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COMPARISON OF DEXMEDETOMIDINE AND CLONIDINE INFUSION ON HAEMODYNAMIC STABILITY OF PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY- A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

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KEYWORDS :

INTRODUCTION

Haemodynamic stability during perioperative period is of paramount importance as there are many patients who have a compromised cardiovascular status and are on medication. Critical events during perioperative period like induction, intubation and surgical stimulus initiate metabolic response to trauma that need 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 haemodynamic instability.

The anaesthesiologist's traditional approach to anaesthesia for laparoscopic cholecystectomy has been the emphasis on the maintaining haemodynamic stability by avoiding hypertension, hypotension or tachycardia.

The problem has been more complex than has been originally thought and most of the haemodynamic instability is persistent during the duration of Pneumoperitoneum (PNP) namely Carbon Dioxide (CO_2) insufflations.Numerous agents and combination of agents has been used in an effort to minimize the haemodynamic instability during this period. Volatile agents like isoflurane and sevoflurane[1] have been used with limited success in maintaining haemodynamic stability as volatile agents decrease surgical stimulus induced catecholamine secretion. Opiods have traditionally been used for blunting the perioperative stress response during general anaesthesia. Although general anaesthesia prevents haemodynamic instability by rendering patients insensate to pain of surgery and discomfort, it is unable to completely eliminate theperioperative stress response.General anaesthesia has been supplemented on occasions with intraoperative infusions of Propofol due to its intrinsic ability to inhibit catecholamine secretion, infusions of Nitro glycerine or Beta blockers, to control preioperative stress. Again combined general anaesthesia with epidural anaesthesia[2] is yet another strategy employed by anaesthesiologists to control perioperative haemodynamic instability, with limited success. But the search for the ideal agent to control this instability in haemodynamics is still on Laparoscopic surgeries require creation of pneumoperitoneum (PNP) which is produced by insufflations of Carbon Dioxide (CO_2) in the abdominal cavity by using automated flow controlled Carbon Dioxide Insufflator which supply gas till the required intrabdominal pressure is reached. Inflation pressure can be varied from 0 – 30 mm Hg where as the total gas flow volume can be set from 0 – 9.9 L/min.Problems encountered during laparoscopic surgeries result from the combined effects of PNP with insufflations of carbon dioxide and patient positioning[3].

After creation of PNP, Intra abdominal pressure increases along with the increase in circulating blood volume which is due to shifting of blood from the splanchnic capacitance blood vessel. Also, there is moderate increase in Intra Abdominal pressure which raises cardiac output and mean arterial pressure[4]. As abdominal pressures rises circulating blood volume falls as venous return and there is a fall in cardiac output.

This fall in cardiac output is troublesome in hypovolemic patients and patients receiving anaesthetic agents with cardiac depressant effects. Laparoscopy induces significant haemodynamic changes and leads to increased Systemic Vascular Resistance (SVR) and Pulmonary Vascular Resistance (PVR), increases in Mean Arterial Pressure (MAP), reduction in Stroke Volume, Cardiac Output, and the mechanism is mechanically and humoral Mediated[5].Alpha 2 Agonists produce diverse responses, including analgesia, anxiolysis, sedation, and sympatholysis, each of which has been reported in the treatment of surgical and chronic pain patients and in panic disorders as well. Recently, the Food and Drug Administration registered two novel alpha 2- adrenergic agonists Clonidine and Dexmedetomidine[6].Clonidine with a elimination half life of 6 to 10 hours is a centrally acting selective partial alpha 2 agonist (220:1 alpha 2 to alpha 1). It is known to induce sedation, decrease anaesthetic drug requirement and improve perioperative haemodynamics by attenuating blood pressure and heart rate responses to surgical stimulation, and protection against perioperative myocardial ischaemia.It provides sympathoadrenal stability and suppresses renin angiotensin activity.

There are studies indicating benefits of using Clonidine for maintenance of haemodynamic stability in laparoscopic cholecystectomy.

Dexmedetomidine with a elimination half life of two to three hours is a highly selective and potent and specific alpha 2 agonist (1620 : 1 alpha 2 to alpha1), and is seven to ten times more selective for alpha 2 receptors compared to Clonidine, and has a shorter duration of action.

Dexmedtomidine is considered full agonist at alpha 2 receptors as compared to Clonidine which is considered as a partial agonist. Similar to Clonidine, Dexmedetomidine, also attenuates the haemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anaesthesia and decreases perioperative requirements of inhaled anaesthetics[7].

As Laparoscopic Cholecystectomy is a routinely performed surgery,

it is desirable to have a stable intraoperative haemodynamic status. Hence in this study, it has been attempted to compare the beneficial effect of the two alpha 2 agonists Clonidine and Dexmedetomidine in maintaining the perioperative parameters like MAP, Heart Rate (HR).

AIMS AND OBJECTIVES

To compare the efficacy of Dexmedetomidine versus Clonidine on Cardiovascular System stability in patients undergoing Laparoscopic Cholecytectomy.

MATERIAL AND METHODS

The present study was conducted in the Department of Anaesthesiology, NIMS Medical College & Super Speciality Hospital, Jaipur during the period of January 2013 to August 2014..

Study Design

Study design was Double Blind Randomized Control Trial.

Study period

The present study was conducted between December 2012 to August 2014.

Place

This study was carried out at Department of Anaesthesiology, NIMS Medical College & Super Speciality Hospital, Jaipur.

Source of Data

Patients undergoing elective laparoscopic cholecystectomy, under general anaesthesia during the study period.

Sample Size

A sample size of 30 patients each, randomly allocated in three groups using computerized randomization.

Selection Criteria

Inclusion

1. ASA Grade I and II.
2. Age between 20 to 60 years

Exclusion

1. Patient refusal.
2. Patient with known allergy to drug.
3. Patients with IHD, valvular heart diseases.
4. Hypertensive patients on treatment with Beta Blockers, Methyl Dopa, MAO inhibitors.
5. Patients with Renal dysfunction.
6. Patients with elevated AST, ALT values.
7. Pregnant and lactating patient.

Randomization

Based on the computer generated randomization, patients were randomly allocated to three group as below.

- Group I (Placebo group; n=30) - Received normal saline
- Group II (Clonidine group; n=30) – Received 4 mcg/kg/hr of Inj Clonidine in 0.9% normal saline
- Group III (Dexmedetomidine group; n=30) – Received 0.4 mcg/kg/hr of Inj Dexmedetomidine in 0.9% normal saline.

Methodology

The ethical clearance for the study was obtained from the Institutional Ethics Committee, NIMS Medical College, Jaipur. Patients undergoing elective laparoscopic cholecystectomy, under general anaesthesia were screened for the eligibility. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anaesthetic procedure. A written informed consent was obtained from the patient. A thorough pre-anaesthetic 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. Patients were randomized according to the computer generated randomization procedure.The study drug was provided as prefilled and coded identical 50 ml syringes containing study drugs, as per the randomization protocol, in dilutions of:

1. Normal saline 0.9% - 20 ml
2. Clonidine – 20 ml (50 mcg/ml)
3. Dexmedetomidine 20 ml (5 mcg/ml)

The doses of Clonidine and Dexmedetomidine were intended to be equipotent. All prefilling, coding and decoding was done in the Department of Clinical Pharmacy. The investigators involved in the study did not knew about the content of the syringes. Patients were explained about the study, but did not know which drug was used. The study drug prefilled and coded Syringes were obtained from the Clinical Pharmacy on the day of the surgery. Two IV line were secured, one 20 G IV canula in right hand for the infusion and another 18 G IV canula in 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 intraoperatively and kept between 25 to 30 mm of Hg. The study drug in the prefilled coded 50 ml Syringe was started 30 minute 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 premedicated with Inj Midazolam 0.05mg/kg, Inj Fentanyl 1.5 mcg/kg followed by preoxygenation for three minutes. Induced with Propofol 2 mg/kg, muscle relaxation was facilitated with Inj Vecuron 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.

Mean arterial pressure and HR was measured at;

- 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 being 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.

Statistical analysis

Data was expressed as mean and standard deviation (SD). The homogenecity in three groups of mean and SD was analysed using SSPS version 17.0, one way analysis of variance for each parameter. Scheffe's test is used to compare pair wise data. Tables of mean and standard deviation were prepared for meaningful comparison of the three groups. A p value of less than or equal to 0.05 was considered as significant.

RESULTS

A comparative study between dexmedetomidine and clonidine was done for assessing the cardiovascular system stability on 90 patients undergoing elective laparoscopic cholecystectomy at NIMS Medical College & Super Speciality Hospital during the period of January 2013 to August 2014 under general anaesthesia. The results were noted

Table 1. Patient characteristics

Characteristics	Group I	Group II	Group III	'p' value
Age (years)	43.27+/- 13.14	44.93+/- 8.16	45.93+/-11.20	0.800
Weight (kg)	59.47+/- 8.57	59.27+/-4.96	53.80+/-7.31	0.057
Duration of Surgery (min.)	68.13+/- 12.38	83.47+/-27.67	79.53+/-19.89	**0.127**

Table 2. Sex distribution

Sex	Group I	Group II	Group III
Female	14(46.67%)	12(40%)	18 (60%)
Male	16 (53.33%)	18(60%)	12(40%)

Table 3. Heart rate

Time interval	Group I	Group II	Group III	' P' value
M1	88.13+/- 13.88	77.87 +/- 8.03	87.73 +/- 16.35	0.936
M2	86.27 +/- 12.49	81.00 +/- 12.07	86.80 +/- 14.99	0.423
M3	87.73 +/- 16.05	77.47 +/- 13.13	84.00 +/- 15.73	0.179
M4	108.47 +/- 17.35	81.60 +/- 10.40	87.00 +/- 19.65	0.0001
M5	93.67 +/- 15.50	73.47 +/- 12.56	81.07 +/- 19.18	0.005
M6	90.87 +/- 12.55	69.73 +/- 11.55	83.57 +/- 22.38	0.004
M7	90.87 +/- 12.55	69.73 +/- 11.55	83.57 +/- 22.38	0.003
M8	94.20 +/- 14.25	69.80 +/- 11.35	80.93 +/- 20.62	0.001
N1	83.00 +/- 11.10	67.53 +/- 12.22	82.93 +/- 18.73	0.006
N2	102.93 +/- 10.52	80.60 +/- 8.83	97.64 +/- 19.02	0.0002
N3	86.40 +/- 10.45	67.93 +/- 9.87	76.29 +/- 16.43	**0.001**

Table 4. Mean arterial pressure

Time interval	Group I	Group II	Group III	'P' value
M1	95.18 +/- 8.65	96.07 +/- 9.47	94.91 +/- 8.67	0.936
M2	98.53 +/- 8.36	96.67 +/- 7.52	96.58 +/- 8.86	0.779
M3	85.09 +/- 11.64	84.20 +/- 9.44	86.20 +/- 8.39	0.860
M4	117.98 +/-14.03	91.69 +/- 10.97	90.22 +/- 8.94	0.0001
M5	100.27 +/- 18.52	90.51 +/- 12.70	90.06 +/- 12.86	0.209
M6	109.64 +/- 12.03	94.62 +/- 11.08	99.50 +/- 17.05	0.014
M7	103.67 +/- 6.82	92.33 +/- 9.32	97.64 +/- 16.34	0.034
M8	102.71 +/- 8.93	90.60 +/- 10.25	93.52 +/- 11.87	0.007
N1	101.87 +/- 6.15	91.60 +/- 10.15	95.55 +/- 13.01	0.025
N2	111.62 +/- 8.70	97.69 +/- 7.23	105.66 +/- 14.22	0.003
N3	101.64 +/- 8.26	90.00 +/- 6.19	91.95 +/- 11.08	0.001

Table 5. Recovery time following extubation

Time (min)	Group I	Group II	Group III	'p' value
Ability to vocalize following extubation	6.8 +/- 2.40	2.67 +/- 0.98	3.46 +/- 2.03	< 0.0001

Table 5. Recovery time following extubation

Time (min)	Group I	Group II	Group III	'p' value
Ability to vocalize following extubation	6.8 +/- 2.40	2.67 +/- 0.98	3.46 +/- 2.03	< 0.0001

Table 7. Use of Atropine (0.6 mg IV)

Drugs	Group I	Group II	Group III
Atropine	0.(0%)	6(20%)	2 (6.67%)

DISCUSSION

Intraoperative hypertension and tachycardia are common hemodynamic disturbances in patients undergoing laparoscopic cholecystectomy. In addition there is increase in systemic vascular resistance, and is associated with a decrease in cardiac index and metabolic changes. Various studies have been conducted with various pharmacological interventions that results in reduced incidence of tachycardia, hypertension during laparoscopic cholecystectomy and provide a stable haemodynamic state, without significant undesirable effects. In our study we compared the efficacy of Dexmedetomidine and Clonidine infusions on haemodynamic stability in patients undergoing Laparoscopic Cholecystectomy.

We 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 end of pneumoperitoneum (N1), after reversal (N2), and post operative in recovery (N3) the change in heart rate were found to be significant. As regards to mean arterial blood pressure statistically significant changes were found between Placebo (Group I) and Clonidine (Group III) groups similar to heart rate changes viz after laryngoscopy and intubation (M4),10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8). Again at end of pneumoperitoneum (N1), and after reversal (N2) the changes were found to be significant. When Dexmedetomidine group (Group III) was compared to Placebo Group (Group I) the heart rate and mean arterial blood pressure were found to be statistically significant only after laryngoscopy and intubation (M4) and post operative in recovery (N3) and not at other intervals. The decrease in heart rate appeared more in Clonidine group at all intervals when compared to Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4), at end of pneumoperitoneum (N1), and after reversal (N2). Similarly the fall in mean arterial pressure appeared more in Clonidine group at all intervals when compared to Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4), and during post operative period in recovery (N3).

Taittonen T, Kirvela OA, et al[1] conducted a study in 1997 Clonidine 4 mcg/kg and Dexmedetomidine 2.5 mcg/kg were given 40-50 min before the anticipated induction of anaesthesia and it was found that heart rate and mean arterial pressure were found to be lower in Clonidine and Dexmedetomidine group when compared to placebo group. In our study we found that heart rate and mean arterial pressure were significantly lower in the Clonidine group when compared to saline group than the Dexmedetomidine group. We used a lower dose of Dexmedetomidine.

Aantaa R Jaakola ML, et al[2] conducted a study in 1997 found the intraoperative 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 mcg/kg orally 90 minute before induction. They found the heart rate and mean systolic and diastolic blood pressure consistently lower in Clonidine group when compared to control group during the intraoperative period. In our study too we found similar results.

Hall JE, Uhrich TD, Ebert TJ [3] conducted a study in 2001 compared the dose response relationship for one hour infusions of Clonidine 1, 2, and 4 mcg/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 4mcg/kg/hr. In our study also in the placebo group the mean arterial pressure raised by 15 % above the baseline 60 mins after starting the infusion and decrease in mean arterial blood pressure was found to be 6.2%.

Jorris JL[4] conducted a study in 1998 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 intraoperative hemodynamic stability Clonidine before creation of pneumoperitoneum, reduces catecholamine release thus significantly attenuated the increase in mean arterial pressure and heart rate in

comparison to placebo in a study where patients received 8 mcg/kg Clonidine infused over one hour before pneumoperitoneum. It was intended to study the propensity of Clonidine to modulate the haemodynamic changes during laparoscopic cholecystectomy. We had used a dose of 4 mcg/kg/hr of Clonidine and our findings are correlated by this study.

The effect of 150 mcg of oral Clonidine 90 min prior to induction in patients undergoing laparoscopic cholecystectomy was studied with placebo and found that the perioperative mean arterial blood pressure and heart rate were significantly lower in Clonidine group at all time points. Our results are also similar to the above said study.

Laisalmi M, Koivusalo AM, et al[5] conducted a study in 2001 and compared in healthy individuals undergoing laparoscopic cholecystectomy who received intramuscular Clonidine 4.5 mcg/kg or saline preoperatively, the heart rate and arterial blood pressure were lower during and after pneumoperitoneum in patients who received Clonidine, consistent with the findings of our study. 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 diminished release of norepinephrine from the nerve endings towards the vasculature and reducing the peripheral sympathetic tone towards the heart. Clonidine therefore serves as a 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 value during the pneumoperitoneum thus indicating the haemodynamic stability during pneumoperitoneum with Dexmedetomidine when compared to Placebo group.

However statistically significant difference was found only during laryngoscopy and intubation (M4)

Tufanogullari B, White PF,et al [6] conducted a study in 2008: compared three infusion doses of Dexmedetomidine 0.2, 0.4 and 0.8 mcg/kg/hr with saline in morbidly obese patients undergoing Laparoscopic Bariatric surgery. Mean arterial blood pressure values were maintained within ±25% of the preinduction baseline values by varying the inspired Desflurane concentration. It was found that intraoperative hemodynamic values were similar in the four groups, arterial blood pressure values were significantly reduced in the Dex 0.2, 0.4, and 0.8 groups compared with the control group on admission to the postanesthesia care unit (PACU) ($p<0.05$). In our study also, the mean arterial pressure in Dexmedetomidine group was significantly less in PACU ($p<0.05$).

Bhattacharjee DP, Nayak SK,et al [7] conducted a study in 2010 showed the effects of Dexmedetomidine infusion (0.2 mcg/kg/hour) for haemodynamic stability in patients undergoing laparoscopic cholecystectomy and found that mean arterial pressure and heart rate in Dexmedetomidine group were significantly less after intubation and throughout the period of pneumoperitoneum. We found similar result only after intubation but there was no statistically significant difference during the period of pneumoperitoneum between the Dexmedetomidine and saline group. It appears that Dexmedetomidine group maintained mean arterial blood pressure and heart rate throughout the pneumoperitoneum without additional isoflurane requirement, whereas in saline group, higher MAC values of isoflurane were required to control 20% rise above pre operative values. Mean recovery time as indicated by ability to vocalize following extubation was found to be significantly less in both Dexmedetomidine (Group III) and Clonidine (Group II) groups in our study as there was a reduction in isoflurane requirement in the two groups as compared to Placebo group. Isoflurane was used in 4 of 15 patients (23%) in Clonidine group, 5 of 15 patients (33%) in Dexmedetomidine group and in all the patients (100%) in the saline group. A reduction of isoflurane requirement was observed in our study. The patients required significantly lower concentrations of isoflurane in Clonidine and Dexmedetomidine group. Our findings were in accordance with other studies, in which there was decrease in MAC and inhalational agent requirement[8].

Delayed recovery in Placebo group compared to Clonidine and Dexmedetomidine group appears to be due to higher consumption of Isoflurane. Atropine was used in 3 out of 15 patients (20% patients) in Clonidine group, 1 out of 15 patients (6.67% patients) in Dexmedetomidine group, when the heart rate decreased to less than 50 per minute. Previous studies[9] demonstrated severe bradycardia associated with Clonidine administration. Even Dexmedetomidine required atropine in some studies[10].In one patient receiving Dexmedetomidine infusion, the ECG rhythm became irregular and the infusion was stopped. We did not perform intra group comparisons between time intervals, which can be the limitation of the study. Further studies need to be conducted with a larger sample size to corroborate the findings of this study, which mayenlighten further the usefulness of two alpha 2 agonists in the anaesthetic management of Laparoscopic Cholecystectomy.

CONCLUSION

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. In addition Clonidine being more cost effective than Dexmedetomidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy

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