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Comparison Of The Effects Of Intravenously Administered Dexmedetomidine With Clonidine On Hemodynamic Responses During Laparoscopic Cholecystectomy.

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ABSTRACT

Clonidine, a selective alpha-2 adrenergic agonist, and dexmedetomidine, a new generation highly selective alpha-2 adrenoreceptor agonist, are well known to inhibit catecholamine release. The present study compares the effects of intravenously administered clonidine versus dexmedetomidine to attenuate hemodynamic responses to pneumoperitoneum during laparoscopic cholecystectomy under general anesthesia.60 patients of ASA physical status I and II, aged between 18 to 50 years, of either sex. Scheduled for elective laparoscopic cholecystectomy were randomized into 3 groups (Group C, D, and K) in a double-blind fashion, to receive either clonidine 1 µg/kg in normal saline, dexmedetomidine 1 µg/kg in normal saline or normal saline IV respectively. The total volume of the study drug was adjusted to 50 ml and administered 15 minutes before induction. Following pneumoperitoneum, a significant rise in heart rate and arterial pressure was observed in group K. Patients in group D showed the best control of arterial pressure. No significant episodes of hypotension were found in any group. Administration of clonidine or dexmedetomidine attenuates the hemodynamic response to pneumoperitoneum, dexmedetomidine being more effective in this regard.

Keywords: Clonidine; Dexmedetomidine; Laparoscopic cholecystectomy; Hemodynamic response; Pneumoperitoneum.

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INTRODUCTION

Laparoscopy has now become the standard technique of choice for cholecystectomy. The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide (CO_2) [1, 2]. The pneumoperitoneum results in pathophysiological changes characterized by an increase in arterial pressure and systemic and pulmonary vascular resistance (SVR and PVR) early after the beginning of intra-abdominal insufflation with little change in heart rate (HR) [1-3]. A 10% to 30% reduction in cardiac output has been reported in most studies [3]. Severe increases in arterial pressure can be a risk factor for adverse cardiologic events in patients with pre-existing essential hypertension, ischemic cardiac disease, or increased intracranial or intra-ocular pressure [4]. Problems encountered during laparoscopic surgeries may result from the combined effects of pneumoperitoneum and patient positioning [5].

Hypercapnia and pneumoperitoneum cause stimulation of the sympathetic nervous system causing catecholamine and vasopressin release [6]. Different pharmacological agents like α_2 adrenergic agonists1, beta-blockers [7], and opioids [8] are often used to attenuate circulatory response due to pneumoperitoneum. Clonidine is a selective α_2 adrenergic agonist that causes a fall in the heart rate and blood pressure with decreased systemic vascular resistance and cardiac output [9]. Dexmedetomidine is a highly selective, potent, and specific α_2 agonist with a shorter duration of action [10].

The present study was designed in a prospective, randomized, double-blind fashion to compare the efficacy of intravenously administered clonidine versus dexmedetomidine in attenuation of hemodynamic responses during laparoscopic cholecystectomy. The secondary objective was to study the side effects associated with these drugs.

METHODOLOGY

The study was conducted in the year 2024 at the Department Of Anesthesiology & Critical Care, Sri Lalithambigai Medical College And Hospital, Adayalampattu, Maduravoyal, Chennai, Tamil Nadu, India.60 ASA physical status I and II patients aged between 18 to 50 years of both sexes scheduled for elective laparoscopic cholecystectomy were enrolled in the study. Power calculations suggested that a minimum of 16 subjects per group was required to detect a 10% difference in arterial pressure between groups (taking type I or α error of 5%, type II or β error of 20%, and Standard Deviation=10). To be on the safer side, 20 patients were included in each group (n=20). Patients with any degree of heart block, pre-existing hypertension, cardiovascular, hepatic, or renal disease, allergies to the drugs used, or acute cholecystitis as well as pregnant ladies and lactating mothers were excluded from the study. Patients concomitantly taking clonidine, methyl-dopa, beta-blocking drugs, benzodiazepines, and MAO inhibitors, patients in whom surgery could not be completed laparoscopically, and open cholecystectomy had to be performed were also excluded from the study. Patients who showed exaggerated hypertensive responses (taken as systolic BP > 160 mmHg or diastolic BP > 100 mmHg) during surgery were administered nitroglycerine infusion. Patients were admitted one day before the scheduled surgery and examined, interviewed, and written consent taken. No hypnotic medication was given on the evening before surgery. Patients were premedicated with glycopyrrolate 0.02 mg/kg in the preoperative room. Upon arrival in the operating room, monitors were attached and baseline parameters, e.g. heart rate, NIBP, oxygen saturation, and ECG, were recorded. Immediately before induction, patients were randomly divided into three equal groups (n=20) using sealed envelopes chosen by the patients. The groups were;

- Control group (group K) – received 50 ml of normal saline.
- Clonidine group (group C) – received clonidine 1 µg/ kg in normal saline.
- The dexmedetomidine group (group D) – received dexmedetomidine 1 µg/kg in normal saline.

The total volume of the study drug was adjusted to 50 ml and administered over 15 min before induction. The preparation, labeling, and administration of the study drugs were performed by an anesthesiologist who was not directly involved in this study. After pre-oxygenation for 3 minutes, anesthesia was induced with a standard anesthetic protocol using midazolam 0.05 mg/kg, fentanyl 1 µg/kg, thiopentone sodium 3-5 mg/ kg, and tracheal intubation was facilitated by vecuronium bromide0.1mg/kg intravenously. Anesthesia was maintained by N_2O: O_2 (60:40) with controlled ventilation. After 1 hour of surgery, each patient received 1 gm of paracetamol infused over 30 minutes intravenously. Throughout the laparoscopic surgery, carbon dioxide pneumoperitoneum was established and maintained at a pressure of 14 mm Hg and $ETCO_2$ was maintained between 25-45 mm Hg. The surgical techniques were identical in

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all the three groups. During surgery, Ringer's lactate solution was administered in maintenance dose as per the Holiday Segar formula. At the end of the operation, neuromuscular blockade was antagonized with the injection of neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg intravenously and the patient was extubated when respiration was deemed sufficient and they were able to obey commands. Arterial pressures and heart rates were measured upon arrival in the OT (baseline), before induction, 3 minutes after endotracheal intubation, before pneumoperitonium (P0); at 10 (P10), 20 (P20) and 30 (P30) minutes after pneumoperitoneum and then every 20 minutes till the end of surgery, ten minutes after release of CO_2 and ten minutes after extubation.

Statistical Analysis

Data was expressed as mean and standard deviation. The homogeneity in 3 groups of mean and SD was analyzed using SPSS version 16.0 software. Comparisons amongst the same group were done using the Student- T-test while inter-group comparisons were done using one-way analysis of variance (ANOVA). Categorical data were compared using the Chi-square test. A p-value of less than or equal to 0.05 was considered statistically 'significant'.

RESULTS

There were no significant differences between the three groups concerning demographic data such as age, sex, weight, ASA grade, and duration of surgery (Table 1). Preoperative vital parameters were compared among the three groups of patients and no significant difference was found (Baseline values of Table 2, 3, 4, and 5). Mean intra-abdominal pressure was maintained at 14 mm Hg throughout the laparoscopic surgery. No patient was excluded from the study. However, 4 out of 20 patients (20%) in group K required intra-operative NTG drip for control of hypertension. It was not required in group C or D patients, because they remained hemodynamically stable. Upon statistical comparison of heart rate in three groups of patients, significant variation was observed throughout the intraoperative period except for the baseline and before induction values where no significant difference was observed (Table 2). In group K, the heart rate was significantly higher after intubation and after extubation (105.55±10.20 and 105.45±8.99 respectively). The mean heart rate was lowest for group D. 3 out of 20 patients (15%) in group D required intravenous atropine due to bradycardia. Systolic arterial pressure was significantly higher in group K (especially after intubation, at P30, and after extubation) except for the baseline value (Table 3). No significant episode of hypotension was found in any of the groups post-pneumoperitoneum. Mean and diastolic arterial pressure was significantly higher in group K (especially after intubation, at P20, P30, and after extubation). It was significantly lower in group D (Tables 4 and 5).

Table 1: Demographic profile (Mean ± SD).

Demographic profile	Group C	Group D	Group K	P value	Significance
Age (years)	37.7±9.59	37.3±9.41	35.4±10.34	0.7309	NS
Sex (F: M)	18: 2	18: 2	17 : 3	0.8505	NS
Weight (Kg)	60.65±6.21	61.05±6.86	60.15±7.97	0.92157	NS
ASA Grade (I : II)	16 : 4	15 : 5	16 : 4	0.90616	NS
Duration of surgery (min)	47.95±9.20	45.70±12.59	48.50±10.74	0.69354	NS

Table 2: Changes in heart rate in three groups (Mean ± SD).

Heart Rate (bpm)	Group C	Group D	Group K	P value	Significance
Baseline	76.60±6.76	77.85±6.84	76.30±7.75	0.76746	NS
Before Induction	72.95±6.68	71.40±6.71	76.55±8.05	0.07499	NS
After Intubation	86.10±7.21	74.65±7.03	105.55±10.20	<0.00001	HS
P 0	74.80±10.25	70.95±8.51	83.60±11.03	0.00062	HS
P 10	78.15±11.01	73±9.24	85.80±9.62	0.00068	HS
P 20	77.40±6.08	72.05±10.67	85.20±6.97	0.00002	HS
P 30	76.10±5.66	70.83±8.42	87.95±6.07	<0.00001	HS
After Release of CO_2	71.75±5.70	69.70±5.14	75.60±5.62	0.00452	HS
After Extubation	77.75±8.03	71.95±8.68	105.45±8.99	<0.00001	HS

P0, P10, P20, P30 = before & 10, 20, 30 minutes after pneumoperitoneum, respectively; NS = Not significant, HS = Highly significant

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Table 3: Changes in systolic arterial pressure in three groups (Mean ± SD).

SAP (mm Hg)	Group C	Group D	Group K	P value	Significance
Baseline	121.95±7.75	121.05±8.12	118.80±8.82	0.46557	NS
Before Induction	112.80±6.49	109.15±6.89	116.50±8.62	0.01048	S
After Intubation	124.50±9.36	115.10±6.20	144.05±7.13	<0.00001	HS
P 0	114.80±6.68	112.35±7.82	124.10±7.35	0.0033	HS
P 10	122.95±7.82	119.85±8.37	129.35±7.03	0.00102	HS
P 20	122.10±7.91	116.35±10.41	134.20±10.82	<0.00001	HS
P 30	119.35±7.74	113.72±10.27	140.20±9.49	<0.00001	HS
After Release of CO_2	114.15±8.13	110.40±9.91	121.95±8.83	0.00055	HS
After Extubation	124.55±7.34	118.60±10.57	138.75±10.46	<0.00001	HS

P0, P10, P20, P30 = before & 10, 20, 30 minutes after pneumoperitoneum, respectively;
NS = Not significant, HS = Highly significant, S = Significant, SAP = Systolic arterial pressure

Table 4: Changes in mean arterial pressure in three groups (Mean ± SD).

MAP (mm Hg)	Group C	Group D	Group K	P value	Significance
Baseline	94.50±9.54	93.25±8.03	92.60±9.63	0.79895	NS
Before Induction	86.85±8.83	83.25±7.87	92.45±9.57	0.00617	HS
After Intubation	97.75±11.10	88.50±6.85	107.40±8.18	<0.00001	HS
P 0	89.75±6.07	85.70±6.84	94.15±8.36	0.00194	HS
P 10	94.70±6.49	89.15±6.66	101.95±6.70	<0.00001	HS
P 20	93.60±6.31	86.45±7.52	105.20±9.68	<0.00001	HS
P 30	92.10±6.56	84.50±7.59	106.75±8.90	<0.00001	HS
After Release of CO_2	88.65±7.33	82.65±8.55	93.20±6.57	0.00021	HS
After Extubation	95.60±6.68	90.10±8.93	107.75±7.99	<0.00001	HS

P0, P10, P20, P30 = before & 10, 20, 30 minutes after pneumoperitoneum, respectively; NS = Not significant, HS = Highly significant, MAP = Mean arterial pressure

Table 5: Changes in diastolic arterial pressure in three groups (Mean ± SD).

DAP (mm Hg)	Group C	Group D	Group K	P value	Significance
Baseline	80.10±10.86	79.45±9.01	79.60±10.37	0.9776	NS
Before Induction	73.80±10.72	70.35±9.61	80.25±10.67	0.0127	S
After Intubation	80.85±6.23	75.35±8.86	89.35±9.15	0.00001	HS
P 0	77.10±6.28	72.40±8.11	81.10±9.60	0.00525	HS
P 10	80.55±6.44	73.85±8.25	88.25±7.21	<0.00001	HS
P 20	79.70±6.10	71.50±9.03	90.75±10.35	<0.00001	HS
P 30	78.60±6.42	70.11±8.54	90.05±10.36	<0.00001	HS
After Release of CO_2	76.15±7.20	69.15±9.33	78.80±8.13	0.00153	HS
After Extubation	81.05±7.01	75.85±9.49	92.25±9.39	<0.00001	HS

P0, P10, P20, P30 = before & 10, 20, 30 minutes after pneumoperitoneum, respectively; NS = Not significant, HS = Highly significant, S = Significant, DAP = Diastolic arterial pressure

DISCUSSION

Hemodynamic changes with pneumoperitoneum were first recognized in 1947 [11]. Increased intra-abdominal pressure due to insufflation of gas may compress venous capacitance vessels causing an initial increase followed by a sustained decrease in preload as venous return decreases, while arterial compression may increase after-load and systemic vascular resistance [6]. At intra-abdominal pressure of 15 mm Hg, Joris et al4 found a 35% increase in mean arterial pressure, a 65% increase in systemic vascular resistance, and a 90% increase in pulmonary vascular resistance, while there was a 20% decrease in cardiac output. Ishizaki et al [12] tried to determine the safe range of intra-abdominal pressures during laparoscopic surgery. At 16 mm Hg of intra-abdominal pressure, a significant fall in cardiac output was observed. However, at 12 mm Hg of intra-abdominal pressure, hemodynamic alterations were not observed. During laparoscopy, the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible. In this present study, mean intra-abdominal pressure was maintained at 14 mm Hg throughout surgery. Hemodynamic perturbations during pneumoperitoneum can be harmful, especially in elderly and hemodynamically compromised patients [23]. Joris JL et al [13] opined that vasopressin and catecholamines, more particularly norepinephrine, probably mediate the increase in systemic vascular resistance in pneumoperitoneum. To date, many

different techniques and pharmacological agents have been used to reduce the detrimental effects of pneumoperitoneum. Techniques like reduction in intra-abdominal pressure during pneumoperitoneum and gasless laparoscopy using abdominal elevators have been tried [24]. Pharmacological agents like β-blockers, opioids, increasing concentration of inhalational anesthetic agents, nitroglycerine, and α2-adrenergic agonists have been tried [1, 7, 8]. The α2-agonists, including clonidine and dexmedetomidine, decrease central sympathetic outflow by acting like a brake and modify intraoperative cardiovascular and endocrine responses favorably to surgical stimuli, laryngoscopy, and laparoscopy [14]. Both clonidine and dexmedetomidine have been shown to reduce sympathetic nervous system activity and plasma catecholamine concentrations. Clonidine, with an elimination half-life of 6 to 10 hours, is a centrally acting selective partial α2-agonist (α2: α1 = 220: 1). It is known to induce sedation, decrease anesthetic drug requirement and improve perioperative hemodynamics by attenuating blood pressure and heart rate responses to surgical stimulation, and protecting against perioperative myocardial ischemia [9]. It provides sympathoadrenal stability and suppresses renin-angiotensin activity. There are studies indicating the benefits of using clonidine for the maintenance of hemodynamic stability in laparoscopic cholecystectomy. Malek et al [15] used 150 µg of clonidine as an intravenous infusion and intramuscularly while Sung et al16 and Yu et al17 used 150 µg of oral clonidine as premedication for the maintenance of hemodynamic stability during pneumoperitoneum. Yu et al even recommended its routine use as premedication in laparoscopic surgeries. Das et al [18] also used 150 µg of oral clonidine 90 minutes before surgery to prevent hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy. Kalra et a [19] used clonidine 1 µg/kg intravenously for 15 minutes before pneumoperitoneum and clonidine group patients showed significantly better hemodynamic control than the control group. Similar findings were obtained in the present study. However, higher doses of clonidine resulted in significant bradycardia and hypotension [25]. Dexmedetomidine, with an elimination half-life of 2 to 3 hours is a highly selective, potent, and specific α2-agonist (α2: α1 = 1620: 1), and is 7 to 10 times more selective for α2 receptors compared to clonidine with a shorter duration of action. It is considered a full agonist at α2 receptors as compared to clonidine, which is considered a partial agonist. Similar to clonidine, dexmedetomidine also attenuates the hemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anesthesia, and decreases perioperative requirements of inhaled anesthetics [10]. Jaakola et al [19] found decreased BP and heart rate during intubations following the administration of 0.6 µg/kg bolus of dexmedetomidine preoperatively. Lawrence et al [20] found a decreased hemodynamic response to tracheal intubation or extubation following a single high dose of dexmedetomidine (2 µg/kg). Ghodki et al [21] used dexmedetomidine 1 µg/kg intravenously over 15 minutes before induction followed by a maintenance infusion of 0.2 µg/kg/h and observed favorable vasopressor response during laryngoscopy, with minimal change in BP with pneumoperitoneum. In the present study, a single dexmedetomidine bolus of 1 µg/kg was used before induction, and similar hemodynamic control was noted. α2-agonists have also been reported to increase the risk of hypotension and bradycardia, especially in young healthy volunteers during rapid bolus administration [20, 22]. In this study, 3 patients of group D required intravenous atropine administration due to bradycardia.

CONCLUSION

Administration of clonidine or dexmedetomidine before the commencement of pneumoperitoneum effectively attenuates the hemodynamic response to pneumoperitoneum. However, dexmedetomidine blunts the hemodynamic response to pneumoperitoneum more effectively with a greater chance of developing hypotension and bradycardia.

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