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Research Article

EFFECTS OF CLONIDINE ON HAEMODYNAMICS IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY- A COMPARATIVE STUDY

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ABSTRACT

A randomized double blind prospective trial designed to evaluate the efficacy of clonidine in achieving haemodynamic stability in patients undergoing laparoscopic cholecystectomy. Sixty patients, of both sex (31-60 yrs of age) undergoing elective laparoscopic cholecystectomy were randomly allocated equally in one of the two parallel groups: C & P. Group C received clonidine 1.5 µg /kg intravenously over a period of 15 minutes before induction followed by 1 µg/kg /hr by continuous i.v. infusion. Group P received isotonic saline 0.9% in the same volume. Mean arterial pressure and heart rate in Group C was significantly less after intubation and throughout the period of pneumoperitonium. No significant difference in the parameters of recovery was observed between the two groups. Clonidine improves intra and post-operative haemodynamic stability during laparoscopic surgery without prolonging recovery.

Keywords: clonidine, haemodynamics, laparoscopic surgery.

INTRODUCTION

Clonidine is an imidazoline derivative with α_2 agonist activity. It has intrinsic analgesic effects and produces preoperative sedation and anxiolysis. The intravenous administration of clonidine before induction of anaesthesia attenuates sympatho-adrenal responses to laryngoscopy and endotracheal intubation. It also provides improved haemodynamic stability during intraoperative period.

Carbon dioxide (CO_2) is usually used to produce pneumoperitoneum during laparoscopic surgical procedures[1, 2]. Both CO_2 and pneumoperitoneum causes adverse cardiovascular and renal effects[3]. Some of these effects are related to CO_2 and some to elevated intra abdominal pressure. Immediately after creation of pneumoperitonium, plasma level of norepinephrine, epinephrine and plasma renin activity increases[4]. Increased catecholamine level activates the renin–angiotensin–aldosterone–system. All these changes together contribute to elevated arterial pressure, increased systemic and pulmonary vascular resistance and reduced cardiac output[5]. Laparoscopic cholecystectomy is performed in reverse Trendelenburg position[6]. Cardiac output is further decreased secondary to decreased venous return caused by the above said position. Clonidine decreases sympathetic tone, arterial pressure, and heart rate and produces sedation[7]. It also diminishes intraoperative requirement of analgesics.

This placebo controlled, double blind prospective study is designed to evaluate the efficacy of clonidine in bringing haemodynamic stability in patients undergoing laparoscopic cholecystectomy.

METHODS

The present study was done in Calcutta National Medical College and Hospitals, Kolkata, West Bengal, India. The study protocol was approved by the Institutional Ethical Committee of Calcutta National Medical College and Hospital. Written Informed Consent was taken from each subject willing to enter the study. Sixty ASA grade I and II patients undergoing elective laparoscopic cholecystectomy were randomly assigned to of the two groups: Group C (Clonidine group) and Group P (Control group) Patients with hypertension, morbid obesity, alcohol / drug abuse and severe hepatic, renal, endocrine and cardiac dysfunction were excluded from the study.

On arrival to operation theatre, routine monitoring (ECG, Pulse oxymetry, NIBP) was started and baseline vital parameters like heart rate, mean arterial blood pressure (MAP) and arterial oxygen saturation (SpO_2) were recorded. An intravenous line was started. Group C patients received clonidine 1.5µg/kg i.v. before induction over a period of 15 minutes and followed by 1µg/kg/hr by continuous i.v. infusion intraoperatively. Group P patients were given isotonic saline 0.9% in the same volume as the study drug.

After preoxygenation for 3 minutes, patients were induced with fentanyl 1 µg/kg and propofol, 2 mg/kg. Endotracheal intubation was facilitated by muscle relaxant vecuronium bromide. Anaesthesia was maintained with O_2 in N_2O, intermittent bolus dose of fentanyl citrate (0.5µg/kg) and vecuronium bromide (0.01mg/kg). CO_2 was insufflated into the peritoneal cavity (at a rate of 2 lit/min) to create pneumoperitoneum. Intra-abdominal pressure was maintained to 14 mmHg throughout the laparoscopic procedure. The patients were mechanically ventilated to keep $ETCO_2$ between 35-40 mmHg. Normothermia was maintained during operation. All patients received intravenous lactated ringer's solution at a rate of 5ml/kg/hr as maintenance fluid. Intraoerative hypertension was managed by infusion of nitroglycerine.

At the end of the operation the infusion of clonidine / isotonic saline was stopped, residual neuromuscular block was reversed by appropriate dose of neostigmine and glycopyrrolate and tracheal extubation was performed. Timings of the following events were noted as i) time to tracheal extubation ii) time to respond to verbal command iii) Orientation time. Heart rate, MAP and SPO_2 were also recorded throughout the surgical procedure at an interval of 15 minutes. Patients were observed for any adverse events during postoperative period.

STATISTICAL ANALYSIS

The results obtained from the study are presented in the following section in a tabulated manner. The results are expressed in Mean ± SD. Comparison between groups were performed with the Kruskal-Wallis one way ANOVA by ranks or Fisher's exact test for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when normal tests failed. P value<0.05 was considered to be statistically significant [Graph Pad InStat version 3.05, Graph Pad Software, SanDiego, CA]

RESULTS

Ten patients of group P developed severe hypertension (SBP > 170 mm of Hg, DBP > 110 mm of Hg and had to be controlled by nitroglycerine infusion. They were excluded from the final tabulation. The groups were comparable with respect to age, sex, weight and duration of surgery (Table 1). There was no significant difference in the preoperative MAP values between the two groups. After infusion of clonidine / isotonic saline, MAP values are lower in group C than in group P ($P < 0.001$, Table 2). Map values in group C fell significantly after induction ($P < 0.01$, Table 2). MAP values in group P were significantly higher ($P < 0.05$) after intubation and pneumoperitoneum and remained higher throughout the pneumoperitoneum (Table 2).

The preoperative heart rate is comparable between the two groups (Table 3). In group P, heart rate increased significantly after intubation and pneumoperitoneum ($P<0.01$) and remained higher throughout the peumoperitoneum in comparison to group C ($P < 0.05$, Table 3).

There is no significant difference in the parameters of recovery between the two groups ($P > 0.05$), Table 4).

Table 1: Patient's characteristics and duration of surgery in two groups (Mean ± SD)

	Group C(n=30)	Group P(n=20)
Age (mean; range)	41.4(35-65)	46.7(35-65)
Sex (M/F)	6/24	7/23
Weight (Kg)	57.28 ± 10.76	59.88 ± 10.4
Duration of surgery (min)	76.52 ± 9.2	81.17 ± 9.56

Table 2: Changes in Mean Arterial Pressure (Mean ± SD)

	Group C	Group P	Statistical Significance
Preoperative	104.4 ± 13	103 ± 10.7	P>0.05; NS
After infusion	8 ± 16.7	107.2 ± 13.3	P<0.01; HS
1 min after induction	60 ± 16.8	92 ± 25.4	P<0.01; HS
1 min after intubation	89.5 ± 25.1	118.2 ± 16.3	P<0.05; S
After pneumoperitoneum	96 ± 13.6	132 ± 16.3	P<0.05; S
15 min			
30 min	90 ± 14.6	128 ± 15.7	P<0.05; S
45 min	81 ± 13.8	126 ± 16	P<0.05; S
60 min	86 ± 12.2	130 ± 13.3	P<0.05;
	91 ± 16.8	126 ± 10.8	P<0.05; S
End of pneumoperitoneum	82.2 ± 12.2	102 ± 10.9	P<0.05; S
Postoperative period	86.1 ± 7.6	110.1 ± 18.7	P<0.05; S

S –Significant; NS –Not Significant; HS –Highly Significant

Table 3: Changes in Heart Rate (Mean ± SD)

	Group C	Group P	Statistical Significance
Preoperative	76 ± 12.2	80.1 ± 10.0	P>0.05; NS
After infusion	74 ± 11.4	82 ± 9.6	P>0.05; NS
1 min after induction	66.23± 16.1	79.4 ± 13	P<0.05; S
1 min after intubation	79.1 ± 12	98.2 ± 14.7	P<0.01; HS
After pneumoperitoneum	74 ± 9.5	96 ± 12.6	P<0.01; HS
15 min			
30 min	78 ± 9.1	90 ± 14.7	P<0.05; S
45 min	76 ± 13.6	94 ± 13.1	P<0.05; S
60 min	75 ± 7.3	96 ± 11.5	P<0.05; S
	75 ± 7.9	94 ± 10.8	P<0.05; S
End of pneumoperitoneum	68 ± 12.4	84 ± 1.4	P<0.05; S
Postoperative period	76 ± 11.6	96 ± 16.8	P<0.01; HS

S –Significant; NS –Not Significant; HS –Highly Significant

Table 4: Recovery time (min), Mean ± SD

	Group C	Group P	Statistical significance
Extubation time (min)	5.53 ± 0.8	6.12 ± 1.48	P>0.05; NS
Response to level command	7.79 ± 1.69	7.74 ± 1.68	P>0.05; NS
Time for orientation	9.33 ± 1.41	8.72 ± 1.07	P>0.05; NS

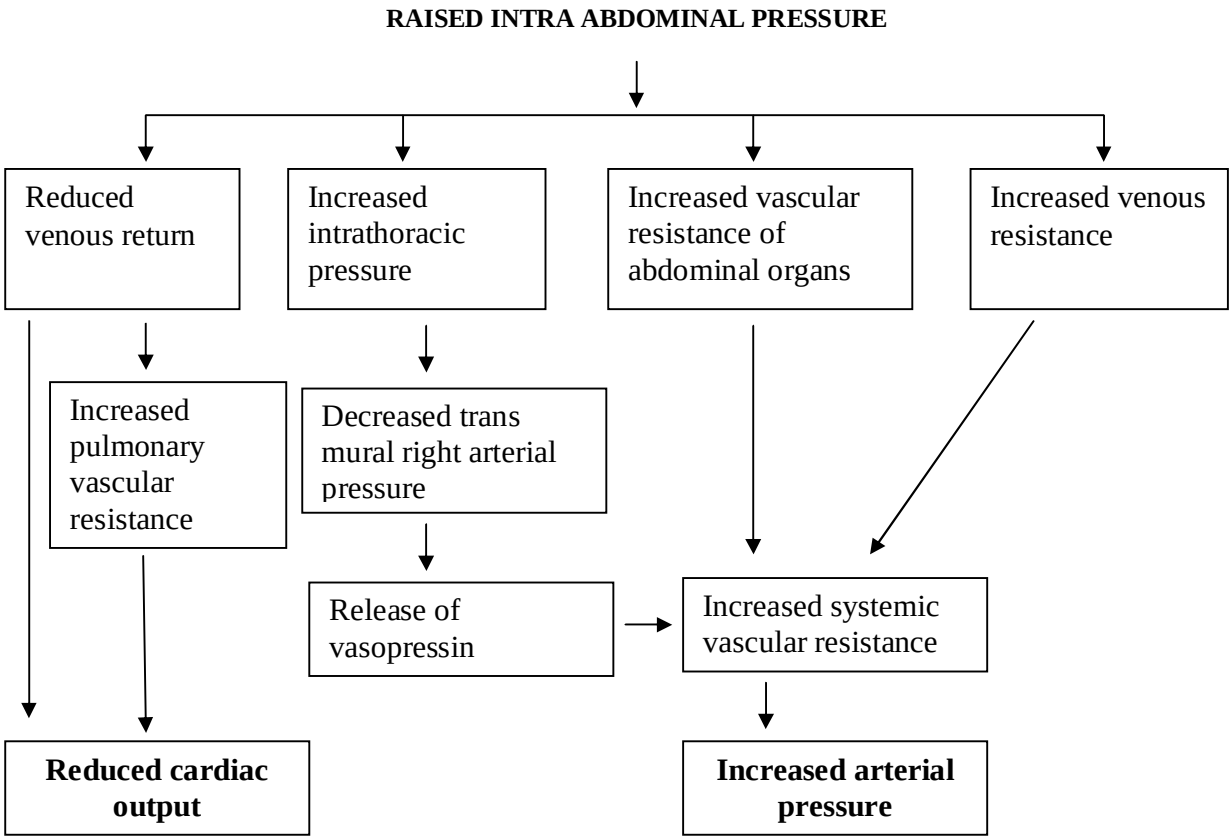
S –Significant; NS –Not Significant

DISCUSSION

In this study, we observed the effects of clonidine on haemodynamics in patients undergoing laparoscopic cholecystectomy. Clonidine is a partial α_2 adrenergic agonist that has sedative, analgesic and antihypertensive effects[8]. Clonidine provides its haemodynamic effects acting both on brain and periphery. Clonidine activates the postsynaptic α_2 adrenoceptors in nucleus tractus solitarius and locus ceruleus of the brain stem and reduces the sympathetic drive. It also activates nonadrenergic imidazoline preferring binding sites in the lateral radicular nucleus, thereby producing hypotension and an antiarrythmogenic action[9, 10]. In the periphery activation of presynaptic α_2 adrenoceptors at sympathetic terminals reduces their release of nor-epinephrine by the sympathetic nerve terminal, which could cause vasorelaxation and reduced chronotropic drive[11]. Clonidine reduces heart rate partly by a presynaptically mediated inhibition of nor-epinephrine release at the neuroreceptor junctions and partly by a vagomimetic action[12]. Although clonidine depress atrioventricular nodal

conduction, severe bradyarrythmias are rare with clonidine use[12]. Clonidine may reduce myocardial oxygen demand and has been shown to reduce infarct size when administered to patients in the acute phase of myocardial infarction[13]. Delayed onset of hypotension has not been observed with the use of clonidine.

CO_2 is routinely used to create pneumoperitoneum during laparoscopic surgery. Elevated intraabdominal pressure induced by pneumoperitoneum and CO_2 itself adversely effects the cardiovascular system[3].



Schematic representation of haemodynamic changes due to raised intraabdominal pressure.

Plasma level of norepinephrine, epinephrine and plasma renin activity increases immediately after pneumoperitoneum. Increased catecholamine level activates the renin - angiotensin – aldosterone – system (RAAS) leading to some characteristic[4,5] haemodynamic alterations which include decreased cardiac output (25-35%), elevated arterial pressure, increased systemic / pulmonary vascular resistance

Laparoscopic cholecystectomy is performed in reverse Trendlenburg position. This particular position leads to diminished venous return which is turn leads to further decrease in cardiac output[6]. Although normal heart rate tolerates the increase in afterload under physiologic conditions, the changes in afterload produced by pneumoperitoneum may result in deleterious effects in patients with compromised cardiac function. Clonidine significantly reduces the release of catecholamines and almost completely blocks norepinephrine release, attenuates the increase in systemic vascular resistance. Clonidine improves intraoperative and postoperative haemodynamic stability by stabilizing the changes in arterial pressure, heart rate and cardiac output.

CONCLUSION

This study confirms that haemodynamic changes (rise in mean arterial pressure and heart rate) are attenuated by clonidine infusion during laparoscopic cholecystectomy. Clonidine causes sedation but it does not delay the recovery time as shown in the study.

To conclude, clonidine improves intraoperative and postoperative haemodynamic stability during laparoscopic surgery. It reduces the increase in mean arterial pressure and heart rate during and after pneumoperitoneum. The haemodynamic stability provided by clonidine should be helpful in patients with compromised cardiac function, thereby allowing these patients to benefit from all the advantages of the laparoscopic approach.

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