Original Article

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Effect of Clonidine and Nitroglycerine Infusion on Haemodynamic and Intraocular Pressure in Laparoscopic Cholecystectomy

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Abstract

Background: In comparison to open surgery laparoscopic cholecystectomy is beneficial. Nevertheless, pneumoperitoneum and the alteration because of patient position causing pathophysiological offers limitation in anaesthetic management. We designed a study to observe the changes on heart rate and blood pressure, intraocular pressure and end-tidal carbon dioxide pressure due to use of clonidine and nitroglycerin during laparoscopic cholecystectomy.

Method: The study included 60 patients belonging to American Society of Anesthesiologists class I-II, planned for elective laparoscopic cholecystectomy were randomly divided into 2 groups: Clonidine infusion was given in group 1 at the rate of 1.5 µg/kg/hr and Group II received nitroglycerine infusion at the rate of 0.5 µg/kg/min (30µg/kg/hr). The parameters observed included mean arterial blood pressure, heart rate, end tidal CO_2, and intraocular pressure.

Results: The groups were comparable with no significant differences in gender and age. Heart rate of the patients were observed at preinduction, at intubation and after intubation at at interval of 5 minutes onwards upto reversal. Heart rate comparison after 15 minutes onwards upto reversal between group I and II showed statistically significant difference. Mean arterial pressure comparison between group I and II showed insignificant difference. Mean IOP at the time of induction in group I and II was 16.27±3.06 and 18.13±2.80 respectively, which was significant statistically. ETCO2 difference between the groups was not statistically significant.

Conclusion: The findings in our study suggested that clonidine surpass nitroglycerin in effectiveness with regard to prevent hemodynamic parameters changes and IOP induced by insufflations of CO2 in laparoscopic cholecystectomy. Also there is no significant hypotension requiring stopping of infusion or further treatment.

Keywords: Clonidine; Nitroglycerin; Laparoscopy; Cholecystectomy; Intraocular Pressure**.**

Introduction

The benefits of laparoscopy cholecystectomy has made it the gold standard for treatment of cholelithiasis [1]. Laparoscopy however requires CO2 for pneumoperitoneum.

Pneumoperitoneum causes physiological changes comprising of increase in arterial pressure and increase in pulmonary and systemic vascular resistance (PVR and SVR) early after the beginning of intra-abdominal insufflation with minor change in heart rate (HR).Studies have shown a reduction of 10% to 30% in cardiac output[2-4]. Any major alteration in arterial pressure can be detrimental for increase chances of adverse events in patients with pre-existing ischemic cardiac disease, essential hypertension, or increased intra-ocular or intra-cranial pressure.

Both pneumoperitoneum and patient positioning can synergistically increase the problems encountered during laparoscopic surgeries. [2,3]. Stimulation of the sympathetic nervous system by pneumoperitoneum and hypercapnia cause vasopressin and catecholamine release[5,6]. Drugs like beta-blockers, α_2 adrenergic agonists and opioids are used often to overcome the pneumoperitoneum induced

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circulatory response [2,7,8].

Clonidine has 9-12 hrs of half life and is a selective α_2 adrenergic agonist. It has central sympatholytic effect and causes fall in the blood pressure and hear rate with decreased cardiac output and systemic vascular resistance. In addition it nullifies the surgical stimuli induced and reduces the anesthetic and narcotic drug doses [9].

Intraocular pressure (IOP) normal range varies from 10-22 mm Hg andmaintained by several factorswhich includes the volume of intraocular fluid such as blood, venous congestion of the orbital veins, aqueous humor, the lens and the vitreous [10]. There is increase in IOP during laparoscopic surgerydue to physiological changes such as increase of blood pressure, end tidal carbon dioxide pressure and central venous pressure, which are the results of the postural changes and increased pressure in intrathoracic compartment [11]. The effects of nitroglycerine (NTG)on IOP have been studied with variable results [12-15].

Therefore, we designed randomized cross sectional to study the changes in heart rate, blood pressure , end tidal carbon dioxide ($EtCO_2$) pressure, and IOP associated with clonidine and nitroglycerin during laparoscopic cholecystectomy.

Methodology

Sixty patients(n=60) [American Society of Anesthesiologists class I or II] undergoing elective laparoscopic cholecystectomy were included in the study. The study was conducted after approval from the Institutional Ethics Committee. We excluded the patients who were younger than 20 years and older than 65 years; having acute or chronic opthalmic disease; pre-existing ocular hypertension and chronic lung diseases. This trial was registered by with Central Trial Registry of India (www.ctri.nic.in) having the registration number ***CTRI/2015/01/005434***

The patients were randomly divided into 2 groups: Group I received clonidine infusion at the rate of 1.5 µg/kg/hr and Group II received nitroglycerine infusion at the rate of 0.5 µg/kg/min (30µg/kg/hr). Randomization of the patients was achieved using a computer generated table.

Tablet alprazolam 0.5mg and tablet ranitidine 150 mg orally in night before surgery as pre-medication. All baseline readings were taken in the operating theater monitors displaying heart rate, electrocardiogram, noninvasive blood pressure, oxygen saturation, and $EtCO_2$ pressure. Patients were given intravenous pentazocine in a dose of 0.5 to 0.7 mg/kg body weight. After preoxygenation, the patients were induced with injection propofol 2mg/kg. Tracheal intubation was facilitated with vecuronium in dose of 100µg/kg body weight. Anaesthesia was maintained with oxygen, N_2O, isoflurane along with intermittent positive pressure ventilation (IPPV) and intermittent vecuronium. After induction and beforecreating pneumoperitonium infusion was started.

Rate of infusion was decreased to half if the value of mean arterial blood pressure decreases by 20% of baseline value, rate of infusion was doubled if the value of mean arterial blood pressure increases by 20% of baseline value. Infusion was terminated if the value of mean arterial blood pressure becomes less than 60mmHg. Infusion was stopped in all patients before reversal of neuromuscular blockade. Ringer lactate was administered at the rate of 15ml/kg in 1st hour followed by 7.5ml/kg/hr till the end of surgery to all patients.

The parameters observed were heart rate, mean arterial blood pressure, $EtCO_2$ pressure, and IOP. The heart rate, mean arterial blood pressure were measured just before induction, after induction, and therafter every 5 minutes until reversal. The $EtCO_2$was also observed every 5 minutes after induction until reversal. IOP was measured before induction, after startingthe infusion and 15minute thereafter, by Schiotz tonometer.

The mean and standard deviation of the parameters studied during observation period were calculated for two treatment groups and compared using Student t test. Intragroup comparison was done with Paired t- test. The critical value of 'p' indicating the probability of significant difference was taken as<0.05 for comparisons.

Results

There were no significant differences between two groups with respect to age and gender. Table 1 shows patient's heart rate in 2 groups. The patient's heart rate was observed preinduction, at the time of intubation and after intubation at every 5 minutes onwards upto reversal. The comparison of heart rate between group I and II showed statistically significant difference after 15 minutes onwards upto reversal.

Table 2 compares intergroup mean arterial pressure. Intergroup comparison of mean arterial

pressure between group I and II showed no significant difference.

Table 3 shows comparison of inter group IOP. At the time of pre induction mean IOP between group I and II was statistically not significant. At intubation mean IOP between group I and II was 16.27±3.06 and 18.13±2.80 respectively. At the time of reversal mean IOP in group I and II was 14.07±2.51 and 14.87±2.06 respectively (p = 0.184).

Table 4 compares intergroup $EtCO_2$ which is not significant. The mean change in $EtCO_2$ at 5 minutes between group I and II was 40.77±3.14 and40.80±2.14 respectively and at the time of reversal mean $EtCO_2$ was 34.27±1.17 and 34.77±1.07 respectively.

Table 1: Intergroup comparison of heart rate

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
Preinduction	76.07±16.98	71.00±16.65	1.167	0.248
Induction	77.97±14.28	73.03±16.01	1.259	0.213
5min	74.60±14.43	76.50±16.08	-0.482	0.632
10min	71.87±13.42	78.27±15.47	-1.711	0.092
15min	69.50±13.74	80.23±15.54	-2.833	0.006
20min	67.53±13.14	83.47±15.41	-4.308	<0.001
25min	66.83±12.30	86.07±15.93	-5.147	<0.001
30min	62.65±12.25	87.67±13.27	-6.262	<0.001
35min	64.73±11.51	91.47±14.89	-5.499	<0.001
40min	62.83±13.23	90.90±19.02	-4.072	0.001
Reversal	65.77±10.38	94.00±15.70	-8.214	<0.001

Table 2: Intergroup comparison of mean arterial pressure (MAP)

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
Preinduction	82.60±9.05	79.53±8.13	1.380	0.173
Induction	82.00±8.32	78.13±7.76	1.861	0.068
5min	103.47±133.84	75.60±7.43	1.139	0.260
10min	77.17±7.34	72.90±7.32	2.253	0.028
15min	74.87±7.00	71.30±6.95	1.979	0.053
20min	72.53±6.61	69.27±7.28	1.818	0.074
25min	70.34±6.80	66.97±8.02	1.729	0.089
30min	68.50±6.45	67.83±6.63	0.337	0.738
35min	65.20±5.69	66.00±6.09	-.371	0.713
40min	63.33±4.11	62.00±4.89	0.694	0.496
Reversal	65.80±6.33	63.87±6.01	1.213	0.230

Table 3: Intergroup comparison of intraocular pressure (IOP)

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
Preinduction	17.80±1.90	18.50±2.06	-1.366	0.177
Induction	16.27±3.06	18.13±2.80	-2.464	0.017
5min	-	-	-	-
10min	-	-	-	-
15min	14.73±2.76	16.03±2.37	-1.955	0.055
20min	-	-	-	-
25min	-	-	-	-
30min	14.05±2.97	14.95±1.93	-1.145	0.259
35min	-	-	-	-
40min	-	-	-	-
Reversal	14.07±2.51	14.87±2.06	-1.346	0.184

Table 4: Intergroup comparison of end- tidal carbon dioxide($EtCO_2$)

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	T-value	P-value
Preinduction	-	-	-	-
Induction	-	-	-	-
5min	40.77±3.14	40.80±2.14	-.048	0.962
10min	39.30±2.43	39.57±1.97	-.465	0.643
15min	37.73±2.10	37.87±1.83	-.262	0.794
20min	35.80±1.86	36.33±1.70	-1.155	0.253
25min	35.62±1.49	35.41±1.52	0.521	0.604
30min	35.00±1.29	35.14±1.76	-.294	0.771
35min	35.40±1.29	35.27±1.10	0.303	0.764
40min	33.83±0.93	34.40±0.96	-1.392	0.179
Reversal	34.27±1.17	34.77±1.07	-1.723	0.090

Discussion

In recent years, laparoscopic surgery has become a common clinical practice with laparoscopic cholecystectomy being the most frequent. From anesthetic point of view an appraisal of the complication of hemodynamic alterations due to pneumoperitoneum, increase in intra-abdominal pressure and procedure related are essential. For upper abdominal laparoscopic surgery general anesthesia is the choice of anesthesia. Protection of airway is done by tracheal intubation and intermittent positive pressure ventilation(IPPV) and for normocarbia control of pulmonary ventilation is required. To control these haemodynamic changes which could be devastating present study was done to compare effects of clonidine and nitroglycerine.

In group I clonidine showed significant decrease in heart rate($p<0.05$). Clonidine, when used as intravenous infusion, intramuscular or orally, maintains haemodynamic stability during pneumoperitoneum by minimizing the heart rate variability as found in other studies [16-18].

In clonidine group out of 30 patients, heart rate was increased in 15 patients (50%) as response to intubation. However, heart rate fell significantly after 10 minutes of intubation ($p <0.05$). In our study Clonidine onset of action was more than 5 minutes. Fall in heart rate was observed after 20-30 minutes which was statistically significant. The peak plasma concentration of clonidine occur after 30 minutes. Heart rate was slightly increased during reversal as before reversal clonidine infusion was stopped.

In nitroglycerin group after intubation upto reversal increase in heart rate was observed which was statistically significant ($p<0.05$). The onset of action was observed to be 1-3 minutes. Nitroglycerine infusion was used in low dose in our study. As NTG at low doses preferentially dilate the veins more than the arterioles, it causes fall in mean arterial pressure, a decrease in blood pressure and might increases heart rate. Venodilation decrease size of both ventricles and end-diastolic pressures, however there is only minor change in systemic vascular resistance. Studies have shown that intravenous NTG causes vasodilation in coronaries before any changes in systemic haemodynamic. Also in another studythe heart rate began to augment after 1min in the healthy subjects after sublingual administration which became normal within 30minute [19-21].

After15 minutes of intubation and up to reversal heart rate difference between both groups was found statistically significant, as nitroglycerine causes rise in heart rate wheras clonidine attenutes heart rate (Table 1). Both clonidine and NTG caused decrease in mean arterial pressure however the difference was not significant (Table 2). Similar studies have shown the effect of premedication with clonidine in maintaining perioperative haemodynamic stability.

NTG has vasodilator effect on both veins and arteries. NTG nullify the rise in MAP and SVR . In laparoscopic surgery NTG infusion causes decrease in after load which cause marked haemodynamic improvement as it causes vascular smooth muscle relaxation. NTG infusion was stopped in 6 patients out of 30 (20%) because MAP fall less than 60mmHg. None of the patient in clonidine group developed hypotension.

Nitroglycerine decreases IOP by preventing increase of SVR and modulating aqueous humor dynamics. Preinfusion and postintubation rise in IOP in both groups due to intubation response. In laparoscopic cholecystectomy low dose nitroglycerin infusion might be beneficial to decrease IOP at the time of pneumoperitoneum. There was fall in IOP by both clonidine and nitroglycerine (Table 3) which is consistent with studies done elsewhere [22,23].

There is significant decrease in $EtCO_2$ by both clonidine and nitroglycerine infusion which persisted upto reversal. The fall in $EtCO_2$ was due to decrease in blood pressure that can decreases lung perfusion.

The findings of our study suggested that, clonidine was found more effective than nitroglycerine preventing change in haemodynamic parameter and IOP. Comparative studies between clonidine and NTG are sparse. Limitations of the study includes low sample size. More studies with large population is needed to validate this result.

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