Dexmedetomidine 0.4µg/kg/hr respectively at the rate of 0.08ml/kg/hr.* ***Results:*** *Sex, age, weight and duration of surgery were comparable in all the three groups. Both the drugs, Clonidine and Dexmedetomidine, maintained cardiovascular stability during laparoscopic cholecystectomy. But clonidine appears more effective in maintaining perioperative cardiovascular system stability during laparoscopic cholecystectomy. Besides, the isoflurane requirement in Clonidine Group and Dexmedetomidine Group was found to be considerably lower when compared to the Placebo Group. Also, the mean recovery time as indicated by the ability to vocalize the following extubation was found to be significantly less in Clonidine Group and Dexmedetomidine Group.* ***Conclusion:*** *Clonidine being more cost-effective than Clonidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy.*

Keywords*: Clonidine, Dexmedetomidine, Haemodynamic parameters, Laparoscopy cholecystectomy.*

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Introduction

Hemodynamic stability during the perioperative period is of paramount importance as many patients may have a compromised cardiovascular status. Critical events during a peri-operative period like induction, intubation, and surgical stimulus initiate a metabolic response to trauma that needs to be considered and attended. In recent years the laparoscopic surgeries which once upon a time were considered to cause least trauma are reported to have hemodynamic instability [1]. The traditional approach to anesthesia for laparoscopic cholecystectomy has been the emphasis on maintaining hemodynamic stability by avoiding hypertension, hypotension or tachycardia. Numerous agents and a combination of agents have been used to minimize the hemodynamic instability during this period. Volatile agents like isoflurane and sevoflurane have been used with limited success in maintaining hemodynamic stability as volatile agents decrease surgical stimulus-induced catecholamine secretion [2]. The hemodynamic response during general anesthesia is

traditionally blunted by the use of opioids however; they are not able to eliminate peri-operative stress response. General anesthesia has been supplemented on occasions with intra-operative infusions of Propofol due to its intrinsic ability to inhibit catecholamine secretion, infusions of Nitroglycerine or Beta-blockers, to control peri-operative stress. Laparoscopic surgeries require the creation of pneumoperitoneum (PNP) which is produced by insufflations of Carbon Dioxide CO_2. Problems encountered during laparoscopic surgeries result from the combined effects of PNP with the insufflation of carbon dioxide and patient positioning [3]. There is a moderate increase in Intra Abdominal pressures which raises cardiac output and means arterial pressure [4]. As intra-abdominal pressures raise circulating blood volume falls as venous return decreases and there is a fall in cardiac output. This fall in cardiac output is troublesome in hypovolemic patients and patients receiving anesthetic agents with cardiac depressant effects.

Clonidine is an alpha 2 adrenergic agonist is a centrally acting selective partial alpha 2 agonists. It is known to induce sedation, decrease anesthetic drug requirement and improve peri-operative hemodynamics by attenuating blood pressure and heart rate responses to surgical stimulation, and protection against peri-operative myocardial ischemia. It provides sympathoadrenal stability and suppresses renin-angiotensin activity [5]. Dexmedetomidine is seven to ten times more selective for alpha 2 receptors compared to Clonidine and has a shorter duration of action. Dexmedetomidine is considered a full agonist at alpha 2 receptors as compared to Clonidine which is considered as a partial agonist. Similar to Clonidine, Dexmedetomidine also attenuates the hemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anesthesia and decreases peri-operative requirements of inhaled anesthetics [6]. With this background, we in the present study tried to evaluate the efficacy of Dexmedetomidine versus Clonidine on Cardiovascular System stability in patients undergoing Laparoscopic Cholecystectomy.

Materials and Methods

The present study was conducted in the Department of Anesthesiology, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. The study design was a double-blind randomized control trial. Institutional Ethical committee permission was obtained for the study. Written consent was obtained from all the participants of the study. Inclusion criteria all the patients undergoing elective laparoscopic cholecystectomy, patients ASA Grade I and II, age group between 20 to 60 years. Exclusion criteria: patients with known allergy to drugs, patients with IHD, patients with valvular heart diseases, hypertensive patients on beta-blockers, patients on MAO inhibitors, emergency laparoscopic cholecystectomy. Based on the computer-generated randomization, patients were randomly allocated to three groups as below. Group I (Placebo Group n=15 Received normal saline), Group II (Clonidine group n=15), Received 4 mcg/kg/hr of Inj Clonidine in 0.9% normal saline, Group III (Dexmedetomidine group n=15), Received 0.4 mcg/kg/hr of Inj Dexmedetomidine in 0.9% normal saline. A thorough pre-anesthetic evaluation was performed by taking history and clinical examination and recorded on predesigned and pretested proforma.

In all patients, age, weight, height, SBP, DBP, and HR were recorded. Two IV lines were secured, one 20 G IV cannula in the right hand for the infusion and another 18 G IV cannula in the left hand for Intravenous fluids and drug administration. 500 ml of crystalloids (Ringer Lactate) was started. HR, MAP, and SpO_2 using pulse oximeter were monitored before, during and after the surgery. End Tidal Carbon Dioxide was monitored intra-operatively and kept between 25 to 30 mmHg. The study drug in the prefilled coded 50 ml Syringe was started 30 minutes before induction using infusion pump at the rate of 0.08 ml/kg body weight /hour and the code number of the study drug Syringe was noted down in the proforma. After shifting to operating room monitors, ECG, NIBP and Pulse Oximeter were attached. Patients were pre-medicated with Inj Midazolam 0.05mg/kg, Inj Fentanyl 1.5 µg/kg followed by pre-oxygenation for three minutes. Induced with Propofol 2mg/kg, muscle relaxation was facilitated with

Inj Vecuronium 0.1 mg/kg. Patients were intubated using an appropriate size endotracheal tube and maintained on O_2: N_2O (30:70) and Isoflurane 1% was started. Throughout the procedure any 20% rise in MAP above the basal MAP, Isoflurane concentration was increased to maintain the basal MAP. For fall in MAP of more than 20% of basal MAP, Isoflurane was stopped. Heart rate less than 50 bpm was treated with atropine 0.6 mg intravenous. The MAP and HR were recorded at various intervals from preoperative session Preoperative (M1), 10 min after starting Study Drug Infusion (M2), At Induction(M3), After intubation (M4), before Pneumoperitoneum (M5), 10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8), Then every 30 min till end of surgery, End of Pneumoperitoneum N1), After Reversal (N2), Postoperative in Recovery room (N3), Study drug infusion was discontinued at the end of pneumoperitoneum. After surgery patients were reversed with Inj. Glycopyrrolate 0.01 mg/kg and Inj. Neostigmine 0.05mg/kg. Patients were extubated and time to recovery was measured, recovery is defined as the time to vocalize after extubation. At the end of the study, the data were decoded and analysis was done as per the analysis plan. The recorded data was then analyzed with statistical software SSPS version 17.0 on windows platform. The level of significance of p values was <0.05.

Results

The average age in Group I (Placebo Group) was 47.23 years, in Group II (Clonidine Group) was 44.93 years and Group III (Dexmedetomidine Group) was 45.93years. The average weight in Group I (Placebo Group) was 59.47Kg, in Group II (Clonidine Group) was 63.60 Kg and Group III (Dexmedetomidine Group) was 53.80 Kg, the other demographic details are given in table 1.

Table 1: Demographic details

	Group I Mean ± SD	**Group II Mean ± SD**	**Group III Mean ± SD**	***p* values**
Age in years	43.27 ± 13.14	44.93 ± 8.16	45.93 ± 11.20	0.800
Weight in Kgs	59.47 ± 8.57	63.60 ± 4.96	53.80 ± 7.31	0.057
Duration of surgery	68.13 ± 12.38	83.47 ± 27.67	79.53 ± 19.89	0.127

Table 2: Heart rate recording at various time intervals

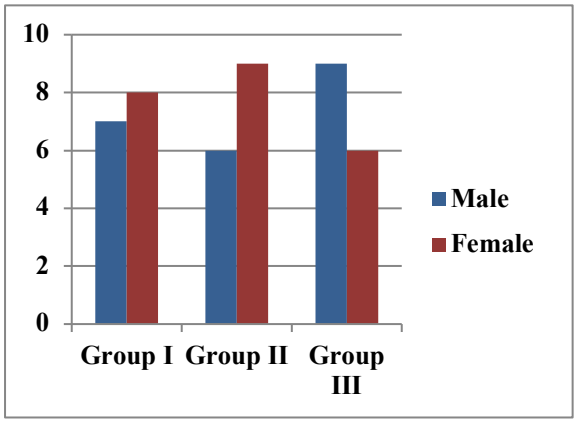
Heart Rate	**Group I**	**Group II**	**Group III**
M1	88.13 ±13.88	77.87 ±8.03	87.73 ±16.35
M2	86.27 ±12.49	81.00 ±12.07	86.80 ±14.99
M3	87.73 ±16.05	77.47 ±13.13	84.00 ±15.73
M4	108.47 ±17.35*	81.60 ±10.40	87.00 ±19.65
M5	93.67 ±15.50*	73.47 ±12.56*	81.07 ±19.18
M6	90.87 ±12.55*	69.73 ±11.55*	83.57 ±22.38
M7	90.87 ±12.55*	69.73 ±11.55*	83.57 ±22.38
M8	94.20 ±14.25	69.80 ±11.35	80.93 ±20.62
N1	83.00 ±11.10	67.53 ±12.22*	82.93 ±18.73
N2	102.93 ±10.52	80.60 ±8.83*	97.64 ±19.02
N3	86.40 ±10.45*	67.93 ±9.87*	76.29 ±16.43

* P values <0.05 hence significant

Heart rate in Group I (placebo group) increased significantly when compared to Group II (Clonidine group), after intubation (M4), before pneumoperitoneum (M5), 10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8), end of pneumoperitoneum (N1), after reversal (N2) and postoperatively in recovery (N3) (p=<0.05) Group I (Placebo Group) and Group III (Dexmedetomidine Group) No statistically difference in heart rate was found between the two groups except after intubation (M4) (p<0.05), when heart rate increased significantly

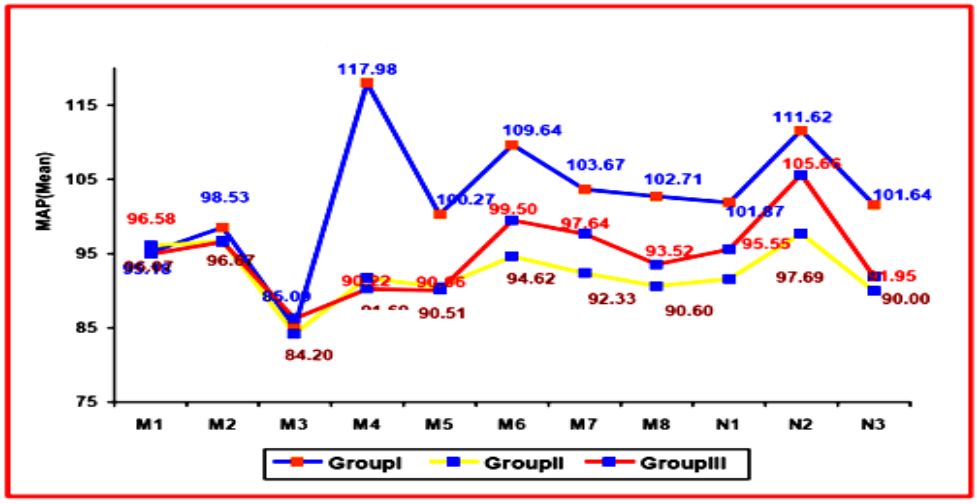
in Group I (Placebo Group) compared to Group III (Dexmedetomidine Group) Group II (Clonidine Group) and Group III (Dexmedetomidine Group) The decrease in heart rate appeared more in Group II (Clonidine Group) at all intervals when compared to Group III (Dexmedetomidine Group) but the decrease was found to be statistically significant only at end of pneumoperitoneum (N1) and after reversal (N2) ($p<0.05$) when heart rate was found to be more in Group III (Dexmedetomidine group).

Chart 1: Sex-wise distribution



Group I (Placebo Group) and Group II (Clonidine Group) Mean arterial pressure (MAP) in Group I (Placebo Group) were significantly higher after intubation (M4), 10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8), end of pneumoperitoneum (N1), after reversal (N2) and postoperatively in recovery (N3) ($p<0.05$)

Chart 2: Mean Arterial Pressure (MAP)



compared to Group II (Clonidine group). Group I (Placebo Group) and Group III (Dexmedetomidine Group), Mean Arterial Pressure (MAP) in Group I (Placebo Group) were significantly higher after intubation (M4) and postoperatively in recovery(N3) ($p=<0.05$) compared to Group III (Dexmedetomidine group) Group II (Clonidine Group) and Group III (Dexmedetomidine Group) There was no statistically significant difference in MAP between two groups. MAP between the two groups was found to be comparable (chart 2).

Ability to vocalize following extubation was significantly prolonged in Group I (Placebo Group) when compared to Group II (Clonidine Group) and Group III(Dexmedetomidine group).There was no significant difference in the recovery profile between Group II (Clonidine Group) and Group III (Dexmedetomidine group).All the patients in group I required 1 to 1.5% isoflurane during the intraoperative period whereas 26.67% of patients in group II and 33.33% patient in group III required isoflurane 1 to 1.5% isoflurane during the intraoperative period. In this study atropine requirement was found in 20% of the patients (3/15) in group II whereas, 6.67% patients (1/15) required atropine in group III.

Table 3: Drug requirements

Drug requirements	Group I	Group II	Group III
Isoflurane (1-1.5%)	15 (100%)	4 (26.67%)	5 (33.33%)
Atropine 0.6mg IV	0(0%)	3 (20%)	1(6.67%)

Discussion

Intra-operative hypertension and tachycardia are common hemodynamic instabilities encountered in patients undergoing laparoscopic cholecystectomy. Increased systemic vascular resistance with decreased cardiac output and metabolic changes are also observed [7]. Pharmacological interventions to reduce the incidence of hemodynamic instabilities without undesirable side effects are therefore needed. We in the present study used Dexmedetomidine and Clonidine infusions on hemodynamic stability in patients undergoing Laparoscopic Cholecystectomy. The results of this study were found a statistically significant change between Placebo (Group I) and Clonidine (Group III) groups as regards to heart rate after laryngoscopy and intubation (M4), before pneumoperitoneum (M5), 10 min after pneumoperitoneum (M6) and throughout the period of pneumoperitoneum i.e. 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8). At the end of pneumoperitoneum (N1), after the reversal (N2), and post-operative in recovery (N3) the change in Heart Rate [HR] was found to be significant. When the Dexmedetomidine group (Group III) was compared to Placebo Group (Group I) the heart rate and Mean Arterial Blood Pressure was found to be statistically significant only after laryngoscopy and intubation time (M4) and postoperative in recovery (N3) and not at other intervals. The decrease in heart rate appeared more in the Clonidine group at all intervals when compared to the Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4), at end of pneumoperitoneum (N1), and after the reversal (N2). Similarly, the fall in mean arterial pressure appeared more in the Clonidine group at all intervals when compared to the Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4) and during postoperative period in recovery (N3). Taittonen T et al; [8] found Clonidine 4 µg/Kg and Dexmedetomidine 2.5 µg/Kg were given 40-50 min before the anticipated induction of anesthesia and it was found that heart rate and mean arterial pressure were found to be lower in Clonidine and Dexmedetomidine group when compared to a placebo group. The findings of this study are in agreement with the results of the present study. In our study, we found that heart rate and mean arterial pressure were significantly lower in the Clonidine group when compared to the saline group and the Dexmedetomidine group. A study by Ghignone M et al; [9] found the intra-operative fluctuation in both Heart rate and Blood pressure to less than 20% of the pre-induction values, and also blunted the cardiovascular response to intubation effectively, in patients receiving Clonidine 5 µg/Kg orally 90 minutes before induction. They found the heart rate and mean systolic and diastolic blood pressure consistently lower in the Clonidine group when compared to the control group during the intra-operative period. In our study too we have found similar results. Hall JE et al; [10]compared the dose-response relationship for one-hour infusions of Clonidine 1, 2, and 4 µg/Kg/hr and placebo. Mean arterial pressure had increased by 10% over the baseline in the placebo group and mean arterial pressure decreased by 13% of the baseline in Clonidine 4 µg/Kg/hr. In our study, the placebo group the mean arterial pressure raised by 15% above the baseline mins after starting the infusion and decrease in mean arterial blood pressure was found to be 6.2%. JorrisJL et al; [7] found that Pneumoperitoneum results in an increase in MAP, SVR, and PVR and a decrease in cardiac output. The increase in SVR is associated with a marked release of vasopressin and catecholamines. Clonidine given before pneumoperitoneum reduces the release of catecholamines and provides intra-operative hemodynamic stability Clonidine before the creation of pneumoperitoneum reduces catecholamine release thus significantly attenuated the increase in mean arterial pressure and heart rate in comparison to placebo. Prevention of tachycardia, slowing of the heart rate and preventing hypertension is probably due to a complex mechanism. Centrally the activation of alpha 2 adrenoreceptors cause a reduction in peripheral sympathetic tone and an increase of vagally induced reflex bradycardia and peripherally it causes stimulation of presynaptic alpha 2 adrenoreceptors and which leads to the diminished release of nor-

epinephrine from the nerve endings towards the vasculature and reducing the peripheral sympathetic tone towards the heart [11]. Clonidine, therefore, serves as an effective and specific regimen to blunt the cardiovascular response. In our study, we found that in the Dexmedetomidine group (Group III), the heart rate and mean arterial pressure remained similar to the pre-operative values during the pneumoperitoneum thus indicating the hemodynamic stability during pneumoperitoneum with Dexmedetomidine when compared to Placebo group. Further studies need to be conducted with a larger sample size to corroborate the findings of this study, which may enlighten further the usefulness of two alpha 2 agonists in the anesthetic management of Laparoscopic Cholecystectomy.

Conclusion

Clonidine and Dexmedetomidine were able to maintain cardiovascular stability during laparoscopic cholecystectomy. But Clonidine appears more effective in maintaining perioperative cardiovascular system stability furthermore Clonidine is more cost-effective than Dexmedetomidine. Hence Clonidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy.

Conflict of Interest: *None declared*
Source of Support: *Nil*
Ethical Permission: *Obtained*

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